

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

202080Orig1s000

ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS

EXCLUSIVITY SUMMARY

NDA # 202080

SUPPL #

HFD # 170

Trade Name OXECTA

Generic Name Oxycodone Hydrochloride Tablets

Applicant Name King Pharmaceuticals Research and Development Inc.

Approval Date, If Known

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.

Applicant bridged the proposed Oxycodone HCl Tablets with the reference product, Roxycodone Tablets by submitting the data from a Bioequivalence study. The study evaluated the Bioequivalence between Oxycodone HCl Tablets (2 x 7.5 mg) and Roxycodone Tablets (15 mg).

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:

d) Did the applicant request exclusivity?

YES ☒ NO ☐

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

3

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?

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES ☐ NO ☒

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES ☒ NO ☐

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

NDA# 021011	Roxicodone (oxycodone HCl) Tablets, 5, 15, 30 mg
NDA# 022272	OxyContin (oxycodone HCl Controlled-Release) Tablets, 10, 15, 20, 30, 40, 60, 80 mg
NDA# 200534 & 200535	Oxycodone HCl Capsules (5 mg) & Oral Solution (100 mg/5 mL), respectively

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.)

YES ☐ NO ☐

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

NDA#

NDA#

NDA#

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.)
IF "YES," GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer

to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES ☒ NO ☐

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES ☐ NO ☒

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

The product is bioequivalent to the listed drug referenced by the applicant.

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES ☐ NO ☐

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES ☐ NO ☐

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES ☐ NO ☐

If yes, explain:

- (c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

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

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES ☐ NO ☐

Investigation #2 YES ☐ NO ☐

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES ☐ NO ☐

Investigation #2 YES ☐ NO ☐

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

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

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 !
 !
 IND # YES ☐ ! NO ☐
 ! Explain:

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

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1

YES ☐

Explain:

!

!

! NO ☐

! Explain:

Investigation #2

YES ☐

Explain:

!

!

! NO ☐

! 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: Lisa E. Basham
Title: Senior Regulatory Health Project Manager
Date: 6/2/11

Name of Division Director signing form: Bob A. Rappaport, M.D.

Title: Director, Division of Anesthesia, Analgesia and Addiction Products; ODE II; CDER

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05

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

/s/

LISA E BASHAM
06/17/2011

BOB A RAPPAPORT
06/17/2011

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION ¹		
NDA # 202080 BLA #	NDA Supplement # BLA STN #	If NDA, Efficacy Supplement Type:
Proprietary Name: Oxecta Established/Proper Name: oxycodone HCl Dosage Form: tablets		Applicant: King Pharmaceuticals Research and Development, Inc. Agent for Applicant (if applicable):
RPM: Lisa E. Basham		Division: DAAAP
<u>NDA:</u> NDA Application Type: ☐ 505(b)(1) ☒ 505(b)(2) Efficacy Supplement: ☐ 505(b)(1) ☐ 505(b)(2) (A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). Consult page 1 of the 505(b)(2) Assessment or the Appendix to this Action Package Checklist.) <u>505(b)(2) Original NDAs and 505(b)(2) NDA supplements:</u> Listed drug(s) relied upon for approval (include NDA #(s) and drug name(s)): 21011 Roxicodone Provide a brief explanation of how this product is different from the listed drug. reformulation If no listed drug, explain. ☐ This application relies on literature. ☐ This application relies on a final OTC monograph. ☐ Other (explain) <u>Two months prior to each action, review the information in the 505(b)(2) Assessment and submit the draft to CDER OND IO for clearance. Finalize the 505(b)(2) Assessment at the time of the approval action.</u> <u>On the day of approval, check the Orange Book again for any new patents or pediatric exclusivity.</u> ☒ No changes ☐ Updated Date of check: 6/17/11 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 <u>6-17-11</u>		☒ AP ☐ TA ☐ CR
Previous actions (<i>specify type and date for each action taken</i>)		☐ None
❖ If accelerated approval or approval based on efficacy studies in animals, were promotional materials received? Note: Promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf). If not submitted, explain _____		☐ Received

¹ The **Application Information** section is (only) a checklist. The **Contents of Action Package** section (beginning on page 5) lists the documents to be included in the Action Package.

❖ Application Characteristics ²		
Review priority: ☐ Standard ☒ Priority Chemical classification (new NDAs only): 5 ☐ Fast Track ☐ Rolling Review ☐ Orphan drug 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 ☒ REMS not required Comments:		
❖ BLAs only: Ensure <i>RMS-BLA Product Information Sheet for TBP</i> and <i>RMS-BLA Facility Information Sheet for TBP</i> have been completed and forwarded to OPI/OBI/DRM (Vicky Carter)	☐ Yes, dates	
❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 (<i>approvals only</i>)	☐ Yes ☐ No	
❖ Public communications (<i>approvals only</i>)		
• Office of Executive Programs (OEP) liaison has been notified of action	☐ Yes ☒ No	
• Press Office notified of action (by OEP)	☐ Yes ☒ No	
• Indicate what types (if any) of information dissemination are anticipated	☒ None ☐ HHS Press Release ☐ FDA Talk Paper ☐ CDER Q&As ☐ Other	

² 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.

❖ Exclusivity	
Is approval of this application blocked by any type of exclusivity?	☒ No ☐ Yes
NDA and BLA: Is there existing orphan drug exclusivity for the “same” drug or biologic for the proposed indication(s)? <i>Refer to 21 CFR 316.3(b)(13) for the definition of “same drug” for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification.</i>	☒ No ☐ Yes If, yes, NDA/BLA # _____ and date exclusivity expires: _____
(b)(2) NDAs only: Is there remaining 5-year exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i>	☒ No ☐ Yes If yes, NDA # _____ and date exclusivity expires: _____
(b)(2) NDAs only: Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i>	☒ No ☐ Yes If yes, NDA # _____ and date exclusivity expires: _____
(b)(2) NDAs only: Is there remaining 6-month pediatric exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i>	☒ No ☐ Yes If yes, NDA # _____ and date exclusivity expires: _____
NDAs only: Is this a single enantiomer that falls under the 10-year approval limitation of 505(u)? <i>(Note that, even if the 10-year approval limitation period has not expired, the application may be tentatively approved if it is otherwise ready for approval.)</i>	☒ No ☐ Yes If yes, NDA # _____ and date 10-year limitation expires: _____
❖ Patent Information (NDAs only)	
Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought. If the drug is an old antibiotic, skip the Patent Certification questions.	☒ Verified ☐ Not applicable because drug is an old antibiotic.
Patent Certification [505(b)(2) applications]: Verify that a certification was submitted for each patent for the listed drug(s) in the Orange Book and identify the type of certification submitted for each patent. NO RELEVANT PATENTS	21 CFR 314.50(i)(1)(i)(A) ☐ Verified 21 CFR 314.50(i)(1) ☒ (ii) ☐ (iii)
[505(b)(2) applications] If the application includes a paragraph III certification, it cannot be approved until the date that the patent to which the certification pertains expires (but may be tentatively approved if it is otherwise ready for approval).	☐ No paragraph III certification Date patent will expire _____
[505(b)(2) applications] For each paragraph IV certification, verify that the applicant notified the NDA holder and patent owner(s) of its certification that the patent(s) is invalid, unenforceable, or will not be infringed (review documentation of notification by applicant and documentation of receipt of notice by patent owner and NDA holder). <i>(If the application does not include any paragraph IV certifications, mark “N/A” and skip to the next section below (Summary Reviews)).</i>	☒ N/A (no paragraph IV certification) ☐ Verified

- [505(b)(2) applications] For **each paragraph IV** certification, based on the questions below, determine whether a 30-month stay of approval is in effect due to patent infringement litigation.

Answer the following questions for **each** paragraph IV certification:

- (1) Have 45 days passed since the patent owner's receipt of the applicant's notice of certification?

☐ Yes ☐ No

(Note: The date that the patent owner received the applicant's notice of certification can be determined by checking the application. The applicant is required to amend its 505(b)(2) application to include documentation of this date (e.g., copy of return receipt or letter from recipient acknowledging its receipt of the notice) (see 21 CFR 314.52(e)).

If "Yes," skip to question (4) below. If "No," continue with question (2).

- (2) Has the patent owner (or NDA holder, if it is an exclusive patent licensee) submitted a written waiver of its right to file a legal action for patent infringement after receiving the applicant's notice of certification, as provided for by 21 CFR 314.107(f)(3)?

☐ Yes ☐ No

If "Yes," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip the rest of the patent questions.

If "No," continue with question (3).

- (3) Has the patent owner, its representative, or the exclusive patent licensee filed a lawsuit for patent infringement against the applicant?

☐ Yes ☐ No

(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)).

If "No," the patent owner (or NDA holder, if it is an exclusive patent licensee) has until the expiration of the 45-day period described in question (1) to waive its right to bring a patent infringement action or to bring such an action. After the 45-day period expires, continue with question (4) below.

- (4) Did the patent owner (or NDA holder, if it is an exclusive patent licensee) submit a written waiver of its right to file a legal action for patent infringement within the 45-day period described in question (1), as provided for by 21 CFR 314.107(f)(3)?

☐ Yes ☐ No

If "Yes," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (Summary Reviews).

If "No," continue with question (5).

(5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the (b)(2) applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification? (Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced within the 45-day period). <i>If "No," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (Summary Reviews).</i> <i>If "Yes," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the OND ADRA and attach a summary of the response.</i>	☐ Yes ☐ No
CONTENTS OF ACTION PACKAGE	
❖ Copy of this Action Package Checklist ³	Yes
Officer/Employee List	
❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list (<i>approvals only</i>)	☒ Included 4-11-11
Documentation of consent/non-consent by officers/employees	☒ Included 5-25-11
Action Letters	
❖ Copies of all action letters (<i>including approval letter with final labeling</i>)	Approval Letter 6-17-11
Labeling	
❖ Package Insert (<i>write submission/communication date at upper right of first page of PI</i>)	
Most recent draft labeling. If it is division-proposed labeling, it should be in track-changes format.	
Original applicant-proposed labeling	Yes
Example of class labeling, if applicable	Roxicodone

³ Fill in blanks with dates of reviews, letters, etc.

❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling (<i>write submission/communication date at upper right of first page of each piece</i>)	☐ Medication Guide ☐ Patient Package Insert ☐ Instructions for Use ☐ Device Labeling ☒ None
Most-recent draft labeling. If it is division-proposed labeling, it should be in track-changes format.	
Original applicant-proposed labeling	
Example of class labeling, if applicable	
❖ Labels (full color carton and immediate-container labels) (<i>write submission/communication date on upper right of first page of each submission</i>)	Attached to Approval Letter C&C Labels submitted 6-9-11
Most-recent draft labeling	
❖ Proprietary Name - Acceptability/non-acceptability letter(s) (<i>indicate date(s)</i>) - Review(s) (<i>indicate date(s)</i>)	Oxecta Acceptable Letter: 6/8/11 Oxecta Review: 6/8/11
❖ Labeling reviews (<i>indicate dates of reviews and meetings</i>)	☐ RPM ☐ DMEPA ☐ DRISK ☐ DDMAC ☐ SEALD ☐ CSS ☐ Other reviews
Administrative / Regulatory Documents	
❖ Administrative Reviews (<i>e.g., RPM Filing Review⁴/Memo of Filing Meeting</i>) (<i>indicate date of each review</i>)	3-7-11
❖ All NDA (b)(2) Actions: Date each action cleared by (b)(2) Clearance Cmte	☐ Not a (b)(2) 5-26-11
❖ NDAs only: Exclusivity Summary (<i>signed by Division Director</i>)	☐ Not a (b)(2) 5-31-11
❖ Application Integrity Policy (AIP) Status and Related Documents http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm	☒ Included
Applicant is on the AIP	☐ Yes ☒ No
- This application is on the AIP - If yes, Center Director's Exception for Review memo (<i>indicate date</i>) - If yes, OC clearance for approval (<i>indicate date of clearance communication</i>)	☐ Yes ☐ No ☐ Not an AP action
❖ Pediatrics (<i>approvals only</i>) - Date reviewed by PeRC _____ If PeRC review not necessary, explain: <u>reformulation-does not trigger PREA</u> - Pediatric Page/Record (<i>approvals only, must be reviewed by PERC before finalized</i>)	☐ Included
❖ Debarment certification (original applications only): verified that qualifying language was not used in certification and that certifications from foreign applicants are cosigned by U.S. agent (<i>include certification</i>)	☒ Verified, statement is acceptable
❖ Outgoing communications (<i>letters (except action letters), emails, faxes, telecons</i>)	filing letter

⁴ Filing reviews for scientific disciplines should be filed behind the respective discipline tab.

❖ Internal memoranda, telecons, etc.	N/A
❖ Minutes of Meetings	
• Regulatory Briefing (<i>indicate date of mtg</i>)	☒ No mtg
• If not the first review cycle, any end-of-review meeting (<i>indicate date of mtg</i>)	☒ N/A or no mtg
• Pre-NDA/BLA meeting (<i>indicate date of mtg</i>)	☐ No mtg 9/27/10
• EOP2 meeting (<i>indicate date of mtg</i>)	☒ No mtg
• Other milestone meetings (e.g., EOP2a, CMC pilots) (<i>indicate dates of mtgs</i>)	
❖ Advisory Committee Meeting(s)	☒ No AC meeting
• Date(s) of Meeting(s)	
• 48-hour alert or minutes, if available (<i>do not include transcript</i>)	
Decisional and Summary Memos	
❖ Office Director Decisional Memo (<i>indicate date for each review</i>)	☒ None
Division Director Summary Review (<i>indicate date for each review</i>)	☒ None 6/17/11
Cross-Discipline Team Leader Review (<i>indicate date for each review</i>)	☒ None
PMR/PMC Development Templates (<i>indicate total number</i>)	☒ None
Clinical Information⁵	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) (<i>indicate date for each review</i>)	N/A
• Clinical review(s) (<i>indicate date for each review</i>)	Frank Pucino 5/24/11
• Social scientist review(s) (if OTC drug) (<i>indicate date for each review</i>)	☒ None
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here ☐ and include a review/memo explaining why not (<i>indicate date of review/memo</i>)	Page 13 of clinical review
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers (<i>indicate date of each review</i>)	☒ None
❖ Controlled Substance Staff review(s) and Scheduling Recommendation (<i>indicate date of each review</i>)	☐ Not applicable Jovita Randall-Thompson 5/24/11 CSS Stats: Ling Chen 4/1/11
❖ Risk Management • REMS Documents and Supporting Statement (<i>indicate date(s) of submission(s)</i>) • REMS Memo(s) and letter(s) (<i>indicate date(s)</i>) • Risk management review(s) and recommendations (including those by OSE and CSS) (<i>indicate date of each review and indicate location/date if incorporated into another review</i>)	☒ None
❖ DSI Clinical Inspection Review Summary(ies) (<i>include copies of DSI letters to investigators</i>)	☒ None requested

⁵ Filing reviews should be filed with the discipline reviews.

Clinical Microbiology ☒ None	
❖ Clinical Microbiology Team Leader Review(s) (indicate date for each review)	☒ None
Clinical Microbiology Review(s) (indicate date for each review)	☒ None
Biostatistics ☒ None	
❖ Statistical Division Director Review(s) (indicate date for each review)	☒ None
Statistical Team Leader Review(s) (indicate date for each review)	☒ None
Statistical Review(s) (indicate date for each review)	☒ None
Clinical Pharmacology ☐ None	
❖ Clinical Pharmacology Division Director Review(s) (indicate date for each review)	☒ None
Clinical Pharmacology Team Leader Review(s) (indicate date for each review)	☒ None
Clinical Pharmacology review(s) (indicate date for each review)	☐ None Suresh B Narahariseti 5/16/11
❖ DSI Clinical Pharmacology Inspection Review Summary (include copies of DSI letters)	☐ None Analytical Site 6/3/11 Clinical Site: 6/10/11
Nonclinical ☐ None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) (indicate date for each review)	☒ None
• Supervisory Review(s) (indicate date for each review)	☒ None
• Pharm/tox review(s), including referenced IND reviews (indicate date for each review)	☐ None Jay Chang 5/20/11
❖ 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)	☐ No carc
❖ ECAC/CAC report/memo of meeting	☐ None Included in P/T review, page
❖ DSI Nonclinical Inspection Review Summary (include copies of DSI letters)	☐ None requested
Product Quality ☐ None	
❖ Product Quality Discipline Reviews	
• ONDQA/OBP Division Director Review(s) (indicate date for each review)	☒ None
• Branch Chief/Team Leader Review(s) (indicate date for each review)	☐ None Prasad Peri 5/28/11
• Product quality review(s) including ONDQA biopharmaceutics reviews (indicate date for each review)	☐ None Julia Pinto 5/24/11
❖ Microbiology Reviews ☐ NDAs: Microbiology reviews (sterility & pyrogenicity) (OPS/NDMS) (indicate date of each review) ☐ BLAs: Sterility assurance, microbiology, facilities reviews (DMPQ/MAPCB/BMT) (indicate date of each review)	☒ Not needed
❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer (indicate date of each review)	☐ None CMC Biopharm: Houda Mahayni 5/16/11

❖ Environmental Assessment (check one) (original and supplemental applications)	
☒ Categorical Exclusion (<i>indicate review date</i>)(<i>all original applications and all efficacy supplements that could increase the patient population</i>)	page 51 of CMC review
☐ Review & FONSI (<i>indicate date of review</i>)	
☐ Review & Environmental Impact Statement (<i>indicate date of each review</i>)	
❖ Facilities Review/Inspection	
☒ NDAs: Facilities inspections (include EER printout) (<i>date completed must be within 2 years of action date</i>) (<i>only original NDAs and supplements that include a new facility or a change that affects the manufacturing sites⁶</i>)	Date completed: 2/17/11 ☒ Acceptable ☐ Withhold recommendation ☐ Not applicable
☐ BLAs: TB-EER (<i>date of most recent TB-EER must be within 30 days of action date</i>) (<i>original and supplemental BLAs</i>)	Date completed: ☐ Acceptable ☐ Withhold recommendation
❖ NDAs: Methods Validation (<i>check box only, do not include documents</i>)	☐ Completed ☒ Requested ☐ Not yet requested ☐ Not needed (per review)

⁶ 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.

Appendix to Action Package Checklist

An NDA or NDA supplemental application is likely to be a 505(b)(2) application if:

- (1) It relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application.
- (2) **Or** it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval.
- (3) **Or** it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations (see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

- (1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies).
- (2) **And** no additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application.
- (3) **And** all other "criteria" are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

- (1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication **AND** a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2).
- (2) **Or** the applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement.
- (3) **Or** the applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your ODE's ADRA.

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/s/

LISA E BASHAM
06/21/2011

PARINDA JANI
06/21/2011

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION		REQUEST FOR CONSULTATION			
TO (Office/Division): Contolled Substance Staff Attention: Corinne Moody & Michael Klein			FROM (Name, Office/Division, and Phone Number of Requestor): Lisa Basham; DAARP		
DATE January 4, 2011	IND NO.	NDA NO. 202080	TYPE OF DOCUMENT New NDA	DATE OF DOCUMENT 12/17/10	
NAME OF DRUG Acurox (without Niacin)		PRIORITY CONSIDERATION high	CLASSIFICATION OF DRUG opioid analgesic		DESIRED COMPLETION DATE PDUFA Date 6/17/11
NAME OF FIRM: King Pharmaceuticals, Inc.					
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):					
COMMENTS / SPECIAL INSTRUCTIONS: Please evaluate this new NDA from a CSS perspective. It is located in the EDR at: \\CDSESUB1\EVSPROD\NDA202080\202080.enx This will be a PRIORITY review with a PDUFA date of 6/17/11. It is an immediate-release purportedly abuse-deterrent formulation. It contains SLS (b) (4) As an immediate-release formulation, it will not, under current standards, require a REMS based upon abuse liability alone. Please let me know ASAP who will be assigned from CSS (Jovita/Silvia reviewed the Acurox with niacin product) Below is additional pertinent info: Acurox (immediate-release oxycodone HCl), 5 mg & 7.5 mg. Indication: management of moderate to severe pain where the use of an opioid analgesic is appropriate. 505(b)(2) referencing Roxycodone (Xanodyne NDA 21-011) PEDS: Req. waiver from conducting studies in all pediatric age groups Receipt Date: December 17, 2010 Filing Date: February 15, 2011 PDUFA DATE: June 17, 2011 Reviewers: PM: Lisa Basham MO: Frank Pucino/Rob Shibuya PT: Jay Chang/Adam Wasserman CMC: TBD CMC Biopharm: Houda Mahayni Clin Pharm: Suresh Naraharisetti/Suresh Doddapaneni Stats: TBD					
SIGNATURE OF REQUESTOR Lisa Basham; RPM; DAARP			METHOD OF DELIVERY (Check one) ☒ DARRTS ☐ EMAIL ☐ MAIL ☐ HAND		
PRINTED NAME AND SIGNATURE OF RECEIVER			PRINTED NAME AND SIGNATURE OF DELIVERER		

Reference ID: 2886628

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/s/

LISA E BASHAM
01/04/2011

Basham, Lisa

From: Basham, Lisa
Sent: Monday, June 06, 2011 2:14 PM
To: 'Maher, Catherine'
Subject: NDA 202080 PI for your review!
Attachments: FDA version of draft PI for NDA 202080 sent to King on 6-6-11.doc

Hi Catherine!

Here is the draft PI for your all's review. Beside's the content, you will need to do some cleaning up (I'm sure) of format, etc., and make sure that the Highlight references are correct. We did some, but it is such a mess right now, it'll be easier to fix once the edits are managed a bit. When you send back (ASAP!), please send a clean version with only the changes tracked that differ from this version. Thanks!

Lisa Basham, MS

Senior Regulatory Health Project Manager
Division of Anesthesia, Analgesia, and Addiction Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
301-796-1175
email: lisa.basham@fda.hhs.gov

28 pages of draft labeling has been withheld in full as
B(4) CCI/TS immediately following this page

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/s/

LISA E BASHAM
06/06/2011



NDA 202080

**PROPRIETARY NAME REQUEST
ACCEPTABLE**

King Pharmaceuticals Research and Development, Inc.
4000 CentreGreen Way, Suite 300
Cary, NC 27513

ATTENTION: Catherine E. Maher, Ph.D., R.A.C.
Senior Director, Regulatory Affairs

Dear Dr. Maher:

Please refer to your New Drug Application (NDA) dated December 17, 2010, received December 17, 2010, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Oxycodone HCl Tablets, USP, 5 mg and 7.5 mg.

We also refer to your May 9, 2011 correspondence, received May 10, 2011, requesting review of your proposed proprietary name, Oxecta. We have completed our review of the proposed proprietary name, Oxecta and have concluded that it is acceptable.

The proposed proprietary name, Oxecta, will be re-reviewed 90 days prior to the approval of the NDA. If we find the name unacceptable following the re-review, we will notify you.

If **any** of the proposed product characteristics as stated in your May 9, 2011 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 Danyal Chaudhry, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-3813. For any other information regarding this application contact the Office of New Drugs (OND) Regulatory Project Manager, Lisa Basham at (301) 796-1175.

Sincerely,

{See appended electronic signature page}

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

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/s/

CAROL A HOLQUIST
06/08/2011

Basham, Lisa

From: Basham, Lisa
Sent: Friday, June 10, 2011 6:14 PM
To: 'Maher, Catherine'
Subject: PI for NDA 202080 back to you.
Attachments: Pfizer version of draft PI received 6-9-11 FDA changes.doc

Catherine, Here you go!

Your alternate proposal for the C&C labels is acceptable. We are still discussing the PMR.

Lisa Basham, MS

Senior Regulatory Health Project Manager
Division of Anesthesia, Analgesia, and Addiction Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
301-796-1175
email: lisa.basham@fda.hhs.gov

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/s/

LISA E BASHAM
06/10/2011

Basham, Lisa

From: Basham, Lisa
Sent: Tuesday, May 24, 2011 3:47 PM
To: 'Maher, Catherine'
Subject: 5/24/11 CMC request for NDA 202080....

Hi Catherine,

Please send a commitment ASAP (via email) to do the following and follow up with a formal submission to the NDA:

Update the batch release and stability data tables to reflect the (b) (4) specifications for (b) (4) and dissolution.

Thanks!!

Lisa Basham, MS

Senior Regulatory Health Project Manager
Division of Anesthesia, Analgesia, and Addiction Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
301-796-1175
email: lisa.basham@fda.hhs.gov

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/s/

LISA E BASHAM
05/25/2011



NDA 202080

DISCIPLINE REVIEW LETTER

King Pharmaceuticals Research and Development, Inc.
4000 CentreGreen Way, Suite 300
Cary, NC 27513

Attention: Catherine E. Maher, Ph.D.
Senior Director, Regulatory Affairs

Dear Dr. Maher:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Oxycodone Hydrochloride Tablets, 5 mg and 7.5 mg.

The Division of Medication Error Prevention and Analysis has completed their review of your proposed carton and container labels and have the following comments:

1. Revise your established name presentation to be in accordance with 21 CFR 201.10(g)(2) which states “The established name shall be printed in letters that are at least half as large as the letters comprising the proprietary name or designation with which it is joined, and the established name shall have a prominence commensurate which such proprietary name or designation appears taking into account all pertinent factors, including typography, layout, contrast and other printing features.”
2. Although you utilize a blue and yellow color on the top of your labels the different strengths appear in the same black font. To ensure adequate differentiation between the two strengths, we request the blue and yellow color be utilized in conjunction with the strength presentation statement (5 mg and 7.5 mg) on the principal display panel. Ensure the strength is presented in a color that will be legible against the colored background. Decrease the prominence of the King Pharmaceuticals symbol, so that it does not compete with the prominence of the proprietary name, established name, or strength presentation.
3. Change the phrase, (b) (4) to “TRADENAME tablets are to be swallowed whole and are not to be administered via nasogastric or any other feeding tubes.”

4. Relocate the phrase “TRADENAME tablets are to be swallowed whole and are not to be administered via nasogastric or any other feeding tubes” to the principal display panel, to increase the prominence of this important statement.
5. Unbold the text of the Rx Only and container size statements.
6. Reduce the size of the graphic above the proprietary name so that it does not compete with its prominence.

We are providing these comments to you before we complete our review of the entire application to give you preliminary notice of issues that we have identified. In conformance with the prescription drug user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and subject to change as we finalize our review of your application. In addition, we may identify other information that must be provided before we can approve this application. If you respond to these issues during this review cycle, depending on the timing of your response, and in conformance with the user fee reauthorization agreements, we may not be able to consider your response before we take an action on your application during this review cycle.

If you have any questions, call Lisa Basham, Senior Regulatory Health Project Manager, at (301) 796-1175.

Sincerely,

{See appended electronic signature page}

Parinda Jani
Chief, Project Management Staff
Division of Anesthesia, Analgesia,
and Addiction Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

PARINDA JANI
05/20/2011



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Silver Spring, MD 20993

NDA 202080

**PROPRIETARY NAME REQUEST
UNACCEPTABLE**

King Pharmaceuticals Research and Development, Inc.
4000 CentreGreen Way, Suite 300
Cary, NC 27513

ATTENTION: Catherine Maher, Ph.D., RAC
Senior Director, Regulatory Affairs

Dear Dr. Maher:

Please refer to your New Drug Application (NDA) dated December 17, 2010, received December 17, 2010, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Oxycodone HCl Tablets, 5 mg and 7.5 mg.

We also refer to your January 21, 2011, correspondence, received January 21, 2011, requesting review of your proposed proprietary name, Acurox. We note that the name Acurox was previously reviewed as a two ingredient product (5 mg/30 mg and 7.5 mg/30 mg) and found to be conditionally acceptable. However, Acurox has been reformulated to contain only one active ingredient, Oxycodone (and no Niacin) and the proposed new strengths are 5 mg and 7.5 mg. Thus, the new product characteristics were evaluated for this proposed proprietary name and we have concluded that this name is unacceptable for the following reasons:

(b) (4)

We note that you have not proposed an alternate proprietary name for review. If you intend to have a proprietary name for this product, we recommend that you submit a new request for a proposed proprietary name review. (See the Guidance for Industry, *Contents of a Complete Submission for the Evaluation of Proprietary Names*, <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM075068.pdf> and “PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2008 through 2012”.)

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Danyal Chaudhry, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-3813. For any other information regarding this application contact the Office of New Drugs (OND) Regulatory Project Manager, Lisa Basham, at (301) 796-1175.

Sincerely,

{See appended electronic signature page}

Carol Holquist, RPh
Director
Division of Medication Error Prevention and Analysis
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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/s/

CAROL A HOLQUIST
04/08/2011



NDA 202,080

INFORMATION REQUEST

King Pharmaceuticals Research and Development, Inc.
Attention: Catherine Maher, Ph.D.
Senior Director, Regulatory Affairs
4000 CentreGreen Way, Suite 300
Cary, NC 27513

Dear Dr. Maher:

Please refer to your New Drug Application (NDA) submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act, for Acurox (Oxycodone HCl) Tablets, 5 mg and 7.5 mg.

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

1. The stability data provided does not justify a specification of NMT (b) (4) for (b) (4) (b) (4) and a specification of NMT (b) (4) for Total Impurities minus (b) (4). The data also does not support a (b) (4) specification of NMT (b) (4) these specifications to be consistent with the release and stability data.
2. The drug substance particle size distribution includes (b) (4). Include the data and propose a specification for the (b) (4).

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

Sincerely,

{See appended electronic signature page}

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

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/s/

PRASAD PERI
03/18/2011

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION		REQUEST FOR CONSULTATION		
TO (Office/Division): Badrul Chowdhury, M.D., Director - Division of Pulmonary, Allergy and Rheumatology Products			FROM (Name, Office/Division, and Phone Number of Requestor): Corinne P. Moody, Science Policy Analyst - Controlled Substance Staff (301) 796-3152	
DATE 02-18-11	IND NO.	NDA NO. 202080	TYPE OF DOCUMENT	DATE OF DOCUMENT 12-17-10
NAME OF DRUG Acurox		PRIORITY CONSIDERATION High	CLASSIFICATION OF DRUG Opioid	DESIRED COMPLETION DATE 03-18-11
NAME OF FIRM: King Pharmacueticals Research Development, Inc.				
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: BACKGROUND: For NDA 202080 - Acurox (Oxycodone HCl w/o niacin), CSS was consulted by DAAP for evaluation of an immediate-release opioid that contains sodium lauryl sulfate and/or other excipients that is/are purportedly a nasal irritant if the formulation is crushed and intranasally inhaled (snorted). Acurox (oxycodone WITH niacin) was previously CR'd last fall but was resubmitted after removal of niacin from the formulation. NDA 202080 represents the formulation without niacin. There are 2 abuse liability studies that include these "nasal" measures (6-point severity scale of multiple adverse events AND a listing of AEs) that are somewhat related: 1. (previous submission) study #AP-ADF-106 (IR oxycodone w/niacin). 2. NDA 202080, study #K234-10-1002 (IR oxycodone w/o niacin). Reference ID: 2908151				

CONSULT QUESTIONS:

1. In NDA 202080, study #K234-10-1002 (IR oxycodone w/o niacin), is the 6-point Subject-Rated Scale for Nasal Effects for burning, need to blow nose, runny nose/nasal discharge, facial pain/pressure, and nasal congestion (at pre-dose, 0.5, 1, 2, 4h) considered a validated assessment tool?
2. If not, what are the appropriate measures for evaluating nasal absorption irritancy and toxicity, e.g. are there any validated tools?
3. What are the thresholds for concern and can such "intranassal" adverse events simply be accomodated over repeated exposure? (exhibit only first-time irritancy if mild degree)
4. Sodium lauryl sulfate is listed as an inactive excipient. What are the known effects of sodium lauryl sulfate on nasal inhalation and/or the respiratory tract?

If you have any questions, please feel free to e-mail me or call me.

SIGNATURE OF REQUESTOR

Corinne P. Moody, Science Policy Analyst

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/

CORINNE P MOODY
02/18/2011



NDA 202080

FILING COMMUNICATION

King Pharmaceuticals Research and Development, Inc.
4000 CentreGreen Way, Suite 300
Cary, NC 27513

Attention: Catherine E. Maher, Ph.D.
Senior Director, Regulatory Affairs

Please refer to your New Drug Application (NDA) dated December 17, 2010, received December 17, 2010, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act, for Acurox (Oxycodone HCL) Tablets, 5 mg and 7.5 mg.

We also refer to your submissions dated January 21 and 26, 2011.

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 June 17, 2011.

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, midcycle, 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 May 27, 2011.

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

1. The proposed label describes the deterrent effects of [REDACTED] (b) (4)
[REDACTED]
However, your study, Intranasal Abuse Liability (K234-10-1002), does not provide justification for the addition of sodium lauryl sulfate (SLS) [REDACTED] (b) (4)
[REDACTED]

2. In reviewing the data of your Phase 1 Intranasal Abuse Liability Study (K234-10-1002), a sequence (AB/BA) effect was observed. The findings show that subjects given Roxycodone in Period 1 and Acurox in Period 2 reported much lower scores on Emax of Drug Liking VAS for Acurox than those who were given Acurox in Period 1 and Roxycodone in Period 2.
3. As presented on page 32 of K234-10-1002 Study Report (11/04/2010), you indicated that all treatment tablets were crushed (b) (4).
Data on the particle size of crushed tablets, sample uniformity and sample appearance for Acurox and Roxycodone to validate equal sample homogeneity was not found in the submission.
4. For Study K234-10-1002, pharmacokinetic parameters such as oxycodone plasma concentration, Cmax and Tmax were not provided. Therefore, the PK and PD for Drug Liking cannot be correlated.
5. Subject ID 9028 was not included in the statistical analysis because of vomiting during Acurox treatment. This subject had an episode of moderate vomiting during Acurox treatment, recorded at Hour 0 (resolved in less than 1 minute), and also had an episode of mild vomiting during Roxycodone treatment at Hour 0.9 (resolved at 0 minute). However, the subject responded to the Drug liking VAS at all planned time points. The Emax of Drug Liking, Overall Drug Liking and Take Drug Again for Acurox were scored at 100, 93 and 100, respectively. Therefore, it is unclear why this subject was not included in the analysis.

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.

We also request that you submit the following information:

1. A detailed description of the measures and standards taken during Study K234-10-1002 discrimination and treatment testing to maintain the concealment of your treatment and control for treatment bias due to subjects and caregivers becoming aware of assigned treatments.
2. For Study K234-10-1002 (discrimination and treatment phase) submit the protocol followed for study drug preparation and administration to subjects. Include a description of crushing conditions, crushed material consistency and average particle size for both administered crushed treatments.
3. For Study K234-10-1002, provide the location in the EDR for Pharmacokinetic Concentrations and Pharmacokinetic Parameters datasets.
4. Provide photostability data as per ICH Q1B.

5. The proposed dissolution specification of NLT (b) (4) is not acceptable. (b) (4)
the dissolution specification to NLT (b) (4) in 15 minutes.

Please respond only to the above requests for information. While we anticipate that any response submitted in a timely manner will be reviewed during this review cycle, such review decisions will be made on a case-by-case basis at the time of receipt of the submission.

REQUIRED PEDIATRIC ASSESSMENTS

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

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

If you have any questions, call Lisa Basham, Senior Regulatory Health Project Manager, at (301) 796-1175.

Sincerely,

{See appended electronic signature page}

Bob A. Rappaport, M.D.
Division of Anesthesia and Analgesia Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

BOB A RAPPAPORT
02/10/2011

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION		REQUEST FOR CONSULTATION			
TO (Office/Division): OSE Mail Attention: Bola Adeolu			FROM (Name, Office/Division, and Phone Number of Requestor): Lisa Basham; DAAP		
DATE January 11, 2011	IND NO.	NDA NO. 202080	TYPE OF DOCUMENT New NDA	DATE OF DOCUMENT 12/17/10	
NAME OF DRUG Acurox (without Niacin)		PRIORITY CONSIDERATION high	CLASSIFICATION OF DRUG opioid analgesic		DESIRED COMPLETION DATE PDUFA Date 6/17/11
NAME OF FIRM: King Pharmaceuticals, Inc.					
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):					
COMMENTS / SPECIAL INSTRUCTIONS: Please evaluate this new NDA from an OSE perspective. It is located in the EDR at: \\CDSESUB1\EVSPROD\NDA202080\202080.enx					
This will be a PRIORITY review with a PDUFA date of 6/17/11. It is an immediate-release purportedly abuse-deterrent formulation. It contains (b) (4) As an immediate-release formulation, it will not, under current standards, require a REMS based upon abuse liability alone. Please let me know ASAP who will be assigned from OSE and please specify what parts of the application that the assigned reviewers will be responsible for. Below is additional pertinent info: Acurox (immediate-release oxycodone HCl), 5 mg & 7.5 mg. Indication: management of moderate to severe pain where the use of an opioid analgesic is appropriate. 505(b)(2) referencing Roxycodone (Xanodyne NDA 21-011) PEDS: Req. waiver from conducting studies in all pediatric age groups Receipt Date: December 17, 2010 Filing Date: February 15, 2011 PDUFA DATE: June 17, 2011 Reviewers: PM: Lisa Basham MO: Frank Pucino/Rob Shibuya PT: Jay Chang/Adam Wasserman CMC: TBD CMC Biopharm: Houda Mahayni Clin Pharm: Suresh Naraharisetti/Suresh Doddapaneni Stats: Kate Meaker/Dionne Price					
SIGNATURE OF REQUESTOR Lisa Basham; RPM; DAARP			METHOD OF DELIVERY (Check one) ☒ DARRTS ☐ EMAIL ☐ MAIL ☐ HAND		
PRINTED NAME AND SIGNATURE OF RECEIVER			PRINTED NAME AND SIGNATURE OF DELIVERER		

Reference ID: 2890181

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/s/

LISA E BASHAM
01/11/2011



NDA 202080

NDA ACKNOWLEDGMENT

King Pharmaceuticals Research and Development, Inc.
4000 CentreGreen Way, Suite 300
Cary, NC 27513

Attention: Catherine E. Maher, Ph.D.
Senior Director, Regulatory Affairs

Dear Dr. Maher:

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: Acurox (Oxycodone HCL) Tablets, 5 mg and 7.5 mg

Date of Application: December 17, 2010

Date of Receipt: December 17, 2010

Our Reference Number: NDA 202080

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on February 15, 2011, 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 responsible for complying with the applicable provisions of sections 402(i) and 402(j) of the Public Health Service Act (PHS Act) [42 USC §§ 282 (i) and (j)], which was amended by Title VIII of the Food and Drug Administration Amendments Act of 2007 (FDAAA) (Public Law No. 110-85, 121 Stat. 904). Title VIII of FDAAA amended the PHS Act by adding new section 402(j) [42 USC § 282(j)], which expanded the current database known as ClinicalTrials.gov to include mandatory registration and reporting of results for applicable clinical trials of human drugs (including biological products) and devices.

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

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

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

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

When submitting the certification for this application, **do not** include the certification with other submissions to the application. Submit the certification within 30 days of the date of this letter. In the cover letter of the certification submission clearly identify that it pertains to **NDA 202080**, submitted on December 17, 2010, and that it contains the FDA Form 3674 that was to accompany that application.

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

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

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

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

If you have any questions, call me at (301) 796-1175.

Sincerely,

{See appended electronic signature page}

Lisa E. Basham, M.S.
Senior Regulatory Health Project Manager
Division of Anesthesia and Analgesia Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

LISA E BASHAM
01/07/2011

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION		REQUEST FOR CONSULTATION					
TO (Office/Division): Contolled Substance Staff Attention: Corinne Moody & Michael Klein			FROM (Name, Office/Division, and Phone Number of Requestor): Lisa Basham; DAARP				
DATE January 4, 2011	IND NO.	NDA NO. 202080	TYPE OF DOCUMENT New NDA	DATE OF DOCUMENT 12/17/10			
NAME OF DRUG Acurox (without Niacin)	PRIORITY CONSIDERATION high		CLASSIFICATION OF DRUG opioid analgesic	DESIRED COMPLETION DATE PDUFA Date 6/17/11			
NAME OF FIRM: King Pharmaceuticals, Inc.							
REASON FOR REQUEST							
I. GENERAL							
<table style="width: 100%; border: none;"> <tr> <td style="vertical-align: top; width: 33%;"> ☐ NEW PROTOCOL ☐ PROGRESS REPORT ☐ NEW CORRESPONDENCE ☐ DRUG ADVERTISING ☐ ADVERSE REACTION REPORT ☐ MANUFACTURING CHANGE / ADDITION ☐ MEETING PLANNED BY </td> <td style="vertical-align: top; width: 33%;"> ☐ PRE-NDA MEETING ☐ END-OF-PHASE 2a MEETING ☐ END-OF-PHASE 2 MEETING ☐ RESUBMISSION ☐ SAFETY / EFFICACY ☐ PAPER NDA ☐ CONTROL SUPPLEMENT </td> <td style="vertical-align: top; width: 33%;"> ☐ RESPONSE TO DEFICIENCY LETTER ☐ FINAL PRINTED LABELING ☐ LABELING REVISION ☐ ORIGINAL NEW CORRESPONDENCE ☐ FORMULATIVE REVIEW ☒ OTHER (SPECIFY BELOW): </td> </tr> </table>					☐ 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):
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COMMENTS / SPECIAL INSTRUCTIONS: Please evaluate this new NDA from a CSS perspective. It is located in the EDR at: \\CDSESUB1\EVSPROD\NDA202080\202080.enx							
This will be a PRIORITY review with a PDUFA date of 6/17/11. It is an immediate-release purportedly abuse-deterrent formulation. It contains (b) (4) As an immediate-release formulation, it will not, under current standards, require a REMS based upon abuse liability alone. Please let me know ASAP who will be assigned from CSS (Jovita/Silvia reviewed the Acurox with niacin product) Below is additional pertinent info: Acurox (immediate-release oxycodone HCl), 5 mg & 7.5 mg. Indication: management of moderate to severe pain where the use of an opioid analgesic is appropriate. 505(b)(2) referencing Roxycodone (Xanodyne NDA 21-011) PEDS: Req. waiver from conducting studies in all pediatric age groups Receipt Date: December 17, 2010 Filing Date: February 15, 2011 PDUFA DATE: June 17, 2011 Reviewers: PM: Lisa Basham MO: Frank Pucino/Rob Shibuya PT: Jay Chang/Adam Wasserman CMC: TBD CMC Biopharm: Houda Mahayni Clin Pharm: Suresh Naraharisetti/Suresh Doddapaneni Stats: TBD							
SIGNATURE OF REQUESTOR Lisa Basham; RPM; DAARP			METHOD OF DELIVERY (Check one) ☒ DARRTS ☐ EMAIL ☐ MAIL ☐ HAND				
PRINTED NAME AND SIGNATURE OF RECEIVER			PRINTED NAME AND SIGNATURE OF DELIVERER				

Reference ID: 2886628

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/s/

LISA E BASHAM
01/04/2011



PNDA 202080

MEETING MINUTES

King Pharmaceuticals
Research and Development, Inc.
4000 CentreGreen Way, Suite 300
Cary, NC 27513

Attention: Catherine Maher, PhD, RAC
Senior Director, Regulatory Affairs

Please refer to your Pre-New Drug Application (PNDA) file for Act for Acurox (oxycodone HCL, USP) Tablets.

We also refer to the meeting between representatives of your firm and the FDA on September 27, 2010. The purpose of the meeting was to discuss the development program to support submission of an NDA.

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

If you have any questions, call me at (301) 796-1175.

Sincerely,

{See appended electronic signature page}

Lisa E. Basham, M.S.
Senior Regulatory Health Project Manager
Division of Anesthesia and Analgesia Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

SPONSOR MEETING AGENDA

MEETING DATE/TIME: September 27, 2010 (2:30-3:30 PM)
LOCATION: 10903 New Hampshire Ave., Silver Spring, MD; Bldg 22; Room 1421
APPLICATION: **Pre-NDA 202080/Acurox** (Oxycodone HCl) Tablets
STATUS OF APPLICATION: Pre-submission
SPONSOR: King Pharmaceuticals
TYPE OF MEETING: Type B/Pre-NDA
MEETING CHAIR: Sharon Hertz, M.D.; Deputy Director, Division of Anesthesia and Analgesia Products (DAAP)
MEETING RECORDER: Lisa Basham, Senior Regulatory Health Project Manager

FDA Attendees	Title
Curtis Rosebraugh, MD	Director, Office of Drug Evaluation II (ODE II)
Bob Rappaport, MD	Division Director, DAAP
Sharon Hertz, MD	Deputy Division Director, DAAP
Michael Klein, PhD	Director, Controlled Substance Staff (CSS)
Suresh Doddapaneni, PhD	Clinical Pharmacology Team Leader
Dionne Price, PhD	Biostatistics Team Leader
Adam Wasserman, PhD	Supervisory Pharmacologist
Prasad Peri, PhD	Acting Branch Chief, ONDQA
Danae Christodoulou, PhD	Pharmaceutical Assessment Lead, ONDQA
Silvia Calderon, PhD	Team Leader, CSS
Igor Cerny, Pharm.D.	Clinical Reviewer
David Lee, PhD	Clinical Pharmacology Reviewer
Katherine Meaker, PhD	Statistics Reviewer
Jay Chang, PhD	Preclinical Reviewer
Ling Chen, PhD	Mathematical Statistician, Special Projects Team, Division of Biostatistics VI (DBVI), Office of Biostatistics (OB)
Jovita Randall-Thompson, PhD	Pharmacologist, CSS
Corinne Moody	Policy Analyst, CSS
Leah Ripper	Associate Director of Regulatory Affairs, ODE2
Lisa Basham, MS	Senior Regulatory Project Manager

Sponsor Attendees	Title
Eric Carter, PhD, MD	Chief Scientific Officer, King R&D
Robert Rolleri, PharmD	Sr. Director of Clinical Research, King R&D
Kenneth W. Sommerville, MD	Vice President of Clinical Development, King R&D
Catherine Maher, PhD	Sr. Director of Reg. Affairs, King R&D
Glenn Pixton, MS	Director of Statistics, King R&D
Stephen MacLennan, PhD	Sr. Dir. of Pharmacology, King R&D
Mike Lamson, PhD	Sr. Dir. of Pharmacokinetics and Clinical Research, King R&D
Almasa Bass, PharmD	Sr. Scientist, Pharmacokinetics and Clinical Research, King R&D
Andrew Reddick	President and CEO, Acura Pharmaceuticals, Inc.
Al Brzezsko, PhD	Vice President, Technical Affairs, Acura Pharmaceuticals, Inc.
Ken Touw, PhD	Senior VP, King R&D

MEETING MINUTES

NOTE: The sponsor's questions are shown below in normal text, followed by the Agency's responses, provided to the sponsor prior to the meeting, in bolded text. The sponsor provided clarification/responses to the Agency responses prior to the meeting and those are shown in italicized text as well. Discussion is shown in normal text and is labeled as such. After the meeting, the sponsor provided some follow-up questions and some requested data via email. The questions, and the Agency responses, are shown following the meeting minutes in a similar format. The emailed data is attached at the end of the document.

CLINICAL

Question 1

In accordance with 21 CFR §314.54(a)(1)(iii), King R&D plans to submit a 505(b)(2) application for an oxycodone HCl immediate-release tablet. Functional excipients in the product may have the potential to deter oxycodone abuse and misuse by providing limits and impediments to intranasal and intravenous administration of the product. The application will reference NDA 21-011 (Roxicodone[®] [oxycodone HCl tablets USP]) and establish safety and efficacy based on bioequivalence to Roxicodone[®].

Because there will be no new studies in the proposed pain patient population, King R&D proposes to review the safety and efficacy of Acurox[®] Tablets within Sections 2.7.3 and 2.7.4 of the NDA. King R&D also proposes to omit from the NDA a formal Integrated Summary of Efficacy and Integrated Summary of Safety.

- a) *Does the Division agree that the safety and efficacy of Acurox[®] Tablets may be established by demonstrating bioequivalence to Roxicodone[®]? If not, what would the Division consider to be an acceptable approach?*

FDA Response:

Yes, as long as the submitted bioequivalence data are scientifically rigorous and demonstrate bioequivalence and no new safety concerns are raised by the formulation. However, if the formulation does raise the possibility of novel risks, e.g. GI obstruction due to a non-dissolving tablet, additional safety data may be required.

Sponsor Response:

Novel risks, such as GI obstruction, have not been observed in clinical trials with Acurox[®] Tablets or other products using the same technology in single doses up to 8 tablets. Are there any other specific concerns that the Agency has in this regard?

DISCUSSION: The Division stated that there are no specific safety concerns at this time.

- b) *Does the Division agree that reviewing the safety and efficacy of Acurox[®] Tablets within Sections 2.7.3 and 2.7.4 of the NDA is acceptable? If not, what would the Division consider to be an acceptable approach?*

FDA Response:

According to the Guidances for Industry, M4E: The CTD-Efficacy (<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm073290.pdf>) and M4S: The CTD-Safety (<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm073299.pdf>), the Clinical Summary is intended to provide a detailed, factual summarization of all of the clinical information in the CTD. This includes information provided in ICH E3 clinical study reports; information obtained from any meta-analyses or other cross-study analyses for which full reports have been included in Module 5; and postmarketing data for products that have been marketed in other regions. The comparisons and analyses of results across studies provided in this document should focus on factual observations. As long as your plans for the efficacy and safety submission for Acurox tablets complies with the guidance, the safety and efficacy reviews may be placed in Sections 2.7.3 and 2.7.4.

Sponsor Response:
No discussion is necessary.

- c) *Does the Division agree that the Integrated Summaries of Efficacy and Safety may be omitted from the NDA? If not, what would the Division consider to be an acceptable approach?*

FDA Response:

In the absence of novel clinical efficacy studies, an Integrated Summary of Efficacy need not be included in your NDA submission. Describe how you plan to report the safety data from the studies you conduct with Acurox in which patients are not blocked with naltrexone.

Sponsor Response:
Three clinical studies will be included in the NDA. Studies AP-ADD-100 and K234-10-1001 are pharmacokinetic studies in which a naltrexone block was administered.

Study K234-10-1002 is the intranasal abuse liability study that did not use a naltrexone block. The safety data for this study will be reported in the clinical study report as described in the Statistical Analysis Plan for the study. These

data will also be presented in Sections 2.7.2 (Summary of Clinical Pharmacology Studies), 2.7.4 (Summary of Clinical Safety), and 2.5 (Clinical Overview).

Is this approach acceptable?

DISCUSSION: The Division stated that this approach is acceptable.

Question 2

NDA 20-2080 will include a dose-proportionality / food-effect study (Appendix B) and a bioequivalence study to the reference listed drug Roxicodone[®] (Appendix C). The designs of the pharmacokinetic studies are consistent with the guidance documents for conducting bioequivalence and dose-proportionality studies.

The definitive intranasal abuse liability study for Acurox[®] (oxycodone HCl, USP) Tablets (NDA 20-2080) is Study K234-10-1002 (Appendix A). Study AP-ADF-106 was previously reviewed by FDA (Acurox[®] with Niacin NDA 22-451), was considered adequate by the Division, and will be considered a supportive study for this application. The designs and endpoints of both Study K234-10-1002 and Study AP-ADF-106 are consistent with the January 2010 draft guidance for industry regarding "Assessment of Abuse Potential of Drugs".

(b) (4)

- a) *Does the Division agree that the proposed bioequivalence and dose-proportionality studies are adequate to support an NDA filing, and assuming favorable review, an eventual approval? If not, why not and what modifications to the plan does the Division propose?*

FDA Response:

In theory, the type of information obtained from the proposed studies would be expected to be adequate for filing. However, modify your protocol for food-effect Study K234-10-1001 so that the Roxicodone arm is administered under a *fasting* state. Whether the data are capable of supporting an approval will be a review issue.

Sponsor Response:

The bioequivalence of Acurox[®] Tablets to Roxicodone[®] was established under fasted conditions in Study AP-ADD-100. Is this an acceptable approach to satisfy the filing requirements for bioequivalence?

To clarify, Study K234-10-1001 included a comparison to Roxicodone[®] in order to determine the relative bioavailability of Acurox[®] Tablets under fed conditions.

DISCUSSION: The Sponsor clarified that study AP-ADD-100 was conducted with the to-be-marketed formulation. The Division stated that, with this clarification, there is no need to administer Roxicodone tablets in the fasted state in Study K234-10-1001, and that Study AP-ADD-100 will be considered a pivotal bioequivalence study, for which an inspection by the Division of Scientific Investigation will be required.

- b) *Does the Division agree that the proposed new intranasal abuse liability study (K234-10-1002) is adequate to support an NDA filing, and assuming favorable review, an eventual approval?* (b) (4)

FDA Response:

In response to question 2(b), your proposed new intranasal abuse liability study, Protocol K234-10-1002, is acceptable for NDA filing. The adequacy of these data, and whether the study can support an approval will be determined during NDA review. Though you have not provided a full protocol for the proposed new intranasal abuse liability study (Protocol K234-10-1002), we have the following comments for you to address:

- **Provide justification for using the single dose of 15 mg of oxycodone (3 tablets of Roxicodone) in the prequalification phase and in the second phase of Protocol K234-10-1002.**

Sponsor Response:
No discussion is necessary.

- **Provide information on the total amount of crushed material that would have to be snorted under Treatment B and how this amount compares to the amount of crushed material under Treatment A. Drug treatments need to be equivalent not only on the dose of oxycodone to be snorted but in terms of the total amount of crushed material to be snorted. As proposed, Treatment A requires two crushed Acurox (15 mg of oxycodone, 980 mg of crushed material) whereas Treatment B requires the crushing of three immediate-release Roxicodone tablets (15 mg of oxycodone). Provide information on the average weight of a Roxicodone 5 mg tablet.**

Sponsor Response:
The total amount of crushed material in three 5 mg Roxicodone® Tablets in Treatment B is approximately 300 mg. The total amount of crushed material in two 7.5 mg Acurox® Tablets in Treatment A is approximately 980 mg. Two 7.5 mg tablets was the maximum tolerated intranasal dose in Study AP-ADF-106.

The difference in the amount of crushed material snorted in Treatment A and Treatment B is intended to simulate real world conditions. Snorting three crushed 5 mg Roxicodone® Tablets provides the maximum quantity of crushed material available in a 15 mg oxycodone HCl dose. We anticipate that, in addition to the functional inactive ingredients in Acurox® Tablets, the increased mass of crushed material will contribute to a lower abuse potential. Protocol K234-10-1002 ensures that subjects in the trial can not visually distinguish Treatment A (two crushed 7.5 mg Acurox® Tablets) from Treatment B (three crushed 5 mg Roxicodone® Tablets) based on the amount of crushed material to be snorted.

DISCUSSION: The Agency stated that, as the test conditions are meant to simulate real-world conditions, the difference in the amount of crushed material in the two treatments is acceptable.

- **We recommend that you consider exploring the possibility of including a placebo arm in Part II of your abuse liability study (Protocol K234-10-1002). A placebo tablet that represents the new formulation without the active ingredient would contain the same amount of sodium lauryl sulfate as formulated in Acurox but have no oxycodone. We recognize that you will have to manufacture these placebo tablets.**

Sponsor Response:

A placebo arm (lactose) is included in the Drug Discrimination Phase of Protocol K234-10-1002 to ensure subjects can discriminate between oxycodone and placebo. Only subjects who have demonstrated the ability to discriminate will be enrolled in the Treatment Phase. In view of this design, does the Agency agree that a placebo arm is not necessary?

DISCUSSION: The Agency stated that a validation arm with placebo containing SLS is needed to determine how patients respond to SLS alone, and how oxycodone will impact that reaction. The Sponsor explained that the critical comparison in the Treatment Phase of the protocol is Acurox (oxycodone HCl with SLS) compared with Roxicodone (oxycodone HCl without SLS) and that a placebo arm is not necessary for this comparison. They continued that the safety of SLS and other functional excipients will be assessed by comparing adverse event profiles between crushed Acurox and crushed Roxicodone and through a 6-point Subject Rated Scale for Nasal Effects. The Agency stated that they would discuss the matter internally and provide further comment in the meeting minutes (See Post Meeting Note at the end of section for Question 2).

- **Provide supportive information to justify the use of the following questionnaires. You have proposed to use the subjective questionnaires entitled “Take Drug Again Assessment (TDAA) and “Global Assessment of Overall Drug Liking.” Also, provide supportive information, including any research data, on the**

validity and reliability of these subjective questionnaires in assessing the abuse liability of Acurox under the experimental parameters you propose.

- **We recommend that you evaluate Drug Liking at time points 5, 25 and 30 minutes and 1, 1.5, 2, 2.5 and 3 hours.**

Sponsor Response:

Please confirm that a time point of 15 minutes is recommended instead of 25 minutes.

DISCUSSION: The Agency clarified that the recommended time points are 5, 15, and 30 minutes and 1, 1.5, 2, 2.5, and 3 hours.

- **We recommend that you include additional co-primary subjective measures such as Drug Effect and Drug High in your assessment. These measures should be given at the same time points we recommend for evaluating Drug Liking.**

Sponsor Response:

No discussion is necessary.

- **Describe the statistical model you will use in the data analysis of Protocol K234-10-1002. In the synopsis of Protocol K234-10-1002, you state that the study will be a crossover design study, yet you do not provide the statistical model which you propose to use in the data analysis.**

Sponsor Response:

No discussion is necessary.

- **There is no need to adjust alpha when conducting the statistical analysis of your abuse liability study (Protocol K234-10-1002).**

Sponsor Response:

No adjustment to alpha implies that all co-primary endpoints need to be statistically significant for the study to be 'successful'. Is the Agency suggesting that all co-primary endpoints need to be statistically significant? If not, then what is the rationale for suggesting no alpha adjustment, given the proposed testing strategy requires one co-primary endpoint (E_{max}) to be significant, but only one of the other two (Take Drug Again Assessment-TDAA and Overall Drug Liking-ODL) to be significant?

DISCUSSION: The Agency stated that, in drug-liking studies, drug effect and high are appropriate to use as co-primary endpoints with many secondary endpoints. Results from the primary endpoints alone are not necessarily sufficient to support the success of the study. The

totality of evidence from all endpoints (primary and secondary) will be used to determine the success of the study. Abuse liability studies can be viewed more as safety studies. The Agency also recommended that the sponsor compare subject percent change of $E_{\max}$ between treatment arms.

- **Our recommendations on the content of Section (b) (4) of the proposed drug label for the product will be provided after all submitted data are reviewed.**

Sponsor Response:

No discussion is necessary.

(b) (4)

POST MEETING NOTE: The Division of Biometrics IV within the Office of Biostatistics and the Controlled Substance Staff recommend the following:

1. **A placebo treatment should be included in the treatment phase of the abuse potential study (Part I of *Protocol K234-10-1002*) for assay sensitivity. In the qualification phase of the abuse potential study (Part I of *Protocol K234-10-1002*), a drug discrimination test will be performed to ensure that subjects can differentiate between intranasally administered crushed Roxicodone® tablets and placebo. In the treatment phase of the abuse potential study (Part I of *Protocol K234-10-1002*), however, it is still possible that some subjects may not respond to Roxicodone®.**
2. **A sodium lauryl sulfate (SLS) treatment should be included in the treatment phase of the abuse potential study (Part II of *Protocol K234-10-1002*) for assay sensitivity. Although SLS is not considered an active ingredient in terms of drug efficacy, as proposed by the Sponsor, (b) (4)**

3. **A 4x4 Williams square design may be used after adding two treatments, the placebo and SLS, to the treatment phase of the abuse potential study.**
4. **You should consider longer washout periods between treatments, taking under consideration the crossover testing of the study and the route of administration. In addition, a urine test and a nasal mucosal examination before each treatment may be needed.**
5. **We recommend that you include all of the following comparisons:**
 - a. **Compare Roxicodone® to Placebo (Assay sensitivity)**
 - b. **Compare SLS to Placebo (Assay sensitivity)**
 - c. **Compare Acurox® to Roxicodone®**
 - d. **Compare Acurox® to Placebo**

Question 3

(b) (4)

(b) (4)

Question 4

King R&D proposes to submit SAS[®] datasets only for the two intranasal abuse liability studies. SAS[®] datasets for Study AP-ADF-106 will be included in NDA 20-2080 in the same format as in NDA 22-451. The SAS[®] datasets for Study K234-10-1002 entitled “Randomized, Double-Blind, Active-Controlled Study to Evaluate the Relative Abuse Potential and Safety of Intranasally Administered Crushed Acurox[®] Tablets in Non-Dependent Recreational Opioid Users” will be submitted in accordance with the Guidances for Industry Providing Regulatory Submissions in Electronic Format- Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (June 2008) and Providing Regulatory Submissions in Electronic Format General Considerations (October 2003). Each dataset will be provided as a SAS[®] transport file in accordance with the above referenced guidances. Datasets will be modeled in accordance with the Clinical Data Interchange Standards Consortium (CDISC) Study Data Tabulation Model (SDTM) Implementation Guide: Human Clinical Trials v1.2, which comprises version 3.1.2 of the submission data standards.

- a) Does the Division agree with this proposal for only submitting SAS[®] datasets for the intranasal abuse liability studies? If not, what does the Division propose?*
- b) Does the Division agree with the proposal to submit the SAS dataset for Study AP-ADF-106 in the format in NDA 22-451? If not, what does the Division propose?*

FDA Response:

No to both questions.

(b) (4)

Sponsor Response:

Thank you for the guidance on datasets for Protocol K234-10-1002. King R&D will submit datasets (SAS xpt files) in a similar format to those submitted in NDA 022451.

In addition, King R&D proposes to submit study data from the 2 pharmacokinetic studies as follows:

- AP-ADD-100 (bioequivalence study): pharmacokinetic, adverse event, and demographic data in Excel spreadsheets*
- K234-10-1001 (dose proportionality and food effect study): all data as SAS xpt files in accordance with CDISC SDTM standards, in a similar format to those submitted in NDA 022451*

Is this acceptable?

DISCUSSION: The Sponsor agreed to format the analysis datasets for Study K234-10-1002 as requested for Studies AP-ADF-102 and AP-ADF-111 during the review of NDA 022451. The Sponsor also agreed to submit SAS datasets in accordance with CDISC SDTM Implementation Guide for the pharmacokinetic studies AP-ADD-100 and K234-10-1001.

REGULATORY

Question 5

NDA 22-451 for Acurox[®] with Niacin Tablets included a laboratory study evaluating the volume of various solvents required to draw crushed/dissolved Acurox[®] with Niacin Tablets into a syringe and a laboratory study evaluating the difficulty of extracting oxycodone from Acurox[®] with Niacin Tablets. The only difference between Acurox[®] with Niacin Tablets and Acurox[®] (oxycodone HCl, USP) Tablets is that (b) (4)

The design and conduct of these laboratory studies were reviewed in NDA 22-451, and no issues were identified.

(b) (4)

FDA Response:

No.

(b) (4)

ADDITIONAL COMMENTS:

- **Evaluate the feasibility of preparing a solution for injection and the health risks associated with the injection of that solution.**

Sponsor Response:

No discussion is necessary.

- **Provide toxicological information on the intravenous administration of sodium lauryl sulfate.**

Sponsor Response:

Please clarify what type of information is being requested.

DISCUSSION: The Agency clarified that the sponsor should evaluate the feasibility of preparing samples for I.V. injection, and provide an evaluation of the consequences of I.V. use. If the drug is syringeable and able to be injected, any safety information, particularly with regard to the safety of injecting sodium laurel sulfate, will be useful. The Agency offered to make every effort to review the information on acute toxicity prior to the NDA submission and identify additional follow-up needed.

Question 6

As FDA noted in its presentation at the 22 April 2010 Joint Meeting of the Anesthetic and Life Support Drugs Advisory Committee and the Drug Safety and Risk Management Advisory Committee, the abuse of prescription opioid products is a significant public health concern. FDA has encouraged pharmaceutical companies to develop novel abuse-resistant formulations of opioids because of the therapeutic importance of opioids in relieving moderate to severe pain. Because of the medical need for opioid analgesic products that deter misuse, abuse, and diversion, King R&D will be requesting a Priority Review Classification for this NDA.

Does the Division foresee any reason why a Priority Review Classification would not be granted for the Acurox[®] (oxycodone HCl, USP) Tablets NDA based on inclusion of a unique mixture of functional excipients that may limit or impede oxycodone abuse and misuse?

FDA Response:

No. This application will be granted a priority review classification.

Sponsor Response:

No discussion is necessary.

NONCLINICAL

Question 7

As agreed during discussions with the Division during the development of Acurox[®] with Niacin (oxycodone HCl USP and niacin USP) Tablets, King R&D has not conducted nonclinical studies with the active or inactive ingredients in Acurox[®] (oxycodone HCl, USP) Tablets. Based on feedback from the Division on the Acurox[®] with Niacin Tablets development program (FDA letter from Dr. Rappaport to Acura Pharmaceuticals on 25 October 2005 and the NDA 22-451 Complete Response letter dated 30 June 2009), this course of action was acceptable.

Please confirm that the Division does not require any nonclinical studies in support of the NDA submission and filing acceptance for Acurox[®] (oxycodone HCl, USP) Tablets.

FDA Response:

No new nonclinical studies with the active ingredient are required to support the submission and filing of NDA 202080 for Acurox tablets. Refer to Question 8 regarding nonclinical information which may be necessary to support the safety of the inactive ingredients in Acurox for the NDA submission.

Sponsor Response:

No discussion is necessary.

Question 8

No review issues relating to the excipients used in Acurox[®] with Niacin Tablets were identified in the Complete Response letter for NDA 22-451. Since the amounts of (b) (4) in Acurox (oxycodone HCl, USP) Tablets, and the safety evaluation conducted for NDA 22-451 uncovered no toxicity concerns (Appendix E), King R&D plans to provide a similar safety assessment in NDA 20-2080 for Acurox[®] (oxycodone HCl, USP) Tablets.

Please confirm that this approach is acceptable to the Division. If not, please indicate why not and provide guidance on what would be acceptable.

FDA Response:

A similar safety assessment as used for NDA 022451 may be acceptable to justify the level of excipients in Acurox for the NDA 202080 submission. However, without niacin in the current Acurox formulation to discourage excessive administration, the maximum theoretical daily dose for an opioid-tolerant patient must be considered when determining the acceptable levels of excipients. You will need to research prescribing patterns to determine the maximum theoretical dose for your IR product and provide support that excipient levels are within the FDA Inactive

Ingredient Guide limits at that maximal dose level. Otherwise you will need to support the safety of these excipients according to the following Agency Guidance: Guidance for Industry: Nonclinical Studies for Safety Evaluation of Pharmaceutical Excipients (May 2005), which is available on the CDER web page at the following <http://www.fda.gov/RegulatoryInformation/Guidances/default.htm>

Sponsor Response:

IMS data (National Disease Therapeutic Index) for immediate release oxycodone HCl tablets indicate that 12 tablets (2 tablets q4h) is the maximum daily prescribed dose regardless of dosage strength. Opioid tolerant patients may require fewer tablets of higher strength oxycodone HCl (e.g., 15 mg or 30 mg). Therefore, twelve tablets per day is the anticipated daily tablet load for Acurox[®] Tablets (e.g., 5 mg and 7.5 mg). Does the Agency agree that the above-referenced safety assessment could be based on 12 Acurox[®] Tablets per day?

DISCUSSION: The Agency stated that 200 mg of immediate-release oxycodone HCl is the total daily dose on which to base the safety assessment of the functional excipients of Acurox. The sponsor noted that, at the 2010 Joint Meeting of the Anesthetic and Life Support and Drug Safety and Risk Management Advisory Committees to discuss Acurox with Niacin NDA 22451, the Agency presented data in their Drug Utilization Summary indicating that the daily tablet load of IR oxycodone HCl rarely exceeds 12 tablets. They added that, furthermore, IMS data for IR oxycodone HCl indicate that 12 tablets is the maximum daily prescribed dose regardless of dosage strength. The Agency stated that there is evidence of dosing beyond what one may consider practical. For a safety assessment, the Agency must consider the highest possible prescribed dose. The sponsor noted that dosages of greater than 12 tablets per day may be possible for higher-dose drugs, but believe that, with their highest proposed dose being 7.5 mg, that the vast majority of patients would not exceed 12 tablets per day. They also noted that 200 mgs would be more than 20 tablets of Acurox. The sponsor inquired whether a safety margin analysis using current literature would suffice. The Agency responded that the sponsor may submit this analysis and references for the 12 tablet daily dose of IR oxycodone HCl tablets (see email attachment) and that the Agency will review such data as soon as possible to determine the maximum number of tablets to be evaluated by the Sponsor in a safety assessment for the functional excipients in Acurox[®] Tablets.

CHEMISTRY, MANUFACTURING, AND CONTROLS

Question 9

Three lots of each strength of Acurox[®] (oxycodone HCl, USP) Tablets have been or will be placed on stability according to the protocol outlined in Section 11 of this document. Included in the original NDA submission will be stability data for 6 months of storage at 40°C/75% relative humidity (RH) and 9 months of storage at 25°C/60%RH for product packaged in bottles.

Does the Agency agree to accept for filing an NDA submission with such 9-month real-time stability data and accept an amendment submitted within 3 months before the PDUFA date containing 12 months of real time stability data for storage at 25°C/60%RH ?”

FDA Response:

No, we do not agree.

(b) (4)

Sponsor Response:

No discussion is necessary.

ADDITIONAL COMMENTS:

Provide a list of all manufacturing facilities, in alphabetical order, a statement about their cGMP status, and whether they are ready for inspections at the time of NDA submission. For all manufacturing sites, provide a contact name with telephone and facsimile number at the site. Clearly specify the responsibilities of each facility, and which sites are intended to be primary or alternate sites. Note that facilities with unacceptable cGMP compliance may risk approvability of the NDA.

Dissolution Method:

Provide in your NDA submission the dissolution method report. The report should include the following information;

- **Detailed description of the dissolution method proposed for your product and the developmental parameters (i.e., selection of the equipment/ apparatus, in vitro dissolution media, agitation/rotation speed, pH, assay, sink conditions, etc.) used to select/identify the proposed dissolution method as the most optimal. The conditions used for each test should be clearly specified.**
- **Include the testing conducted to demonstrate the discriminating capability of the selected dissolution test.**
- **Provide the complete dissolution profile data (individual, mean, SD, and profiles) collected during the development/validation of the dissolution test. Also, include the data supporting the robustness of the dissolution test and the validation of the analytical method (precision, accuracy, etc.).**

Dissolution Acceptance Criterion:

Please note that the setting of the dissolution acceptance criterion for your product should be based on the dissolution profile data from clinical and primary stability batches. Therefore, in the NDA, please provide the complete dissolution profile data

supporting the selection of the proposed dissolution acceptance criterion for your product (i.e., specification-sampling time point and specification value).

Sponsor Response:

No discussion is necessary.

Post-Meeting Follow-Up questions received via email on 9/30/10

1. *First, thank you again for agreeing to review information relating to the excipients in Acurox[®] Tablets (NDA 202080). The team has one question at this time about information provided in our briefing package, specifically the safety qualification document for Acurox[®] with Niacin (Appendix E of the preNDA document – see p79). As part of the safety qualification of the excipients used in Acurox with Niacin, our research noted that sodium lauryl sulfate (SLS) once was present in a marketed US product at the maximum potency value of 308.0 mg in an oral capsule [1996 Inactive Ingredient List (Redacted) and last updated March 8, 2001; please see email attachment #2]. King R&D and Acura believe this information is relevant to assessing the safety of Acurox[®] because it is unlikely that the product with the 308.0 mg of SLS was withdrawn from the marketplace due to the presence of SLS. The team would like to know how the Division views the IIG list for products that are no longer marketed.*

FDA Response:

Upon further internal evaluation, no further justification is required for the levels of SLS and microcrystalline cellulose in Acurox without Niacin. However, you must provide a safety assessment for the level of crospovidone in Acurox tablets without Niacin based on a total daily intake of 16 tablets.

2. *Previously the Division had accommodated reviewing stability data during the review cycle (FDA response to Pre-NDA question 9), as long as it is submitted before the final three months of the review period. Does this signify a change in approach by the Division? For this particular NDA, we would be submitting data on one additional time point (12 months) for 6 batches of drug product. Can the Division accommodate submission of data on this one time point two to three months after NDA submission?*

FDA Response:

This is acceptable, provided that the amended data is limited to one time point, and is submitted early in the review cycle.

3. *As promised during the discussion of Question 8, attachment #3 is the latest IMS NDTI data (7/1/09 to 6/30/10) for IR oxycodone IR tablets 5 mg take into consideration before making a final determination of the maximum daily tablet load. This data supports our view that 12 tabs/day for Acurox[®] should be used when analyzing the safety of the inactive excipient load.*

Summary (details in attached excel spreadsheet):

(b) (4)

FDA Response: See response to question 4, below.

4. *Also referenced in the discussion of Question 8 is the Drug Utilization Summary for IR oxycodone (attachment #4, page 13) presented by the Division at the 22 April 2010 Advisory Committee Meeting for Acurox[®] with Niacin Tablets. This data also supports our view that 12 tabs/day for Acurox[®] should be used when analyzing the safety of the inactive excipient load.*

FDA Response: Upon further internal discussion, it would be acceptable to base safety assessments on a total daily intake of Acurox of 16 tablets per day. This takes into account the data that dosing generally does not exceed 12 tablets per day and builds in an additional safety factor.

Attachments:

- 1996 Inactive Ingredients List, update March 8, 2001
- IMS NDTI Data (7/1/09-6/30/10)
- Drug Utilization Summary for IR Oxycodone from April 22, 2010 Advisory Committee Meeting for Acurox with Niacin Tablets

INACTIVE INGREDIENTS FOR CURRENTLY MARKETED DRUG PRODUCTS

INGREDIENT ROUTE/DOSAGE FORM	CAS #	NDA COUNT	LAST NDA	APPROVAL DATE	DIV	POTENCY RANGE
SODIUM HYPOCHLORITE IV(INFUSION); INJECTION	007681529	1				
ORAL; SUSPENSION		1				
SODIUM IODIDE INTRAVENOUS; POWDER, FOR INJECTION SOLUTION	007681825	1				
SODIUM L-CYSTEINATE HYDROCHLORIDE INTRADISCAL; POWDER, FOR INJECTION SOLUTION		1				
SODIUM L-LACTATE EPIDURAL; INJECTION	000867561	1				
IM - IV - SC; INJECTION		1		01/06/76	600	0.18%
IM - IV; INJECTION		2				
INTRACARDIAC; INJECTION		1				
INTRAPERITONEAL; SOLUTION		2		01/06/76	600	0.18%
IV(INFUSION); INJECTION		2				
NERVE BLOCK; INJECTION		1				
SODIUM LACTATE CAUDAL BLOCK; INJECTION	000072173	1				
IM - IV - SC; INJECTION		1				
INTRACARDIAC; INJECTION		1				
INTRAPERITONEAL; SOLUTION		1				
NERVE BLOCK; INJECTION		1				
TOPICAL; SOLUTION		1				
SODIUM LAURETH SULFATE ORAL; CAPSULE COATED	001335724	1				
ORAL; TABLET		1				
TOPICAL; EMULSION, CREAM		1				
SODIUM LAURETH-5 SULFATE TOPICAL; EMULSION, CREAM	009004824	1				
TOPICAL; SHAMPOO		1				
SODIUM LAUROYL SARCOSINATE TOPICAL; LOTION	000137166	1				
SODIUM LAURYL SULFATE BUCCAL/SUBLINGUAL; TABLET	000151213	1				
DENTAL; GEL		1				
DENTAL; PASTE		1				
ORAL; CAPLET		1				
ORAL; CAPSULE		1				
ORAL; CAPSULE, ENTERIC COATED PELLETS		246		12/20/95	520	0.15MG - 308.0MG
ORAL; CAPSULE, HARD GELATIN		1				
ORAL; CAPSULE, SUSTAINED ACTION		5		05/03/95	530	
ORAL; DROPS		17		04/25/95	UNK	0.004MG - 0.6MG
ORAL; GRANULE		1				
ORAL; POWDER, FOR RECONSTITUTION		1		04/28/95	600	0.01% - 0.066%
ORAL; SUSPENSION		11		01/05/78	520	
ORAL; TABLET		317		10/06/95	UNK	0.025MG - 50.0MG
ORAL; TABLET (IMMED./COMP. RELEASE), UNCOATED,		5		01/04/95	600	0.5MG - 5.0MG
ORAL; TABLET, COATED		10		06/23/95	600	0.5MG - 4.0MG
ORAL; TABLET, DELAYED ACTION, ENTERIC COATED		3		05/15/90	600	5.39MG - 8.09MG

INACTIVE INGREDIENTS FOR CURRENTLY MARKETED DRUG PRODUCTS

INGREDIENT ROUTE/DOSAGE FORM	CAS #	NDA COUNT	LAST NDA	APPROVAL DATE	DIV	POTENCY RANGE
SODIUM LAURYL SULFATE	000151213	21		05/30/95	600	0.13MG - 4.5MG
ORAL; TABLET, FILM COATED		5		11/25/91	600	1.76MG - 15.0MG
ORAL; TABLET, SUSTAINED ACTION		3		07/07/80	600	0.01MG - 0.02MG
SUBLINGUAL; TABLET		12		09/28/92	600	0.1% - 2.5%
TOPICAL; EMULSION, CREAM		5		01/24/92	600	0.25%
TOPICAL; LOTION		2		01/24/92	UNK	0.15% - 1.0%
TOPICAL; OINTMENT		1		01/10/91	600	
TOPICAL; SPONGE		2		09/19/85	600	0.3% - 0.333%
TOPICAL; SUSPENSION, SHAMPOO		3				
VAGINAL; EMULSION, CREAM	001847581	1				
SODIUM LAURYL SULFOACETATE	007757746	4		10/13/87	600	0.05% - 0.183%
TOPICAL; SHAMPOO		6		02/26/93	600	0.05% - 0.183%
SODIUM METABISULFITE		5		04/10/89	600	0.1% - 0.15%
CAUDAL BLOCK; INJECTION		37		12/14/95	UNK	0.007% - 0.66%
EPIDURAL; INJECTION		1		11/15/74	600	0.09% - 0.1%
IM - IV; INJECTION		2		06/26/95	600	0.0025% - 0.66%
IM - IV; INJECTION		16		05/18/92	600	0.01% - 0.32%
INHALATION; SOLUTION		1		06/26/95	600	0.024% - 1.0%
INTRACARDIAC; INJECTION		48		02/26/93	600	0.05% - 0.5%
INTRAMUSCULAR; INJECTION		33		03/06/92	UNK	0.01% - 0.3%
INTRAVENOUS; INJECTION		6		08/30/91	600	0.36MG
INTRAVENOUS; SOLUTION		2		12/10/81	600	0.1% - 0.2%
IONTOPHORESIS; SOLUTION		1		01/15/86	600	0.2MG - 4.1MG
IV(INFUSION); INJECTION		3		07/22/82	600	0.3% - 1.0%
NERVE BLOCK; INJECTION		1		05/28/81	UNK	
OPHTHALMIC; SOLUTION		1		02/27/79	600	0.58% - 1.0%
OPHTHALMIC; SUSPENSION		2		02/08/77	UNK	0.25%
ORAL; CAPSULE		1		01/01/83	600	0.29% - 0.58%
ORAL; CONCENTRATE		1		12/24/81	UNK	0.16%
ORAL; SUSPENSION		1		12/24/84	UNK	0.18%
ORAL; SYRUP		1		10/04/82	UNK	
ORAL; TABLET		8		03/31/95	UNK	0.075% - 0.81%
SODIUM PHOSPHATE	007632055	3				
IM - IV; INJECTION		1				
IM - IV; POWDER, FOR INJECTION SOLUTION		1				
IM - IV; SOLUTION, INJECTION		1				
INTRA-ARTICULAR; INJECTION		1				
INTRADERMAL; INJECTION		1				
INTRALESIONAL; INJECTION		1				
INTRAMUSCULAR; INJECTION		1				
INTRAMUSCULAR; POWDER, FOR INJECTION SOLUTION		1				
INTRAVENOUS; INJECTION		1				
INTRAVENOUS; POWDER, FOR INJECTION SOLUTION		1				
IV(INFUSION); INJECTION		1				
IV(INFUSION); POWDER, FOR INJECTION SOLUTION		1				
NASAL; SOLUTION		1				
OPHTHALMIC; SOLUTION		1				

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/s/

LISA E BASHAM
11/05/2010



PNDA 202080

MEETING PRELIMINARY COMMENTS

King Pharmaceuticals
Research and Development, Inc.
4000 CentreGreen Way, Suite 300
Cary, NC 27513

Attention: Catherine Maher, PhD, RAC
Senior Director, Regulatory Affairs

Dear Dr. Maher:

Please refer to your Pre-New Drug Application (PNDA) file for Acurox (oxycodone HCL, USP) Tablets.

We also refer to your June 11, 2010, correspondence, received June 16, 2010, requesting a meeting to discuss the development program to support submission of an NDA.

This material consists of our preliminary responses to your questions and any additional comments in preparation for the discussion at the meeting scheduled for September 27, 2010, between King Pharmaceuticals and the Division of Anesthesia and Analgesia Products. We are sharing this material to promote a collaborative and successful discussion at the meeting. The meeting minutes will reflect agreements, important issues, and any action items discussed during the meeting and may not be identical to these preliminary comments following substantive discussion at the meeting. However, if these answers and comments are clear to you and you determine that further discussion is not required, you have the option of cancelling the meeting (contact the regulatory project manager (RPM)). If you choose to cancel the meeting, this document will represent the official record of the meeting. If you determine that discussion is needed for only some of the original questions, you have the option of reducing the agenda and/or changing the format of the meeting (e.g., from face to face to teleconference). It is important to remember that some meetings, particularly milestone meetings, can be valuable even if the premeeting communications are considered sufficient to answer the questions. Note that if there are any major changes to your development plan, the purpose of the meeting, or the questions based on our preliminary responses, we may not be prepared to discuss or reach agreement on such changes at the meeting although we will try to do so if possible. If any modifications to the development plan or additional questions for which you would like CDER feedback arise before the meeting, contact the RPM to discuss the possibility of including these items for discussion at the meeting.

Clinical

Question 1

In accordance with 21 CFR §314.54(a)(1)(iii), King R&D plans to submit a 505(b)(2) application for an oxycodone HCl immediate-release tablet. Functional excipients in the product may have the potential to deter oxycodone abuse and misuse by providing limits and impediments to intranasal and intravenous administration of the product. The application will reference NDA 21-011 (Roxicodone[®] [oxycodone HCl tablets USP]) and establish safety and efficacy based on bioequivalence to Roxicodone[®].

Because there will be no new studies in the proposed pain patient population, King R&D proposes to review the safety and efficacy of Acurox[®] Tablets within Sections 2.7.3 and 2.7.4 of the NDA. King R&D also proposes to omit from the NDA a formal Integrated Summary of Efficacy and Integrated Summary of Safety.

- a) *Does the Division agree that the safety and efficacy of Acurox[®] Tablets may be established by demonstrating bioequivalence to Roxicodone[®]? If not, what would the Division consider to be an acceptable approach?*

FDA Response:

Yes, as long as the submitted bioequivalence data are scientifically rigorous and demonstrate bioequivalence and no new safety concerns are raised by the formulation. However, if the formulation does raise the possibility of novel risks, e.g. GI obstruction due to a non-dissolving tablet, additional safety data may be required.

- b) *Does the Division agree that reviewing the safety and efficacy of Acurox[®] Tablets within Sections 2.7.3 and 2.7.4 of the NDA is acceptable? If not, what would the Division consider to be an acceptable approach?*

FDA Response:

According to the Guidances for Industry, M4E: The CTD-Efficacy (<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm073290.pdf>) and M4S: The CTD-Safety (<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm073299.pdf>), the Clinical Summary is intended to provide a detailed, factual summarization of all of the clinical information in the CTD. This includes information provided in ICH E3 clinical study reports; information obtained from any meta-analyses or other cross-study analyses for which full reports have been included in Module 5; and postmarketing data for products that have been marketed in other regions. The comparisons and analyses of results across studies provided in this document should focus on factual observations. As long as your plans for the efficacy and safety submission for Acurox tablets complies

with the guidance, the safety and efficacy reviews may be placed in Sections 2.7.3 and 2.7.4.

- c) *Does the Division agree that the Integrated Summaries of Efficacy and Safety may be omitted from the NDA? If not, what would the Division consider to be an acceptable approach?*

FDA Response:

In the absence of novel clinical efficacy studies, an Integrated Summary of Efficacy need not be included in your NDA submission. Describe how you plan to report the safety data from the studies you conduct with Acurox in which patients are not blocked with naltrexone.

Question 2

NDA 20-2080 will include a dose-proportionality / food-effect study (Appendix B) and a bioequivalence study to the reference listed drug Roxicodone[®] (Appendix C). The designs of the pharmacokinetic studies are consistent with the guidance documents for conducting bioequivalence and dose-proportionality studies.

The definitive intranasal abuse liability study for Acurox[®] (oxycodone HCl, USP) Tablets (NDA 20-2080) is Study K234-10-1002 (Appendix A). Study AP-ADF-106 was previously reviewed by FDA (Acurox[®] with Niacin NDA 22-451), was considered adequate by the Division, and will be considered a supportive study for this application. The designs and endpoints of both Study K234-10-1002 and Study AP-ADF-106 are consistent with the January 2010 draft guidance for industry regarding "Assessment of Abuse Potential of Drugs".

(b) (4)

- a) *Does the Division agree that the proposed bioequivalence and dose-proportionality studies are adequate to support an NDA filing, and assuming favorable review, an eventual approval? If not, why not and what modifications to the plan does the Division propose?*

FDA Response:

In theory, the type of information obtained from the proposed studies would be expected to be adequate for filing. However, modify your protocol for food-effect Study K234-10-1001 so that the Roxicodone arm is administered under a *fasting* state. Whether the data are capable of supporting an approval will be a review issue.

- b) *Does the Division agree that the proposed new intranasal abuse liability study (K234-10-1002) is adequate to support an NDA filing, and assuming favorable review, an eventual*

approval

(b) (4)

FDA Response:

In response to question 2(b), your proposed new intranasal abuse liability study, Protocol K234-10-1002, is acceptable for NDA filing. The adequacy of these data, and whether the study can support an approval will be determined during NDA review. Though you have not provided a full protocol for the proposed new intranasal abuse liability study (Protocol K234-10-1002), we have the following comments for you to address:

- Provide justification for using the single dose of 15 mg of oxycodone (3 tablets of Roxicodone) in the prequalification phase and in the second phase of Protocol K234-10-1002.
- Provide information on the total amount of crushed material that would have to be snorted under Treatment B and how this amount compares to the amount of crushed material under Treatment A. Drug treatments need to be equivalent not only on the dose of oxycodone to be snorted but in terms of the total amount of crushed material to be snorted. As proposed, Treatment A requires two crushed Acurox (15 mg of oxycodone, 980 mg of crushed material) whereas Treatment B requires the crushing of three immediate-release Roxicodone tablets (15 mg of oxycodone). Provide information on the average weight of a Roxicodone 5 mg tablet.
- We recommend that you consider exploring the possibility of including a placebo arm in Part II of your abuse liability study (Protocol K234-10-1002). A placebo tablet that represents the new formulation without the active ingredient would contain the same amount of sodium lauryl sulfate as formulated in Acurox but have no oxycodone. We recognize that you will have to manufacture these placebo tablets.
- Provide supportive information to justify the use of the following questionnaires. You have proposed to use the subjective questionnaires entitled "Take Drug Again Assessment (TDAA) and "Global Assessment of Overall Drug Liking." Also, provide supportive information, including any research data, on the validity and reliability of these subjective questionnaires in assessing the abuse liability of Acurox under the experimental parameters you propose.
- We recommend that you evaluate Drug Liking at time points 5, 25 and 30 minutes and 1, 1.5, 2, 2.5 and 3 hours.
- We recommend that you include additional co-primary subjective measures such as Drug Effect and Drug High in your assessment. These measures should be given at the same time points we recommend for evaluating Drug Liking.
- Describe the statistical model you will use in the data analysis of Protocol K234-10-1002. In the synopsis of Protocol K234-10-1002, you state that the study will

be a crossover design study, yet you do not provide the statistical model which you propose to use in the data analysis.

- **There is no need to adjust alpha when conducting the statistical analysis of your abuse liability study (Protocol K234-10-1002).**
- **Our recommendations on the content of Section (b) (4) of the proposed drug label for the product will be provided after all submitted data are reviewed.**

(b) (4)

Question 3

(b) (4)

(b) (4)

(b) (4)

Question 4

King R&D proposes to submit SAS[®] datasets only for the two intranasal abuse liability studies. SAS[®] datasets for Study AP-ADF-106 will be included in NDA 20-2080 in the same format as in NDA 22-451. The SAS[®] datasets for Study K234-10-1002 entitled “Randomized, Double-Blind, Active-Controlled Study to Evaluate the Relative Abuse Potential and Safety of Intranasally Administered Crushed Acurox[®] Tablets in Non-Dependent Recreational Opioid Users” will be submitted in accordance with the Guidances for Industry – Providing Regulatory Submissions in Electronic Format- Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (June 2008) and Providing Regulatory Submissions in Electronic Format – General Considerations (October 2003). Each dataset will be provided as a SAS[®] transport file in accordance with the above referenced guidances. Datasets will be modeled in accordance with the Clinical Data Interchange Standards Consortium (CDISC) Study Data Tabulation Model (SDTM) Implementation Guide: Human Clinical Trials v1.2, which comprises version 3.1.2 of the submission data standards.

- a) *Does the Division agree with this proposal for only submitting SAS[®] datasets for the intranasal abuse liability studies? If not, what does the Division propose?*
- b) *Does the Division agree with the proposal to submit the SAS dataset for Study AP-ADF-106 in the format in NDA 22-451? If not, what does the Division propose?*

FDA Response:**No to both questions.**

(b) (4)

Regulatory

Question 5

NDA 22-451 for Acurox[®] with Niacin Tablets included a laboratory study evaluating the volume of various solvents required to draw crushed/dissolved Acurox[®] with Niacin Tablets into a syringe and a laboratory study evaluating the difficulty of extracting oxycodone from Acurox[®] with Niacin Tablets. The only difference between Acurox[®] with Niacin Tablets and Acurox[®] (oxycodone HCl, USP) Tablets is that

(b) (4)

(b) (4) The design and conduct of these laboratory studies were reviewed in NDA 22-451, and no issues were identified.

(b) (4)

FDA Response:

No.

(b) (4)

ADDITIONAL COMMENTS:

- **Evaluate the feasibility of preparing a solution for injection and the health risks associated with the injection of that solution.**
- **Provide toxicological information on the intravenous administration of sodium lauryl sulfate.**

Question 6

As FDA noted in its presentation at the 22 April 2010 Joint Meeting of the Anesthetic and Life Support Drugs Advisory Committee and the Drug Safety and Risk Management Advisory Committee, the abuse of prescription opioid products is a significant public health concern. FDA has encouraged pharmaceutical companies to develop novel abuse-resistant formulations of opioids because of the therapeutic importance of opioids in relieving moderate to severe pain. Because of the medical need for opioid analgesic products that deter misuse, abuse, and diversion, King R&D will be requesting a Priority Review Classification for this NDA.

Does the Division foresee any reason why a Priority Review Classification would not be granted for the Acurox[®] (oxycodone HCl, USP) Tablets NDA based on inclusion of a unique mixture of functional excipients that may limit or impede oxycodone abuse and misuse?

FDA Response:

No. This application will be granted a priority review classification.

Nonclinical

Question 7

As agreed during discussions with the Division during the development of Acurox[®] with Niacin (oxycodone HCl USP and niacin USP) Tablets, King R&D has not conducted nonclinical studies with the active or inactive ingredients in Acurox[®] (oxycodone HCl, USP) Tablets. Based on feedback from the Division on the Acurox[®] with Niacin Tablets development program (FDA letter from Dr. Rappaport to Acura Pharmaceuticals on 25 October 2005 and the NDA 22-451 Complete Response letter dated 30 June 2009), this course of action was acceptable.

Please confirm that the Division does not require any nonclinical studies in support of the NDA submission and filing acceptance for Acurox[®] (oxycodone HCl, USP) Tablets.

FDA Response:

No new nonclinical studies with the active ingredient are required to support the submission and filing of NDA 202080 for Acurox tablets. Refer to Question 8 regarding nonclinical information which may be necessary to support the safety of the inactive ingredients in Acurox for the NDA submission.

Question 8

No review issues relating to the excipients used in Acurox[®] with Niacin Tablets were identified in the Complete Response letter for NDA 22-451. Since the amounts of (b) (4) in Acurox (oxycodone HCl, USP) Tablets, and the safety evaluation conducted for NDA 22-451 uncovered no toxicity concerns (Appendix E), King R&D plans to provide a similar safety assessment in NDA 20-2080 for Acurox[®] (oxycodone HCl, USP) Tablets.

Please confirm that this approach is acceptable to the Division. If not, please indicate why not and provide guidance on what would be acceptable.

FDA Response:

A similar safety assessment as used for NDA 022451 may be acceptable to justify the level of excipients in Acurox for the NDA 202080 submission. However, without niacin in the current Acurox formulation to discourage excessive administration, the maximum theoretical daily dose for an opioid-tolerant patient must be considered when determining the acceptable levels of excipients. You will need to research prescribing patterns to determine the maximum theoretical dose for your IR product and provide support that excipient levels are within the FDA Inactive Ingredient Guide limits at that maximal dose level. Otherwise you will need to support the safety of these excipients according to the following Agency Guidance: *Guidance for Industry: Nonclinical Studies for Safety Evaluation of Pharmaceutical Excipients (May 2005)*, which is available on the CDER web page at the following <http://www.fda.gov/RegulatoryInformation/Guidances/default.htm>

Chemistry, Manufacturing, and Controls

Question 9

Three lots of each strength of Acurox[®] (oxycodone HCl, USP) Tablets have been or will be placed on stability according to the protocol outlined in Section 11 of this document. Included in the original NDA submission will be stability data for 6 months of storage at 40°C/75% relative humidity (RH) and 9 months of storage at 25°C/60%RH for product packaged in bottles.

Does the Agency agree to accept for filing an NDA submission with such 9-month real-time stability data and accept an amendment submitted within 3 months before the PDUFA date containing 12 months of real time stability data for storage at 25°C/60%RH ?”

FDA Response:

No, we do not agree.

(b) (4)

ADDITIONAL COMMENTS:

Provide a list of all manufacturing facilities, in alphabetical order, a statement about their cGMP status, and whether they are ready for inspections at the time of NDA submission. For all manufacturing sites, provide a contact name with telephone and facsimile number at the site. Clearly specify the responsibilities of each facility, and which sites are intended to be primary or alternate sites. Note that facilities with unacceptable cGMP compliance may risk approvability of the NDA.

Dissolution Method:

Provide in your NDA submission the dissolution method report. The report should include the following information;

- **Detailed description of the dissolution method proposed for your product and the developmental parameters (i.e., selection of the equipment/ apparatus, in vitro dissolution media, agitation/rotation speed, pH, assay, sink conditions, etc.) used to select/identify the proposed dissolution method as the most optimal. The conditions used for each test should be clearly specified.**
- **Include the testing conducted to demonstrate the discriminating capability of the selected dissolution test.**
- **Provide the complete dissolution profile data (individual, mean, SD, and profiles) collected during the development/validation of the dissolution test. Also, include the data supporting the robustness of the dissolution test and the validation of the analytical method (precision, accuracy, etc.).**

Dissolution Acceptance Criterion:

Please note that the setting of the dissolution acceptance criterion for your product should be based on the dissolution profile data from clinical and primary stability batches. Therefore, in the NDA, please provide the complete dissolution profile data supporting the selection of the proposed dissolution acceptance criterion for your product (i.e., specification-sampling time point and specification value).

You should provide me with a hardcopy or electronic version of any materials (i.e., slides or handouts) to be presented and/or discussed at the meeting.

If you have any questions, call me at (301) 796-1175.

Sincerely,

{See appended electronic signature page}

Lisa E. Basham, M.S.
Senior Regulatory Health Project Manager
Division of Anesthesia and Analgesia Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

LISA E BASHAM
09/23/2010



NDA 202080

MEETING REQUEST GRANTED

King Pharmaceuticals
Research and Development, Inc.
4000 CentreGreen Way, Suite 300
Cary, NC 27513

Attention: Catherine Maher, PhD, RAC
Senior Director, Regulatory affairs

Dear Ms. Maher:

Please refer to your Pre-New Drug Application (PNDA) file for Acurox (oxycodone HCL) Tablets.

We also refer to your June 11, 2010, correspondence requesting a Pre-NDA meeting to discuss the requirements for an NDA submission for Acurox (without Niacin). Based on the statement of purpose, objectives, and proposed agenda, we consider the meeting a type B meeting.

The meeting is scheduled as follows:

Date: September 27, 2010
Time: 2:30-3:30
Location: 10903 New Hampshire Avenue
White Oak Building 22, Conference Room: 1421
Silver Spring, Maryland 20903

CDER participants:

Bob A. Rappaport, MD	Division Director
Sharon Hertz, MD	Deputy Division Director
Michael Klein, PhD	Director, Controlled Substance Staff (CSS)
Robert Shibuya, MD	Clinical Team Leader
Adam Wasserman, PhD	Supervisory Pharmacologist
Prasad Peri, PhD	Branch Chief, ONDQA
Suresh Doddapaneni, PhD	Team Leader, Clinical Pharmacology
Dionne Price, PhD	Team Leader, Statistics
Silvia Calderon, PhD	Team Leader, CSS
Parinda Jani	Chief, Project Management Staff
Igor Cerny, PhD	Clinical Reviewer
Jay Chang, PhD	Preclinical Reviewer
Danae Christodoulou, PhD	Pharmaceutical Assessment Lead
David Lee, PhD	Clinical Pharmacology Reviewer

Katherine Meaker, PhD	Statistics Reviewer
Jovita Randall Thompson, PhD	Reviewer, CSS
Corinne Moody	Policy Analyst; CSS
Lisa Basham, MS	Senior Regulatory Health Project Manager

Please e-mail me any updates to your attendees at lisa.basham@fda.hhs.gov, at least one week prior to the meeting. For each foreign visitor, complete and email me the enclosed Foreign Visitor Data Request Form, at least two weeks prior to the meeting. A foreign visitor is defined as any non-U.S. citizen or dual citizen who does not have a valid U.S. Federal Government Agency issued Security Identification Access Badge. If we do not receive the above requested information in a timely manner, attendees may be denied access.

Please have all attendees bring valid photo identification and allow 15-30 minutes to complete security clearance. Upon arrival at FDA, provide the guards with either of the following numbers to request an escort to the conference room: Lisa Basham at 301-796-1175 or Cynthia Olsen, the Division Secretary, at 301-796-2280.

We acknowledge receipt of your meeting background package with your June 11, 2010 meeting request.

If you have any questions, call me at (301) 796-1175.

Sincerely,

{See appended electronic signature page}

Lisa Basham, MS
Senior Regulatory Health Project Manager
Division of Anesthesia and Analgesia Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

ENCLOSURE: Foreign Visitor Data Request Form

FOREIGN VISITOR DATA REQUEST FORM

VISITORS FULL NAME (First, Middle, Last)	
GENDER	
COUNTRY OF ORIGIN/CITZENSHIP	
DATE OF BIRTH (MM/DD/YYYY)	
PLACE OF BIRTH (city and country)	
PASSPORT NUMBER COUNTRY THAT ISSUED PASSPORT ISSUANCE DATE: EXPIRATION DATE:	
VISITOR ORGANIZATION/EMPLOYER	
MEETING START DATE AND TIME	
MEETING ENDING DATE AND TIME	
PURPOSE OF MEETING	
BUILDING(S) & ROOM NUMBER(S) TO BE VISITED	
WILL CRITICAL INFRASTRUCTURE AND/OR FDA LABORATORIES BE VISITED?	
HOSTING OFFICIAL (name, title, office/bldg, room number, and phone number)	
ESCORT INFORMATION (If different from Hosting Official)	

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-202080	GI-1	KING PHARMACEUTICA LS RESEARCH DEVELOPMENT INC	Acurox (oxycodone hydrochloride, USP) Tablets

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/s/

LISA E BASHAM
08/16/2010

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION		REQUEST FOR CONSULTATION																							
TO (Office/Division): Contolled Substance Staff Attention: Corinne Moody & Michael Klein			FROM (Name, Office/Division, and Phone Number of Requestor): Lisa Basham; DAARP																						
DATE July 28, 2010	IND NO.	NDA NO. 202080 (presubmission)	TYPE OF DOCUMENT Pre-NDA Meeting Pkg	DATE OF DOCUMENT June 11, 2010; received June 14, 2010																					
NAME OF DRUG Acurox (WITHOUT Niacin))		PRIORITY CONSIDERATION standard	CLASSIFICATION OF DRUG opioid analgesic	DESIRED COMPLETION DATE Internal Meeting: 9/14/10 Industry Meeting 9/27/10																					
NAME OF FIRM: King Pharmaceuticals																									
REASON FOR REQUEST I. GENERAL																									
<table border="0"> <tr> <td>☐ NEW PROTOCOL</td> <td>☒ PRE-NDA MEETING</td> <td>☐ RESPONSE TO DEFICIENCY LETTER</td> </tr> <tr> <td>☐ PROGRESS REPORT</td> <td>☐ END-OF-PHASE 2a MEETING</td> <td>☐ FINAL PRINTED LABELING</td> </tr> <tr> <td>☐ NEW CORRESPONDENCE</td> <td>☐ END-OF-PHASE 2 MEETING</td> <td>☐ LABELING REVISION</td> </tr> <tr> <td>☐ DRUG ADVERTISING</td> <td>☐ RESUBMISSION</td> <td>☐ ORIGINAL NEW CORRESPONDENCE</td> </tr> <tr> <td>☐ ADVERSE REACTION REPORT</td> <td>☐ SAFETY / EFFICACY</td> <td>☐ FORMULATIVE REVIEW</td> </tr> <tr> <td>☐ MANUFACTURING CHANGE / ADDITION</td> <td>☐ PAPER NDA</td> <td>☐ OTHER (SPECIFY BELOW):</td> </tr> <tr> <td>☐ MEETING PLANNED BY</td> <td>☐ CONTROL SUPPLEMENT</td> <td></td> </tr> </table>					☐ NEW PROTOCOL	☒ PRE-NDA MEETING	☐ RESPONSE TO DEFICIENCY LETTER	☐ PROGRESS REPORT	☐ END-OF-PHASE 2a MEETING	☐ FINAL PRINTED LABELING	☐ NEW CORRESPONDENCE	☐ END-OF-PHASE 2 MEETING	☐ LABELING REVISION	☐ DRUG ADVERTISING	☐ RESUBMISSION	☐ ORIGINAL NEW CORRESPONDENCE	☐ ADVERSE REACTION REPORT	☐ SAFETY / EFFICACY	☐ FORMULATIVE REVIEW	☐ MANUFACTURING CHANGE / ADDITION	☐ PAPER NDA	☐ OTHER (SPECIFY BELOW):	☐ MEETING PLANNED BY	☐ CONTROL SUPPLEMENT	
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COMMENTS / SPECIAL INSTRUCTIONS: King Pharmaceuticals is planning to submit an NDA for Acurox (without Niacin). From here on, the name Acurox will refer to this product (without Niacin), and the older product, for which we had an AC meeting (April 22, 2010) and issued a CR letter, will be referred to as Acurox with Niacin (NDA 022451). Aside from the removal of niacin from the formulation, the formulation remains unchanged (b) (4). Please look over the meeting package (submitted with the meeting request) and evaluate, from a CSS perspective, their plans for the NDA. Please let me know ASAP whether you will be consulting CSS stats and whether I should add reviewers from that group to the meetings, as well as whether Jovita Randall-Thompson and Silvia Calderon will also review this product as they did Acurox with Niacin. As you'll recall, Ling Chen was the CSS stats reviewer for Acurox without Niacin (NDA 022451). I will forward the meeting package ASAP. They sent it directly to me via email and I have placed it on the common drive at the following link: <\\fdfs01\ode2\Lisa Basham\NDA 202080 (ACUROX_King)\PreNDA Meeting\Pre-NDA Meeting package> Feel free to call/email with any questions! Thank you!!																									
SIGNATURE OF REQUESTOR Lisa Basham; RPM; DAARP (ext. 61175)			METHOD OF DELIVERY (Check one) ☒ DARRTS ☐ EMAIL ☐ MAIL ☐ HAND																						
PRINTED NAME AND SIGNATURE OF RECEIVER			PRINTED NAME AND SIGNATURE OF DELIVERER																						

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-202080	GI-1	KING PHARMACEUTICA LS RESEARCH DEVELOPMENT INC	Acurox (oxycodone hydrochloride, USP) Tablets

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/s/

LISA E BASHAM
06/28/2010

For Internal Use Only

Meeting Request Granted Form**

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

Complete the information below and check form into DFS.

Application Type	☐ P-IND IND X presubmission NDA
Application Number	NDA 202080
DATE Sponsor informed of meeting granted	June 21, 2010
Sponsor was informed of: - date/time & meeting location - expected FDA attendees - meeting briefing package due date - number of copies	☐ X Yes ☐ No ☐ X Yes ☐ No ☐ N/A: already submitted ☐ X Yes ☐ No Other: please indicate: pre-meeting on 9/14/10 Industry meeting on 9/27/10
Project Manager	Lisa Basham

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

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-202080	GI-1	KING PHARMACEUTICA LS RESEARCH DEVELOPMENT INC	Acurox (oxycodone hydrochloride, USP) Tablets

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/s/

LISA E BASHAM
06/23/2010