CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

206627Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

EXCLUSIVITY SUMMARY

NDA # 206627 SUPPL # N/A HFD # 170

Trade Name: Hysingla ER

Generic Name: hydrocodone bitartrate extended-release tablets

Applicant Name: Purdue Pharma LP

Approval Date, If Known: November 20, 2014

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)(2)

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES ☒ NO ☐

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

N/A

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:

N/A

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d) Did the applicant request exclusivity?

YES ☒ NO ☐

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

The applicant did not specify, they only referenced 21 CFR 314.50(j) , but in the context of their 505(b)(2) application, a 3 year period of exclusivity is appropriate for consideration.

e) Has pediatric exclusivity been granted for this Active Moiety?

YES ☐ NO ☒

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

N/A

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 ☐

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

NDA#	202880	Zohydro ER (hydrocodone bitartrate) extended-release tablets
NDA#	020716	Vicoprofen (hydrocodone bitartrate/ibuprofen) tablets
NDA#	204307	Vituz (Chlorpheniramine maleate/hydrocodone bitartrate) oral solution
NDA#	022439	Zutripro (Chlorpheniramine maleate/ hydrocodone bitartrate/pseudoephedrine hydrochloride) oral solution
NDA#	022442	Rizera (hydrocodone bitartrate/ pseudoephedrine hydrochloride) oral solution
NDA#	020716	Vicoprofen (hydrocodone bitartrate/ibuprofen) tablets

And many ANDA products containing hydrocodone bitartrate in combination with other drug moieties, e.g., acetaminophen, homatropine methylbromide, ibuprofen

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

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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

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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?

N/A 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:

HYD3002: "A Multicenter, Randomized, Double-blind, Placebo-controlled Study With an Open-label Run-in to Assess the Efficacy and Safety of Hydrocodone Bitartrate (HYD) Tablets 20 to 120 mg Once-daily in Subjects with Moderate to Severe Chronic Low Back Pain"

HYD1013: "A Single-Center, Randomized, Double-Blind, Crossover Study to Evaluate the Abuse Potential, Phannacokinetics, and Safety of Oral Crushed and Intact Controlled Release Hydrocodone (HYD) Tablets in Recreational Opioid Users"

HYD1014: "A Single-Center, Randomized, Double-Blind, Crossover Study to Evaluate the Abuse Potential, Pharmacokinetics, and Safety of Crushed and Intranasally Administered Controlled Release Hydrocodone in Recreational Opioid Users"

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

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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 (HYD3002)	YES ☐	NO ☒
Investigation #2 (HYD1013)	YES ☐	NO ☒
Investigation #3 (HYD1014)	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:

N/A

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 (HYD3002)	YES ☐	NO ☒
Investigation #2 (HYD1013)	YES ☐	NO ☒
Investigation #3 (HYD1014)	YES ☐	NO ☒

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

N/A

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"):

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HYD3002: "A Multicenter, Randomized, Double-blind, Placebo-controlled Study With an Open-label Run-in to Assess the Efficacy and Safety of Hydrocodone Bitartrate (HYD) Tablets 20 to 120 mg Once-daily in Subjects with Moderate to Severe Chronic Low Back Pain"
HYD1013: "A Single-Center, Randomized, Double-Blind, Crossover Study to Evaluate the Abuse Potential, Phannacokinetics, and Safety of Oral Crushed and Intact Controlled Release Hydrocodone (HYD) Tablets in Recreational Opioid Users"

HYD1014: "A Single-Center, Randomized, Double-Blind, Crossover Study to Evaluate the Abuse Potential, Pharmacokinetics, and Safety of Crushed and Intranasally Administered Controlled Release Hydrocodone in Recreational Opioid Users"

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1 (HYD3002) !
!
IND # 059175 YES ☒ ! NO ☐
! Explain:

Investigation #2 (HYD1013) !
!
IND # 059175 YES ☒ ! NO ☐
! Explain:

Investigation #3 (HYD1014) !
!
IND # 059175 YES ☒ ! NO ☐
! Explain:

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(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?

N/A

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: Dominic Chiapperino, PhD

Title: Regulatory Project Manager, DAAAP
Date: signed electronically

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Name of Office/Division Director signing form: Sharon Hertz, MD
Title: Acting Director, DAAAP

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

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

/s/

DOMINIC CHIAPPERINO
11/20/2014

SHARON H HERTZ
11/20/2014

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION[1]		
NDA # 206627	NDA Supplement # Not applicable (N/A)	If NDA, Efficacy Supplement Type: N/A *(an action package is not required for SE8 or SE9 supplements)*
Proprietary Name: Hysingla ER Established/Proper Name: hydrocodone bitartrate Dosage Form: Extended-release oral tablets		Applicant: Purdue Pharma LP Agent for Applicant (if applicable): N/A
RPM: Dominic Chiapperino, PhD		Division: Division of Anesthesia, Analgesia, and Addiction Products

NDA Application Type: ☐ 505(b)(1) ☒ 505(b)(2) Efficacy Supplement: ☐ 505(b)(1) ☐ 505(b)(2) BLA Application Type: ☐ 351(k) ☐ 351(a) Efficacy Supplement: ☐ 351(k) ☐ 351(a)	**For ALL 505(b)(2) applications, two months prior to EVERY action:** • **Review the information in the 505(b)(2) Assessment and submit the draft[2] to CDER OND IO for clearance.** • **Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity)** ☒ No changes ☐ New patent/exclusivity *(notify CDER OND IO)* Date of check: 11/20/14 ***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.***

❖ Actions	
• Proposed action • User Fee Goal Date is October 28, 2014	☒ AP ☐ TA ☐ CR
• Previous actions *(specify type and date for each action taken)*	☒ 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. For example, if the application is a pending BLA supplement, then a new *RMS-BLA Product Information Sheet for TBP* must be completed.

Review priority: ☐ Standard ☒ Priority
Chemical classification (new NDAs only): 3
(confirm chemical classification at time of approval)

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

NDAs: Subpart H
☐ Accelerated approval (21 CFR 314.510)
☐ Restricted distribution (21 CFR 314.520)
Subpart I
☐ Approval based on animal studies

BLAs: Subpart E
☐ Accelerated approval (21 CFR 601.41)
☐ Restricted distribution (21 CFR 601.42)
Subpart H
☐ 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

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

Comments:

❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 *(approvals only)*	☐ Yes ☐ No
❖ 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 (The potential for being blocked by Zohydro ER (NDA 202880) 3-year exclusivity was considered, but no FDA final assessment was made as to the scope of Zohydro ER exclusivity because the two sponsors, Purdue and Zogenix, negotiated a waiver of Zohydro ER 3-year exclusivity to allow approval of Hysingla ER.)
❖ 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.

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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)*	AP, 11/20/14
Labeling	
❖ Package Insert *(write submission/communication date at upper right of first page of PI)*	
• Most recent draft labeling *(if it is division-proposed labeling, it should be in track-changes format)*	☒ Included
• Original applicant-proposed labeling	☒ Included
❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling *(write submission/communication date at upper right of first page of each piece)*	☒ Medication Guide ☐ Patient Package Insert ☐ Instructions for Use ☐ Device Labeling ☐ None
• Most-recent draft labeling *(if it is division-proposed labeling, it should be in track-changes format)*	☒ Included
• Original applicant-proposed labeling	☒ Included
❖ Labels (**full color** carton and immediate-container labels) *(write submission/communication date on upper right of first page of each submission)*	
• Most-recent draft labeling	☒ Included
❖ Proprietary Name • Acceptability/non-acceptability letter(s) *(indicate date(s))* • Review(s) *(indicate date(s)*	Letter, Acceptable, 7/18/14 Review of J.Schlick, I.Chan, and K.Taylor, 7/2/14
❖ Labeling reviews *(indicate dates of reviews)*	RPM: ☒ None DMEPA: J.Schlick, I.Chan, 10/22/14 DMPP/PLT (DRISK): M.Walker, E.Chung-Davies, B.Fuller, L.Griffiths, 8/7/14 OPDP: E.Chung-Davies, 8/7/14 SEALD: ☒ None CSS: ☒ None (See labeling comments in general review) Other: (PMHS/Peds) D.Snyder, H.Sachs, L.Yao 7/31/14; (PMHS/MH) C.Kasten, M.Tassinari,L.Yao, 7/31/14
Administrative / Regulatory Documents	

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❖ RPM Filing Review[4]/Memo of Filing Meeting *(indicate date of each review)* ❖ All NDA 505(b)(2) Actions: Date each action cleared by 505(b)(2) Clearance Committee	505(b)(2) Assessment, D.Chiapperino, 11/20/14 Cleared by Committee on 10/14/14 Filing reviews: D.Chiapperino, 6/30/14 J.Tolliver, M.Rusinowitz, S.Calderon, M.Klein, 6/11/14 J.Pinto, 6/6/14 J.Spaulding, E.Fields, 6/4/14 D.Mellon, 6/4/14 S.Nallani, Y.Xu, 6/3/14 Y.Zhou, J.Derr, 6/3/14 J.Metcalfe, B.Riley, 5/16/14 A.Khairuzzaman, T.Ghosg, 5/7/14
❖ NDAs only: Exclusivity Summary *(signed by Division Director)*	☒ 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 ○ If yes, Center Director's Exception for Review memo *(indicate date)* ○ If yes, OC clearance for approval *(indicate date of clearance communication)*	☐ Yes ☒ No ☐ Not an AP action
❖ Pediatrics *(approvals only)* • Date reviewed by PeRC July 9, 2014 If PeRC review not necessary, explain: _____	Minutes, J.Inglese, 7/21/14
❖ 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, etc.) *(do not include previous action letters, as these are located elsewhere in package)*	In reverse chronology: various, numerous "Information Request" emails; Filing/74-day letter, 6/13/14; NDA Acknowledgement letter, 4/30/14
❖ 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)	None
❖ Minutes of Meetings	
• If not the first review cycle, any end-of-review meeting *(indicate date of mtg)*	☒ N/A or no mtg
• Pre-NDA/BLA meeting *(indicate date of mtg)*	Minutes, 8/8/13 (meeting held 7/10/13)
• EOP2 meeting *(indicate date of mtg)*	Minutes, 5/31/11 (meeting held 5/4/11)
• Mid-cycle Communication *(indicate date of mtg)*	☒ N/A
• Late-cycle Meeting *(indicate date of mtg)*	☒ N/A
• Other milestone meetings (e.g., EOP2a, CMC pilots) *(indicate dates of mtgs)*	

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

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❖ Advisory Committee Meeting(s)	☒ No AC meeting
• Date(s) of Meeting(s)	
Decisional and Summary Memos	
❖ Office Director Decisional Memo *(indicate date for each review)*	☒ None
Division Director Summary Review *(indicate date for each review)*	S.Hertz, 11/20/14
Cross-Discipline Team Leader Review *(indicate date for each review)*	E.Fields, 10/28/14
PMR/PMC Development Templates *(indicate total number)*	4 groupings of template forms in DARRTS, all signed on 11/19/14 by J.Racoosin, to capture 2808-1 through 2808-6 and 2065-1 through 2065-5
Clinical	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) *(indicate date for each review)*	☒ No separate review
• Clinical review(s) *(indicate date for each review)*	J.Spaulding, E.Fields, 8/14/14
• Social scientist review(s) (if OTC drug) *(indicate date for each review)*	☒ 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 *(indicate date of review/memo)*	(see p.27 of clinical review)
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers *(indicate date of each review)*	CDRH/ENTB consult review, C.Gusto, S.Nandkumar, 6/26/14 CDER/IRT-QT consult review, M.J.Ng, Q.Dang, F.Li, J.Liu, N.Stockbridge, 7/1/14
❖ Controlled Substance Staff review(s) and Scheduling Recommendation *(indicate date of each review)*	M.Rusinowitz, S.Calderon, J.Tolliver, M.Klein, 10/29/14 J.Tolliver, M.Rusinowitz, S.Calderon, M.Klein, 9/2/14
❖ Risk Management • REMS Documents and REMS Supporting Document *(indicate date(s) of submission(s))* • REMS Memo(s) and letter(s) *(indicate date(s))* • Risk management review(s) and recommendations (including those by OSE and CSS) *(indicate date of each review and indicate location/date if incorporated into another review)*	REMS and REMS materials, submitted 10/30/14 REMS Supporting Document, submitted 10/30/14 REMS DRISK review, D.Gonzalez, R.Mehta, 11/6/14 REMS, OPDP consult review, E.Chung-Davies, 8/15/14 REMS Memo, J.Racoosin, 7/30/14
❖ OSI Clinical Inspection Review Summary(ies) *(include copies of OSI letters to investigators)*	In reverse chronology, various OSI letters, and clinical inspection summary of C.Kleppinger, J.Pohlman, K.Ayalew 10/24/14

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Clinical Microbiology ☒ None	
❖ Clinical Microbiology Team Leader Review(s) *(indicate date for each review)*	☐ No separate review
Clinical Microbiology Review(s) *(indicate date for each review)*	☐ None
Biostatistics ☐ None	
❖ Statistical Division Director Review(s) *(indicate date for each review)*	☒ No separate review
Statistical Team Leader Review(s) *(indicate date for each review)*	☒ No separate review
Statistical Review(s) *(indicate date for each review)*	Y.Zhou, J.Derr, 7/28/14 W.Liu, Q.Dang, Y.Tsong, 6/20/14 (consult review requested by CSS)
Clinical Pharmacology ☐ None	
❖ Clinical Pharmacology Division Director Review(s) *(indicate date for each review)*	☒ No separate review
Clinical Pharmacology Team Leader Review(s) *(indicate date for each review)*	☒ No separate review
Clinical Pharmacology review(s) *(indicate date for each review)*	S.Nallani, Y.Xu, 7/31/14
❖ OSI Clinical Pharmacology Inspection Review Summary *(include copies of OSI letters)*	☒ None requested
Nonclinical ☐ None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) *(indicate date for each review)*	☒ No separate review
• Supervisory Review(s) *(indicate date for each review)*	D.Mellon, 10/30/14
• Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)*	E.Bolan, D.Mellon, 10/10/14
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer *(indicate date for each review)*	☒ None
❖ Statistical review(s) of carcinogenicity studies *(indicate date for each review)*	M.Min, K.Lin, 9/24/14
❖ ECAC/CAC report/memo of meeting	A.Seifried, A.Jacobs, 6/26/14
❖ OSI Nonclinical Inspection Review Summary *(include copies of OSI letters)*	☒ None requested
Product Quality ☐ None	
❖ Product Quality Discipline Reviews	
• ONDQA/OBP Division Director Review(s) *(indicate date for each review)*	☒ No separate review
• Branch Chief/Team Leader Review(s) *(indicate date for each review)*	☒ No separate review
• Product quality review(s) including ONDQA biopharmaceutics reviews *(indicate date for each review)*	X.Shen, J.Pinto, 8/1/14 A.Khairuzzaman, T.Ghosh, 7/31/14
❖ Microbiology Reviews ☒ NDAs: Microbiology reviews (sterility & pyrogenicity) (OPS/NDMS) *(indicate date of each review)* ☐ BLAs: Sterility assurance, microbiology, facilities reviews (OMPQ/MAPCB/BMT) *(indicate date of each review)*	J.Metcalfe, B.Riley, 7/30/14
❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer *(indicate date of each review)*	☒ None

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❖ Environmental Assessment (check one) (original and supplemental applications)	
☒ Categorical Exclusion *(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)*	(see page 84 of Shen/Pinto product quality review)
☐ Review & FONSI *(indicate date of review)*	
☐ Review & Environmental Impact Statement *(indicate date of each review)*	
❖ Facilities Review/Inspection	
☒ NDAs: Facilities inspections (include EER printout or EER Summary Report only; do NOT include EER Detailed Report; date completed must be within **2 years** of action date) *(only original NDAs and supplements that include a new facility or a change that affects the manufacturing sites[5])*	Date completed: Memo, J.Williams, M.Ramanadham, 10/16/14, recommending approval. ☐ Acceptable ☐ Withhold recommendation ☐ Not applicable
☐ BLAs: TB-EER (date of most recent TB-EER must be within **30 days** of action date) *(original and supplemental BLAs)*	Date completed: ☐ Acceptable ☐ Withhold recommendation
❖ NDAs: Methods Validation *(check box only, do not include documents)*	☐ Completed ☐ Requested ☐ Not yet requested ☒ Not needed (per review)

[5] i.e., a new facility or a change in the facility, or a change in the manufacturing process in a way that impacts the Quality Management Systems of the facility.

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 *(Notify CDER OND IO)*
• Finalize 505(b)(2) assessment	☐ 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 *Application Product Names* 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

Reference ID: 3663208

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/s/

DOMINIC CHIAPPERINO
11/24/2014

Chiapperino, Dominic

From: Chiapperino, Dominic
Sent: Wednesday, October 22, 2014 8:25 PM
To: Liao, Edward (Edward.Liao@pharma.com)
Subject: NDA 206627, postmarketing requirements

Dear Ed,

Concerning your NDA for Hysingla ER, we are seeking Purdue's agreement to the following postmarketing requirements (PMRs), which we have determined to be necessary.

Deferred pediatric study under PREA:

Conduct a pharmacokinetic and safety study of an age-appropriate formulation of hydrocodone extended-release tablets in patients from ages 12 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

Final Protocol Submission: July 31, 2015
Study Completion: January 31, 2019
Final Report Submission: July 31, 2019

The five PMRs associated with all ER/LA opioid products:

1. Conduct one or more studies to provide quantitative estimates of the serious risks of misuse, abuse, addiction, overdose, and death associated with long-term use of opioid analgesics for management of chronic pain, among patients prescribed ER/LA opioid products. Include an assessment of risk relative to efficacy.

   These studies should address at a minimum the following specific aims:

   a. Estimate the incidence of misuse, abuse, addiction, overdose, and death associated with long-term use of opioids for chronic pain. Stratify misuse and overdose by intentionality wherever possible. Examine the effect of product/formulation, dose and duration of opioid use, prescriber specialty, indication, and other clinical factors (e.g., concomitant psychotropic medications, personal or family history of substance abuse, history of psychiatric illness) on the risk of misuse, abuse, addiction, overdose, and death.

   b. Evaluate and quantify other risk factors for misuse, abuse, addiction, overdose, and death associated with long-term use of opioids for chronic pain, including but not limited to the following: demographic factors, psychosocial/behavioral factors, medical factors, and genetic factors. Identify confounders and effect modifiers of individual risk factor/outcome relationships. Stratify misuse and overdose by intentionality wherever possible.

   The following timetable proposes the schedule by which you will conduct these studies:

Reference ID: 3647104

Final Protocol Submission: Submitted.
Study Completion: 01/2018
Final Report Submission: 06/2018

2. Develop and validate measures of the following opioid-related adverse events: misuse, abuse, addiction, overdose and death (based on DHHS definition, or any agreed-upon definition), which will be used to inform the design and analysis for PMR # 2065-1 and any future post-marketing safety studies and clinical trials to assess these risks. This can be achieved by conducting an instrument development study or a validation study of an algorithm based on secondary data sources.

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

   Final Protocol Submission: Submitted.
   Study Completion: 08/2015
   Final Report Submission: 11/2015

3. Conduct a study to validate coded medical terminologies (e.g., ICD9, ICD10, SNOMED) used to identify the following opioid-related adverse events: misuse, abuse, addiction, overdose, and death in any existing post-marketing databases to be employed in the studies. Stratify misuse and overdose by intentionality wherever possible. These validated codes will be used to inform the design and analysis for PMR # 1.

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

   Final Protocol Submission: Submitted.
   Study Completion: 08/2015
   Final Report Submission: 11/2015

4. Conduct a study to define and validate "doctor/pharmacy shopping" as outcomes suggestive of misuse, abuse and/or addiction. These validated codes will be used to inform the design and analysis for PMR # 1.

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

   Final Protocol Submission: Submitted.
   Study Completion: 08/2015
   Final Report Submission: 11/2015

5. Conduct a clinical trial to estimate the serious risk for the development of hyperalgesia following use of ER/LA opioid analgesics for at least one year to treat chronic pain. We strongly encourage you to use the same trial to assess the development of tolerance following use of ER/LA opioid analgesics. Include an assessment of risk relative to efficacy.

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

   Final Protocol Submission: Submitted.
   Trial Completion: 08/2016

Reference ID: 3647104

Final Report Submission: 02/2017

An additional PMR to assess abuse-deterrent properties of Hysingla ER:

Conduct epidemiologic investigations to address whether the properties intended to deter misuse and abuse of Hysingla ER (hydrocodone bitartrate extended-release tablets) actually result in a significant and meaningful decrease in misuse and abuse, and their consequences, addiction, overdose, and death, in the community. The post-marketing study program must allow FDA to assess the impact, if any, that is attributable to the abuse-deterrent properties of Hysingla ER. To meet this objective, investigations should incorporate recommendations contained in the FDA draft guidance, *Abuse-Deterrent Opioids—Evaluation and Labeling* (January 2013) and proposed comparators need to be mutually agreed upon prior to initiating epidemiologic investigations. There must be sufficient drug utilization to allow a meaningful epidemiological assessment of overall and route-specific abuse deterrence.

Please review and respond as soon as possible that Purdue is agreeable to the above list of PMRs. A formal amendment should be submitted stating your agreement, with the above list reproduced in your cover letter.

Contact me if you have any questions or need for further discussion of these PMRs.

Kind regards,
Dominic

Dominic Chiapperino, Ph.D.
Senior Regulatory Health Project Manager
Division of Anesthesia, Analgesia, and Addiction Products
Office of Drug Evaluation II
FDA, Center for Drug Evaluation and Research
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Reference ID: 3647104

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/s/

DOMINIC CHIAPPERINO
10/22/2014

Chiapperino, Dominic

From: Chiapperino, Dominic
Sent: Wednesday, October 22, 2014 1:20 PM
To: 'Liao, Edward'
Cc: Fanelli, Richard (Richard.Fanelli@pharma.com)
Subject: NDA 206627, Hysingla tablets strengths, request for comment

Hi Ed,

We note your response in below email and have follow up questions, as noted here in bold font.

1. "The abuse-deterrent features of Hysingla ER address the risk of misuse and abuse of this product."

Describe how the abuse-deterrent features will address the concerns conveyed to you about the risk of medication errors from prescribers dosing this once daily formulation twice daily, a form of misuse.

2. "Approving only the lower dosage strengths of Hysingle ER would result in a larger pill burden for patients requiring higher doses to alleviate their pain."

Provide an estimate of the number of patients that would require dosing beyond 60 mg per day, and beyond 120 mg per day. As you suggest that taking two pills once daily represents a pill burden, do you propose to limit dosing to no more than 120 mg per day?

3. "ER/LA opioids are approved and marketed at dosages that are about as potent as the highest dosage unit of Hysingla ER."

Describe how the presence of approved products at similar potency, most of which are dosed twice daily, addresses the concerns conveyed about the risk of mis-prescribing Hysingla ER.

4. We will monitor public reaction and offer to work closely with FDA to address the public concern.

Describe how you propose to address public concerns that may arise concerning the higher strengths.

Response to our questions is need at your earliest possible opportunity.

Kind regards,
Dominic

Dominic Chiapperino, Ph.D.
Senior Regulatory Health Project Manager
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Dominic.Chiapperino@fda.hhs.gov

Reference ID: 3647103

From: Liao, Edward [mailto:Edward.Liao@pharma.com]
Sent: Tuesday, October 21, 2014 12:39 PM
To: Chiapperino, Dominic
Cc: Fanelli, Richard
Subject: RE: Hysingla tablets strengths

Hi Dominic:

We did consider your proposal, but decided that all dose strengths should be approved without delay.

As we mentioned in the t-con, we understand the public concern and have developed plans to ensure that the risks/benefits of this medicine are properly communicated. We will also offer to work with FDA's public affairs office to coordinate communications about the product.

The medical need and benefit/risks of the higher strengths are fully supported by the data in the NDA. The ISE/ISS describe a number of subjects enrolled in the pivotal trial who titrated to and required these higher doses. The abuse-deterrent features of Hysingla ER address the risk of misuse and abuse of this product. Approving only the lower dosage strengths of Hysingle ER would result in a larger pill burden for patients requiring higher doses to alleviate their pain. ER/LA opioids are approved and marketed at dosages that are about as potent as the highest dosage unit of Hysingla ER. Finally, this product will be part of the class-wide REMS and post-marketing studies requirements. We will monitor for any signals of safety and abuse based on dose.

Therefore, we believe that the full dose range of Hysingla ER should be approved by the PDUFA date. We will monitor public reaction and offer to work closely with FDA to address the public concern.

Thanks.
ed

From: Chiapperino, Dominic [mailto:Dominic.Chiapperino@fda.hhs.gov]
Sent: Monday, October 20, 2014 9:23 AM
To: Liao, Edward
Subject: Hysingla tablets strengths

Hi Ed,

When we had our t-con with you a couple weeks ago we discussed the upper strengths of Hysingla ER tablets and the possibility of delaying approval of upper strengths. Has Purdue given further consideration to this issue? I believe your position was that you would consider, and get back to us.

Thanks and regards,
Dominic

Dominic Chiapperino, Ph.D.
Senior Regulatory Health Project Manager
Division of Anesthesia, Analgesia, and Addiction Products

Reference ID: 3647103

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Reference ID: 3647103

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/s/

DOMINIC CHIAPPERINO
10/22/2014

Chiapperino, Dominic

From: Chiapperino, Dominic
Sent: Tuesday, October 07, 2014 12:54 PM
To: Liao, Edward (Edward.Liao@pharma.com)
Cc: Dettelbach, Kim; Sitlani, Jay; Hertz, Sharon H
Subject: NDA 206627, follow-up request for comment from Purdue

Dear Ed,

We note that that the "Approved Drug Products with Therapeutic Equivalence Evaluations" lists "NP" or new product exclusivity for Zohydro, the approved single-entity hydrocodone product (NDA # 202880), that expires October 25, 2016. Please submit in writing your position on the implications of Zohydro's exclusivity for approval of your application. Specifically, please address the following characteristics of Zohydro that may be considered that drug's condition(s) of approval for which new clinical studies were essential (section 505(c)(3)(E)(iii) of the FD&C Act; 21 CFR 314.108(b)(4)): single-entity hydrocodone; long-acting (extended-release) formulation; strengths of hydrocodone up to 50 mg or up to 100 mg daily; and the indication for management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate.

Kind regards,
Dominic

Dominic Chiapperino, Ph.D.
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Reference ID: 3645788

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/s/

DOMINIC CHIAPPERINO
10/20/2014
Archiving 10/7/14 email

Chiapperino, Dominic

From: Chiapperino, Dominic
Sent: Monday, October 20, 2014 1:56 PM
To: Liao, Edward (Edward.Liao@pharma.com)
Subject: NDA 206627, information request, container labels

Hi Ed,

As I mentioned by phone today, regarding NDA 206627, we do in fact have an additional comment about the container labels submitted for Hysingla ER, as follows:

> Increase the font size of the statement "Swallow tablets whole." to the same font size as the current net quantity statement, "60 tablets". This will help increase the prominence of this important information. The remaining portion, "Do not cut, break, chew, crush, or dissolve." can begin on a new line, with its current font size unchanged. In order to accommodate the larger font size of "Swallow tablets whole.", decrease the font size of the net quantity and "Rx Only" statements.

You may submit a mock-up by email of one representative label for one of the tablet strengths. We will confirm its acceptability and you may then update the NDA with revised container labels.

Kind regards,
Dominic

Dominic Chiapperino, Ph.D.
Senior Regulatory Health Project Manager
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/s/

DOMINIC CHIAPPERINO
10/20/2014

Chiapperino, Dominic

From: Chiapperino, Dominic
Sent: Wednesday, October 08, 2014 2:55 PM
To: Liao, Edward (Edward.Liao@pharma.com)
Subject: NDA 206627, FDA-revised prescribing information
Attachments: Hysingla ER with FDA revisions 10-8-14 CLEAN.docx

Hi Ed,

Referring to your NDA 206627 for Hysingla ER, we are now providing you with a Word file that has our substantial revisions to your proposed product labeling (package insert and Medication Guide). The revisions are not shown with tracked changes because of the extensive revisions and multiple file versions that had to be merged from our consulted groups.

We are not yet certain that this label represents our final recommendations for the label, but this is substantially complete so that we may share with you and have meaningful dialog as necessary.

Contact me if you have any questions.

Kind regards,
Dominic

Dominic Chiapperino, Ph.D.
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/s/

DOMINIC CHIAPPERINO
10/08/2014

Chiapperino, Dominic

From: Chiapperino, Dominic
Sent: Tuesday, September 30, 2014 10:03 AM
To: Liao, Edward (Edward.Liao@pharma.com)
Subject: NDA 206627, Request for comment from Purdue

Hi Ed,

Concerning your NDA 206627, we have the following request for comment from Purdue:

We note that that the "Approved Drug Products with Therapeutic Equivalence Evaluations" lists new product exclusivity for Zohydro ER, the approved single-entity hydrocodone product (NDA # 202880), that expires October 25, 2016. Please comment on the implications of that exclusivity for approval of your application.

Please respond at your earliest opportunity… An email to me is sufficient at this time.

Kind regards,
Dominic

Dominic Chiapperino, Ph.D.
Senior Regulatory Health Project Manager
Division of Anesthesia, Analgesia, and Addiction Products
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Dominic.Chiapperino@fda.hhs.gov

Reference ID: 3637434

Chiapperino, Dominic

From: Chiapperino, Dominic
Sent: Tuesday, September 30, 2014 12:07 PM
To: 'Liao, Edward'
Subject: RE: T-con with FDA, Hysingla ER application

Hi Ed,

Regarding the t-con we have scheduled for tomorrow, the following items are what we have in mind as an agenda:

- What are Purdue's plans to address likely public concern about the introduction of higher doses of hydrocodone into the market (even though Hysingla ER represents a once daily dosing regimen)?
- What is Purdue's current understanding about clinical study site and API manufacturing site inspections?
- FDA is planning to provide by end of this week the revised Hysingla ER labeling with our edits and recommendations. We plan to discuss our broad view of the content in Section 9 in advance of sending the revised label.
- Discussion of our request for comment sent to Purdue previously by email today [i.e., "We note that that the "Approved Drug Products with Therapeutic Equivalence Evaluations" lists new product exclusivity for Zohydro, the approved single-entity hydrocodone product (NDA # 202880), that expires October 25, 2016. Please comment on the implications of that exclusivity for approval of your application."].

Thanks, and speak with you tomorrow.

Regards,
Dominic

From: Liao, Edward [mailto:Edward.Liao@pharma.com]
Sent: Wednesday, September 24, 2014 12:43 PM
To: Chiapperino, Dominic
Subject: RE: T-con with FDA, Hysingla ER application

Hi Dominic:
Next Wednesday, 10/1, at 2pm is okay for us. Do you have any additional information on discussion topics, so that we can ensure that the right people are on this call?

For this call, please use the following dial-in: 1-800-591-2259, Participant Code: (b) (4)).

Thanks.
ed

From: Chiapperino, Dominic [mailto:Dominic.Chiapperino@fda.hhs.gov]
Sent: Wednesday, September 24, 2014 11:38 AM
To: Liao, Edward
Subject: RE: T-con with FDA, Hysingla ER application

Hi Ed,

Sorry tomorrow will not work for our team. How about next week, Wednesday, Oct. 1st, 2:00 to 3:00 PM (EST)?

Reference ID: 3637434

Thanks,
Dominic

From: Liao, Edward [mailto:Edward.Liao@pharma.com]
Sent: Wednesday, September 24, 2014 11:11 AM
To: Chiapperino, Dominic
Subject: RE: T-con with FDA, Hysingla ER application

Hi Dominic:
Just following up on my note to you from yesterday. Is a t-con tomorrow possible?
Thanks.
ed

From: Liao, Edward
Sent: Tuesday, September 23, 2014 11:20 AM
To: 'Chiapperino, Dominic'
Subject: RE: T-con with FDA, Hysingla ER application

Hi Dominic:
Unfortunately, Todd and Rich will be on a plane for most of Friday, so we will not have our senior regulatory team available on Friday.
Is anytime on Thursday possible?
Also, can you please provide some more details regarding agenda/discussion items, so that I can make sure that the necessary people are available on the call?
Thanks.
ed

From: Chiapperino, Dominic [mailto:Dominic.Chiapperino@fda.hhs.gov]
Sent: Tuesday, September 23, 2014 10:23 AM
To: Liao, Edward
Subject: T-con with FDA, Hysingla ER application

Hi Ed,

We are interested in having some dialog with Purdue on various topics concerning your NDA 206627 for Hysingla ER. I have reserved time for this coming Friday, 9/26, at 1:30 PM (EST). Some topics will be broad and require your senior regulatory team, and we may need to touch base concerning DMFs supporting the application.

Please let me know of your availability for Friday, and I can probably provide additional details of agenda items by Friday.

Thank you,
Dominic

Dominic Chiapperino, Ph.D.
Senior Regulatory Health Project Manager
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Reference ID: 3637434

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/s/

DOMINIC CHIAPPERINO
09/30/2014

Chiapperino, Dominic

From: Chiapperino, Dominic
Sent: Thursday, September 04, 2014 12:32 PM
To: Liao, Edward (Edward.Liao@pharma.com)
Subject: NDA 206627, information request - study sites

Hi Ed,

Referring to the Hysingla ER application, we have the following requests for additional information:

1. We note in the 120-day safety update for NDA 206627 that you discovered missing ECG data that was not included in the original NDA submission. We acknowledge your recognition of the issue and that the majority of ECGs were retrieved and analyzed. However, we have concerns regarding the process that allowed for these tracings to be missing. The vendor was to receive three ECG tracings at least 20 minutes apart for each subject; if those were not received, did the vendor query the study site? Please describe the procedures involved with the ECG transmissions and what checks were in place to document that all ECGS were transmitted. More so, according to the protocol, the investigator was to review and sign upon receipt all ECG reports from the central ECG provider. It appears that investigators did not notice the missing ECGs. Were these missing ECGs picked up by the site monitors?

   Please address the above issues so we can better understand the reasons for the missing data.

2. During the inspection of the Taber study site, the FDA inspector had some concerns regarding the reliability of audiologic assessment data from that site. Address how removal of all audiologic assessment data gathered from that site affects the overall audiologic assessment findings. Provide the number subjects who had audiologic assessments at that site, and provide reanalyses of relevant audiologic data excluding data from the Taber site.

Contact me if you have questions, but submit this information by September 26, 2014.

Kind regards,
Dominic

Dominic Chiapperino, Ph.D.
Senior Regulatory Health Project Manager
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/s/

DOMINIC CHIAPPERINO
09/04/2014

Chiapperino, Dominic

From: Chiapperino, Dominic
Sent: Friday, August 29, 2014 11:33 AM
To: Liao, Edward (Edward.Liao@pharma.com)
Subject: NDA 206627, information request, REMS

Hi Ed,

Referring to the Hysingla ER application, NDA 206627, I have confirmed with our team that you should submit the REMS materials as a formal amendment at your earliest opportunity, as previously submitted to us by email, but with one correction to make. In the Blueprint drug-specific information for Hysingla, there is one instance of referring to Hysingla ER as "HYD" (in the last bullet of "Key Instructions" section). Please correct this to instead read "Hysingla ER". This are the only revision needed at this time.

Also, as discussed by phone, I look forward to receiving your amendment with proof of patent-holder notification for the two Paragraph IV patent certifications concerning Vicoprofen patents.

Kind regards,
Dominic

Dominic Chiapperino, Ph.D.
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Reference ID: 3619597

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/s/

DOMINIC CHIAPPERINO
08/29/2014

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

REQUEST FOR CONSULTATION

TO *(Office/Division)*:	FROM (*Name, Office/Division, and Phone Number of Requestor)*:
Division of Biostatistics VI, Attn: Karl Lin	Dominic Chiapperino, DAAAP/ODE2, 6-1183

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
April 28, 2014		N 206627/S-000	NDA	April 28, 2014

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
Hydrocodone bitartrate q24h film-coated tablets	Priority	Opioid analgesic	June 10, 2014

NAME OF FIRM: Purdue Pharma, LP

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE / ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE-NDA MEETING
- ☐ END-OF-PHASE 2a MEETING
- ☐ END-OF-PHASE 2 MEETING
- ☐ RESUBMISSION
- ☐ SAFETY / EFFICACY
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☐ OTHER *(SPECIFY BELOW)*:

II. BIOMETRICS

- ☐ PRIORITY P NDA REVIEW
- ☐ END-OF-PHASE 2 MEETING
- ☐ CONTROLLED STUDIES
- ☐ PROTOCOL REVIEW
- ☐ OTHER (SPECIFY BELOW):
- ☐ CHEMISTRY REVIEW
- ☒ PHARMACOLOGY
- ☐ BIOPHARMACEUTICS
- ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE 4 STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL - BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG SAFETY

- ☐ PHASE 4 SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE, e.g., POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ NONCLINICAL

COMMENTS / SPECIAL INSTRUCTIONS: DAAAP is requesting a PHARMACOLOGY-CAC statistical data consult for NDA 206627/S-000.

Please review and comment on the acceptability of the carcinogenicity statistical information for the 2-year carcinogenicity bioassay in mouse (study NDSE-558-GLP) and the 2-year carcinogenicity bioassay in rat (study NDSE 559-GLP) submitted in NDA 206627/S-000 on April 28, 2014. The study reports and SAS transport files are located
In Global Submit Review under NDA 206627 in section 4.2.3.4.1.
EDR location: <**\\CDSESUB1\evsprod\NDA206627\206627.enx**>

NOTE: We ask that this review be completed by June 10, 2014. The Division has scheduled a meeting with the ECAC on June 17, 2014. Elizabeth Bolan (301-796-2203; Elizabeth.Bolan@FDA.HHS.GOV) will be the primary reviewer for these studies. For questions, please contact Dominic Chiapperino, DAAAP Project Manager, at 301-796-1183.

SIGNATURE OF REQUESTOR Dominic Chiapperino	METHOD OF DELIVERY (Check all that apply) ☒ DARRTS ☐ EMAIL ☐ MAIL ☐ HAND
PRINTED NAME AND SIGNATURE OF RECEIVER	PRINTED NAME AND SIGNATURE OF DELIVERER

06/18/2013

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

/s/

DOMINIC CHIAPPERINO
04/28/2014

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

IND 059175

MEETING MINUTES

Purdue Pharma L.P.
One Stamford Forum
Stamford, CT 06901-3431

Attention: Edward Liao, Pharm.D.
Associate Director, Regulatory Affairs

Dear Dr. Liao:

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 q24h Film-Coated Tablets (HYD).

We also refer to the meeting between representatives of your firm and the FDA July 10, 2013. The purpose of the meeting was to discuss the development program for HYD and your planned 505(b)(2) NDA submission.

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) 796-1183

Sincerely,

{See appended electronic signature page}

Dominic Chiapperino, Ph.D.
Senior Regulatory Health Project Manager
Division of Anesthesia, Analgesia, and
Addiction Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes

Reference ID: 3566752

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type: Type B

Meeting Category: Pre-NDA

Meeting Date and Time: July 10, 2013, 1:30 – 2:30 PM (EST)

Meeting Location: 10903 New Hampshire Avenue
White Oak Building 22, Conference Room 1315
Silver Spring, Maryland 20903

Application Number: IND 059175

Product Name: HYD (hydrocodone bitartrate q24h film-coated tablets)

Indications: Management of moderate to severe pain when a continuous, around-the-clock analgesic is needed for an extended period of time

Sponsor/Applicant Name: Purdue Pharma L.P.

Meeting Chair: Ellen W. Fields, MD, MPH, Clinical Team Leader, Division of Anesthesia, Analgesia, and Addiction products (DAAAP)

Meeting Recorder: Dominic Chiapperino, PhD, Senior Regulatory Health Project Manager, DAAAP

Meeting Attendees:

FDA Attendees	Title
Bob A. Rappaport, MD	Director, Division of Anesthesia, Analgesia, and Addiction Products (DAAAP)
Sharon Hertz, MD	Deputy Director, DAAAP
Sara Stradley, MS	(Acting) Associate Director Regulatory Affairs, Office of Drug Evaluation II
Ellen W. Fields, MD, MPH	Clinical Team Leader, DAAAP
Jacqueline Spaulding, MD	Medical Officer, DAAAP
Dan Mellon, PhD	Nonclinical Supervisor, DAAAP
Elizabeth Bolan, PhD	Nonclinical Reviewer, DAAAP
Dominic Chiapperino, PhD	Senior Regulatory Health Project Manager, DAAAP
Yun Xu, PhD	Team Leader, Division of Clinical Pharmacology II (DCP-II)
Srikanth Nallani, PhD	Clinical Pharmacology Reviewer, DCP-II
Janice Derr, PhD	(Acting) Statistics Team Leader, Division of Biometrics II (DB-II)
Yan Zhou, PhD	Statistics Reviewer, DB-II
Michael Klein, PhD	Director, Controlled Substance Staff (CSS)
Lori A. Love, MD, PhD	Senior Medical Officer, CSS
Prasad Peri, PhD	Branch Chief, Branch VIII, Office of New Drug Quality Assessment (ONDQA)

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Julia Pinto, PhD	CMC Lead, Branch VIII, ONDQA
Edwin Jao, PhD	Review Chemist, Branch VIII, ONDQA
Angelica Dorantes, PhD	Team Leader, Biopharmaceutics, ONDQA
Elsbeth G. Chikhale, PhD	Biopharmaceutics Reviewer, ONDQA
Cynthia Kornegay, PhD	Epidemiologist Team Lead, Division of Epidemiology II (DEPI-II)
Catherine Dormitzer, PhD, MPH	Epidemiologist, OSE, DEPI II
Jamie Wilkins Parker, PharmD	Team Leader, Division of Medication Error Prevention and Analysis (DMEPA)
Vicky Borders-Hemphill, PharmD	Safety Evaluator, DMEPA
Kimberly Lehrfeld, PharmD, BCPS	(Acting) Team Leader, Division of Risk Management (DRISK)
Danielle Smith, PharmD, MS	Risk Management Analyst, DRISK
Mark Liberatore, PharmD	Safety Regulatory Project Manager, Office of Surveillance and Epidemiology (OSE)
Purdue Attendees	**Title**
Gary Stiles, MD	Senior Vice-President, R&D
Craig Landau, MD	Vice President and Chief Medical Officer
Todd Baumgartner, MD	Vice President, Regulatory Affairs
Stephen Harris, MD	Executive Medical Director, Clinical Pharmacology
Steven Ripa, MD	Executive Medical Director
Kimberly Pendino, PhD, DABT	Executive Director, Toxicology
Paul Coplan, PhD	Executive Director, Risk Management
Warren Wen, PhD	Director, Clinical Research
Catherine Munera, PhD	Director, Biostatistics and Statistical Programming
Andrew Albright	Director, Project Management
Edward Liao, PharmD	Director, Regulatory Affairs
(b) (4)	Audiology Consultant, (b) (4)
(b) (4)	Audiology Consultant, (b) (4)
(b) (4)	Audiology Consultant, (b) (4) r
Paul Coplan, PhD	Executive Director, Risk Management & Epidemiology

1.0 BACKGROUND

Purdue Pharma L.P. requested a Pre-NDA meeting to discuss their clinical development program and planned NDA submission for HYD, indicated for management of moderate to severe pain when a continuous, around-the-clock analgesic is needed for an extended period of time.

Purdue anticipates eventual submission of a 505(b)(2) new drug application (NDA) in early 2014, with reference to FDA-approved product, Vicoprofen (NDA 020716), for reliance on FDA's prior findings to support their NDA submission for HYD.

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Purdue submitted a meeting briefing package, dated May 29, 2013, containing questions shown below in Section 2 in italic font, which will be the basis of discussion during the meeting to be held on July 10, 2013. DAAAP's preliminary responses to the questions, in bold font in Section 2, were provided to Purdue On July 5, 2013, ahead of this scheduled meeting.

Purdue has identified the topics/questions for which they would like further discussion. Purdue's additional information and follow-up questions for discussion are shown as boxed text in Section 2. Discussion during the meeting is summarized in Section 2 in normal font. Questions and responses not identified for discussion during the meeting are included at the end of Section 2 for reference.

2.0 DISCUSSION

Purdue began the meeting discussion with a brief statement of broader goals within the company. Purdue stated their interest in more clearly establishing the role of opioids in treating chronic non-cancer pain. Toward this goal, they are expanding treatment of chronic pain in clinical trials to 18 months to generate long-term data that have not so far been available. Secondly, Purdue stated that their clinical programs for all opioid formulations are moving in the direction of replacement of approved non-abuse-deterrent opioid formulations with formulations offering abuse-deterrent features expected to reduce the incidence of abuse and misuse associated with these drug products.

Original Question 4:

Question 4. Does the Agency agree that the proposed package of pre-clinical studies, as described in the 505(b)(2) HYD NDA plan document, will be adequate for approval of this 505(b)(2) NDA?

FDA Response to Question 4:

For a 505(b)(2) application, no further nonclinical studies are needed for hydrocodone. However, at the maximum theoretical daily dose of 3 g for hydrocodone, some excipients in your formulation (b) (4) **levels of those in approved products. Specifically,** (b) (4)

The drug substance and drug product impurity specifications must meet ICH Q3A and ICH Q3B thresholds for qualification based on a maximum daily dose of 3 g or justification must be provided. Refer to nonclinical comments for details.

Failure to address the levels of the drug substance or drug product impurity specifications or provide justification for the levels of excipients will result in a nonclinical recommendation of refusal-to-file for the NDA.

Purdue Follow-up Responses and Questions for July 10, 2013:

4(a) In the approved label for Vicoprofen as well as in the Vicoprofen NDA, there is no non clinical section or summaries of non-clinical pharmacology/safety. To this end, Purdue has conducted a full non-clinical assessment of HYD as a single agent, including a full battery of toxicology studies. We will submit these data in the NDA, and propose label text around these data. We would be willing to discuss this with the Agency.

4(b) FDA correspondence regarding maximum total daily dose (mg salt form) for HYD cites a value of 3000 mg/day. Purdue believes [redacted] (b) (4) [redacted]. Does FDA agree with this approach to establishing a maximum daily dose value for HYD?

4(c) Purdue has drafted a toxicology risk assessment based on nonclinical toxicology summaries provided by [redacted] (b) (4) [redacted] the supplier of PEO, and assuming a maximum ingestion of HYD of 3000 mg/day (25 tablets of 120 mg). The toxicology database for PEO is replete and includes chronic toxicity/carcinogenicity data. Using the most conservative NOAEL value provided from a 2-year dog toxicity study, a safety margin of 2X is obtained. No target organs of toxicity were noted in any study and maximum (limit) doses were tested. Is this approach in qualifying PEO in line with your expectations?

Discussion of Question 4:

Question 4a. Purdue stated that they have conducted a full battery of nonclinical assessments with hydrocodone to submit with their NDA. FDA acknowledged that the Vicoprofen label is not a good source for appropriately labeling HYD based on current data and labeling requirements. There was agreement that the full nonclinical assessment of HYD, including a full battery of toxicology studies, would be submitted in the NDA with proposed annotated labeling text for FDA review. Because of the extensive clinical history with hydrocodone, a chronic toxicology study with hydrocodone in a second species will not be required for this product if Purdue confirms that all standard toxicological endpoints were included in the rat carcinogenicity study and if the rat carcinogenicity study data can define a NOAEL.

Question 4b. Regarding the suggestion by Purdue that [redacted] (b) (4) [redacted], FDA stated that establishing the maximum daily dose is ideally based on clinical use data which are not available for a single-entity hydrocodone drug product. FDA recognized that 3,000 mg/day of hydrocodone bitartrate is a large amount but confirmed

that, in the absence of data, 3,000 mg/day will be used as the Maximum Theoretical Daily Dose (MTDD). Purdue stated that they plan to submit appropriate justification for the drug substance and drug product specifications with their NDA submission. FDA indicated that if Purdue proposes specifications above the ICH qualification thresholds along with justification for the specification, the Agency will not consider that a filing issue as long as the justification is reviewable. However, the acceptability of the proposed specifications and justification will be a review issue for the NDA.

Question 4c. Purdue stated that they plan to support the justification and safety margin for the PEO used in the HYD drug product by providing the toxicological risk assessment performed by (b) (4) and that currently only summary information is available. FDA stated that summaries are not acceptable and access to the full study reports and data from these studies is required. The study reports can be submitted as part of the NDA or referenced via a letter of authorization to a master file containing the reports. If the data or right of reference cannot be provided, Purdue must document the attempts to get access and provide a weight-of-evidence approach in qualifying the PEO.

Original Question 13:

Question 13. Does the Agency agree that the audiology data, consisting of 3 months of placebo-controlled and up to 18 months of open-label exposure to hydrocodone, acquired by licensed, independent audiologists at conventional and ultra-high frequencies, analyzed in accordance with the proposed plan, can provide the data to evaluate ototoxicity of hydrocodone?

FDA Response to Question 13:

In general, we agree that the audiology data analyzed in accordance with the proposed plan should provide an adequate evaluation of the ototoxicity of hydrocodone. However, we have some additional questions and comments regarding your proposed analyses:

1. **In the Analysis and Reporting of Adverse Event "Audiogram Abnormal" section (page 55 of 61), you state, "For careful and ongoing monitoring of hearing related events, Purdue requested that all audiometry changes from baseline, upon confirmation from the central ENT consultant, be reported as AEs of "changes in audiometry". These AEs are coded to the preferred term of "audiogram abnormal" per MedDRA v16.0." It is appropriate to record all audiometric changes from baseline as adverse events; however, all audiometry changes from baseline should be reported as "changes in hearing sensitivity" rather than "changes in audiometry." Audiometry is a tool to assess hearing sensitivity, rather than a description of the characteristics of a hearing related event. "Changes in hearing sensitivity" is a more accurate reporting of a hearing related adverse event.**

2. **Regarding Cohort 2B described in Table 11 (page 53 of 61), it is unclear why this dataset will not be incorporated in the supportive data analysis. Clarify your rationale for not including this cohort in your data analysis. In addition to providing your rationale, these subjects, who were tested by audiologists while on**

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treatment, should not be completely disregarded from your reporting. We acknowledge that these data may not be suitable for use to determine the ototoxicity of hydrocodone. Describe how you will track these subjects and report the data from this cohort (e.g., descriptive reports). Also, note that if your primary and/or supporting cohort data do not include a sufficient number of subjects with pre-treatment hearing loss, you may not be able to make claims about the safety of hydrocodone with respect to ototoxicity in patients with preexisting hearing loss.

Purdue Follow-up Response and Questions for July 10, 2013

13(a). We agree with changing the terminology from "change in audiometry" to "change in hearing sensitivity". Originally we used the terminology "audiometric changes" which for the formal report was altered to "changes in audiometry". We agree that "change in hearing sensitivity" is clearer. We have analyzed the changes from baseline in 2 ways. The ASHA [American Speech-Language-Hearing Association] criteria are designed specifically for early detection of possible ototoxic change but were not designed for detection or classification of adverse events. Therefore we have used the ASHA criteria for early detection of those subjects requiring follow-up. Then the CTCAE [Common Terminology Criteria for Adverse Events] criteria will be used for classification of actual AEs. Does the Agency agree with this approach?

13(b). Cohort 1 from the HYD3003 study provides superior data for determining if pre-existent hearing loss preferentially predisposes subjects to hydrocodone induced ototoxicity if it exists. In Cohort 1 we deliberately included subjects with both normal hearing and a range of pre-existent hearing loss at baseline. We designed the study in this manner so that we could address the issue of potential ototoxicity across the range of potential patients eligible for hydrocodone therapy. In Cohort 1 we have reliable baseline audiologic data performed by licensed audiologists in sound booths with calibrated equipment meeting all ANSI criteria. Not only did the Cohort 1 patients not have HYD exposure prior to baseline, but they were also screened for other factors that could confound audiologic analyses over time. These factors include exposure to other ototoxins in the previous 6 months, conductive hearing loss, concomitant noise exposure, and other medical conditions (eg, Meniere's Disease) that could cause hearing fluctuation unrelated to study drug. In Cohort 2B, the baseline evaluation under properly controlled audiologic conditions was conducted not only after HYD administration but was also conducted in patients that were not screened prior to HYD administration for the other factors that could confound audiologic data interpretation. At this time point, we cannot retrospectively fully capture any history of other ototoxic drug exposure, recent or concomitant noise exposure, conductive hearing loss history or other ongoing otologic disorders. We believe that analysis of Cohort 1 data can accurately address the issue of any influence of pre-existent hearing loss but that analysis of Cohort 2B data will not serve to further elucidate the issue and could confound it. However, data from Cohort 2B will be summarized and be included as supplemental data in the HYD3003 CSR. In addition, all subjects from HYD3002 study had appropriate audiology baseline and will be analyzed similarly by hearing status. Does the Agency agree with this approach?

Discussion of Question 13:
Question 13a. With regard to the follow-up proposal in Purdue's Item 13a, FDA presented the viewpoint of the consulted expert in CDRH [reading text from internal email], as follows:

> "The sponsor states that they "have used the ASHA criteria for early detection of those subjects requiring follow-up. Then the CTCAE criteria will be used for classification of actual AEs." This implies that they will not report those subjects with changes in hearing sensitivity per ASHA criteria as adverse events. We do not agree with this approach. We believe that any significant changes in hearing sensitivity as defined by ASHA criteria should be reported as an adverse event. The adverse event is not related to the temporal onset of the change in hearing (i.e., early detection of a change), it is related to the amount of change in hearing sensitivity, which is what ASHA criteria provide. If the sponsor would subsequently like to utilize the CTCAE criteria for a grading of the adverse events, that is acceptable. But any confirmed change in hearing sensitivity per ASHA criteria should be reported as an adverse event."

Purdue stated that they were conducting a comprehensive audiologic testing program in their Phase 3 clinical program based on FDA guidance and Purdue's consultation with third party experts. In order to properly assess the ototoxic potential of hydrocodone, Purdue has contracted with licensed audiologists who conducted hearing tests using standardized equipment under controlled conditions, e.g. sound-treated booths. Prior to implementing the comprehensive ototoxicity monitoring program under the guidance of audiologic and otolaryngologic consultants, initial audiologic data collected at the investigative sites provided highly variable results that could not be adequately interpreted by experts in the field. Purdue also plans to include data from high frequency monitoring as an important component of early detection of potential ototoxicity.

There was agreement to use the "change in hearing sensitivity" terminology in reporting results. Purdue plans to report all changes in hearing sensitivity related to ASHA criteria for early detection of possible otoxotic change and plans to use the CTCAE to identify and classify ASHA events as Adverse Events.

Question 13b. Data analysis from all cohorts from the clinical program (including Cohort 2b) will be submitted with the NDA application for FDA review. Purdue will evaluate the results from the 3-month placebo-controlled study (HYD3002) and from Cohort 1 from the long-term safety study (HYD3003) by pretreatment hearing level where there are reliable baseline audiologic data. FDA stated that this approach was acceptable.

Original Question 14:

Question 14. Does the Agency agree with the primary efficacy analysis for HYD3002, as described in the HYD3002 Statistical Analysis Plan?

FDA Response to Question 14:

Similar to our responses in the End-of-Phase 2 meeting dated May 4, 2011, you should provide a justification for your assumption that patients who drop out due to reasons other than AEs have responses similar to the average response at Week 3, Week 4 and Week 5.

You have proposed to conduct subgroup analyses based on age (< 65 and ≥ 65 years), dose level (HYD 20 mg, 40 mg, 60 mg, 80 mg and 120 mg), baseline opioid status (naïve and experienced) and prior hydrocodone product. Also conduct subgroup analyses for gender and race.

Purdue Follow-up Responses and Questions for July 10, 2013:

Purdue will provide a justification for our approach to the treatment of missing data in the submission.

Analysis of efficacy and safety data from studies HYD3002 and HYD3003 by age, gender, and race will be provided in the ISE and ISS, respectively. Although the HYD3002 SAP mentioned that analysis of efficacy by incoming opioid dose, HYD dose at end-of-titration, and previous opioid experience may be conducted, Purdue is currently not planning to include results of these analyses in the submission. Does the Agency agree that the presentation of subgroups analyses in the integrated summaries rather than in the study CSR is an appropriate approach?

Discussion of Question 14:
FDA clarified the expectation that all analyses conducted must be included in the full study reports. There was agreement that Purdue will provide a justification for their approach to the treatment of missing data for patients who discontinue due to reasons other than adverse events in the NDA submission. Purdue will include study-level subgroup analyses of efficacy data by age, gender, and race as part of the HYD3002 study report. The ISE section that describes subgroup analyses can cross-reference the HYD3002 study report.

Original Question 17:

Question 17. Does the Agency agree that if Purdue elects to file the HYD NDA as a (b) (4) [redacted]

FDA Response to Question 17:

In your letter to the Division dated September 21, 2011 (Serial No. 0123), you asked the Division the following:

"…. (b) (4) [redacted]

In an email response from the Division dated October 17, 2011, we stated the following:

(b) (4)

Purdue Follow-up Response and Questions for July 10, 2013:

(b) (4)

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(b) (4)
. Does the Agency agree with this assessment?

Discussion of Question 17:

Question 17a. As per prior guidance, FDA confirmed that a (b) (4)

Question 17b. Purdue expressed concern that (b) (4)

Post-meeting note:

(b) (4)

Additional CMC Comments:

Demonstrate whether the intact tablet will swell in water and in simulated gastric fluids over time. Provide tablet dimensions and photos of the tablet at various time points.

Purdue Follow-up Response and Questions for July 10, 2013:

HYD tablets will swell over time when placed in water or simulated gastric fluid. To ensure that we optimally address this request, could FDA provide some insight on what questions the Agency is trying to answer with these data?

Discussion of CMC Additional Comments:
There was discussion regarding the HYD formulation and continued efforts to further understand the characteristics of abuse-deterrent PEO-based formulations. FDA stated that the relationship between in vitro behavior and in vivo performance is not well understood for these formulations and is trying to collect as much information as possible. Purdue noted that up to 18 months of clinical safety data would be provided, including GI-related adverse events, and they will also address FDA's request regarding intact tablet swelling when placed in water and simulated gastric fluid.

Other questions/responses not requiring discussion during the meeting:

Abuse Deterrence
Question 1. Does the Agency agree Abuse Deterrence Studies currently underway and the associated study design principles will provide an adequate pre-marketing assessment of the abuse-deterrent properties of HYD, and are there any critical pre-marketing modalities of testing absent from Purdue's investigational plan?

FDA Response:
You have submitted only summary information about your proposed approach for in vitro abuse-deterrent testing for HYD. It appears that your proposed studies are similar to those recommended in the draft Guidance for Industry: *Abuse-Deterrent Opioids — Evaluation and Labeling* http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM334743.pdf. **We have not noted any obvious omissions; however, we cannot confirm the approach is complete in the absence of an opportunity to review complete protocols. Submit complete protocols for in vitro studies along with the data when you submit the NDA for HYD. The adequacy of the data from these in vitro studies to support conclusions is a review issue.**

Question 2. Does the Agency agree that if the results from the pre-marketing studies of abuse deterrence outlined in Section 11.1 are similar to those seen for reformulated OxyContin, the HYD abuse-deterrence studies would be appropriate for depiction in labeling and should allow (b) (4) *claims in the label?*

FDA Response:
It is possible that, if the results from the pre-marketing studies with HYD are similar to the results with OxyContin, information from the studies may be suitable for labeling. However, this will depend on the totality of data for HYD, along with an understanding of how any differences in abuse patterns for hydrocodone and oxycodone may impact interpretation of the relevance of the study results.

Question 3. Does the Agency agree that, since HYD has intended abuse-deterrent properties, this NDA may be considered for priority review?

FDA Response:
Yes, we agree that the purported abuse-deterrent properties of HYD would warrant a priority review for your planned NDA submission.

Question 5. Does the Agency agree that a biowaiver for the 30 mg and 100 mg tablet strengths, based on conformance to the principles in Guidance for Industry Extended Release Oral Dosage Forms: Development, Evaluation, and Application of In Vitro/In Vivo Correlations, September 1997 (Section VII(A)(1) Biowaivers for Changes in the Manufacturing of a Drug Product, Category 1 Biowaivers Without an IVIVC), is acceptable?

FDA Response:
Yes, we agree that a biowaiver request for the 30 mg and 100 mg tablets is appropriate. Submit the biowaiver request in the NDA, along with a justification and supportive data.

Clinical Pharmacology
Question 6. Does the Agency agree that the proposed Clinical Pharmacology package, consisting of 11 Phase 1 studies, including a Thorough QT study, is adequate for approval of this 505(b)(2) NDA?

FDA Response:
Provide data from all of the conducted clinical pharmacology studies for review with the NDA submission. Note the specific submission recommendations for review of a Thorough QT Study Report in the QT IRT Reference Document (Appendix 1).
http://www.fda.gov/downloads/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ManualofPoliciesProcedures/ucm082015.pdf

We note that you completed an in vitro alcohol-drug interaction study. We remind you that you must conduct in vivo alcohol interaction studies if an in vitro study demonstrated dose-dumping in alcohol. Also refer to "Additional Biopharmaceutics Comments" concerning in vitro testing of alcohol dose-dumping.

Clinical
Question 7. Does the Agency agree that the proposed 505(b)(2) NDA submission is adequate to support an approval for the proposed indication?

FDA Response:
You plan to submit a 505(b)(2) NDA submission that will reference Vicoprofen (NDA 20716) as the listed drug. You intend to submit one adequate and well-controlled efficacy and safety study (HYD3002) and one uncontrolled long-term safety study (HYD3003).

Based on the information you have provided, these studies appear to be adequate to support submission of your NDA. The proposed organization of the ISS and ISE appears acceptable.

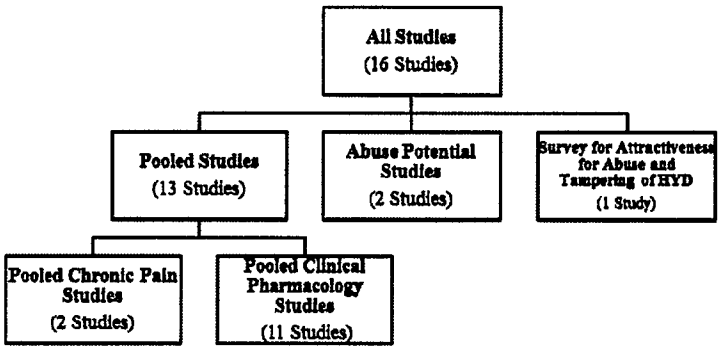
Question 8. Does the Agency agree that, for the HYD NDA, the narrative text of the Integrated Summary of Effectiveness (ISE) can be presented in Module 2, and the tables, appendices, and

datasets can be contained in Module 5, as described in Example 4 (page 7) of the guidance, "Integrated Summaries of Effectiveness and Safety: Location Within the Common Technical Document" (April 2009)?

FDA Response:
Yes, we agree that, for the HYD NDA, the narrative text of the Integrated Summary of Effectiveness (ISE) can be presented in Module 2, and the tables, appendices, and datasets can be contained in Module 5, as long as there are working hyperlinks between the two modules.

Question 9. Does the Agency agree with the proposed data grouping/pooling of subjects for the Integrated Summary of Safety (ISS)?

FDA Response:
The briefing document states that the HYD clinical program consists of 16 studies, and the following graphic depicts the proposed pooling of studies for the ISS:



- **All studies (16 studies)**
- **Pooled all studies (Phase 1 and Phase 3 studies)**
- **Studies not pooled (Abuse liability studies)**
- **Pooled Chronic Pain Studies (Phase 3 studies)**
- **Pooled Clinical Pharmacology Studies group (the Phase 1 studies)**

The proposed data grouping/pooling of subjects for the ISS appears generally reasonable. However, it is not useful to pool Phase 1 and Phase 3 studies for safety analyses, as the study populations and dosing regimens differ.

Question 10. Does the Agency agree that the number of subjects exposed and the duration of exposures in the HYD clinical development program are adequate and sufficient to assess the safety of HYD for approval?

FDA Response:
Your proposed safety database includes more than 1700 subjects that have been exposed to HYD in Phase 1 and Phase 3 studies. You report that for Study HYD3003, 910 subjects

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have been exposed to at least one dose of HYD, 495 subjects to multiple dosing for 6 months or longer, 216 subjects for 12 months or longer, and that greater than 50% of those subjects received an average HYD dose of 60 mg or greater during the 12-month maintenance period. In addition, you report that as of April 22, 2013, approximately 170 subjects are still active in the HYD3003 maintenance period and it is expected that more than 100 of those subjects will complete the 12-month maintenance period (based on an estimated attrition rate), which will bring the total number of subjects with 12-month exposure to more than 300.

Provided that there are no unforeseen safety signals, the safety database size appears adequate.

Other formulations containing PEO have been associated with gastrointestinal adverse events including obstruction, sticking, and choking. Given the (b) (4) level of polyethylene oxide in the HYD formulation, provide an analysis of gastrointestinal adverse events occurring in all clinical studies in order to assess whether the presence of PEO results in an excess of these events. The events of interest include, obstruction, choking, vomiting, retching, atypical chest pain, and difficult or painful swallowing, tracheal obstruction, tracheal obstruction extrinsic, regurgitation, gagging, foreign body, foreign body reaction/sensation, removal of foreign body from throat, removal of foreign body from esophagus, removal of foreign body from larynx, esophageal obstruction, colonic obstruction, duodenal obstruction, gastrointestinal obstruction, intestinal obstruction, large intestinal obstruction, obstruction gastric, small intestinal obstruction, and removal of foreign body from gastrointestinal tract.

Question 11. Does the Agency agree that the safety data from the 6 month extension phase of HYD3003 (Protocol Amendment #3), which will provide duration of treatment for up to 18 months, can be included in the 120-day safety update of the NDA?

FDA Response:
The original NDA submission must include all safety data intended to support the approval of your product. Additional data beyond the required safety database may be submitted in the 120-day safety update.

Question 12. Does the Agency agree that the conversion table and conversion instructions that guided the HYD clinical investigators in converting subjects from other opioid analgesics to HYD can be included in the HYD label?

FDA Response:
You propose to include the conversion table and instructions used during the clinical trials in the product label. This information may be included in the label. However, the final decision will be based on review of the efficacy and safety data submitted in the NDA.

Risk Management
Question 15. Does the Agency agree that the class REMS for extended-release/ long-acting (ER/LA) opioids will apply to HYD?

FDA Response:
Yes, we agree that the class REMS for ER/LA opioids will apply to HYD. We encourage you to submit the most recently approved ER/LA Opioid Analgesics REMS at the time you submit your NDA, which is located on FDA's Approved REMS website. A complete review of the REMS, in conjunction with the full clinical review of the NDA will be necessary to determine that the REMS adequately addresses the safety risks and meets the criteria set forth in section 505-1 of the Federal Food, Drug, and Cosmetic Act.

Question 16. When developing the NDA Module 1 drug abuse liability assessment for HYD, can Purdue specifically reference information from the 8-factor analysis of hydrocodone included in the FDA Briefing Document for the Drug Safety and Risk Management Advisory Committee (DSaRM) Meeting on the potential rescheduling of hydrocodone?

FDA Response:
An 8-factor analysis of hydrocodone, as conducted for the referenced DSaRM Advisory Committee meeting for purposes of considering rescheduling combination hydrocodone products, is not required for your HYD NDA submission. Under the Controlled Substances Act, single-entity opioid products such as HYD are Schedule II.

Additional Biopharmaceutics Comments:
Provide the following information in your NDA regarding the development of the dissolution method, establishing dissolution acceptance criteria, conducting in vitro alcohol dose-dumping studies, and the extended-release claim for your proposed drug product:

Dissolution Method:
Submit the dissolution method report supporting the selection of the proposed test and include the following information:

a. **Solubility data for the drug substance as a function of pH range;**

b. **Detailed description of the dissolution method proposed for the evaluation of your product and the developmental parameters (*i.e., selection of the equipment/apparatus, dissolution media, agitation/rotation speed, pH, assay, and sink conditions.*). 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. If possible, the dissolution profile should be complete and cover at least (b) (4) 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. **The complete dissolution profile data (*individual, mean, SD, profiles*) for your product. Report the dissolution data as the cumulative drug release with time; and**

d. **The testing conducted to demonstrate the discriminating capability of the selected dissolution test as well as the supportive validation data for the dissolution method (i.e., method robustness,) and analytical method (precision, accuracy, linearity, stability). The chosen method should be discriminating and sensitive enough to reject lots that would have less than acceptable clinical performance.**

Dissolution Acceptance Criteria:

Provide the complete dissolution profile data (i.e., 10, 20, and 30 minutes; 1, 2, 4, 6, 8, 10, and 12 hours) from the clinical and stability registration batches supporting the selection of the dissolution acceptance criteria. For the setting of the drug dissolution acceptance criteria, consider the following points:

a. **The in vitro dissolution specifications should encompass the timeframe over which at least (b) (4) of the drug is dissolved or where the plateau of drug dissolved is reached if incomplete dissolution is occurring.**

b. **Data from the lots used in the clinical trials and primary stability studies must be used.**

c. **For extended-release products, the establishment of at least three specification time-points covering the initial, middle, and terminal phases of the complete dissolution profile data must be set. The acceptance criteria ranges must be based on the overall dissolution data generated at these times.**

d. **In general, selection of the dissolution acceptance criteria ranges is based on mean target value ± (b)(4)% and NLT (b)(4)% for the last specification time-point. Wider specification ranges may be acceptable if they are supported by an approved In Vitro-In Vivo Correlation (IVIVC) model.**

e. **Set the dissolution acceptance criteria in a way to ensure consistent performance from lot to lot and these criteria should not allow the release of any lots with dissolution profiles outside those that were tested clinically.**

Note that the final determination of the acceptability of the dissolution method is a review issue during the IND or NDA phase of development. However, the acceptability of the proposed dissolution acceptance criteria for your product will be made during the NDA review process based on the totality of the data provided.

In Vitro Alcohol-Induced Dose Dumping:

Evaluate the potential for alcohol-induced dose dumping for the highest and lowest strength of your proposed ER product by first conducting an in vitro alcohol dose-dumping test. Depending on the results of the in vitro testing, you may have to follow-up with an in vivo alcohol dose-dumping study. Note that, if the results show an

interaction of your ER product with alcohol, you should discuss these results with FDA prior to NDA submission.

Consider the following points during the evaluation of the in vitro alcohol-induced dose dumping of your ER product:

a. **Conduct dissolution testing using the optimal dissolution apparatus and agitation speed. Dissolution data should be generated from 12 dosage units (n=12) at multiple time points to obtain a complete dissolution profile.**

b. **Use the following alcohol concentrations for the in vitro dissolution studies: 0 %, 5 %, 10 %, 20 %, and 40 %.**

c. **In general;**
   - **If the optimal dissolution medium is 0.1 N HCl, dissolution profiles in this 0.1 N HCl containing the above range of alcohol concentrations would be sufficient.**
   - **If the optimal dissolution medium is NOT 0.1 N HCl, dissolution profiles using the above range of alcohol concentrations in 0.1 N HCl and in the optimal dissolution medium are recommended.**
   - **If the optimal dissolution medium has not been identified; 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.**
   - **If the dissolution of the ER product is pH independent; then dissolution data in 0.1 N HCl with the above range of alcohol concentrations is sufficient.**

d. **Compare the shape of the dissolution profiles to determine if the modified-release characteristics are maintained, especially in the first 2 hours.**

e. **Estimate the f2 values assessing the similarity (or lack thereof) between the dissolution profiles (using 0% alcohol as the reference).**

f. **Provide the report with the complete data (i.e., individual, mean, SD, comparison plots, f2 values, etc.) collected during the evaluation of the in vitro alcohol-induced, dose-dumping study to FDA for review and comments.**

Extended-Release Claim:
Based on the Code of Federal Regulations, [21 CFR 320.25 (f)], if any part of your drug product includes an extended-release component, provide the data supporting the approval of the controlled-release claim made for your drug.

Additional Nonclinical comments:
We note that you have submitted the final study reports of the two carcinogenicity assessments. Please submit the data in SAS transport files. Data files should be submitted electronically, following Section E of the Guidance for Industry: *Providing Regulatory Submission in Electronic Format- NDAs.*
http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM163187.pdf

New or novel excipients in your drug must be adequately qualified for safety. Studies must be submitted to the IND in accordance as per the Guidance for Industry: *Nonclinical Studies for Safety Evaluation of Pharmaceutical Excipients.*
http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM079250.pdf

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).

For the NDA submission, any impurity or degradation product that exceeds ICH thresholds must be adequately qualified for safety as per ICH Q3A(R2), ICH Q3B(R2) or be demonstrated to be within the specifications of the referenced drug used for approval through the 505(b)(2) pathway. Unless otherwise justified, adequate qualification must include:

- **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.**
- **Repeat dose toxicology study of appropriate duration to support the proposed indication.**

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(R2) and ICH Q3B(R2) qualification thresholds and determination if the impurity contains 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.**

Potentially genotoxic impurities or degradation products pose an additional risk; therefore, a specification which provides for a maximal daily intake of NMT 1.5 mcg/day must be set for genotoxic or potentially genotoxic impurities in the drug substance and drug product unless otherwise adequately justified. Adequate safety qualification for any potential genotoxic impurities identified via a structural alert for mutagenicity must be provided with the NDA submission and must include an in vitro bacterial reverse mutation assay (Ames assay) with the isolated impurity, tested up to the limit dose for the assay. Should this qualification produce positive or equivocal results, the impurity specification must be set such that the maximal daily intake of the impurity is NMT 1.5 mcg/day, or otherwise justified. Justification may require an assessment for carcinogenic potential in either a standard 2-year rodent bioassay or in an appropriate transgenic mouse model.

- **NOTE: We may refuse to file your application if your NDA submission does not contain adequate safety qualification data for any identified impurity containing a structural alert for mutagenicity that exceeds 1.5 mcg/day.**

If the drug substance batch(es) proposed for use in your clinical study are not the same batches as those used in your nonclinical toxicology studies, your IND submission should include a table that compares the impurity profile across batches. Include justification for why the levels of impurities in the pivotal nonclinical toxicology studies provide adequate coverage for the proposed levels in the clinical batches or do not otherwise represent a safety concern.

Drug substance manufacturing process intermediates may include compounds with structural alerts for genotoxicity. Refer to the 2008 Draft FDA Guidance for Industry: *Genotoxic and Carcinogenic Impurities in Drug Substances and Products: Recommended Approaches* http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm079235.pdf **for acceptable levels of potentially genotoxic impurities over the course of drug development. Your IND should include initial evaluation of your synthetic pathway to identify potentially genotoxic impurities and justification for why you believe these impurities should not be regulated as per the 2008 Draft Guidance.**

Your NDA submission should include a detailed discussion of the nonclinical information in the published literature and should specifically address how the information within the published domain impacts the safety assessment of your drug product. This discussion should be included in Module 2 of the submission. Copies of all referenced citations should be included in the NDA submission in Module 4. Journal articles that are not in English must be translated into English.

The nonclinical information in your proposed drug product labeling must include relevant exposure margins with adequate justification for how these margins were obtained. As 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 labeling.

Additional CSS Comments:
In the NDA, you should provide in tabular form the following information and data related to the abuse potential assessment, including drug diversions and overdose:

1. **Descriptions of all reports and details of all incidents of abuse, misuse, or overdose (intentional or unintentional), or drug that is lost, stolen, missing or unaccounted for in all clinical studies. Include the Study number, site, type of report, subject identifier, and narratives.**
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.**
3. **Any data you have regarding abuse of hydrocodone containing products via non-oral routes including inhalation (smoking), insufflation (snorting) and intravenous injection.**

3.0 ACTION ITEMS/ FINAL UNDERSTANDINGS

3.1 (b) (4)

3.2 Regarding Hatch-Waxman exclusivity conferred on any other hydrocodone formulations that may receive FDA approval prior to an approval of HYD, any formulation that is not a once daily formulation such as HYD will not be considered pharmaceutically equivalent to HYD.

3.3 Purdue's proposed nonclinical package for hydrocodone is complete. In lieu of a second chronic toxicology study with hydrocodone, the rat carcinogenicity study should be discussed in terms of a NOAEL.

3.4 Regarding the maximum daily dose of hydrocodone for purposes of acceptable limits in proposed drug substance and drug product specifications, FDA reiterated that 3,000 mg is considered the appropriate maximum theoretical daily dose. Purdue can submit drug specifications based on an alternative MTDD with justification for review, and this will permit filing of the NDA. However, the acceptability of such specifications and justification for a MTDD of less than 3000 mg/day will be a review issue.

3.5 In order to qualify the PEO excipient, Purdue must provide the full study reports from (b) (4) or must reference the information, e.g., with a letter of authorization to

a Master File containing the full study reports. If this is not possible, Purdue may submit a weight-of-evidence approach for qualifying the PEO. The acceptability of a weight-of-evidence approach will be a review issue.

3.6 Purdue and FDA agree on the planned submission and organization of data concerning the ototoxicity assessments.

3.7 Regarding statistical analyses, Purdue will provide a justification for their approach to the treatment of missing data when patients discontinue for reasons other than adverse events.

3.8 All subgroup analyses conducted would be included in the individual clinical study reports. The ISE section that describes subgroup analyses can cross-reference to the HYD3002 study report.

3.9 Purdue will include information pertaining to possible swelling of HYD tablets in water or gastric fluid, a potential source of GI-related adverse events.

3.10 FDA advice and comments in response to questions/topics not selected for further discussion during the meeting represent final understandings between Purdue and FDA concerning these questions/topics.

4.0 ATTACHMENTS AND HANDOUTS

All content from the Meeting Agenda handout is included in Section 2.

5.0 OTHER IMPORTANT ADVICE AT PRE-NDA STAGE

5.1 PREA REQUIREMENTS

Please be advised that under the Food and Drug Administration Safety and Innovation Act (FDASIA), you must submit a Pediatric Study Plan (PSP) within 60 days of an End-of-Phase 2 (EOP2) meeting held on or after November 6, 2012. If an EOP2 meeting occurred prior to November 6, 2012 or an EOP2 meeting will not occur, then:

- if your marketing application is expected to be submitted prior to January 5, 2014, you may either submit a PSP 210 days prior to submitting your application or you may submit a pediatric plan with your application as was required under the Food and Drug Administration Amendments Act (FDAAA).

- if your marketing application is expected to be submitted on or after January 5, 2014, the PSP should be submitted as early as possible and at a time agreed upon by you and FDA. We strongly encourage you to submit a PSP prior to the initiation of Phase 3 studies. In any case, the PSP must be submitted no later than 210 days prior to the submission of your application.

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. For additional guidance on submission of the PSP, including a PSP Template, please refer to: http://www.fda.gov/DrugsDevelopmentApprovalProcess/DevelopmentResources/ucm049867.htm . In addition, you may contact the Pediatric and Maternal Health Staff at 301-796-2200 or email pdit@fda.hhs.gov.

5.2 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. In particular, please note the following formatting requirements:

- Each summarized statement in the Highlights (HL) must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contains more detailed information.

- The section headings and subheadings (including title of the Boxed Warning) in the Table of Contents must match the headings and subheadings in the FPI.

- The preferred presentation for cross-references in the in the FPI is the section heading (not subsection heading) followed by the numerical identifier in italics. For example, "[*see Warnings and Precautions (5.2)*]".

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/DrugsGuidanceComplianceRegulatoryInformation/LawsActsandRules/ucm084159.htm. We encourage you to review the information at this website and use it as you draft prescribing information for your application.

5.3 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.				

5.4 505(b)(2) REGULATORY PATHWAY

A 505(b)(2) application would be an acceptable approach at this time based on the information provided. 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 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 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 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 is supported by reliance 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.

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.

Reference ID 3366742

Attachment 1:
Additional Comments for Pre-NDA Stage of Drug Development

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. 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.

3. New excipients in your drug must be adequately qualified for safety. Studies must be submitted to the IND in accordance as per the following guidance for industry, *Nonclinical Studies for Safety Evaluation of Pharmaceutical Excipients*.

   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).

4. Any impurity or degradation product that exceeds ICH qualification thresholds must be adequately qualified for safety as described in 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.

5. Genotoxic, carcinogenic or impurities that contain a structural alert for genotoxicity must be either reduced to NMT 1.5 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 ICHS2A 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 1.5 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.

6. In Module 2 of your NDA (2.6.6.8 Toxicology Written Summary/Other Toxicity), 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 ICHQ3A and 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.

7. The NDA submission must contain information on potential leachables and extractables from the drug container closure system and/or drug product formulation, unless specifically waived by the Division. Certain drug products are considered to present a high concern for risk, for example, liquid formulations or drugs in patches or other devices employed for parenteral delivery. The evaluation of extractables and leachables from the drug container closure system or device should include specific assessments for residual monomers, solvents, polymerizers, etc.). Based on identified leachables you will need to provide a toxicological evaluation to determine the safe level of exposure via the label-specified route of administration. The approach for toxicological evaluation of the safety of leachables must be based on good scientific principles and take into account the specific container closure system or patch, drug product formulation, dosage form, route of administration, and dose regimen (chronic or short-term dosing). As many residual monomers are known genotoxic agents, your safety assessment must take into account the potential that these leachables may either be known or suspected highly reactive and/or genotoxic compounds. The safety assessment should be specifically discussed in Module 2.6.6.8 (Toxicology Written Summary/Other Toxicity) of the NDA submission. For additional

guidance on extractables and leachables testing, consult the FDA Guidance documents "Container Closure Systems for Packaging Human Drugs and Biologics" and "Nasal Spray and Inhalation Solution, Suspension, and Spray Drug Products – Chemistry, Manufacturing, and Controls Documentation." For your toxicological risk assessment, any leachable that contains a structural alert for mutagenicity should not exceed 1.5 mcg/day total daily exposure or be adequately qualified for safety. A toxicological risk assessment should be provided for any non-genotoxic leachable that exceeds 5 mcg/day.

8. Failure to submit adequate impurity qualification, justification for the safety of new excipient use, or an extractable leachable safety assessment at the time of NDA submission can result in a Refusal-to-File or other adverse action.

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 (nonclinical 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 nonclinical 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 nonclinical 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

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). This information is requested for all major trials used to support safety and efficacy in the application (i.e., phase 2/3 pivotal trials). Please note that if the requested items are provided elsewhere in the submission in the format described, the Applicant can identify the location(s) and/or provide link(s) to the requested information.

The dataset that is requested in Item III below is for use in a clinical site selection model that is being piloted in CDER. Electronic submission of site level datasets is voluntary and is intended to 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 1, Technical Instructions: Submitting Bioresearch Monitoring (BIMO) Clinical Data in eCTD Format).

I. Request for general study related information and comprehensive 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 pivotal 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. Location of Principal Investigator: Address (e.g. Street, City, State, Country) and contact information (i.e., phone, fax, email). If the Applicant is aware of changes to a clinical investigator's site address or contact information since the time of the clinical investigator's participation in the study, we request that this updated information also be provided.

2. Please include the following information in a tabular format *by site* in the original NDA for each of the completed pivotal clinical trials:
   a. Number of subjects screened at each site
   b. Number of subjects randomized at each site, if appropriate
   c. Number of subjects treated who prematurely discontinued at each site

3. Please include the following information in a tabular format in the NDA for each of the completed pivotal clinical trials:
   a. Location at which sponsor trial documentation is maintained (e.g., monitoring plans and reports, training records, data management plans, drug accountability records, IND safety reports, or other sponsor records as described in ICH E6, Section 8). This is the actual physical site(s) where documents are maintained and would be available for inspection.
   b. Name, address and contact information of all contract research organizations (CROs) used in the conduct of the clinical trials and brief statement of trial related functions transferred to them. If this information has been submitted in eCTD format previously (e.g., as an addendum to a Form FDA 1571) you may identify the location(s) and/or provide link(s) to information previously provided.

c. The location at which trial documentation and records generated by the CROs with respect to their roles and responsibilities in conduct of respective studies is maintained. As above, this is the actual physical site where documents would be available for inspection.

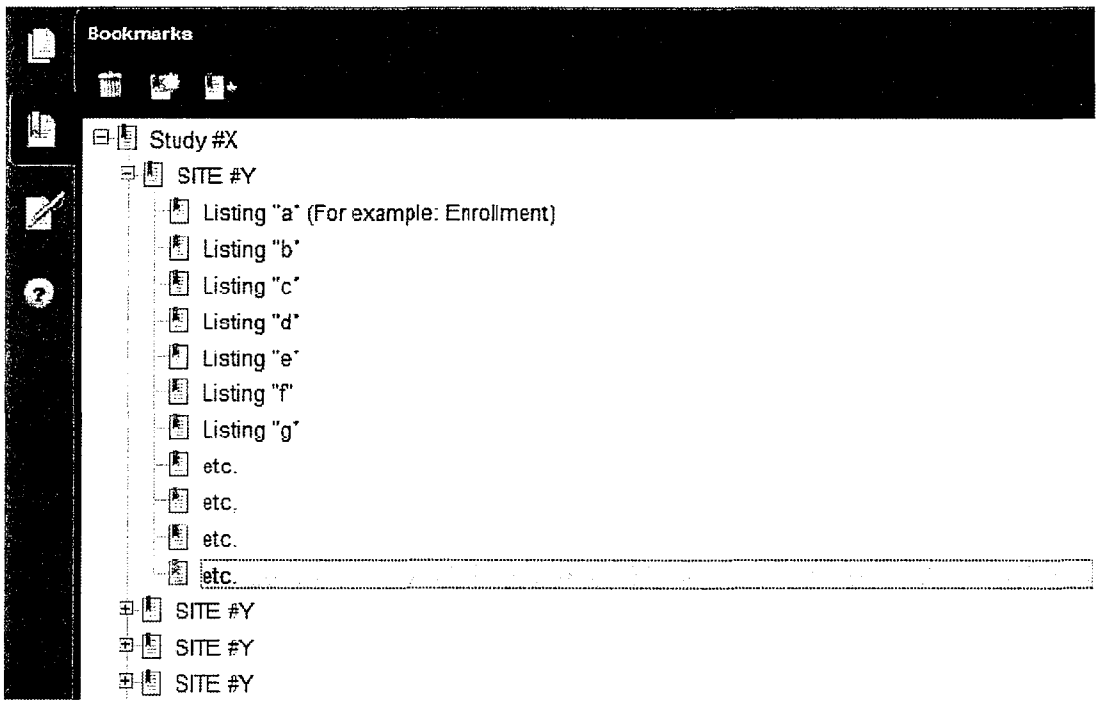
4. For each pivotal trial provide a sample annotated case report form (or identify the location and/or provide a link if provided elsewhere in the submission).

5. For each pivotal trial provide original protocol and all amendments (or identify the location and/or provide a link if provided elsewhere in the submission).

II. Request for Subject Level Data Listings by Site

1. For each pivotal trial: Site-specific individual subject data listings (hereafter referred to as "line listings"). For each site provide:
   a. Listing for each subject consented/enrolled; for subjects who were not randomized to treatment and/or treated with study therapy, include reason not randomized and/or treated
   b. Subject listing for treatment assignment (randomization)
   c. Listing of subjects that discontinued from study treatment and subjects that discontinued from the study completely (i.e., withdrew consent) with date and reason discontinued
   d. Listing of per-protocol subjects/ non per-protocol subjects and reason not per-protocol
   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/BLA, including a 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 testing (e.g., laboratory, ECG) 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

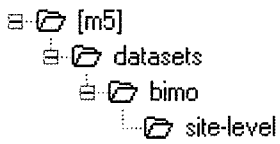
OSI is piloting a risk based model for site selection. Voluntary electronic submission of site level datasets is intended to facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process. If you wish to voluntarily provide a dataset, please refer to the draft "Guidance for Industry Providing Submissions in Electronic Format – Summary Level Clinical Site Data for CDER's Inspection Planning" (available at the following link http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/UCM332468.pdf) for the structure and format of this data set.

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/BLA 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

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).

Reference ID: 3666752

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. [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)

21. 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):

22. 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).

23. 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

24. 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

25. 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]

26. Include only references that are important to the prescriber. [See 21 CFR 201.57(c)(16)]

27. 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)].

28. 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.

29. 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.

30. 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.

31. 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.

Reference ID: 3366752

32. 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.

33. For fictitious examples of labeling in the new format, refer to http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/LawsActsandRules/ucm084159.htm

34. For a list of error-prone abbreviations, symbols, and dose designations, refer to the Institute of Safe Medication Practices' website, http://www.ismp.org/Tools/abbreviationslist.pdf

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,* available at 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,* available at 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,* available at

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

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.

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.

Reference ID: 3594814

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		

Reference ID: 3666752

Reference ID: 3354814

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/s/

DOMINIC CHIAPPERINO
08/08/2013

Chiapperino, Dominic

From: Chiapperino, Dominic
Sent: Monday, July 28, 2014 1:10 PM
To: Liao, Edward (Edward.Liao@pharma.com)
Subject: NDA 206627, information request, REMS revisions
Attachments: ER.LA REMS RPC risk-mang-rems-and-materials-Clean with FDA Edits.7.24.14.doc

Hi Ed,

As you know, since Purdue has approved products that are part of the ER/LA opioid analgesics REMS, manufacturers of ER/LA opioid analgesic products collectively referred to as the REMS Program Companies (RPC) submitted their respective modified REMS documents and REMS materials to the Agency between June 9-13, 2014 to reflect the safety labelling changes approved for all ER/LA opioid analgesics on April 16, 2014. Based on that ongoing review, REMS materials for the ER/LA REMS have been revised since your submission of NDA 206627 and the proposed REMS in that original submission.

For your REMS submitted with NDA 206627, we request that you update the REMS document, using the attached file, to make your proposed REMS consistent with changes also requested of the RPC for the REMS Modification currently under review by FDA. This attached document reflects also the addition of a new dosage strength of Butrans (approved on June 30, 2014) and the addition of Targiniq ER (approved on July 23, 2014).

We ask that you review the attached document and add the drug-specific information for Hysingla ER in the Blueprint – particularly in the product specific information chart, and re-submit this back to FDA by August 1st, or by the same date that RPC is able to respond to similar requested revisions, although they would not be including the Hysingla ER information. They were asked to respond by Aug. 1st as well.

We may have further comments about your proposed REMS at a later date, as far as the drug-specific language included for Hysingla ER. Review of this information is ongoing.

Kind regards,
Dominic

Dominic Chiapperino, Ph.D.
Senior Regulatory Health Project Manager
Division of Anesthesia, Analgesia, and Addiction Products
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Reference ID: 3600275

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/s/

DOMINIC CHIAPPERINO
07/28/2014

Chiapperino, Dominic

From: Chiapperino, Dominic
Sent: Monday, July 28, 2014 9:33 AM
To: Liao, Edward (Edward.Liao@pharma.com)
Subject: NDA 206627, information request, container labels & CMC

Hi Ed,

We have reviewed the container labeling you submitted in response to our July 11, 2014, information request, and had further discussion with DMEPA about the labeling. We have the following additional comments/requests, and also two additional CMC requests, below:

Labeling/Packaging

1. The colors used to differentiate the 20 mg and 40 mg strengths (green and grey) are similar, and the colors used for the 60 mg and 80 mg strengths ((b) (4) and dark pink) are also similar, which may lead to errors when selecting the correct strength. Select a different color within each of these two similar color pairs and ensure the new colors are not similar in color to other strengths.

2. Move the statement "Swallow tablets whole. Do not cut, break, chew, crush or dissolve" to the principal display panel to improve its prominence. Consider moving the statement "Purdue Pharma L.P." to the side panel to make room for this important information.

3. Place the medication guide statement under the strength presentation on the principal display panel. Move the NDC number, proprietary name, established name, and strength up toward the top of the label to increase their prominence.

4. You have not provided carton labels. Confirm that the drug product bottles will not be packaged in cartons or provide carton labels for each product strength.

CMC

5. Update Section 3.2.P.5.1 Specifications with the new acceptance limits of NMT (b) (4) for (b) (4) and NMT (b) (4) for total impurities for all product strengths.

6. In process control acceptance limits are typically tighter than the final limits for the drug product so that there is some room of variation for subsequent manufacturing procedures. Explain how your wider in process control acceptance limit ((b) (4)) of (b) (4) for content uniformity can ensure that the final drug product content uniformity to be (b) (4)

Please respond to the CMC comments and packaging comment #4 by Wednesday, and address the other labeling/packaging comments with revised labels or a proposal at your earliest opportunity.

Kind regards,
Dominic

Dominic Chiapperino, Ph.D.
Senior Regulatory Health Project Manager
Division of Anesthesia, Analgesia, and Addiction Products

Reference ID: 3600264

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/s/

DOMINIC CHIAPPERINO
07/28/2014

Chiapperino, Dominic

From: Chiapperino, Dominic
Sent: Thursday, July 24, 2014 5:08 PM
To: Liao, Edward (Edward.Liao@pharma.com)
Subject: NDA 206627, information request, food effect

Hi Ed,

For NDA 206627, we have an additional request, as follows:

In Food-effect Study HYD1003, we noted that inter-individual variability decreased under fed condition, particularly after high-fat meal consumption. We noted bioavailability (Cmax and or AUC) of subjects 1021, 1034, 1074, 1085 was very low under fasting condition compared to average values in the group. Under high-fat meal consumption these subjects had up to 8-fold higher increase in Cmax and or AUC. We noted that subject 1021 vomited after receiving Hysingla ER under fasting condition. Explain the experimental conditions, subject AEs or other relevant conditions that may have contributed to the low bioavailability in these subjects under fasting condition. Also, explain how you plan to address these observations in labeling.

Please provide response by c.o.b. Monday, July 28th, and also submit the response to the NDA file.

Kind regards,
Dominic

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Reference ID: 3599029

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/s/

DOMINIC CHIAPPERINO
07/24/2014

Chiapperino, Dominic

From: Chiapperino, Dominic
Sent: Thursday, July 24, 2014 3:29 PM
To: Liao, Edward (Edward.Liao@pharma.com)
Subject: NDA 206627, information request, terminology

Hi Ed,

Concerning NDA 206627, we have an additional request for information, to clarify some terminology Purdue has used, as follows:

1. In Section 4.4. 5.4 (Aberrant Drug Behavior Events) of the ISS you have listed abuse, overdose, misuse and medication errors under aberrant drug behavior events. Clarify if the events of abuse, overdose, misuse and medication errors are what you have defined as aberrant drug behavior. If not, provide what you define as aberrant drug behavior.

2. In Section 4.4.5.2 Formulation-related Choking and Obstruction Risks (Table 44) and Section 4.4.5.4 Aberrant Drug Behavior Events (Table 46) of the ISS, the term "additional medical concept" is included in these respective tables. Clarify what the term "additional medical concept" means and any additional information related to use of this terminology.

Please try to include response to this request with the amendments you expect to send tomorrow. You may also send response to me by email.

Kind regards,
Dominic

Dominic Chiapperino, Ph.D.
Senior Regulatory Health Project Manager
Division of Anesthesia, Analgesia, and Addiction Products
Office of Drug Evaluation II
FDA, Center for Drug Evaluation and Research
10903 New Hampshire Avenue
Building 22, Room 3134
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Office phone: (301) 796-1183
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Dominic.Chiapperino@fda.hhs.gov

Reference ID: 3598921

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/s/

DOMINIC CHIAPPERINO
07/24/2014

Chiapperino, Dominic

From: Chiapperino, Dominic
Sent: Tuesday, July 22, 2014 11:28 AM
To: Liao, Edward (Edward.Liao@pharma.com)
Subject: NDA 206627, information request, (b) (4) follow-up

Hi Ed,

We have reviewed the new information provided in response to previous comments about Hysingla ER (b) (4) (b) (4) on tablets. We have the following follow-up comments/requests:

1. From your given description on (b) (4) .

2. In your product development section (section 4.3.1), you have mentioned that you will be using a (b) (4) .

3. Provide detailed clarification on how the (b) (4) .

Please respond to these new requests by Friday if at all possible. We will not be discussing this today during our t-con today as I had suggested we would. Your written response should be submitted as email to me and then as formal amendment as well.

Thank you and regards,

Reference ID: 3597198

Dominic Chiapperino, Ph.D.
Senior Regulatory Health Project Manager
Division of Anesthesia, Analgesia, and Addiction Products
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/s/

DOMINIC CHIAPPERINO
07/22/2014

Chiapperino, Dominic

From: Chiapperino, Dominic
Sent: Tuesday, July 22, 2014 8:03 AM
To: Liao, Edward (Edward.Liao@pharma.com)
Subject: NDA 206627, information request, Labeling

Dear Ed,

Regarding the package insert for Hysingla ER, we have made substantial revisions but are not quite at the point of sending you our complete set of labeling comments and marked-up package insert. However, we have some sections that we would like to address as soon as possible, so I am excerpting from the package insert to request additional information from you related to these sections, as follows:

Provide clarification for the following dosing-related issues, in these sections:

> **2.2 Titration and Maintenance of Therapy**
>
> Individually titrate HYSINGLA ER to a dose that provides adequate analgesia and minimizes adverse reactions. Continually re-evaluate patients receiving HYSINGLA ER to assess the maintenance of pain control and the relative incidence of adverse reactions as well as monitoring for the development of addiction, abuse, or misuse. Frequent communication is important among the prescriber, other members of the healthcare team, the patient, and the caregiver/family during periods of changing analgesic requirements, including initial titration. During chronic therapy, periodically reassess the continued need for the use of opioid analgesics.
>
> Adjust the dose of HYSINGLA ER in <u>increments of […] every 3 to 5 days as needed to achieve adequate analgesia</u>.

1. For the above portion of section 2.2 (as we've revised it thus far), provide clarification as to appropriate dose increments in mg, where we have underlined the text.

> **5.14 QT Interval Prolongation**
>
> (b) (4)

2. For the above section 5.14 that we have added in the package insert, clarify the amount by which the dose would be appropriately reduced, i.e., by modifying underlined text, and giving your rationale.

Please respond by email at your earliest opportunity. A formal amendment is not necessary for this issue.

Kind regards,
Dominic

Reference ID: 3597191

Dominic Chiapperino, Ph.D.
Senior Regulatory Health Project Manager
Division of Anesthesia, Analgesia, and Addiction Products
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/s/

DOMINIC CHIAPPERINO
07/22/2014

PeRC PREA Subcommittee Meeting Minutes
July 9, 2014

PeRC Members Attending:
Lynne Yao
Rosemary Addy
Jane Inglese
Hari Cheryl Sachs
Wiley Chambers
Tom Smith
Karen Davis-Bruno
Andrew Mulberg
Daiva Shetty
Julia Pinto
Lily Mulugeta

Agenda

(b) (4)

NDA	206627	Hysingla (hydrocodone) Partial Waiver/Deferral/Plan	Management of moderate to pain severe enough to require around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate

(b) (4)

(b) (4)

Hysingla (hydrocodone) Partial Waiver/Deferral/Plan

- NDA 206627 seeks marketing approval for Hysingla (hydrocodone) for management of moderate to pain severe enough to require around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate.
- The application triggers PREA as directed to a new dosing regimen.
- The application has a PDUFA a goal date of October 28, 2014.
- The Division noted that this is a high priority review and plan to take an early action (mid-August). The PeRC agreed to review the pediatric plan and not proceed with review of the iPSP that was submitted.

- The PeRC noted the potential serious consequences for development of age appropriate abuse-deterrent opioids formulations to treat chronic and acute pain in children if waivers are granted for abuse-deterrent formulations. Clearly development of abuse-deterrent formulations of opioids and age-appropriate formulations for children are both important public health needs. Further discussion to develop consistent policies will be held.
- (b) (5) Therefore, the Division and PMHS will discuss this potential policy change further.
- *PeRC Recommendations:*
    - The PeRC agreed with a partial waiver for pediatric patients aged birth to less than 7 years because studies would be impossible or highly impracticable for pediatric patients of this age. See bullet above.
    - The PeRC agreed with partial waiver for pediatric patients aged 7 to less than 12 years because reasonable attempts to develop a formulation for pediatric patients of this age have failed. Information documenting the sponsor's failed attempts to develop a pediatric formulation must be posted on FDA's website.
    - There was some disagreement among PeRC members on the appropriate basis for the partial waiver in each pediatric age group, with one PeRC member recommending that the population birth to less than 12 years be waived for failure to develop an age appropriate formulation.
    - The PeRC agreed to a deferral for pediatric patients aged 12 to less than 17 years because adult studies have been completed and the product is ready for approval.
    - The PeRC recommended that the Division consider asking the sponsor to revise the pediatric study timeline to require earlier study completion dates.

(b) (4)

(b) (4)

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/s/

JANE E INGLESE
07/21/2014

Chiapperino, Dominic

From: Chiapperino, Dominic
Sent: Monday, July 21, 2014 1:37 PM
To: Liao, Edward (Edward.Liao@pharma.com)
Subject: RE: NDA 206627, information requests (2)

Hi Ed,

I need to add one question to the Clinical Pharmacology list in my previous email.

6. What is the extent of rescue medications in study HYD 3002 and or study HYD3003 patients in following groups?
   a) strong laxatives (Lactulose etc.,)
   b) mild laxatives (docusate, fiber etc.,)
   c) no laxatives

Thank you,
Dominic

From: Chiapperino, Dominic
Sent: Monday, July 21, 2014 1:19 PM
To: Liao, Edward (Edward.Liao@pharma.com)
Subject: NDA 206627, information requests (2)

Hi Ed,

Regarding NDA 206627 for Hysingla ER, we have additional requests for information, as follows:

Clinical

1. Provide a summary table for subjects who were discontinued during the run-in period and double-blind periods due to confirmed or suspected diversion in Study HYD3002. Include the following information in the summary table: subject identifier, dose of HYD /placebo when discontinuation occurred, circumstance surrounding confirmed or suspected diversion and supporting laboratory data (e.g., urine drug screen). In addition, please attach case report forms for each of these subjects.

2. Provide a summary table for subjects who were discontinued due to confirmed or suspected diversion in Study HYD3003. Include the following information in the summary table: subject identifier, dose of HYD when discontinuation occurred, circumstance surrounding confirmed or suspected diversion and supporting laboratory data (e.g., urine drug screen). In addition, please attach case report forms for each of these subjects.

Clinical Pharmacology:

In study HYD1007, we note that use of lactulose has potentially confounded the effect of severe hepatic impairment on systemic exposure of hydrocodone. Specifically, three subjects taking lactulose had low systemic exposure after receiving Hysingla ER. The rest of the subjects in severe hepatic impairment group had higher plasma systemic exposure (Cmax and AUC) compared to average values noted in healthy subjects.

Discuss the impact of lactulose or other laxative use on safety and efficacy in clinical studies HYD3002 and HYD3003. Specifically, address the following:

Reference ID: 3596577

1. How many subjects receiving Hysingla ER reported constipation as an adverse event? How many of these subjects were treated for constipation?
2. How many subjects received a laxative? Based on search for conmeds in HYD1007, we note that search for "laxative" as a search term may not yield any results. We recommend that you search for specific drugs/supplements used for relieving constipation (docusate, Metamucil, lactulose, etc., etc.).
3. Was the use of rescue medications in HYD 3002 high in patients taking laxatives?
4. In study HYD3003, did you note use of "laxative" in patients receiving Hysingla ER. Was PK data (pre-dose plasma concentrations) available in those subjects? Discuss any impact of laxative use on pre-dose hydrocodone plasma levels?
5. Was the use of rescue medications in HYD3003 high in patients taking laxatives?

We would like response to these requests by c.o.b. Wednesday, July 24th.

Kind regards,
Dominic

Dominic Chiapperino, Ph.D.
Senior Regulatory Health Project Manager
Division of Anesthesia, Analgesia, and Addiction Products
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Reference ID: 3596577

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/s/

DOMINIC CHIAPPERINO
07/21/2014

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

NDA 206627

PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE

Purdue Pharma, L.P.
One Stamford Forum
201 Tresser Blvd.
Stamford, CT 06901-3431

ATTENTION: Edward Liao, Pharm.D.
Director, US Regulatory Affairs

Dear Dr. Liao:

Please refer to your New Drug Application (NDA) dated April 26, 2014, received April 28, 2014, submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Hydrocodone Bitartrate Extended-Release Tablets, 20 mg, 30 mg, 40 mg, 60 mg, 80 mg, 100 mg and 120 mg.

We also refer to your correspondence, dated and received April 30, 2014, requesting review of your proposed proprietary name, Hysingla ER. We have completed our review of the proposed proprietary name, Hysingla ER, and have concluded that it is acceptable.

If any of the proposed product characteristics as stated in your April 30, 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 Dominic Chiapperino, Regulatory Project Manager, in the Office of New Drugs at (301) 796-1183.

Sincerely,

{See appended electronic signature page}

Kellie A. Taylor, Pharm.D., MPH
Deputy Director
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 on behalf of KELLIE A TAYLOR
07/18/2014

Chiapperino, Dominic

From: Chiapperino, Dominic
Sent: Thursday, July 10, 2014 11:49 AM
To: Liao, Edward (Edward.Liao@pharma.com)
Subject: NDA 206627, information request, updates to Section 12 of PI
Attachments: Section 12 Clinical Pharmacology IR.docx

Hi Ed,

Concerning NDA 206627 and your submitted package insert's Section 12, we have preliminary comments and request for updates as indicated in the attached Word document targeting only Section 12 of the PI.

Since our requests include new tabulated data and information, we wanted to provide these comments as soon as possible and have Purdue address these comments and submit with appropriate revisions the attached Word document targeting only Section 12. We will incorporate your new Section 12 into our current working file containing overall labeling revisions for future discussion.

We request these revisions to Section 12 by July 16th if at all possible.

Kind regards,
Dominic

Dominic Chiapperino, Ph.D.
Senior Regulatory Health Project Manager
Division of Anesthesia, Analgesia, and Addiction Products
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5 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

DOMINIC CHIAPPERINO
07/10/2014

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION			**PEDIATRIC AND MATERNAL HEALTH STAFF REQUEST FOR CONSULTATION**	
TO: CDER Pediatric and Maternal Health Staff *(please check)* Pediatrics ☐ Maternal Health ☐ Both ☒			FROM *(Name, Office/Division, and Phone Number of Requestor)*: Division of Anesthesia, Analgesia, and Addiction Products; Bob A. Rappaport, MD, Director Point-of-contact: Dominic Chiapperino, PhD, Senior Regulatory Health Project Manager, DAAAP, 301-796-1183	
DATE 7-10-14	IND NO.	NDA 206627	TYPE OF DOCUMENT Orig. NDA Submission	DATE OF DOCUMENT 4-28-14
NAME OF DRUG Hydrocodone bitartrate	NAME OF FIRM Purdue Pharma LP		CLASSIFICATION OF DRUG Type 3	PDUFA Goal Date 10-28-14, but earlier action targeted in mid-August
Requested Consult Completion Date: July 24, 2014	☐ Urgent* (< 14 days)		☒ Priority (14-29 days)	☐ Routine ≥ 30 days

*Note: Any consult requests with a desired completion date of < 14 days from receipt must receive prior approval from PMHS team leaders. Also, please check one of the three boxes above and also put in a due date.

REASON FOR REQUEST

Pediatrics:	Maternal Health Team:
☒ Labeling Review ☐ Written Request/PPSR ☐ PREA PMR/General Regulatory Question ☐ SPA ☐ Action Letter Review ☐ 30-day IND Review ☐ Other Protocol Review ☐ Meeting Attendance ☐ PeRC Preparation Assistance ☐ Other (please explain):	☒ Labeling Review ☐ Pregnancy Exposure Registry (protocol or report) ☐ Clinical Lactation Study (protocol or report) ☐ Pregnancy PK (protocol or report) ☐ 30-day IND Review ☐ Risk Management – Pregnancy Prevention and Planning ☐ Evaluation of possible safety signal ☐ Guidance development ☐ Other (please explain):
Link to electronic submission (if available): EDR Location: \\CDSESUB1\evsprod\NDA206627\206627.enx Working file for edits: <\\fdsfs01\ode2\DAAAP\NDA and sNDA\NDA 206627 (HYD-ER Purdue)\Labeling\Hysingla ER 4-28-14 label with FDA revisions.docx>	Materials to be reviewed: Section 8.1, 8.2, 8.3, and 8.4 of PI

1. Please briefly describe the submission including drug's indication(s):

   This is a new NDA submission for an extended-release reformulation (with claimed abuse deterrent properties) of hydrocodone bitartrate, indicated for the management of chronic pain

2. Describe in detail the reason for your consult. Include specific questions:

   DAAAP needs input from PMHS for appropriately labeling the product, including risk summary for specific populations (maternal, pregnancy category, etc)

3. Meeting dates:

   Mid-Cycle Meeting: Occurred June 25th
   Labeling: July 16th and 23rd
   Wrap-Up Meeting: July 24th

4. DARRTS Reference ID # for Prior Peds or Maternal Health consults for this product (within the last 3 years):

N/A

Review team:
Project Manager: Dominic Chiapperino, Ph.D.
Clinical reviewer & Team Leader: Jacqueline Spaulding, MD and Ellen Fields, MD, MPH (TL)
Pharmacology/Toxicology reviewer & Team Leader: Elizabeth Bolan, PhD and Dan Mellon, PhD (TL)
Clinical Pharmacology reviewer & Team Leader: Srikanth Nallani, PhD and Yun Xu, PhD (TL)
Other:

PRINTED NAME or SIGNATURE OF REQUESTOR:	METHOD OF DELIVERY (Please check)
Dominic Chiapperino (signed electronically)	☒ DARRTS ☐ EMAIL ☐ HAND ☐ OTHER

Version: DARRTS 06/01/2011

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/s/

DOMINIC CHIAPPERINO
07/10/2014

Chiapperino, Dominic

From: Chiapperino, Dominic
Sent: Friday, June 27, 2014 2:06 PM
To: Liao, Edward (Edward.Liao@pharma.com)
Subject: NDA 206627, information request, CMC

Dear Ed,

I have a CMC-related information request for NDA 206627, as follows:

1. To facilitate the review of your NDA, expand your bottle configuration table in Section 3.2.P.7 to include a list of each material used in the construction of all package components and correlate each to its respective CFR sections.

2. You stated that drug product batch size in addition to the submitted typical size of (b) (4) tablets will be quantitatively proportional and validated. Specify the range of your potential additional batch sizes and confirm how you will update the NDA with additional supporting information.

Contact me if you have questions.

Kind regards,
Dominic

Dominic Chiapperino, Ph.D.
Senior Regulatory Health Project Manager
Division of Anesthesia, Analgesia, and Addiction Products
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Dominic.Chiapperino@fda.hhs.gov

Reference ID: 3533700

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/s/

DOMINIC CHIAPPERINO
06/27/2014

Executive CAC
June 24, 2014

Committee: Abby Jacobs, Ph.D., OND-IO, Acting Chair
Paul Brown, Ph.D., OND-IO, Member
Timothy McGovern, Ph.D., OND-IO, Alternate Member
R. Daniel Mellon, Ph.D., DAAAP, Supervisor
Elizabeth A. Bolan, Ph.D., DAAAP, Presenting Reviewer

Author of Draft: Elizabeth A. Bolan, Ph.D.

The following information reflects a brief summary of the Committee discussion and its recommendations.

NDA #: 206627
Drug Name: Hydrocodone bitartrate extended-release tablets (HYSINGLA ER)
Sponsor: Purdue Pharma, L.P.

Background:
Hydrocodone bitartrate is a semi-synthetic mu opioid agonist. Purdue Pharma is developing a single-entity extended-release hydrocodone product with purported abuse-deterrent properties for the management of moderate to severe pain where the use of an opioid analgesic is appropriate. Hydrocodone bitartrate was found to be negative in the Ames assay, the in vitro mouse lymphoma assay and the in vivo mouse micronucleus assay and is not considered either mutagenic or clastogenic. The Executive CAC provided concurrence on dose selection for both the mouse and rat carcinogenicity study protocols (minutes dated 6/14/02).

Mouse Carcinogenicity Study
In the 2-year carcinogenicity study in CD-1 mice (60-70/sex/group), hydrocodone bitartrate was administered orally by gavage (vehicle: distilled water) at doses of 0, 20, 60, 200 mg/kg in males and 0, 10, 30, 100 mg/kg in females. Dosing of the high dose male group was stopped at Week 94 as a result of increased mortality. The high dose males were sacrificed at the termination of the study The 2-year mouse study is considered valid and no treatment-related increases in any tumor type were observed.

Rat Carcinogenicity Study
In the 2-year carcinogenicity study in Sprague-Dawley rats (70/sex/group), hydrocodone bitartrate was administered orally by gavage (vehicle: distilled water) at doses of 0, 4, 12, and 25 mg/kg in both males and females. The maximally tolerated dose appears to have been exceeded at the mid and high doses in both males and females based on decreases in terminal body weights >10% as compared to controls. The 2-year rat study is considered valid and no treatment-related increases in any tumor type were observed.

Executive CAC Recommendations and Conclusions:

Rat:

- The Committee concurred that the study was valid and acceptable, noting prior Exec CAC concurrence with the protocol. The Committee noted the body weight decrements and low exposure ratios.

- The Committee concurred that there were no drug-related neoplasms in the study.

Mouse:

- The Committee concurred that the study was valid and acceptable, noting prior Exec CAC concurrence with the protocol.

- The Committee concurred that there were no drug-related neoplasms in the study.

Abby Jacobs, Ph.D.
Acting Chair, Executive CAC

cc:\
/Division File, DAAAP, NDA 206627
/RD Mellon, DAAAP
/EA Bolan, DAAAP
/D Chiapperino, DAAAP
/ASeifried, OND-IO

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/s/

ADELE S SEIFRIED
06/26/2014

ABIGAIL C JACOBS
06/26/2014

Chiapperino, Dominic

From: Chiapperino, Dominic
Sent: Tuesday, June 24, 2014 8:38 AM
To: Liao, Edward (Edward.Liao@pharma.com)
Subject: NDA 206627, information request, patient death

Hi Ed,

For NDA 206627, we have an additional information request as follows:

Submit a copy of the death certificate for Subject HYD3003-2198A-3065030 or provide the location of the death certificate in the subject's CRF.

Please provide this by the end of this week.

Kind regards,
Dominic

Dominic Chiapperino, Ph.D.
Senior Regulatory Health Project Manager
Division of Anesthesia, Analgesia, and Addiction Products
Office of Drug Evaluation II
FDA, Center for Drug Evaluation and Research
10903 New Hampshire Avenue
Building 22, Room 3134
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Dominic.Chiapperino@fda.hhs.gov

Reference ID: 3530581

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/s/

DOMINIC CHIAPPERINO
06/24/2014

Chiapperino, Dominic

From: Chiapperino, Dominic
Sent: Monday, June 23, 2014 4:56 PM
To: Liao, Edward (Edward.Liao@pharma.com)
Subject: NDA 206627, information request, pharmacogenomic data

Dear Ed,

We have the following request for additional information. Response is requested by end of this week if at all possible.

We have noted your plan to collect pharmagenomic (pharmacogenetic data) data from subjects participating in protocols for studies HYD1002, HYD1003, HYD1006. We noted the "Pharmacogenomic Sample Collection Manual" for HYD1002. However, we were unable to locate any report on exploratory PG analyses that may have been performed to investigate PK, pharmacodynamic, and/or safety findings or hypotheses from this and related studies.

Provide any information, particularly pharmacogenetic data, that could help explain the variability in PK parameters. If such exploratory analysis reports are already submitted, help us locate these reports.

Kind regards,
Dominic

Dominic Chiapperino, Ph.D.
Senior Regulatory Health Project Manager
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/s/

DOMINIC CHIAPPERINO
06/23/2014

Chiapperino, Dominic

From: Chiapperino, Dominic
Sent: Monday, June 16, 2014 1:28 PM
To: Liao, Edward (Edward.Liao@pharma.com)
Subject: NDA 206627, information request, HYD3002

Dear Ed,

Concerning NDA 206627 for Hysingla ER, we have the following request for additional information:

In the Clinical Study Report for Study HYD3002, Table 6 (Subject Disposition and Reasons for Discontinuations – Safety Population and Randomized Safety Population) located below, it is reported that, during the double-blind period, 5% of the HYD treatment group versus 4% of the placebo treatment group discontinued study drug and study simultaneously due to subject's choice.

Reference ID: 3525392

	Run-in Period (N=905)			Double-bli (N=5	
	Non-randomized (NN=312)	Randomized (NN=593)	Overall (NN=905)	Placebo* (NN=292)	HYD (NN=2
Completed Period on Study Drug*, n (%)		592 (100)	592 (65)	210 (72)	229 (7
Discontinued Study Drug - All Cases, n (%)*	312 (100)	1 (< 1)	313 (35)	82 (28)	67 (23)
Adverse Event	94 (30)	0	94 (10)	10 (3)	17 (6)
ASHA-Related Event*	3 (1)	0	3 (< 1)	1 (< 1)	1 (< 1)
Subject's Choice	49 (16)	0	49 (5)	14 (5)	15 (5)
Lost to Follow-up	19 (6)	0	19 (2)	3 (1)	5 (2)
Lack of Therapeutic Effect	46 (15)	0	46 (5)	44 (15)	16 (5)
Confirmed or Suspected Diversion	23 (7)	0	23 (3)	3 (1)	2 (1)
Administrative	20 (6)	1 (< 1)	21 (2)	7 (2)	11 (4)
Did Not Qualify for Double-blind Period	59 (19)	–	59 (7)	–	–
Discontinued Study Drug and Study Simultaneously, n (%)				51 (17)	46 (16)
Adverse Event				6 (2)	8 (3)
ASHA-Related Event*				0	1 (< 1)
Subject's Choice				12 (4)	15 (5)
Lost to Follow-up				3 (1)	5 (2)
Lack of Therapeutic Effect				21 (7)	7 (2)
Confirmed or Suspected Diversion				3 (1)	2 (1)
Administrative				6 (2)	8 (3)
Discontinued Study Drug and Stayed in Study, n (%)*				31 (11)	21 (7)
Adverse Event				4 (1)	9 (3)
ASHA-Related Event*				1 (< 1)	0
Subject's Choice				2 (1)	0
Lack of Therapeutic Effect				23 (8)	9 (3)
Confirmed or Suspected Diversion				0	0
Administrative				1 (< 1)	3 (1)

Provide an additional summary table (HYD versus placebo group) displaying the specific reasons for a subject's choice (e.g., personal reasons or withdrawal of consent) to discontinue study drug and study simultaneously during the double-blind period as listed in the appendix table and subject's case report form.

Please provide the requested information by c.o.b. June 19, 2014.

Kind regards,
Dominic

Reference ID: 3525392

Dominic Chiapperino, Ph.D.
Senior Regulatory Health Project Manager
Division of Anesthesia, Analgesia, and Addiction Products
Office of Drug Evaluation II
FDA, Center for Drug Evaluation and Research
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/s/

DOMINIC CHIAPPERINO
06/16/2014

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 206627

FILING COMMUNICATION -
FILING REVIEW ISSUES IDENTIFIED

Purdue Pharma L.P.
One Stamford Forum
201 Tresser Blvd.
Stamford, CT 06901-3431

Attention: Edward Liao, PharmD
US Regulatory Affairs

Dear Dr. Liao:

Please refer to your New Drug Application (NDA) dated April 26, 2014, received April 28, 2014, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA), for Hysingla ER (hydrocodone bitartrate) extended-release tablets, 20, 30, 40, 60, 80, 100, and 120 mg.

We also refer to your amendments dated May 6, 9, and 21, and June 3, 2014.

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 **Priority**. Therefore, the user fee goal date is October 28, 2014.

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 requirement/commitment requests by October 7, 2014.

During our filing review of your application, we identified the following potential review issues:

Chemistry, Manufacturing, and Controls

1. We have reviewed DMF (b) (4) in support of NDA 206627 and found that it is deficient. The deficiencies were communicated to the DMF holder on May 30, 2014. Be advised that the outcome of the CMC review of your NDA is dependent upon satisfactory resolution of the identified deficiencies in DMF (b) (4).

2. Include (b) (4) as a Process Control during the manufacture of the drug product, including sampling and testing during the preparation of (b) (4)

3. The release specification for (b) (4) in the drug product is too high and is not supported by the batch release data which demonstrate levels of (b) (4) to be at or below the limit of quantitation. Tighten the specification for (b) (4) to be consistent with the batch data and further tighten the specification for the total impurities which includes the current high specification for (b) (4).

4. Monitor for (b) (4) during stability.

5. Provide (b) (4).

6. You have not provided process validation data for the drug product manufacturing process. Commit to completing the process validation before the release of your commercial product to the market.

Microbiology

7. You propose waiving microbial enumeration release testing for your drug product. This proposal may be acceptable provided that adequate upstream controls are established and documented. We acknowledge your summary of both water activity and microbial limits testing data in module 3.2.P.2. However, a release program that does not include microbial enumeration testing necessitates adequate microbiological controls of both incoming raw materials and the manufacturing process, in addition to the product's low water activity. Provide the following information for your process:

   a. Identify and justify critical control points in the manufacturing process that could affect microbial load of the drug product.

      i. (b) (4)

      ii.

   b. Describe microbiological monitoring and acceptance criteria for the critical control points that you have identified. Verify the suitability of your testing methods for your drug product. Conformance to the acceptance criteria

established for each critical control point should be documented in the batch record in accordance with 21 CFR 211.188.

c. Describe activities taken when microbiological acceptance criteria are not met at control points.

d. At a minimum, perform microbial limits testing at the initial stability testing time point. Provide an updated stability schedule to reflect this testing. In lieu of providing this information, amend the drug product release and stability specifications with microbial enumeration testing of every batch.

Biopharmaceutics

8. Based on insufficient data and information submitted thus far, your proposed specifications and process controls related to (b) (4) and dissolution cannot likely be deemed acceptable. Provide the following information:

   a. Provide data to show how variability in the (b) (4) process parameters, (b) (4) .

   b. Provide a detailed explanation of how you control the (b) (4) (b) (4) .

   c. Provide dissolution data to support your proposed range (b) (4) tablet hardness.

   d. In your submitted dissolution method development report, we could not locate information for the method's discriminating capability that can distinguish a "bad batch." Provide the exact location in the application where this information can be found or submit a study report that demonstrates the method's capability to detect any faulty batch as a result for unacceptable variation in either material attributes (b) (4) or manufacturing process deviation or both.

Clinical

9. In your oral human abuse potential study, HYD1013, we note the absence of information regarding how subjects chewed the test drug. There is no indication that a "vigorous" chewing arm was included in the Treatment Phase. This is important as we note the prior findings from Study OTR1016 that evaluated the pharmacokinetics of reformulated OxyContin and demonstrated substantially higher plasma levels of oxycodone following "vigorous" chewing compared to "normal" chewing of the reformulated product. Therefore, it must be determined whether "vigorous" chewing of HYD tablets could result in significantly higher plasma levels of hydrocodone, and, therefore, possibly higher levels of subjective reinforcing effects (i.e., Drug Liking) compared to when HYD tablets are subjected to "normal" chewing. We recommend that you conduct a pharmacokinetic study examining plasma levels of hydrocodone following "normal" and "vigorous" chewing of HYD tablets to potentially bridge to study HYD1013.

We are providing the above comments to give you preliminary notice of potential review issues. Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review. Issues may be added, deleted, expanded upon, or modified as we review the application. If you respond to these issues during this review cycle, we may not consider your response before we take an action on your application.

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:

1. The "Initial U.S. Approval" date in the Highlights (HL) section is currently left blank, perhaps because you believe the year shown here identifies the approval year of this product (which is not known). However, the year shown here would be for the first FDA approval of the hydrocodone bitartrate moiety, which is 1943, and should be included.

2. Under the ADVERSE REACTIONS heading of the HL section, the required bolded statement, "To report SUSPECTED ADVERSE REACTIONS, contact [name of manufacturer] at [manufacturer's U.S. phone number] or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch." should be revised so that the phrase "SUSPECTED ADVERSE REACTIONS" is in all-caps font.

3. The revision date statement included at the end of the HL statement, i.e., "**Revised: xx/xxxx**," should be right-justified in that column.

The above labeling comments, based on the SRPI checklist, are fairly minor and, therefore, we will not request submission of revised labeling at this time.

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) and 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) and 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.

We acknowledge receipt of your requests for a partial waiver and a partial deferral of pediatric studies for this application. Once we have reviewed your requests, we will notify you if the partial waiver and/or partial deferral requests are denied.

If you have any questions, call Dominic Chiapperino, PhD, Senior Regulatory Health Project Manager, at (301) 796-1183.

Sincerely,

{See appended electronic signature page}

Bob A. Rappaport, MD
Director
Division of Anesthesia, Analgesia, and
Addiction Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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

/s/

BOB A RAPPAPORT
06/13/2014

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

IND 059175

MEETING MINUTES

Purdue Pharma L.P.
One Stamford Forum
Stamford, CT 06901-3431

Attention: Edward Liao, Pharm.D.
Associate Director, Regulatory Affairs

Dear Dr. Liao:

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 q24h Film-coated Tablets (HYD).

We also refer to the meeting between representatives of your firm and the FDA on May 4, 2011. The purpose of the meeting was to discuss the drug development program for HYD, now at the End-of-Phase-2 stage of development.

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) 796-1183.

Sincerely,

{See appended electronic signature page}

Dominic Chiapperino, Ph.D.
Senior Regulatory Health Project Manager
Division of Anesthesia, Analgesia, and
Addiction Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

ENCLOSURE:
Meeting Minutes

MEMORANDUM OF MEETING MINUTES

MEETING DATE:	May 4, 2011
TIME:	4:00 to 5:00 PM
LOCATION:	Building 22, Room 1315 FDA White Oak Campus Silver Spring, MD
APPLICATION:	IND 059175
PRODUCT:	Hydrocodone bitartrate q24h film-coated tablets (HYD)
SPONSOR:	Purdue Pharma L.P.
TYPE OF MEETING:	Type B, End-of-Phase-2
MEETING CHAIR:	Bob A. Rappaport, M.D., Director, Division of Anesthesia, Analgesia, and Addiction Products (DAAAP)
MEETING RECORDER:	Dominic Chiapperino, Ph.D., Senior Regulatory Health Project Manager, DAAAP

ATTENDEES:

FDA Attendees

Bob A. Rappaport, M.D., Director, Division of Anesthesia, Analgesia, and Addiction Products (DAAAP)
Frank Pucino, Pharm.D.,M.P.H., Acting Clinical Team Leader, DAAAP
Jacqueline Spaulding, M.D., M.P.H., Medical Officer, DAAAP
Dan Mellon, Ph.D., Pharmacology Toxicology Supervisor, DAAAP
Dominic Chiapperino, Ph.D., Senior Regulatory Health Project Manager, DAAAP
Srikanth Nallani, Ph.D., Clinical Pharmacology Reviewer, Division of Clinical Pharmacology II
Dionne Price, Ph.D., Biostatistics Team Leader, Division of Biostatistics II (DB2)
Yan Zhou, Ph.D., Biostatistics Reviewer, DB2
Lori Love, M.D., Ph.D., Lead Medical Officer, Controlled Substance Staff

Purdue Attendees

Gary Stiles, M.D., Senior Vice-President, R&D
Craig Landau, M.D., Vice President and Chief Medical Officer
Todd Baumgartner, M.D., Vice President, Regulatory Affairs
Stephen Harris, M.D., Executive Medical Director, Clinical Pharmacology
Paul Coplan, Sc.D., Executive Director, Risk Management and Epidemiology
Warren Wen, Ph.D., Director, Clinical Research
Catherine Munera, Ph.D., Director, Biostatistics and Statistical Programming
Andrew Albright, Director, Project Management
Edward Liao, Pharm.D., Associate Director, Regulatory Affairs
(b) (4) Biostatistics Consultant
(b) (4) Biostatistics Consultant

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BACKGROUND

Purdue is developing HYD (hydrocodone bitartrate q24h film-coated tablets) for the indication of management of moderate to severe pain when a continuous, around-the-clock analgesic is needed for an extended period of time. Purdue is seeking feedback from FDA on its proposed development program for HYD, now at the End-of-Phase-2 stage of development.

Below are the Division's responses to the questions from Purdue's March 25, 2011, meeting package, which were sent to Purdue as "Preliminary Comments" on May 2, 2011, ahead of this May 4, 2011, meeting. Purdue's questions are in italics and the Division's responses are in bolded text. On May 3, 2011, Purdue provided additional information, follow-up questions and/or requests for clarification for each of the questions they specified for further discussion during the meeting. For these specified questions (Questions 6, 8, 10, 13, 15, and 17), the additional information and follow-up questions are inserted below in boxed text. Discussion during the meeting is in normal font.

DISCUSSION

Pre-Clinical

Question 1. Does the Agency agree that a chronic toxicology study in a second species would therefore not be required?

FDA Response:
Given the long clinical history of hydrocodone, your two-year rat carcinogenicity study may be used in lieu of the chronic toxicology study in a second species if the data from the carcinogenicity study are analyzed in an attempt to define a NOAEL. Include in Module 2 a discussion of any standard toxicology study endpoints in the carcinogenicity studies (i.e. histopathology of non-neoplastic lesions) along with the discussion of your general toxicology data.

Discussion:
There was no further discussion of Question 1.

Question 2. Does the Agency agree that the pre-clinical studies conducted with HYD are adequate to support approval of an NDA for HYD?

FDA Response:
No, we do not agree. (b) (4)

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(b) (4)

Final determination of the adequacy of your nonclinical program to support approval of an NDA can only be provided upon review of the entire submission.

Discussion:
There was no further discussion of Question 2.

Question 3. Does the Agency concur that if (b) (4) *is not mutagenic in the bacterial reverse mutation assay,* (b) (4) *will meet the qualification requirement of the FDA draft "Guidance for Industry: Genotoxic and Carcinogenic Impurities in Drug Substances and Products"?*

FDA Response:
The concern for mutagenicity, which the Ames test will address, is based on the structural alert for mutagenicity arising from the (b) (4)
We have also seen the potential for (b) (4) **as a class to cause clastogenicity. Therefore, for qualification of an** (b) (4) **both an in vitro mutagenicity assay as well as an in vitro clastogenicity assay are required.**

<u>Additional Nonclinical Comments:</u>
Due to the development of tolerance to the effects of opioids, there is no maximum daily dose for these products. The Division will consider the maximum theoretical daily dose (MTDD) 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. The current thinking in the Division for an MTDD of hydrocodone in an opioid tolerant individual is 3 g/day. If you can provide a clear rationale to support a different MTDD for this product, submit your justification for review by the Division.

Discussion:
There was no further discussion of Question 3.

<u>Clinical Pharmacology</u>
Question 4. Does the Agency agree that the proposed clinical pharmacology studies conducted with HYD will be adequate to support an HYD NDA approval?

FDA Response:
The proposed studies appear appropriate for the drug development plan. The conduct, results and conclusions of the proposed clinical pharmacology studies will be reviewed after NDA submission.

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We note that you plan to evaluate a variety of intrinsic and extrinsic factor effects on hydrocodone pharmacokinetics (PK). We recommend that you evaluate the effect of body weight on the PK of hydrocodone by employing population PK analysis. Such an attempt could assist you with dose selection in future pediatric PK studies.

Discussion:
There was no further discussion of Question 4.

Question 5. Does the Agency agree that if the in vitro ethanol sensitivity test shows that ethanol does not increase the rate of dissolution of hydrocodone from the HYD formulation, an in vivo ethanol study will not be required?

FDA Response:
Pending review of methods employed and data obtained, we recognize that information from the in vitro alcohol drug interaction study suggests that the hydrocodone ER formulation is not susceptible to dose-dumping in alcohol containing media. We recommend that you discuss the impact of the noted in vitro observations on the safety profile of the product at the time of NDA submission.

Discussion:
There was no further discussion of Question 5.

Clinical
Question 6. Does the Agency agree that the proposed Phase 3 program, consisting of one double-blind, placebo-controlled, analgesic study evaluating the safety and efficacy of HYD in low back pain and a single open-label safety study evaluating chronic non-malignant and non-neuropathic pain, is adequate to support approval of HYD for the proposed indication: "management of moderate to severe pain when a continuous, around-the-clock analgesic is needed for an extended period of time" in the dose range of 20-120 mg once daily?

FDA Response:
No we do not agree with your proposal. (b) (4) **. For a 505(b)(2) application for a modified-release formulation that relies on prior findings of efficacy for an immediate-release product, only one adequate and well controlled study is required to support efficacy.**

Purdue Follow-up Response for May 4, 2011:

Are we correct in concluding that FDA's prior findings regarding efficacy of IR hydrocodone combination analgesics make viable a development program for HYD in which only one adequate and well-controlled study is required to support efficacy as a 505(b)(2) submission?

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If so, could HYD3002, modified as described in your response to Question 7, serve as the one adequate and well-controlled study?

(b) (4)

(b) (4)

Discussion:

(b) (4)

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(b) (4)

Question 7. Does the Agency agree that the study design, the inclusion/exclusion criteria, and study population are adequate to support the proposed analgesia indication for HYD in the dose range of 20-120 mg once daily for approval?

FDA Response:
No, we do not agree. Based on your submission, your proposed inclusion/exclusion criteria and study population appear adequate to support your indication. However, we have the following comments regarding your proposed study design as it relates to safety and efficacy:

1. **During the open-label, run-in period for Study HYD3002, subjects will be converted to HYD based on the dose of their incoming opioid and subsequently titrated at 72-hour or 100-hr intervals (depending on the HYD dose) until adequate analgesia and tolerability are achieved. We note that no opioid rescue is being offered during this study phase. Provide a rationale for not incorporating the use of rescue medication given that your titration intervals may predispose subjects with moderate to severe pain to inadequate analgesia and could result in subject withdrawal from study.**

2. **At the time of randomization, subjects may be taking up to 120 mg/day of hydrocodone. For subjects randomized to the placebo treatment arm, the proposed protocol does not provide for an opioid taper, and opioid rescue medication (immediate-release [IR] hydrocodone) is administered only on an as needed basis for breakthrough pain. This scenario may put subjects at risk for opioid withdrawal. Include an opioid taper at the time of randomization.**

3. **From Weeks 3 through 12 of the double-blind treatment phase, subjects in both treatment arms will be allowed a maximum daily IR hydrocodone dose of 10 mg (5 mg twice daily) as rescue medication for breakthrough low back pain. Restricting rescue medication use to this limit for patients with chronic moderate to severe pain will likely result in a substantial number of dropouts. As noted in the National Academy of Sciences (NAS) Report on Prevention and Treatment of Missing Data in Clinical Trials (http://www.nap.edu/catalog.php) efforts should be made to retain patients**

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in clinical studies in order to minimize dropouts and missing data. Therefore, we strongly urge you to re-consider the limitation on rescue medication use.

Discussion:
There was no further discussion of Question 7.

Question 8. Does the Agency agree that the number of subjects exposed and the duration of exposures in the HYD program are adequate to assess the safety of HYD for approval?

FDA Response:
At the time of your NDA submission, the application must include a safety database consisting of at least 300 patients exposed for at least 6 months and 100 patients exposed for at least one year at the maximum labeled dose. Your safety database should be large enough to provide sufficient exposure data to evaluate potential safety concerns observed with formulations that contain polyethylene oxide, such as gastrointestinal problems (e.g., choking, dysphagia and/or GI obstruction).

We also note that there have been concerns with hypersensitivity reactions with the reformulated OxyContin. Describe any differences in excipients between this formulation and OxyContin and whether similar hypersensitivity reactions would be expected based on the proposed formulation of HYD.

In addition, progressive hearing loss has been associated with the chronic use of hydrocodone/acetaminophen combination products and the potential exposure to hydrocodone from this product is higher than the labeled doses from combination product. As a result, it is necessary that you monitor hearing during the proposed Phase 3 trials. Further, opioids may be associated with changes in cardiac conduction and function. You will need to conduct a thorough QTc study in opioid-tolerant patients during Phase 3 clinical development or provide rigorous scientific data to justify why this may not be necessary. We refer you to the ICH Guidance for Industry: E14 Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs which is available at
http://www.fda.gov/downloads/RegulatoryInformation/Guidances/ucm129357.pdf

Purdue Follow-up Response for May 4, 2011:

The Agency states, "at the time of your NDA submission, the application must include a safety database consisting of at least 300 patients exposed for at least 6 months and 100 patients exposed for at least 1 year at the maximum labeled dose." [emphasis added]

We note that in discussing the required patient numbers for 6 months and 1 year exposure, ICH E1a states "...at dosage levels intended for clinical use...".

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Based on the ICH E1a principle, Purdue proposes that, of the 300 and 100 subjects exposed for 6 months and 1 year, respectively, approximately 1/3 will have received HYD at the upper dose range, 80 and 120 mg/day, representing the dosage levels intended for clinical use.

Does the Agency agree that the number or subjects exposed and the duration of exposures in the HYD program are adequate to assess the safety of HYD for approval?

Discussion:
The Division acknowledged that its response regarding patient dosing was not clearly worded. To clarify, the Division stated that it is not necessary for all 300 patients be exposed at the maximum labeled dose (120 mg/day). Rather, the exposure in the safety database must be representative of the range of exposures typical of patients in this setting. Although the proposal to enroll approximately one-third of patients in the upper dose range (80 to 120 mg of hydrocodone) is reasonable, the Division recommended that a fair number of these patients should be appropriate to receive the maximum labeled dose of 120 mg to support the need for such a high dose.

Biostatistics
Question 9. Does the Agency agree with this choice of estimand?

FDA Response:
Your defined estimand of the difference in means for "average pain over the last 24 hours" score between the placebo and HYD treatment groups at Week 12 for all randomized subjects is acceptable. We acknowledge that this estimand reflects the initially assigned treatment as well as subsequent treatments received after discontinuation for retrieved dropouts. Also, see response to Question 10.

Discussion:
There was no further discussion of Question 9.

Question 10. Does the Agency agree with the primary efficacy analysis for the pivotal Phase 3 study?

FDA Response:
You propose a mixed model repeated measures (MMRM) analysis of the primary variable using a pattern mixture model (PMM) framework. In general, a pattern mixture model is formulated based on missing data patterns. Using the proposed framework, the Week 12 treatment estimate will be derived based on three patterns defined by the disposition status of patients: completing the study, discontinuing the study due to adverse events (AEs), or discontinuing the study due to reasons other than AEs. Furthermore, retrieved dropout data will be collected after a patient's discontinuation from double-blind treatment. Retrieved dropouts who provide a Week 12 pain score will be considered as completers for the analysis. As you state, "the Week 12 HYD estimate is a weighted average of the

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completer estimate at Week 12 and of earlier time-points, with weights determined by the proportion of subjects within a treatment who discontinued study or double-blind treatment and did not provide retrieved dropout pain scores at Week 12." Hence, the primary comparison between HYD and placebo will be based on a weighted average of the estimated mean pain scores for patients categorized by the three patterns.

The proposed analysis approach appears to have a desirable feature in that a bad outcome is attributed to patients that discontinue the study due to AEs. The method additionally appears to account for sources of variability introduced by missing data. Although we cannot be certain which methodologies will be most appropriate for analgesic trials at this time, your proposal seems reasonable and we encourage you to proceed.

Address the following:

1. **Provide a justification for your assumption, though not explicitly stated, that patients who drop out due to reasons other than AEs have responses similar to the average response at Week 2 and Week 4.**

2. **You must thoroughly ascertain and document the reason for discontinuation for dropouts and also thoroughly document medications received after discontinuation for retrieved dropouts.**

3. **Currently, a patient who discontinues the study treatment due to an AE may be included in the analysis as a completer if Week 12 data is collected after he/she drops out. Thus, your weighted average estimate will implicitly assign the mean pain score at Week 12 to this patient. This strategy is consistent with the intent-to-treat principle. However, concern will arise if the data from the study suggest that the use of subsequent analgesic medications after discontinuation for retrieved dropouts results in better pain scores at Week 12 compared to those that continue the study treatment.**

Purdue Follow-up Response for May 4, 2011:

1. We will provide justification for our assumption that the pain score at Week 12 for patients who discontinue due to reasons other than AE and who do no need to complete the study, can be estimated using the average of the pain scores at Week 2 and Week 4 in the Statistical Analysis Plan (SAP). This justification will be based on data from studies where we have collected retrieved dropout data and are able to evaluate the pain profile of patients who discontinue study drug early. Based on these retrieved dropout data we believe the average scores at Weeks 2 and 4 adequately estimate the mean responses at Week 12 for these patients. It could be argued that for patients discontinuing after Week 4, using data closer to the time of dropout would provide a better estimate of Week 12 mean scores. However, pattern mixture models can easily require the estimation of too many parameters, resulting in unacceptable increases in variability and even the inability to estimate all required parameters. Grouping missing data patterns by discontinuation reason alone, and estimating missing means using data from early in the study when data are abundant was deemed an acceptable compromise to provide stable unbiased estimates.

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2. To ensure that a subject's discontinuation is attributed to the appropriate reason, an independent Discontinuation Reasons Adjudication Committee (DRAC) will adjudicate all study drug and study discontinuation reasons during the double-blind phase. A similar process was used in the Butrans® pivotal studies.

We agree that it is important to document medications used for pain after discontinuation for patients who are retrieved dropouts. Our plan is to document the analgesics used for chronic pain weekly.

Does the Agency agree that our proposal to evaluate analgesic medications on a weekly basis is sufficient to thoroughly document medication use after discontinuation for retrieved dropout subjects?

3. We acknowledge the Agency's concern regarding our proposal to use retrieved dropout data in the primary efficacy analysis. We will include an additional sensitivity analysis that will use the PMM approach proposed in our primary efficacy analysis without retrieved dropout data. This analysis will evaluate the sensitivity of the primary analysis to the use of retrieved dropout data.

We note that it is possible the Week 12 pain scores for retrieved dropout patients may be better than those of patients who continue in the study. This is primarily of concern for placebo patients who historically show a higher dropout rate due to lack of efficacy. Therefore this could lead to a conservative estimate of the HYD treatment effect.

Discussion:
Regarding Item 1 [of boxed text above], the Division advised that the detailed Statistical Analysis Plan (SAP) and accompanying rationale for the handling of dropouts and missing data should be submitted for review and comment. Regarding the timing of the SAP submission, it was agreed that the SAP can be submitted in advance of the final full protocol submission; however, if received before the final protocol, sufficient accompanying details and context to evaluate the SAP in the absence of the complete final protocol should be included.

Regarding Item 2, Purdue stated that its proposed DRAC would be established to analyze all reasons for study participant discontinuation. The Division stated that, on its face, the DRAC was potentially useful and acceptable as part of the study conduct and emphasized the importance of both collecting information about dropouts as well as accurately documenting the reasons for dropouts. Regarding the specific proposal to document analgesics used for chronic pain in subjects on a weekly basis, the Division stated that this proposal would need further consideration and internal discussion, and would be addressed in a post-meeting note in the meeting minutes.

> Post-Meeting Note:
> Regarding Item 2, the Division would consider the proposal to evaluate analgesic medications on a weekly basis for documenting medication use of retrieved dropout subjects as an acceptable approach.

Regarding Item 3, the Division acknowledged that the use of retrieved dropout data in the primary efficacy analysis is a relatively new practice in the context of clinical trials for chronic

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pain. The Sponsor stated that the Division's concern outlined in the responses would primarily affect the placebo group and result in a conservative estimate of the HYD treatment effect. The Division clarified that although the dropout rate may be anticipated to be higher in the placebo group, this is often not the case in chronic pain trials. The Division will be concerned if there is a higher rate of dropouts in the HYD arm and the use of subsequent analgesics after discontinuation results in better pain scores for the retrieved dropouts compared to patients remaining on HYD. The additional proposed sensitivity analysis seemed reasonable on its face, but a formal review will be necessary.

Question 11. Does the Agency agree with the proposed sensitivity analyses and their use in the interpretation of study results?

FDA Response:
Your proposed sensitivity analyses appear reasonable.

Discussion:
There was no further discussion of Question 11.

Question 12. Does the Agency agree with the assumptions of sample size for the pivotal Phase 3 study?

FDA Response:
Based on the assumptions, the sample size calculation appears reasonable. However, we notice that the sample size is larger than normally seen in analgesic trials and caution that the magnitude of the beneficial effect will be weighed against risk.

Discussion:
There was no further discussion of Question 12.

Abuse Liability
Question 13. Overall, does the Agency agree that the HYD abuse liability program, consisting of the proposed in vitro, tamper testing, and human clinical studies, is adequate to evaluate the abuse liability of HYD?

FDA Response:
HYD will be controlled as a schedule-II drug under the Controlled Substances Act.

Your preliminary testing plan for assessment of the abuse potential covers aspects of both in vitro and clinical abuse potential testing, but the plan is not comprehensive. Detailed protocols are necessary to evaluate whether the proposed testing can provide appropriate and adequate information for the abuse potential assessment of this product.

Reference ID: 2953866

Reference ID: 3666752

The protocols for the planned Phase 3 clinical studies lack specific details on how aberrant drug behaviors, drug compliance, and potential drug diversion will be monitored and assessed during the clinical trials. This information is a critical component of the abuse potential assessment. Complete protocols, including all ancillary forms (e.g., drug accountability records, CSPC Report Form, etc.) should be submitted for evaluation.

For further information on abuse potential assessment, see our draft "Guidance for Industry: Assessment of Abuse Potential of Drugs" at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM198650.pdf

Purdue Follow-up Response for May 4, 2011:

We plan to monitor and assess aberrant drug behaviors, drug compliance, and potential drug diversion as our planned Phase 3 clinical program.

We understand your need to see detailed descriptions of the in vitro physical and chemical manipulation studies and protocols for the in vivo abuse potential studies. We will submit these documents for your review and would like to discuss a mechanism for getting your feedback.

Discussion:
The Division stated that the mechanism for obtaining feedback on all proposals and documents related to abuse liability is to submit the information, including full protocols, to the IND. DAAAP will then consult the Controlled Substance Staff for review of the materials and to provide comment.

Risk Management
Question 14. Does the Agency agree that HYD would be considered a long-acting opioid that is subject to the class REMS for long-acting opioids?

FDA Response:
Yes. Your product will be considered a long-acting opioid and, therefore, be subject to the class REMS for long-acting opioids that ensures the benefits of the drug product outweigh the risks. The elements of the REMS that may be required for your product include:

- **Medication Guide**
- **Communication Plan**
- **Elements to Assure Safe Use**
- **Implementation Plan**
- **Timetable for Submission of Assessments**

Discussion:
There was no further discussion of Question 14.

Reference ID: 2953866

Reference ID: 3666752

Pediatrics
Question 15. Upon review of the deferral request for the pediatric assessment required for Pediatric Research Equity Act (PREA), will the Agency grant a deferral?

FDA Response:
We recommend that you initiate the pediatric assessment during drug development. Following completion of Phase 2 and clinical pharmacology studies, evaluate the effect of bodyweight on PK of hydrocodone. Conduct PK simulations to derive doses in pediatric patients that would yield plasma levels matching the adult population. Confirm that the planned doses are appropriate based on current medical practice and published safety information for hydrocodone products in pediatric patients. Initiate the pediatric PK studies by age cohorts beginning with pediatric patients who are at the least risk (e.g., adolescent patients, etc.).

Additional comments:

- **With regard to pharmacokinetics, the pediatric studies must be prospectively powered to target a 95% CI within 60% and 140% of the point estimate for the geometric mean estimates of clearance and volume of distribution with 80% power for hydrocodone in each age group to be studied. The number of pediatric patients should be approximately evenly distributed across age and gender.**
- **Provide appropriate justification for the proposed blood sample collection time points based on publications or conduct simulations based on clinical PK experience generated so far.**

Purdue Follow-up Response and Questions for May 4, 2011:

Based on your response to Questions 15 and 16, we plan to initiate our pediatric assessments required for PREA during drug development. However, given the difficulty in enrolling studies in this population, it is unlikely that the studies will be completed by the time of the planned NDA submission for HYD.

Given this plan, will we still need to request a deferral of the PREA commitment, and does the Agency agree that this deferral will be granted?

Discussion:
It was first clarified that, to initiate its pediatric assessments and program, Purdue should submit full protocols, including timelines for study initiation and completion. Purdue further stated that they intend to exceed the PREA requirements by proposing a program that would also satisfy BPCA requirements.

Regarding the status of pediatric assessments at the time of NDA submission, the Division clarified that, provided Purdue could demonstrate due diligence in beginning their program to address required pediatric studies under PREA, Purdue may submit their NDA without having completed the pediatric studies required by PREA and/or BPCA. A request for a deferral of these pediatric studies will be evaluated within the review cycle and deferral may be granted

Reference ID: 2953866

Reference ID: 3666752

within the context of an NDA approval, with the terms of deferred studies specified in the approval letter.

Question 16. Upon review, does the Agency agree that the proposed pediatric development plan for HYD is satisfactory to comply with PREA?

FDA Response:
See the Division's response to Question #15.

Discussion:
There was no further discussion of Question 16.

Question 17. Does the Agency agree that if Purdue submits a proposed (b) (4)

FDA Response:
We note that you may be seeking a (b) (4)

Purdue Follow-up Response for May 4, 2011:

We would like to discuss the timing of (b) (4)

Discussion:
The timing (b) (4). It was agreed that the Division would offer advice in a post-meeting note.

Post-Meeting Note:
(b) (4)

Reference ID: 2953866

Reference ID: 3666752

(b) (4)

[redacted]

FINAL UNDERSTANDINGS AND ACTION ITEMS

1. Purdue stated its understanding that, for a viable (b)(2) NDA submission for HYD, an FDA-approved immediate-release hydrocodone-containing product which also contains another (one or more) active ingredient (e.g., acetaminophen), could be referenced. Such a (b)(2) submission must also address relative bioavailability and must reference a product with an approved NDA, rather than an approved ANDA.

2. Purdue's proposed (revised) Phase 3 program could be sufficient for a fileable NDA. A more complete, detailed proposal will be submitted for Division review and comment. (b) (4) [redacted]

Reference ID: 2953866

Reference ID: 3666752

3. Regarding Question 8 follow-up, the Division has corrected its advice on study subject dosing at the maximum dose range. Purdue's proposal of dosing a third of the 300 study subjects in the upper hydrocodone dose range of 80 to 120 mg is reasonable, and a substantial number of these subjects should receive the maximum dose of 120 mg.

4. Regarding missing data and the efficacy analysis, Purdue will submit a detailed SAP which will include a rationale for the various assumptions that underlie the analysis. The SAP will also outline the sensitivity analyses. Purdue will clearly note in their submission of the SAP that FDA comment is requested.

5. Regarding the specific proposed plan by Purdue to document the analgesics used for chronic pain weekly in retrieved drop-out patients, the Division agreed to provide feedback on this plan in a post-meeting note [The post-meeting note was included in these minutes and the Division stated that Purdue's proposal was reasonable].

6. Regarding detailed proposals related to abuse liability, Purdue will submit these to the IND and will receive comment from the Controlled Substance Staff.

7. Regarding the pediatric studies for PREA and BPCA requirements, Purdue will submit a detailed description of the pediatric plan, including protocols and timelines, and will strive to initiate these studies as soon as possible.

8. The Division agrees to provide, in a post-meeting note, advice regarding the most appropriate timing (b) (4) (b) (4)].

Reference ID: 2953866

Reference ID: 3666752

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/s/

DOMINIC CHIAPPERINO
05/31/2011

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADM NISTRATION

REQUEST FOR OPDP (previously DDMAC) LABELING REVIEW CONSULTATION

****Please send immediately following the Filing/Planning meeting****

TO:	FROM: (Name/Title, Office/Division/Phone number of requestor)
CDER-OPDP-RPM	Joan E. Blair, Health Communications Analyst, DRISK 301-796-9351

REQUEST DATE	IND NO.	NDA/BLA NO.	TYPE OF DOCUMENTS (PLEASE CHECK OFF BELOW)
5/28/14		206627	

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
Hysingla ER (extended release 24 hour hydrocodone bitartrate tablets)	Action Date: Week of August 11-15, 2014	Chronic pain, extended release opioid	6/17/14

NAME OF FIRM:	
Purdue Pharma L.P.	PDUFA Date: 10/28/14

TYPE OF LABEL TO REVIEW

TYPE OF LABELING:
(Check all that apply)
- ☐ PACKAGE INSERT (PI)
- ☐ PATIENT PACKAGE INSERT (PPI)
- ☐ CARTON/CONTAINER LABELING
- ☐ MEDICATION GUIDE
- ☐ INSTRUCTIONS FOR USE(IFU)

TYPE OF APPLICATION/SUBMISSION
- X☐ ORIGINAL NDA/BLA
- ☐ IND
- ☐ EFFICACY SUPPLEMENT
- ☐ SAFETY SUPPLEMENT
- ☐ LABELING SUPPLEMENT
- ☐ PLR CONVERSION

REASON FOR LABELING CONSULT
- ☐ INITIAL PROPOSED LABELING
- ☐ LABELING REVISION

For OSE USE ONLY
- X☐ REMS

EDR link to submission: **\\cdsesub1\evsprod\nda206627\0000\m1\us\hyd-risk-man-plans-final.pdf**

Please Note: There is no need to send labeling at this time. OPDP reviews substantially complete labeling, which has already been marked up by the CDER Review Team. After the disciplines have completed their sections of the labeling, a full review team labeling meeting can be held to go over all of the revisions. Within a week after this meeting, "substantially complete" labeling should be sent to OPDP. Once the substantially complete labeling is received, OPDP will complete its review within 14 calendar days.

OSE/DRISK ONLY: For REMS consults to OPDP, send a word copy of all REMS materials and the most recent labeling to CDER DDMAC RPM. List out all materials included in the consult, broken down by audience (consumer vs provider), in the comments section below.

COMMENTS/SPECIAL INSTRUCTIONS: Please review the following materials to ensure that they are not promotional in any way. Since Hysingla ER plans to join the ER/LA (Extended Release/Long Acting) REMS Single Shared System (SSS), all materials should be consistent with the most current version of the ER/LA REMS materials found here: http://www.er-la-opioidrems.com/IwgUI/rems/home.action). However, *the ER/LA REMS SSS materials are currently being revised to reflect new safety label changes - due back to FDA from the RPC in mid-June 2014.*

Hysingla ER (ER/LA) materials include:
Provider:
Patient Counseling Document (PCD) on Extended-Release/Long-Acting Opioid Analgesics
FDA Blueprint for Prescriber Education for Extended-Release and Long-Acting Opioid Analgesics
Prescriber Letter 1
Prescriber Letter 2
Prescriber Letter 3

Professional Organization/Licensing Board Letter 1
Professional Organization/Licensing Board Letter 2
ER/LA Opioid Analgesic REMS SSS website (www.ER-LA-opioidREMS.com) Upon approval Hysingla ER will be added to the list of ER/LA REMS products on the website here: http://www.er-la-opioidrems.com/IwgUI/rems/products.action

SIGNATURE OF REQUESTER	
SIGNATURE OF RECEIVER	METHOD OF DELIVERY (Check one) ☐ eMAIL ☐ HAND

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/s/

VAISHALI JARRAL
05/29/2014

Chiapperino, Dominic

From: Chiapperino, Dominic
Sent: Friday, May 16, 2014 12:17 PM
To: Liao, Edward (Edward.Liao@pharma.com)
Subject: NDA 206627, information request, clinical study site information

Hi Ed,

Referring to your NDA 206627 submission, we are not able to locate the following information, which was requested at the pre NDA meeting. Either provide us with the location of this information in the submission, or submit it to the NDA by May 23, 2014. This is required in order to determine which study sites will be inspected by the Office of Scientific Investigation.

1. Provide the following in tabular form for both Phase 3 studies, by site:

    a. Number of subjects screened at each site
    b. Number of subjects randomized at each site, if appropriate
    c. Number of subjects treated who prematurely discontinued at each site

2. Also indicate where the following information is located in the submission, or submit it to the NDA for both completed Phase 3 trials:

    a. Location at which sponsor trial documentation is maintained (e.g., monitoring plans and reports, training records, data management plans, drug accountability records, IND safety reports, or other sponsor records as described in ICH E6, Section 8). This is the actual physical site(s) where documents are maintained and would be available for inspection.

    b. Name, address and contact information of all contract research organizations (CROs) used in the conduct of the clinical trials and brief statement of trial related functions transferred to them. If this information has been submitted in eCTD format previously (e.g., as an addendum to a Form FDA 1571) you may identify the location(s) and/or provide link(s) to information previously provided.

    c. The location at which trial documentation and records generated by the CROs with respect to their roles and responsibilities in conduct of respective studies is maintained. As above, this is the actual physical site where documents would be available for inspection.

Contact me if you have any questions.

Kind regards,
Dominic

Dominic Chiapperino, Ph.D.
Senior Regulatory Health Project Manager
Division of Anesthesia, Analgesia, and Addiction Products
Office of Drug Evaluation II
FDA, Center for Drug Evaluation and Research
10903 New Hampshire Avenue
Building 22, Room 3134
Silver Spring, MD 20993

Reference ID: 3508175

Office phone: (301) 796-1183
Facsimile: (301) 796-9723
Dominic.Chiapperino@fda.hhs.gov

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/s/

DOMINIC CHIAPPERINO
05/16/2014

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADM NISTRATION

REQUEST FOR PATIENT LABELING REVIEW CONSULTATION

TO:

CDER/DMPP/Patient Labeling Team (PLT)
ATTN: Chris Wheeler, Carol A. McAlman

FROM: (Name/Title, Office/Division/Phone number of requestor)

Division of Anesthesia, Analgesia, and Addiction Products – Bob A. Rappaport, M.D., Director
Point-of-contact: Dominic Chiapperino, Ph.D., Senior Regulatory Health Project Manager, 301-796-1183

REQUEST DATE: **May 6, 2014**

NDA/BLA NO.: **NDA 206627**

TYPE OF DOCUMENTS:
(PLEASE CHECK OFF BELOW)
Original NDA

NAME OF DRUG: **Hysingla ER (hydrocodone bitartrate) extended-release tablets**

PRIORITY CONSIDERATION: **P**

CLASSIFICATION OF DRUG: **3**

DESIRED COMPLETION DATE
(Generally 2 Weeks after receiving substantially complete labeling)
July 25, 2014

SPONSOR: **Purdue Pharma L.P.**

PDUFA Date:
Oct. 28, 2014 (However, action planned for much earlier, targeting August 11, 2014)

TYPE OF LABEL TO REVIEW

TYPE OF LABELING:
(Check all that apply)
- ☐ PATIENT PACKAGE INSERT (PPI)
- ☒ MEDICATION GUIDE
- ☐ INSTRUCTIONS FOR USE(IFU)

TYPE OF APPLICATION/SUBMISSION
- ☒ ORIGINAL NDA/BLA
- ☐ EFFICACY SUPPLEMENT
- ☐ SAFETY SUPPLEMENT
- ☐ LABELING SUPPLEMENT
- ☐ MANUFACTURING (CMC) SUPPLEMENT
- ☐ PLR CONVERSION

REASON FOR LABELING CONSULT
- ☒ INITIAL PROPOSED LABELING
- ☐ LABELING REVISION

EDR link to submission: \\CDSESUB1\evsprod\NDA206627\206627.enx

Please Note: DMPP uses substantially complete labeling, which has already been marked up by the CDER Review Team, when reviewing MedGuides, IFUs, and PPIs. Once the substantially complete labeling is received, DMPP will complete its review within 14 calendar days. Please provide a copy of the sponsor's proposed patient labeling in Word format.

COMMENTS/SPECIAL INSTRUCTIONS:
Remaining team meetings:
- Filing/Planning: May 22nd
- Mid-Cycle Meeting: June 25th
- Labeling: July 9th, 16th, and 23rd
- Wrap-Up Meeting: July 24th

SIGNATURE OF REQUESTER **Dominic Chiapperino (electronically signed)**

SIGNATURE OF RECEIVER

METHOD OF DELIVERY (Check one)
☐ eMAIL (BLAs Only) ☒ DARRTS

Version: 12/9/2011

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/s/

DOMINIC CHIAPPERINO
05/06/2014

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADM NISTRATION

REQUEST FOR "DDMAC" LABELING REVIEW CONSULTATION

****Please send immediately following the Filing/Planning meeting****

TO:
CDER/OMP/OPDP
c/o CDER-DDMAC-RPM
ATTN: Olga Salis, Eunice Chung-Davies, and Sam Skariah

FROM: (Name/Title, Office/Division/Phone number of requestor)
Division of Anesthesia, Analgesia, and Addiction Products
Dr. Bob A. Rappaport, M.D., Director
Point-of-contact: Dominic Chiapperino, Ph.D.,
Senior Regulatory Health Project Manager, 301-796-1183

REQUEST DATE	IND NO.	NDA/BLA NO.	TYPE OF DOCUMENTS
May 6, 2014		**NDA 206627**	(PLEASE CHECK OFF BELOW) **Original NDA, labeling (recvd. 4/28/14)**

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE (Generally 1 week before the wrap-up meeting)
Hysingla ER (hydrocodone bitartrate) extended-release tablets	**Priority**	**3 (new formulation)**	**July 25, 2014**

NAME OF FIRM:
Purdue Pharma L.P.

PDUFA Date: **Oct. 28, 2014 (However, an action is planned for much earlier, targeting Aug. 11, 2014)**

TYPE OF LABEL TO REVIEW

TYPE OF LABELING:
(Check all that apply)
- ☒ PACKAGE INSERT (PI)
- ☐ PATIENT PACKAGE INSERT (PPI)
- ☒ CARTON/CONTAINER LABELING
- ☒ MEDICATION GUIDE
- ☐ INSTRUCTIONS FOR USE(IFU)

TYPE OF APPLICATION/SUBMISSION
- ☒ ORIGINAL NDA/BLA
- ☐ IND
- ☐ EFFICACY SUPPLEMENT
- ☐ SAFETY SUPPLEMENT
- ☐ LABELING SUPPLEMENT
- ☐ PLR CONVERSION

REASON FOR LABELING CONSULT
- ☒ INITIAL PROPOSED LABELING
- ☐ LABELING REVISION

EDR link to submission: \\CDSESUB1\evsprod\NDA206627\206627.enx

Please Note: There is no need to send labeling at this time. OPDP reviews substantially complete labeling, which has already been marked up by the CDER Review Team. After the disciplines have completed their sections of the labeling, a full review team labeling meeting can be held to go over all of the revisions. Within a week after this meeting, "substantially complete" labeling should be sent to OPDP. Once the substantially complete labeling is received, OPDP will complete its review within 14 calendar days.

COMMENTS/SPECIAL INSTRUCTIONS:
Note: The Medication Guide should follow the format of the ER/LA Opioid REMS products' MedGuides
Team meetings:
- Filing/Planning: May 22nd
- Mid-Cycle Meeting: June 25th
- Labeling: July 9th, 16th, and 23rd
- Wrap-Up Meeting: July 24th

SIGNATURE OF REQUESTER **Dominic Chiapperino (electronically signed)**

SIGNATURE OF RECEIVER

METHOD OF DELIVERY (Check one)
☒ eMAIL ☐ HAND

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/s/

DOMINIC CHIAPPERINO
05/06/2014

Chiapperino, Dominic

From: Chiapperino, Dominic
Sent: Friday, May 02, 2014 5:30 PM
To: Liao, Edward (Edward.Liao@pharma.com)
Subject: NDA 206627, information requests, (1) QT study, (2) pediatric plan
Attachments: Highlights_ClinPharm_and_Cardiac_Safety.doc

Dear Ed,

Although we are still conducting our review for the filing of NDA 206627, we have noted the need for additional information and prefer to request this information now, as follows:

1) Related to your submitted tQT study, HYD-1009, please complete the attached table, "Highlights of Clinical Pharmacology and Cardiac Safety," and provide it to us at your earliest convenience. Also, we are not able to locate related ECG waveforms in the ECG warehouse. Please clarify if these have been provided there, and if not, submit all related ECG waveforms to the ECG warehouse at: www.ecgwarehouse.com at your earliest convenience.

2) We note that you have submitted a pediatric plan with your NDA submission. The plan includes: a request for a waiver of studies under PREA for pediatric patients from birth to 6 years because studies would not be feasible given the small number of patients in this age group with chronic pain who require around the clock opioid treatment; a waiver for patients ages 7 to 11 years because they would not be able to swallow the tablets; and a PK and safety study in patients ages 12 to 17. We agree with your request for a waiver in patients less than 7 years for the reason stated. However, we do not agree with your request for a waiver in patients 7 to 11 years due to their inability to swallow a tablet. Under PREA, you are required to attempt to formulate an age appropriate formulation of your product. If you have attempted to make an age appropriate formulation and failed, you must submit this information along with your waiver request and it will be reviewed. Otherwise, your pediatric plan must include a safety and PK study in patients from 7 to <17 years of age. Efficacy in this age group can be extrapolated from findings in adults. Revise and submit your pediatric plan to include a request for a deferral for PK and safety studies in patients 7 to 11 as well as patients 12 to <17, or provide detailed information describing your attempt to formulate an age appropriate formulation.

Contact me if you have questions.

Kind regards,
Dominic

Dominic Chiapperino, Ph.D.
Senior Regulatory Health Project Manager
Division of Anesthesia, Analgesia, and Addiction Products
Office of Drug Evaluation II
FDA, Center for Drug Evaluation and Research
10903 New Hampshire Avenue
Building 22, Room 3134
Silver Spring, MD 20993
Office phone: (301) 796-1183
Facsimile: (301) 796-9723
Dominic.Chiapperino@fda.hhs.gov

Reference ID: 3500393

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/s/

DOMINIC CHIAPPERINO
05/02/2014

MANDATORY: Send a copy of the consult request form to the Office of Combination Products as follows:
--Originating Center: When the consult request is initiated.
--Consulting Center: When the consult is completed.
Email: combination@fda.gov or FAX: 301-427-1935

For Consulting Center Use Only:

Date Received: _____
Assigned to: _____
Date Assigned: _____
Assigned by: _____

Completed date: _____
Reviewer Initials: _____
Supervisory Concurrence: _____

Intercenter Request for Consultative or Collaborative Review Form

To (Consulting Center):
Center: CDRH
Division: ODE/DOED/ENTB
Mail Code: HF
Consulting Reviewer Name: Srinivas Nandkumar, PhD
Building/Room #: Building 66/ Rm 2436
Phone #: 301-796-6480
Fax #:
Email Address: srinivas nandkumar@fda.hhs.gov
RPM/CSO Name and Mail Code:

From (Originating Center):
Center: CDER
Division: CDER/OND/ODE2/DAAAP
Mail Code: HF -170
Requesting Reviewer Name: Jacqueline Spaulding, MD
Building/Room #: Building 22/Rm 3136
Phone#: 301-796-2248
Fax #: 301-796-9723
Email Address: jacqueline.spaulding@fda hhs.gov
RPM/CSO Name and Mail Code: Dominic Chiapperino, PhD
Requesting Reviewer's Concurring Supervisor's Name: Ellen Fields, MD, MPH

Receiving Division: If you have received this request in error, you must contact the request originator by phone immediately to alert the request originator to the error.

Date of Request: May 1, 2014

Requested Completion Date: July 1, 2014

Submission/Application Number: NDA 206627
(Not Barcode Number)

Submission Type: NDA
(510(k), PMA, NDA, BLA, IND, IDE, etc.)

Type of Product: ☐ Drug-device combination ☐ Drug-biologic combination ☐ Device-biologic combination ☐ Drug-device-biologic combination ☑ Not a combination product

Submission Receipt Date: April 28, 2014

Official Submission Due Date: October 28, 2014

Name of Product: HYD (hydrocodone bitartrate) ER tablets

Name of Firm: Purdue Pharma, L.P.

Intended Use: treatment of chronic pain. Proposed indication: "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"

Brief Description of Documents Being Provided (e.g., clinical data -- include submission dates if appropriate):

1. Study report entitled: "Audiology Report for Hydrocodone Bitartrate Once-Daily, Extended-Release Tablets"
2. Background documents if needed, including: (a) the meeting minutes from the Type C meeting held March 13, 2012; (b) the CDRH review by Dr. Giusto for the pre-NDA meeting held July 10, 2013; and (c) meeting minutes from the same pre-NDA meeting.

Documents to be returned to Requesting Reviewer? ☐ Yes ☑ No

Complete description of the request. Include history and specific issues, (e.g., risks, concerns), if any, and specific question(s) to be answered by the consulted reviewer. The consulted reviewer should contact the request originator if questions/concerns are not clear. Attach extra sheet(s) if necessary:

Type of Request: ☑ Consultative Review ☐ Collaborative Review

Dr. James K. Kane, Ph.D., Dr. Cherish Giusto, Au.D., and Dr. Srinivas Nandkumar, Ph.D., participated with DAAAP in a Type C sponsor teleconference to discuss ototoxicity on March 13, 2012. Dr. Giusto then provided a consult review and guidance for a Pre-NDA industry meeting held July 10, 2013, to advise whether the planned audiology assessments and resulting data would be a complete reviewable package for the NDA to assess ototoxicity.
We now request a consult review by CDRH (ENTB) evaluating the audiology report described above, which is part of the Purdue's recently submitted NDA. The documents listed above will be sent electronically.
Question 1. Do you concur with sponsor's conclusion that there is not an increased risk for hearing impairment or vestibular disorders with HYD?

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/s/

DOMINIC CHIAPPERINO
05/01/2014

JACQUELINE A SPAULDING
05/01/2014

ELLEN W FIELDS
05/02/2014

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

NDA 206627

NDA ACKNOWLEDGMENT

Purdue Pharma L.P.
One Stamford Forum
201 Tresser Blvd.
Stamford, CT 06901-3431

Attention: Edward Liao, PharmD
US Regulatory Affairs

Dear Dr. Liao:

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: [Proprietary name pending] (hydrocodone bitartrate) Extended-Release Tablets, 20, 30, 40, 60, 80, 100, and 120 mg

Date of Application: April 26, 2014

Date of Receipt: April 28, 2014

Our Reference Number: NDA 206627

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 June 27, 2014, in accordance with 21 CFR 314.101(a).

If you have not already done so, promptly submit the content of labeling [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).

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

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If you have any questions, call me at (301) 796-1183.

Sincerely,

{See appended electronic signature page}

Dominic Chiapperino, PhD
Senior Regulatory Health 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/

DOMINIC CHIAPPERINO
04/30/2014

From: Jarral, Vaishali
To: edward.liao@pharma.com
Subject: NDA 206627
Date: Wednesday, April 30, 2014 10:54:00 AM

Hello Mr. Liao,

The Agency has received your new NDA 206627 for HYD (hydrocodone bitartrate) extended-release tablets. Please submit the proprietary name review request to this application as soon as possible so that the review can be completed in a timely manner.

Please confirm the receipt of this email.

Thanks,

Vaishali Jarral, M.S., M.B.A
Safety Regulatory Project Manager
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research
Food and Drug Administration
10903 New Hampshire Avenue
Building 22, Room 4472
Silver Spring, MD 20993

301.796.4248
Vaishali.Jarral@fda.hhs.gov

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/s/

VAISHALI JARRAL
04/30/2014

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

REQUEST FOR CONSULTATION

TO *(Office/Division)*: Yi Tsong, Ph.D. - OTS/OB/DBVI	FROM (*Name, Office/Division, and Phone Number of Requestor)*: Sandra Saltz, Project Manager, CSS, 301-796-3117

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
4/30/2014		206627	2 HAPS	Received April 28, 2014

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
Hydrocodone bitartrate extended-release oral tablets			June 30, 2014, or as soon as possible.

NAME OF FIRM: Purdue Pharma LP

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE / ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE-NDA MEETING
- ☐ END-OF-PHASE 2a MEETING
- ☐ END-OF-PHASE 2 MEETING
- ☐ RESUBMISSION
- ☐ SAFETY / EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☒ OTHER *(SPECIFY BELOW)*:

II. BIOMETRICS

- ☐ PRIORITY P NDA REVIEW
- ☐ END-OF-PHASE 2 MEETING
- ☐ CONTROLLED STUDIES
- ☐ PROTOCOL REVIEW
- ☐ OTHER (SPECIFY BELOW):
- ☐ CHEMISTRY REVIEW
- ☐ PHARMACOLOGY
- ☐ BIOPHARMACEUTICS
- ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE 4 STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL - BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG SAFETY

- ☐ PHASE 4 SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE, e.g., POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ NONCLINICAL

COMMENTS / SPECIAL INSTRUCTIONS: We are in need of statistical reviews for the following two HAP studies submitted under NDA 206627. We need a quick turn-around on these reviews.

1. Clinical Study HYD1013 entitled "A Single-Center, Randomized, Double-Blind, Crossover Study to Evaluate the Abuse Potential, Pharmacokinetcis, and Safety of Oral
Crushed and Intact Controlled Release Hydrocodone (HYD) Tablets in Recreational Opioid Users.

2. Clinical Study HYD1014 entitled "A Single-Center, Randomized, Double-Blind, Crossover Study to Evaluate the Abuse Potential, Pharmacokinetics, and Safety of Crushed and
Intranasally Administered Controlled Release Hydrocodone in Recreational Opioid Users

These studies are found in module 5.3.5.4 of the NDA submission.

Thank you very much.

SIGNATURE OF REQUESTOR Sandra L. Saltz	METHOD OF DELIVERY (Check one) ☐ DFS ☒ EMAIL ☐ MAIL ☐ HAND
PRINTED NAME AND SIGNATURE OF RECEIVER	PRINTED NAME AND SIGNATURE OF DELIVERER

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/s/

SANDRA L SALTZ
04/30/2014

Chiapperino, Dominic

From: Chiapperino, Dominic
Sent: Tuesday, April 29, 2014 2:41 PM
To: 'Liao, Edward'
Subject: NDA 206627, Information Request (Module 3)

Dear Ed,

We have received your new NDA 206627 for HYD (hydrocodone bitartrate) extended-release tablets. The eCTD NDA appears to have loaded successfully as of yesterday morning. Based on our review thus far, I do have a request for additional information to be submitted in Module 3, as follows:

> Provide data or specify a referenced DMF as the source of the required data for the following missing Module 3.2.S sections: Sections 3.2.S.1, Characterization; 3.2.S.3 Manufacturing Process; 3.2.S.7 Container Closure System; and 3.2.S.8 Stability.

Also, I will be following up shortly with a formal letter acknowledging receipt of the application as of yesterday. I am the assigned project manager in DAAAP for NDA 206627, so please contact me with any other questions you may have.

Kind regards,
Dominic

Dominic Chiapperino, Ph.D.
Senior Regulatory Health Project Manager
Division of Anesthesia, Analgesia, and Addiction Products
Office of Drug Evaluation II
FDA, Center for Drug Evaluation and Research
10903 New Hampshire Avenue
Building 22, Room 3134
Silver Spring, MD 20993
Office phone: (301) 796-1183
Facsimile: (301) 796-9723
Dominic.Chiapperino@fda.hhs.gov

Reference ID: 3498011

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/s/

DOMINIC CHIAPPERINO
04/29/2014

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADM NISTRATION

REQUEST FOR CONSULTATION

TO *(Division/Office)*:
Office of Surveillance and Epidemiology
ATTN: Vaishali Jarral, MS, MBA,
FYI: Mark Liberatore, Safety Regulatory Project Manager

FROM:
Division of Anesthesia, Analgesia, and Addiction Products – Bob A. Rappaport, M.D., Director
Point-of-contact: Dominic Chiapperino, Ph.D., Senior Regulatory Health Project Manager, 301-796-1183

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
April 29, 2014		**206627**	**Orig. NDA**	**Recvd. April 28, 2014**

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
[tradename pending] (hydrocodone bitartrate) extended-release tablets	n/a	**Type 3**	**July 14, 2014**

NAME OF FIRM: **Purdue Pharma L.P.**

REASON FOR REQUEST

I. GENERAL

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

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH

- ☐ TYPE A OR B NDA REVIEW
- ☐ END OF PHASE II MEETING
- ☐ CONTROLLED STUDIES
- ☐ PROTOCOL REVIEW
- ☐ OTHER (SPECIFY BELOW):

STATISTICAL APPLICATION BRANCH

- ☐ CHEMISTRY REVIEW
- ☐ PHARMACOLOGY
- ☐ BIOPHARMACEUTICS
- ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

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

IV. DRUG EXPERIENCE

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

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS:
DAAAP received this new NDA for extended-release hydrocodone bitartrate, a formulation with abuse deterrent claims. This will have a priority review and likely an accelerated review cycle (reflected in requested completion date of July 14, 2014).
The eCTD application can be accessed at: <\\CDSESUB1\evsprod\NDA206627\206627.enx>
DAAAP is requesting DRISK review of the submitted REMS (this product would belong in the class ER/LA opioid REMS) and DMEPA review of all proposed product labeling.

SIGNATURE OF REQUESTER
Dominic Chiapperino (signed electronically)

METHOD OF DELIVERY (Check one)
☒ EMAIL ☐ HAND

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/s/

DOMINIC CHIAPPERINO
04/29/2014

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

REQUEST FOR CONSULTATION

TO *(Office/Division)*: QT IRT Team
Attn: Devi Kozeli

FROM (*Name, Office/Division, and Phone Number of Requestor)*:
Bob A. Rappaort, M.D., Director, Division of Anesthesia, Analgesia, and Addiction Products (DAAAP)
Point of Contact: Dominic Chiapperino, PhD
RPM, DAAAP, x6-1183

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
April 29, 2014		NDA 206627	Orig. NDA Submitted tQT study	Received April 28, 2014

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
[tradename pending] hydrocodone bitartrate extended-release tablets	P	3	June 27, 2014

NAME OF FIRM: Purdue Pharma, L.P.

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE / ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE-NDA MEETING
- ☐ END-OF-PHASE 2a MEETING
- ☐ END-OF-PHASE 2 MEETING
- ☐ RESUBMISSION
- ☐ SAFETY / EFFICACY
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☒ OTHER *(SPECIFY BELOW)*: tQT study report

II. BIOMETRICS

- ☐ PRIORITY P NDA REVIEW
- ☐ END-OF-PHASE 2 MEETING
- ☐ CONTROLLED STUDIES
- ☐ PROTOCOL REVIEW
- ☐ OTHER (SPECIFY BELOW):
- ☐ CHEMISTRY REVIEW
- ☐ PHARMACOLOGY
- ☐ BIOPHARMACEUTICS
- ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE 4 STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL - BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG SAFETY

- ☐ PHASE 4 SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE, e.g., POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ NONCLINICAL

COMMENTS / SPECIAL INSTRUCTIONS: DAAAP received new NDA 206627, which includes a tQT study.
The eCTD application link is as follows: <**\\CDSESUB1\evsprod\NDA206627\206627.enx**>
and the link to the tQT study files for Study HYD1009 (entitled "Evaluate the effect of multiple doses (once daily for 3 days each of HYD 80, 120, and 160 mg tablets) on the QT/QTc interval") is:
\\CDSESUB1\evsprod\NDA206627\0000\m5\53-clin-stud-rep\535-rep-effic-safety-stud\management-of-pain\5351-stud-rep-contr\hyd1009
This NDA is of high priority because it is for a (claimed) abuse-deterrent hydrocodone formulation. DAAAP intends to take an action at the earliest possible time, well ahead of the "priority review" 6-month goal date, which is why the consult review due date of June 27, 2014 is requested.
Srikanth Nallani and Jackie Spaulding are the assigned clinical pharmacology and clinical reviewers (respectively).

Reference ID: 3497956

SIGNATURE OF REQUESTOR Dominic Chiapperino (signed electronically)	METHOD OF DELIVERY (Check all that apply) ☒ DARRTS ☐ EMAIL ☐ MAIL ☐ HAND
PRINTED NAME AND SIGNATURE OF RECEIVER	PRINTED NAME AND SIGNATURE OF DELIVERER

06/18/2013

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/s/

DOMINIC CHIAPPERINO
04/29/2014

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

REQUEST FOR CONSULTATION

TO *(Office/Division)*:
Controlled Substance Staff (CSS, HFD-009)
ATTN: Corinne Moody, Sandra Saltz

FROM (*Name, Office/Division, and Phone Number of Requestor)*:
Division of Anesthesia, Analgesia, and Addiction Products;
Bob A. Rappaport, M.D., Director
Point-of-contact: Dominic Chiapperino, Ph.D., Senior Regulatory Health Project Manager, 301-796-1183

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
April 29, 2014		NDA 206627	Original NDA	Received April 28, 2014

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
Hydrocodone bitartrate extended-release oral tablets	P	3	July 14, 2014

NAME OF FIRM: Purdue Pharma LP

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE / ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE-NDA MEETING
- ☐ END-OF-PHASE 2a MEETING
- ☐ END-OF-PHASE 2 MEETING
- ☐ RESUBMISSION
- ☒ SAFETY / EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☒ OTHER *(SPECIFY BELOW)*:

II. BIOMETRICS

- ☐ PRIORITY P NDA REVIEW
- ☐ END-OF-PHASE 2 MEETING
- ☐ CONTROLLED STUDIES
- ☐ PROTOCOL REVIEW
- ☐ OTHER (SPECIFY BELOW):
- ☐ CHEMISTRY REVIEW
- ☐ PHARMACOLOGY
- ☐ BIOPHARMACEUTICS
- ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE 4 STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL - BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG SAFETY

- ☐ PHASE 4 SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE, e.g., POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ NONCLINICAL

COMMENTS / SPECIAL INSTRUCTIONS: DAAAP received this NDA for an extended-release formulation of hydrocodone bitartrate with abuse-deterrent claims. This is expected to get a priority review, and perhaps an accelerated FDA action if possible (reflected in the requested completion date of July 14, 2014). We are requesting CSS review of abuse liability studies and labeling claims. The eCTD application can be accessed at:
<**\\CDSESUB1\evsprod\NDA206627\206627.enx**>

Jackie Spaulding is the assigned clinical reviewer in DAAAP (Ellen Fields is TL).

SIGNATURE OF REQUESTOR
Dominic Chiapperino (electronically signed)

METHOD OF DELIVERY (Check one)
☒ DARRTS ☐ EMAIL ☐ MAIL ☐ HAND

PRINTED NAME AND SIGNATURE OF RECEIVER

PRINTED NAME AND SIGNATURE OF DELIVERER

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/s/

DOMINIC CHIAPPERINO
04/29/2014