

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
202080Orig1s000

CHEMISTRY REVIEW(S)

NDA 202080

Oxecta (Oxycodone Hydrochloride) Tablets

Summary of the Basis for the Recommended Action from Chemistry, Manufacturing, and Controls

Applicant: King Pharmaceuticals R &D, Inc
4000 CenterGreen Way, Suite 300
Cary, NC 27513

Indication:

Management of moderate to severe pain where the use of an opioid analgesic is appropriate.

Presentation: The drug product (tablets 5 mg and 7.5 mg) are packaged in HDPE bottles with (b) (4) child resistant closure.

EER Status:	Recommendations:	Acceptable
Consults:	EA -	Categorical exclusion provided
	CDRH-	N/A
	Statistics -	N/A
	Methods Validation -	Not recommended
	DMETS-	Acceptable
	Biopharm-	N/A
	Microbiology -	Satisfactory
	Pharm/toxicology -	Satisfactory

Original Submission: 17-Dec-2010

Post-Approval CMC Agreements: None

Background:

This is a priority NDA (6 months) for oxycodone tablets with claimed (b) (4) formulation. NDA in electronic format with electronic labeling provided in SPL format. This NDA is filed as a 505(b) 2 application.

Reference is made to the CMC review by Dr. Julia Pinto entered into DARRTS on 5/24 where she had asked the sponsor to provide updated specifications for dissolution and (b) (4). This request was sent to the sponsor on 5/24 and updated specifications along with stability data were provided to the Agency in an amendment dated 5/31/2011. The limits for (b) (4) were revised to NMT

(b) (4) and dissolution acceptance criterion was revised to Q=(b) (4) in 15 minutes as requested by the Agency.

The proposed limits meet the Agency's expectations and the issue is now considered resolved.

In addition, the proprietary name "Oxecta" was found acceptable by the Agency.

Conclusion: The drug product is satisfactory.

Overall Conclusion:

From a CMC perspective, the application is recommended for approval.

Prasad Peri, Ph.D.
Branch Chief,
DPA III/ONDQA

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/s/

PRASAD PERI

06/14/2011

Close out last CMC Amendment with updated specs for dissolutiona

(b) (4)

NDA 202080

TradeName (Oxycodone Hydrochloride) Tablets

Summary of the Basis for the Recommended Action from Chemistry, Manufacturing, and Controls

Applicant: King Pharmaceuticals R &D, Inc
4000 CenterGreen Way, Suite 300
Cary, NC 27513

Indication:

Management of moderate to severe pain where the use of an opioid analgesic is appropriate.

Presentation: The drug product (tablets 5 mg and 7.5 mg) are packaged in HDPE bottles with (b) (4) child resistant closure.

EER Status:	Recommendations:	Acceptable
Consults:	EA -	Categorical exclusion provided
	CDRH-	N/A
	Statistics -	N/A
	Methods Validation -	Not recommended
	DMETS-	Acceptable
	Biopharm-	N/A
	Microbiology -	Satisfactory
	Pharm/toxicology -	Satisfactory

Original Submission: 17-Dec-2010

Post-Approval CMC Agreements: None

Background:

This is a priority NDA (6 months) for oxycodone tablets with claimed (b) (4) formulation. NDA in electronic format with electronic labeling provided in SPL format. This NDA is filed as a 505(b) 2 application.

Drug Substance:

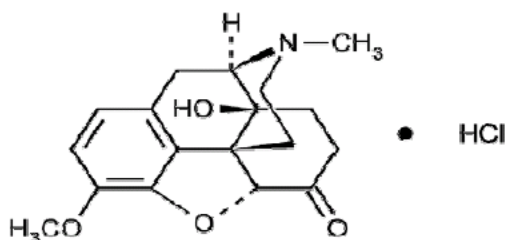
The drug substance is made by (b) (4) and is referenced to DMF (b) (4). This DMF was found adequate in a review dated Jan-4-2011. The drug substance is a white crystalline powder with a melting point between 220°C. Release specifications for Oxycodone HCl by the supplier comply with the USP monograph and include appearance, identification, specific rotation, water content, residue on ignition,

chloride, assay, impurities, organic volatile impurities, assay, related substances (specified and unspecified), residual solvents, particle size, and X-ray, diffraction. Oxycodone HCl is packaged in (b) (4). The retest date is (b) (4) months from the manufacturing date.

Chemical name, structure, molecular weight and molecular formula are provided below.

Chemical Name: Morphinan-6-one, 4,5-epoxy-14-hydroxy-3-methoxy-17-methylhydrochloride, (5□)

Figure 3.2.S.1.2.1 Structural Formula Oxycodone Hydrochloride USP



Molecular Formula
 $C_{18}H_{21}NO_4 \cdot HCl$

Molecular Weight
351.82

Conclusion: The drug substance is satisfactory.

Drug Product:

Tradename (oxycodone HCl) Tablets, are round white, convex tablets that are manufactured in 5 mg and 7.5 mg strengths. The two tablets are distinguished with the strengths being debossed on the tablets. The application references New Drug Application (NDA) 021011 for Roxicodone® (Oxycodone Hydrochloride Tablets USP), and establishes safety and efficacy based on bioequivalence with Roxicodone® Tablets, the reference listed drug (RLD).

The functional excipients used in the preparation of the, oxycodone tablets include

(b) (4)
All are well established, and all but one (b) (4), are currently recognized food additives or Generally Recognized as Safe substances. The functional excipients are intended to introduce limits or impediments to two common methods of opioid analgesic product abuse: (1) intravenous injection of oxycodone extracted from dissolved tablets, and (2) nasal snorting of crushed tablets.

To deter possible intravenous abuse of oxycodone HCl tablets, (b) (4)

(b) (4) These potential abuse deterrent (Aversion Technology) properties have been evaluated by Controlled Substance Staff (CSS).

The drug product is packaged in HDPE bottles with child resistant closures. The recommended storage temperature is 25° C (77° F) with excursions permitted from 15° to 30°C (59°-86°F) and an expiry of 24 months.

The manufacturing process of the drug product uses (b) (4). The product is manufactured by King Pharmaceuticals, Cary, NC. Commercial batches of tablets are about (b) (4) Tablets.

The proposed specifications for the drug product are description, identity, assay, content uniformity, dissolution, impurities, (b) (4), and friability.

The stability data provided in the application support a shelf life of 24 months for the drug product.

CMC issues that are still pending: An update to drug product specifications is being sent by the applicant to reflect the agreed upon dissolution and (b) (4) acceptance criteria.

Conclusion: The drug product is satisfactory.

Overall Conclusion:

From a CMC perspective, the application is recommended for approval.

Prasad Peri, Ph.D.
Branch Chief,
DPA III/ONDQA

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/s/

PRASAD PERI
05/28/2011
recommend Approval

NDA 202080

Tradename (Oxycodone HCl) Tablets

King Pharmaceuticals R&D, Inc.

Julia C. Pinto, Ph.D.

Office of New Drug Quality Assessment, Division III

Division of Anesthesia, Analgesia and Addiction Products

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Chemistry Review Data Sheet

Chemistry Review Sheet

1. NDA 202080
2. REVIEW #: 1
3. REVIEW DATE: April 03, 2011
4. REVIEWER: Julia C. Pinto, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous DocumentsDocument Date

6. SUBMISSIONS BEING REVIEWED:

Submission(s) ReviewedDocument Date

Original NDA Submission

12-17-2010

Amendment

01-26-2011

Amendment

03-09-2011

Amendment

03-14-2011

Amendment

04-01-2011

Amendment

04-08-2011

7. NAME AND ADDRESS OF APPLICANT:

Name: King Pharmaceuticals R &D, Inc
Address: 4000 CenterGreen Way, Suite 300
Cary, NC 27513

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: Tradename under review
- b) Non-Proprietary Name: oxycodone HCl, USP
- c) Code Name/# (ONDC only): N/A
- d) Chem. Type/Submission Priority (ONDC only):
 - Chem. Type: 3
 - Submission Priority: S

Product Drug Code and Name:

- a) Proprietary Name: Tradename under review
- b) Non-Proprietary Name (USAN): oxycodone HCl, USP
- c) Code name/#(ONDQA only):
- d) Chem. Type/Submission Priority (ONDQA only):
 - Chem. Type: Type 2
 - Submission Priority: S

Chemistry Review Data Sheet

9. LEGAL BASIS FOR SUBMISSION: FD&C ACT 505(b)(2)

10. PHARMACOLOGICAL CATEGORY:
Treatment of Moderate to Severe Chronic Pain

11. DOSAGE FORM: Oral tablets

12. STRENGTH/POTENCY: 5mg and 7.5mg

13. ROUTE OF ADMINISTRATION: Orally

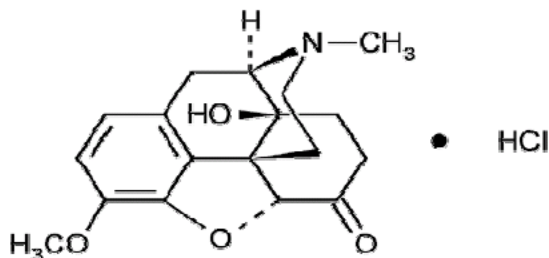
14. Rx/OTC DISPENSED: Rx OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):
 SPOTS product – Form Completed

Not a SPOTS product

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

Figure 3.2.S.1.2-1 Structural Formula Oxycodone Hydrochloride USP



Molecular Formula
 $C_{17}H_{21}NO_4 \cdot HCl$

Molecular Weight
351.82

Chemical name: 4,5 α -Epoxy-14-hydroxy-3-methoxy-17-methylmorphinan-6-one hydrochloride

Or Morphinan-6-one, 4,5-epoxy-14-hydroxy-3-methoxy-17-methyl-, hydrochloride, (5 α)

Other Chemical names: 7,8-Dihydro-14-hydroxycodeinone hydrochloride

14-hydroxydihydrocodeinone hydrochloride

6-Oxo-14-hydroxy-7,8-dihydrocodeine hydrochloride

Dihydro-14-hydroxycodeinone hydrochloride

Dihydrohydroxycodeinone hydrochloride

Dihydrone

Oxycodone

Oxymorphone 3-methyl ether

Chemistry Review Data Sheet

17. RELATED/SUPPORTED DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	Code ¹	Status	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	II		(b) (4)	3	Adequate	May 20, 2009	Reviewed by J. Pinto, Ph.D.
	III		4				
	III		3	Adequate	March 2009	Reviewed by Bogdan Kurtyka, Ph.D.	
	III		4				
	III		3	Adequate	January 2011	Reviewed by George Lunn, Ph.D.	

¹ Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 – Type 1 DMF

3 – Reviewed previously and no revision since last review

4 – Sufficient information in application

5 – Authority to reference not granted

6 – DMF not available

7 – Other (explain under "Comments")

² Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	71895	Acurox with Niacin

18. Status

ONDQA:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	NA		
EES	Adequate	February 17,	Office of Compliance



CHEMISTRY REVIEW



Chemistry Review Data Sheet

Pharm/Tox	Adequate	Rev #1	J. Chang, Ph.D.
Biopharm	Adequate	Rev #1	H. Mahayni, Ph.D.
LNC	NA		
Methods Validation	Adequate	Rev #1	J. Pinto, Ph.D.
DMET/DDMAC			
EA	Categorical exclusion satisfactory	Dec. 17, 2010	J. Pinto, Ph.D.

Executive Summary Section

The Chemistry Review for NDA 202080**The Executive Summary****I. Recommendations****A. Recommendation and Conclusion on Approvability**

Sufficient CMC information, to assure the identity, strength, purity, and quality of the drug product, is provided in this NDA submission. The Office of Compliance has issued an "Acceptable" overall recommendation for all facilities involved in production of the product. The Sponsor has agreed to modified drug product specifications but has not updated the tables to reflect the agreed upon changes. This NDA is recommended as approvable pending the submission of the updated drug product specification tables.

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

No Post Approval commitments are required.

II. Summary of Chemistry Assessment**A. Description of Drug Substance and Drug Product:**

Oxycodone HCl Tablets are an orally administered, immediate-release (IR) composition comprising oxycodone HCl, USP as the drug substance which is referenced to DMF (b) (4). The indication for the drug product is for the management of moderate to severe pain when the use of an opioid analgesic is appropriate. Oxycodone (oxycodone HCl, USP) Tablets, as proposed for marketing, are manufactured in strengths of 5 mg and 7.5 mg oxycodone. The application references New Drug Application (NDA) 021011 for Roxicodone® (Oxycodone Hydrochloride Tablets USP), and establishes safety and efficacy based on bioequivalence with Roxicodone® Tablets, the reference listed drug (RLD).

The functional excipients used in the preparation of the, Oxycodone Tablets drug product include (b) (4)

All are well established, and all but one (b) (4) are currently recognized food additives or Generally Recognized as Safe substances. The functional excipients are intended to introduce limits or impediments to two common methods of opioid analgesic product abuse: (1) intravenous injection of oxycodone extracted from dissolved tablets, and (2) nasal snorting of crushed tablets. To deter possible intravenous abuse of Oxycodone HCl Tablets, (b) (4)

Executive Summary Section

The drug product is stored in 100 count HDPE bottles with child proof closures. The recommended storage temperature is 25° C (77° F) with excursions permitted from 15° to 30°C (59°-86°F) and an expiry of 24 months.

The name proposed for the drug product was “Acurox” tablets. However upon review by DDMAC the name was turned down and a new one is currently under review. Therefore the drug product is referred to as Oxycodone tablets within this review.

B. Description of How the drug is intended to be used:

Oxycodone Tablets is an opioid analgesic indicated only for the management of moderate to severe pain when the use of an opioid analgesic is appropriate. Each tablet of 5mg and 7.5mg, is an immediate release oral dosage form with “abuse deterrent” components.

C. Basis for Approvability Recommendation

The Office of Compliance has issued an “Acceptable” overall recommendation for all facilities. Sufficient CMC information, to assure the identity, strength, purity, and quality of the drug product, is provided in this NDA submission. Sufficient CMC information, to assure the identity, strength, purity, and quality of the drug product, is provided in this NDA submission. The Office of Compliance has issued an “Acceptable” overall recommendation for all facilities involved in production of the product. However, while the Sponsor has agreed to the modified drug product specifications the tables have not been updated to reflect the agreed upon changes. This NDA is recommended as approvable pending the submission of the updated drug product specification tables.

III. Administrative**A. Reviewer’s Signature****B. Endorsement Block**

Chemistry Reviewer: Julia Pinto, Ph.D.

Pharmaceutical Assessment Leader: Danae Christodoulou, Ph.D.

Project Manager: Lisa Basham, RPh.

Branch Chief: Prasad Peri, Ph.D.

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/s/

JULIA C PINTO
05/24/2011

PRASAD PERI
05/24/2011
I concur

Initial Quality Assessment
Division III, Branch VIII
Office of New Drug Quality Assessment
Division of Anesthesia, Analgesia and Addiction Products

OND Division:	Anesthesia, Analgesia and Addiction	
NDA:	202-080	
Type:	3P	
Applicant:	King Pharmaceuticals	
Stamp date:	December 17, 2010	
PDUFA Date:	June 17, 2011 (applicant requested P status)	
Trademark:	ACUROX [®]	
Established Name:	Oxycodone HCl	
Dosage Form:	Tablets (5mg, 7.5mg)	
Route of Administration:	Oral	
Indication:	Management of moderate to severe chronic pain	
Pharmaceutical Assessment Lead:	Danae D. Christodoulou, Ph.D.	
	YES	NO
ONDQA Fileability:	<u>√</u>	___
Comments for 74-Day Letter:	<u>√</u>	___

Summary, Critical Issues and Comments

A. Summary

The application is submitted as a 505(b)(2) with reference to the approved drug, Roxicodone® tablets, NDA 21-011. The applicant requested a priority review (6-month review clock), based on the claim for (b) (4) of this product, namely nasal snorting of crushed tablets and IV injection of crushed or dissolved tablets.

The drug product Acurox® is a (b) (4) tablet formulation of the active ingredient, oxycodone HCl, with the excipients used previously in NDA 22-451 (Acurox® with niacin). The applicant cited the proprietary Aversion® technology, developed by Acura Pharmaceuticals, which uses one or two therapeutic compounds and inactive ingredients which function to discourage misuse or abuse of oxycodone. Acurox® tablets are claimed (b) (4)

The initial Acurox® formulation, contained oxycodone HCl and niacin, and was submitted by Acura in NDA 22-451 in 2008, but was not approved by the Agency. Niacin was assessed not to improve on “dislike” of the drug and presented safety issues. The current product is a reformulation without niacin, (b) (4) Oxycodone HCl is sourced from (b) (4) (b) (4) specification of NMT (b) (4). The applicant cross-references NDA 22-324, Remoxy®, which they currently own, to support safety of certain excipients. The drug product will be marketed in 150 cc white HDPE bottles, containing 100 tablets, (b) (4), and a child resistant (b) (4) closure.

B. Review, Comments and Recommendations

Drug Substance

The drug substances manufacturing process is referenced to Drug Master File:

Oxycodone HCl

DMF (b) (4)

Sections pertaining to characterization, general properties, process validation, reference standards and stability data are also referenced to the (b) (4) DMF. Purity profiles, specifications and batch analysis data are included in the NDA.

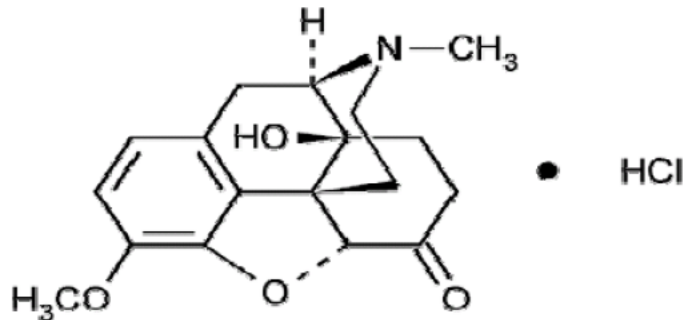
Molecular Structure, Chemical Name, Molecular Formula and Molecular Weight

• 7,8-dihydro-14-hydroxycodeinone hydrochloride

Molecular formula: C₁₈H₂₁NO₄•HCl

Molecular Weight: 351.82 g/mol

Figure 3.2.S.1.2-1 Structural Formula Oxycodone Hydrochloride USP



Molecular Formula
C₁₈H₂₁NO₄•HCl

Molecular Weight
351.82

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DMF (b) (4) has been reviewed and deemed adequate for ANDAs. The impact of critical physical attributes e.g., drug substance solubility, polymorphism, particle size distribution, etc., on dissolution of Acurox® should be assessed.

A summary of (b) (4) API batches in the NDA is provided in the Table below:

Table 3.2.S.4.4-1 Oxycodone Hydrochloride USP Lot Usage

OxyHCl* Batch Number (b) (4)	OxyHCl* Batch Number (King)	Date of Drug Substance Manufacture	Drug Product Lot Number	Lot Use	Drug Product Strength
08EW537	55246	05/13/08	57216	Stability Lot	5mg
08EW537	55246	05/13/08	57217	Stability Lot	5mg
08EW537	55246	05/13/08	57218	Stability Lot	5mg
08EW537	55246	05/13/08	57219	Stability Lot	7.5mg
08EW537	55246	05/13/08	57220	Stability Lot	7.5mg
08EW537	55246	05/13/08	57221	Stability Lot	7.5mg
07JW373-4	53598	06/15/07	Not applicable		
08CW501	53599	03/26/08	Not applicable	-	-

* OxyHCl = Oxycodone Hydrochloride

Batch analysis results are provided. (b) (4)

The suitability of analytical methods (b) (4) and validation should be assessed as per ICHQ2B.

Specifications of Oxycodone HCl (b) (4) (release specifications)

Stability of Oxycodone HCl

Stability data are referenced to the DMF. Retest date for oxycodone HCl is (b) (4) months.

Drug product

Acurox® tablets is an immediate-release oral dosage form of oxycodone HCl with “abuse deterrent” components. (b) (4)
(b) (4) as in NDA 22-451. The applicant stated that the two strengths of tablets meet the definition of *proportionally similar* as described in the FDA “Guidance for Industry: Bioavailability and Bioequivalence Studies for Orally Administered Drug Products – General Considerations.” Quantitative composition of Acurox® tablets is provided below.

Drug Product Composition

Component	Quality Standard	Function	IIG Levels	Strength			
				5 mg		7.5 mg	
				Quantity per Unit mg/tab	%	Quantity per Unit mg/tab	%
Oxycodone Hydrochloride USP	USP	Active pharmaceutical ingredient	Not applicable	5*	(b) (4)	7.5*	(b) (4)
Polyethylene Oxide NF (b) (4)	NF	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)
Sodium Lauryl Sulfate NF (b) (4)	NF						
Microcrystalline Cellulose NF (b) (4)	NF						
Crospovidone NF (b) (4)	NF						
Colloidal Silicon (b) (4)	NF						
Magnesium Stearate NF (b) (4)	NF						

* Actual quantity will be corrected for potency.

There are no novel excipients in Acurox® tablets. However, three inactive ingredients, microcrystalline cellulose NF, sodium lauryl sulfate NF and crospovidone NF, exceed levels in the FDA’s Inactive Ingredient Guide. As discussed during the pre-NDA meeting for NDA 22-451, on August 13, 2008, the applicant has provided a safety evaluation of these ingredients. In addition, as requested in the Pre-NDA meeting for the current NDA, held on September 27, 2010, a safety assessment for the level of Crospovidone NF, based upon a total daily intake of 16 tablets, is included in the NDA. The suitability of the levels of these excipients in the formulation should be assessed in consultation with the Toxicology Division. Excipient compendial specifications, and additional physical attributes such as particle size distribution, (b) (4) should be assessed for impact on drug product manufacturability, quality and performance.

Manufacturing Process:

King Pharmaceuticals, Inc., in Bristol, TN is the proposed commercial manufacturing, primary release, stability testing and packaging site for the drug product. The proposed production scale batches are (b) (4)

The manufacturing process and in-process controls have been described in sufficient detail;

(b) (4)

Container Closure:

Four packaging DMFs (Type III) are supporting the container closure system, i.e., 100-count 150 cc white HDPE bottles, (b) (4)

Since this is a solid oral dosage form, review of the packaging DMFs is not required. (b) (4)

Supporting stability data for the hold time of bulk product (b) (4) should be requested and assessed.

Stability:

Stability testing of Acurox® tablets is performed under standard ICH conditions at 25°C/60% RH, and 40°C/75% RH. Stability protocols are provided. Tests performed are: appearance, assay, (b) (4) dissolution and related compounds. Hardness testing was performed as well, but not included in the

product shelf-life specifications. Longest stability data provided is 12 months under normal storage, and 6 months under accelerated storage. Stability protocols are provided in the NDA. The proposed shelf-life of 24 months was based on real time data from the King batches and statistical analysis evaluation using [REDACTED] (b) (4). The limiting attribute was [REDACTED] (b) (4) with estimated shelf life of 24 months. The expiration dating proposed should be assessed as per ICH Q1E. Photostability testing has not been reported and should be requested.

Labeling: Provided in M1 (draft container labels and annotated package insert). Labeling information on the container labels and packaging insert should be assessed with respect to CMC requirements. Draft labeling text in SPL format has not been provided and should be requested.

C. Critical issues for review and recommendation

During assessment of the CMC information provided in this NDA, the primary reviewer should consider addressing issues identified above and other related ones, summarized here, for their impact on drug product quality and performance throughout the product's life-cycle:

1. The drug substance DMF (b) (4) (oxycodone HCl, (b) (4) should be assessed. The latest review is fairly recent (1/14/2011). The drug substance(s) specifications should be assessed as per ICH Q3A. Any structural alerts for mutagenicity: (b) (4), should be assessed in consultation with the Toxicology division.
2. Impact of physical properties and suitability of the proposed specifications (PSD, polymorph) of the drug substance oxycodone HCl, e.g., solubility, polymorphism, particle size distribution, etc., on the manufacturability of formulation and drug product performance should be assessed. The applicant does not test (b) (4) as acceptance or regulatory specification and relies on the (b) (4) release testing. (b) (4)
3. The amounts and specifications of compendial excipients in the formulation. The safety of excipients that exceed levels in the IIG should be assessed in consultation with the Toxicology division. Evaluation of the suitability of pharmacopeial specifications of excipients for drug product manufacturability, quality and performance. Note that additional physical attributes of excipients have not been discussed.
4. (b) (4)
5. Hold times of the bulk drug product (b) (4) and supporting stability data.
6. The dissolution method should be evaluated for discriminatory ability and robustness, e.g., by supporting data on developmental formulations and validation data. Note that the applicant (b) (4) the dissolution specification based on stability data.
7. Specifications and proposed limits for identified and unidentified impurities/degradants in the drug product. Note that the proposed limit for (b) (4) exceeds ICH Q3B limits. Justification should be based on ICH Q3B guidelines. Specifications and qualification levels should be assessed in consultation with the Toxicology Division.
8. The justification for not proposing microbial controls for the drug product should be assessed.
9. Evaluation of supporting CMC data, e.g., in the Pharmaceutical Development Report for drug product quality and performance as "abuse deterrent".
10. The proposed expiration dating of 24 months and the applicant's statistical analysis should be assessed as per ICH Q1E.
11. Photostability testing has not been reported and should be requested.

D. Comments for the 74-day Letter:

- Provide photostability testing for the drug product, as per ICH Q3B.

E. Recommendation for fileability: The NDA is fileable based on pre-NDA agreements and sufficient number of registration (6) batches and long term data (up to 12 months). The NDA is suitable for evaluation and assessment based on FDA and ICH guidelines for submitting CMC information for New Drug Applications.

Recommendation for Team Review: The NDA is not recommended for team review, since it is a 505(b)(2) application, the drug substances are not NMEs, the formulation does not include novel excipients and the manufacturing process for the drug product does not present complexity, e.g., novel delivery or device issues. However, biopharmaceutics evaluation of the dissolution method has been requested.

Consults

Specifications for impurities should be evaluated in consultation with the Toxicology reviewer.

No statistical consult was deemed necessary. A microbiology consult may be requested by the primary reviewer upon evaluation of the applicant's justification.

<u>Danae D Christodoulou, Ph.D.</u>	<u>2/2/2011</u>
CMC Lead	Date

<u>Prasad Peri, Ph.D.</u>	<u>2/2/2011</u>
Branch VIII Chief (Acting)	Date

NDA Number: 202-080

Supplement Number and Type:
3P

Established/Proper Name:
Acurox®/oxycodone HCl tablets

Applicant: King
Pharmaceuticals

Letter Date: 12/17/10

Stamp Date: 12/17/10

The following parameters are necessary in order to initiate a full review, i.e., complete enough to review but may have deficiencies. On **initial** overview of the NDA application for filing:

A. GENERAL				
	Parameter	Yes	No	Comment
1.	Is the CMC section organized adequately?	X		
2.	Is the CMC section indexed and paginated (including all PDF files) adequately?	X		
3.	Are all the pages in the CMC section legible?	X		
4.	Has all information requested during the IND phase, and at the pre-NDA meetings been included?	X		

B. FACILITIES*				
	Parameter	Yes	No	Comment
5.	Is a single, comprehensive list of all involved facilities available in one location in the application?	X		(M3)
6.	For a naturally-derived API only, are the facilities responsible for critical intermediate or crude API manufacturing, or performing upstream steps, specified in the application? If not, has a justification been provided for this omission? This question is not applicable for synthesized API.			NA

7.	<p>Are drug substance manufacturing sites identified on FDA Form 356h or associated continuation sheet? For each site, does the application list:</p> <ul style="list-style-type: none"> • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable) 	X		
8.	<p>Are drug product manufacturing sites are identified on FDA Form 356h or associated continuation sheet. For each site, does the application list:</p> <ul style="list-style-type: none"> • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable) 	X		Clarifications and communications with OC.
9.	<p>Are additional manufacturing, packaging and control/testing laboratory sites are identified on FDA Form 356h or associated continuation sheet. For each site, does the application list:</p> <ul style="list-style-type: none"> • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable) 		X	Clarifications and communications with OC.

10.	Is a statement provided that all facilities are ready for GMP inspection at the time of submission?		X	
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* If any information regarding the facilities is omitted, this should be addressed ASAP with the applicant and can be a *potential* filing issue or a *potential* review issue.

C. ENVIRONMENTAL ASSESMENT				
	Parameter	Yes	No	Comment
11.	Has an environmental assessment report or categorical exclusion been provided?	X		

D. DRUG SUBSTANCE/ACTIVE PHARMACEUTICAL INGREDIENT (DS/API)				
	Parameter	Yes	No	Comment
12.	Does the section contain a description of the DS manufacturing process?	X		Referenced to DMF (b) (4)
13.	Does the section contain identification and controls of critical steps and intermediates of the DS?	X		Referenced to DMF (b) (4)
14.	Does the section contain information regarding the characterization of the DS?	X		Referenced to DMF (b) (4)
15.	Does the section contain controls for the DS?	X		Referenced to DMF (b) (4)
16.	Has stability data and analysis been provided for the drug substance?			Referenced to DMF (b) (4)
17.	Does the application contain Quality by Design (QbD) information regarding the DS?		X	
18.	Does the application contain Process Analytical Technology (PAT) information regarding the DS?		X	

E. DRUG PRODUCT (DP)				
	Parameter	Yes	No	Comment
19.	Is there a description of manufacturing process and methods for DP production through finishing, including formulation, filling, labeling and packaging?	X		
20.	Does the section contain identification and controls of critical steps and intermediates of the DP, including analytical procedures and method validation reports for assay and related substances if applicable?	X		
21.	Is there a batch production record and a proposed master batch record?	X		
22.	Has an investigational formulations section been provided? Is there adequate linkage between the investigational product and the proposed marketed product?	X		
23.	Have any biowaivers been requested?		X	
24.	Does the section contain description of to-be-marketed container/closure system and presentations)?	X		
25.	Does the section contain controls of the final drug product?	X		
26.	Has stability data and analysis been provided to support the requested expiration date?	X		
27.	Does the application contain Quality by Design (QbD) information regarding the DP?		X	
28.	Does the application contain Process Analytical Technology (PAT) information regarding the DP?		X	

F. METHODS VALIDATION (MV)				
	Parameter	Yes	No	Comment
29.	Is there a methods validation package?	X		

G. MICROBIOLOGY				
	Parameter	Yes	No	Comment
30.	If appropriate, is a separate microbiological section included assuring sterility of the drug product?		X	NA (Solid Oral Dosage Form)

H. MASTER FILES (DMF/MAF)				
	Parameter	Yes	No	Comment
31.	Is information for critical DMF references (i.e., for drug substance and important packaging components for non-solid-oral drug products) complete?	X		

DMF # (b) (4)	TYPE	HOLDER	ITEM REFERENCED	LOA DATE	COMMENTS
	2	Noramco	Oxycodone HCl	6/4/2010	API
	3		(b) (4)	5/12/2010	
	3			6/10/2010	(b) (4)
	3			6/15/2010	
	3			5/12/2010	(b) (4)

I. LABELING				
	Parameter	Yes	No	Comment
32.	Has the draft package insert been provided?	X		
33.	Have the immediate container and carton labels been provided?	X		

J. FILING CONCLUSION				
	Parameter	Yes	No	Comment
34.	IS THE PRODUCT QUALITY SECTION OF THE APPLICATION FILEABLE?			Based on pre-NDA agreements and sufficient body of data
35.	If the NDA is not fileable from the product quality perspective, state the reasons and provide filing comments to be sent to the Applicant.	X		See above
36.	Are there any potential review issues to be forwarded to the Applicant for the 74-day letter?		X	See above

{See appended electronic signature page}

Name of

PAL: Danae Christodoulou 2/2/11

Division III

Office of New Drug Quality Assessment

Date

{See appended electronic signature page}

Name of

Branch Chief (Acting): Prasad Peri

Division III

Office of New Drug Quality Assessment

Date

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

/s/

DANAE D CHRISTODOULOU
02/08/2011
Initial Quality Assessment

PRASAD PERI
02/08/2011
I concur