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APPLICATION NUMBER:

202080Orig1s000

MEDICAL REVIEW(S)

CLINICAL REVIEW

Application Type	NDA
Application Number(s)	202080
Priority or Standard	Priority
Submit Date(s)	December 17, 2010
Received Date(s)	December 17, 2010
PDUFA Goal Date	June 17, 2011
Division / Office	DAAAP/OND
Reviewer Name(s)	Frank Pucino, PharmD, MPH
Review Completion Date	May 24, 2011
Established Name	Oxycodone HCl
(Proposed) Trade Name	Trade Name pending (oxycodone HCl, USP)
Therapeutic Class	Opioid analgesic
Applicant	King Pharmaceuticals Research and Development
Formulation(s)	Immediate-release 5 mg and 7.5 mg tablets
Dosing Regimen	Every 4-6 hours as needed
Indication(s)	Relief of moderate to severe pain
Intended Population(s)	Adults for whom an opioid analgesic is appropriate

Template Version: March 6, 2009

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

I recommend that Tradename (oxycodone HCl, USP) Tablets be approved for the indication: "the management of moderate to severe pain where the use of an opioid analgesic is appropriate."

As a 505(b)(2) application, the findings of safety and efficacy for Tradename can be established by relying on the Agency's prior finding for Roxicodone (oral immediate-release oxycodone HCl tablets), which was approved for the same indication in 2000 as bioequivalence was established for tradename and Roxicodone. A review of the medical literature included in this submission and the TRADENAME (oxycodone HCl, USP) Tablets safety data provided from the biopharmaceutics and abuse liability studies did not reveal any unexpected adverse events that could be attributed to the study drug when administered by the intended route of administration. Tradename appears to be associated with the typical opioid-related adverse events.

1.2 Risk Benefit Assessment

Based on the known efficacy and safety of Roxicodone, as well as the known chemistry, pharmacology and toxicology profiles of this and other oxycodone HCl products, the benefits of Tradename (oxycodone HCl, USP) Tablets outweigh the risks for the intended use and patient population.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

As an immediate-release oxycodone HCl tablet formulation, a REMS will not be required for approval of this NDA.

1.4 Recommendations for Postmarket Requirements and Commitments

The Applicant requested a waiver of the Pediatric Assessment required under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c) (Section 7.6.3), stating that the product:

- Does not represent a meaningful therapeutic benefit over existing opioid therapies for pediatric patients (PREA §505B(a)(4)(A)(iii)(I).

- Is unlikely to be used in a substantial number of pediatric patients (PREA §505B(a)(4)(A)(iii)(II)).

Since Tradename did not include a new active ingredient, new indication, new dosage form, new dosing regimen, or new route of administration, pediatric assessment will not be required for this product.

1.5 Other Phase 4 Requests

There are no additional Phase 4 requests.

2 Introduction and Regulatory Background

2.1 Product Information

Opiate receptors were first identified in the early 1970's followed by the discovery of the first endogenous opiate-like substance, enkephalin. The existence of mu, delta and kappa sub-types of opiate receptors was also confirmed in the 1970's. Oxycodone, along with most of the clinically used opioids, is relatively selective for the mu receptor and it is through the mu receptor that it exerts its clinical effects. In support of this 505(b)(2) application, the Applicant has submitted findings from two clinical pharmacology studies (AP-ADD100 and K234-10-1001). Study AP-ADD100 demonstrated bioequivalence to another immediate-release oxycodone tablet (Roxicodone; NDA 21011), the listed drug that the Applicant relies upon for safety and efficacy. Study K234-10-1001 provides pharmacokinetic information on dose-proportionality and food effect. No new clinical efficacy or safety studies and no new nonclinical studies were performed in support of this application. The Applicant cites the pharmacokinetic data, published, peer-reviewed literature, and the Agency's previous findings of efficacy and safety for Roxicodone (approved in 2000). For immediate-release oxycodone hydrochloride products, such as the subjects of these two NDAs, there is clear evidence of efficacy and safety based on the Agency's prior findings from other products. Therefore, the focus of this type of 505(b)(2) application is the chemistry, manufacturing and controls information, and the individual products' pharmacokinetic characteristics and how these relate to the products referenced in the NDA.

2.2 Tables of Currently Available Treatments for Proposed Indications

The following eight immediate-release tablet opioids are approved for the treatment of "moderate to severe pain" in the U.S.: hydromorphone, levorphanol, meperidine, methadone, morphine, oxycodone, oxymorphone, and tapentadol. In addition, two immediate-release tablet opioids are approved in the U.S. for the treatment of "moderate to moderately severe pain": hydrocodone (only as an opioid analgesic combination) and tramadol. Several of these agents are also approved for the treatment of pain in combination with either acetaminophen, aspirin, or ibuprofen. Table 1 includes the commercially available oxycodone HCl formulations approved in the United States.

2.3 Availability of Proposed Active Ingredient in the United States

Table 1: Currently Marketed Single Entity Oxycodone HCl Products

Trade Name	NDA #	Approval Date	Major Labeling Changes	Pre- and Postmarketing Safety Concerns
Oxycodone HCl Capsule; Oral	200534	October 20, 2010	None	None
Oxycodone HCl Solution; Oral	200535	October 20, 2010	None	None
Oxycodone HCl Tablet; Oral	ANDAs (Various)	Various	None	None
Oxycontin® Tablet, ER; Oral	022272	April 5, 2010	REMS approved 04/2010 and last modified 11/2010 to provide for changes to the Package Insert and Medication Guide to include language on proper administration of the product to minimize the risk of choking.	Postmarketing reports of choking, gagging, regurgitation, tablets stuck in the throat and difficulty swallowing the tablet.
Roxycodone® Tablet; Oral	021011	August 31, 2000	None	None

Source: Modified from Drugs@FDA (http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm); and the Orange Book (http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm).
Abbreviations: ANDA, Abbreviated New Drug Application; ER, extended-release; HCl, hydrochloride; REMS, Risk Evaluation and Mitigation Strategy.

2.4 Important Safety Issues with Consideration to Related Drugs

All opioids have well established adverse event profiles that include sedation, nausea, vomiting, pruritus, and constipation. The most serious adverse reactions associated with all opioids include respiratory depression (potentially leading to apnea or respiratory arrest), circulatory depression, hypotension and shock. Addiction, abuse, tolerance and physical dependence are other recognized risks associated with this class of drugs. Because of the high potential of abuse and misuse of opioids, and experience with products such as OxyContin and methadone, the Agency now requires REMS be part of the approval package for extended-release formulations and long acting opioids.

All opioid labels have warnings regarding co-ingestion with alcohol, based on the additive effects of the two substances; however stronger warnings and/or non-approval of a drug could result from findings of significant dose dumping. For an immediate-release oxycodone formulation, dose dumping is not a concern.

Tradename tablets contain the excipient polyethylene oxide (PEO), which has been associated with reports of choking, gagging, regurgitation, tablets stuck in the throat and difficulty swallowing the tablet for an extended release product. (b) (4) However, as a result, it should not be administered via nasogastric, gastric or other feeding tubes due to concerns for obstruction of feeding tubes. Although the Applicant does not need to rely on other PEO-containing products for approval of Tradename, this potential safety concern should be taken into consideration for all products that contain this excipient.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

The Applicant previously submitted and NDA for a similar formulation of immediate-release oxycodone HCl that also contained niacin (Acurox with Niacin; NDA 22451). This combination product was originally developed under IND 71,895, and submitted to the Agency on March 7, 2005. For details regarding the regulatory history of this product, please refer to the Clinical Review by Dr. Igor Cerny (May 29, 2009).

(b) (4)

Advisory Committee Meeting (April 22, 2010)
A joint meeting of the Anesthetic and Life Support Drugs Advisory Committee and the Drug Safety and Risk Management Committee was convened to address the following:

1. The results of the studies assessing the effects of niacin on drug liking were presented. The committee was asked to discuss what constitutes an adequate degree of abuse-deterrence to warrant description in the product's label and the potential implications regarding overstating these effects.

2. The committee was asked to discuss whether the alteration of the physicochemical properties of an immediate-release opioid is able to act as a deterrent given that oral dosing without manipulation may be sufficient to satisfy the needs of an abuser and whether the presence of niacin in the formulation is a potentially effective deterrent given that ingesting the product with food or aspirin/NSAIDS will minimize the flushing effect.

3. The results of clinical trials in patients with pain were presented with attention given to the adverse events reported. The committee was asked to discuss whether it is acceptable to risk adverse reactions such as flushing in patients in order to produce a product with properties targeted at deterring misuse and abuse.

In a 19 to 1 vote, the committee determined that the abuse-deterrent properties of Acurox with Niacin tablets were not adequate to support approval of this combination product.

Tradename (NDA 202080)

Pre-NDA Meeting (September 27, 2010)
At this meeting, the Applicant was informed that safety and efficacy could be established by demonstrating bioequivalence to Roxicodone tablets using the to-be-marketed formulation of Tradename. Abuse liability studies would be reviewed as safety studies, and assessment of nasal abuse liability, comparing 2 x 7.5 mg crushed Acurox tablets with 3 x 5 mg crushed Roxicodone tablets, would be based on the "totality of data" including both primary and secondary endpoints. Extrapolation of the nasal snorting study and extraction/syringe data generated with Acurox with Niacin tablets (NDA 22451) to Tradename (NDA 202080) would not be acceptable. However, data generated during the formulation development of NDA 22451 would provide important supporting information for the pharmaceutical development of their product. In addition, no new nonclinical studies with Tradename would be required to support the submission and filing of this NDA. However, the Applicant would need to provide a safety assessment for crospovidone assuming a maximum intake of 16 Tradename tablets/day. A safety assessment for other inactive ingredients in the Tradename formulation would not be required.

2.6 Other Relevant Background Information

No other relevant background information was provided with this submission.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

The Division of Scientific Investigations (DSI) was consulted to inspect the clinical and the analytical sites used for the pivotal bioequivalency study (AP-ADD-100) of this NDA. The reports of these inspections are pending at this writing.

3.2 Compliance with Good Clinical Practices

At this writing, the inspection report from DSI is pending.

3.3 Financial Disclosures

The Applicant submitted Form FDA 3454. There were no disclosed financial arrangements with clinical investigators that required further consideration.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

The proposed commercial manufacturer of the oxycodone drug substance is (b) (4) The overall manufacturer of Tradename will be King Pharmaceutical, (b) (4) (b) (4) The oxycodone HCl Drug Master File (DMF (b) (4) was previously reviewed and determined to be adequate by Dr. Julia Pinto (May 20, 2009). The excipients used in the preparation of Tradename include microcrystalline cellulose, polyethylene oxide (PEO), sodium lauryl sulfate, and crospovidone. All are well established, and all but one (PEO), are currently recognized food additives or Generally Recognized as Safe substances.

Several of the excipients are intended to introduce abuse deterrent properties into the tablet formulation. *In vitro* laboratory experiments demonstrate that attempting to dissolve Tradename in common solvents results in the formation of a viscous mixture that impedes or limits the ability to extract oxycodone from the dissolved tablet or to draw the mixture into a syringe in a volume suitable for potential intravenous injection (Studies PR-381 and PR-382). For detailed discussion regarding these two protocols, please refer to Dr. Jovita Randall-Thompson's review. Three impurities were identified in the drug substance specifications: (b) (4) During the review cycle, the Applicant lowered the specification for the (b) (4) A slight increase of (b) (4) was observed from stability data through the 12 month time point. No other degradation or downward trends were observed.

The CMC reviewer felt that the Applicant provided sufficient CMC information, to assure the identity, strength, purity, and quality of the drug product. Further, the Office of Compliance issued an "Acceptable" overall recommendation for all facilities involved in production of the product.

During the review cycle, the Applicant also (b) (4) the dissolution specification of oxycodone HCl to NLT (b) (4) (Q) in 15 minutes. The proposed dissolution method was

considered acceptable by the Office of New Drugs Quality Assessment. The Applicant conducted a bioequivalence (BE) study using the higher strength tablet (7.5 mg). Since the 5 mg and 7.5 mg tablets are dose proportional, the Agency was asked to waive the regulatory requirement to conduct an *in-vivo* study on the lower strength of 5 mg given that the BE study on the higher strength was found acceptable.

The CMC and Biopharmaceutics quality assessment review teams have recommended approval for this product. Please refer to Dr. Julia Pinto's review for a complete discussion of CMC issues. Dr. Houda Mahayni performed the biopharmaceutics review. Please refer to her review for detailed information regarding the quality assessment of Tradename.

4.2 Clinical Microbiology

Based on three batches of drug product, the (b) (4) levels were below that necessary for proliferation of organisms and therefore microbial growth is not supported. Thus, microbial testing of Tradename was not required.

4.3 Preclinical Pharmacology/Toxicology

No new nonclinical studies were required or submitted with this NDA application. The submission included an assessment of several excipients contained in the Tradename formulation that exceeded the maximum quantities listed in the Inactive Ingredients Guide (IIG) when considering the maximum recommended daily dose (MRDD) of 12 Tradename tablets/day. At the Pre-NDA meeting, the Applicant was informed that the maximum theoretical daily dose for an opioid-tolerant patient must be considered when determining the acceptable levels of excipients. Further, based in part on prescribing data from a Drug Utilization Summary presented 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 22-451), the Division determined that the safety assessment should be based on 16 Tradename tablets per day. The Applicant appeared to provide adequate reassurances, including a written justification that cited literature from the public domain, for the inactive ingredients of crospovidone, sodium lauryl sulfate, and microcrystalline cellulose. Oxycodone hydrochloride USP manufactured by (b) (4) (b) (4) meets the (b) (4) limit of (b) (4) (b) (4) requested by FDA and is proposed for use in the manufacture of the commercial drug product. Based on 16 tablets per day, the potential maximum total daily intake (TDI) of (b) (4) (b) (4), which is considered acceptable by the Pharmacology/Toxicology review team. Although the proposed limit for (b) (4) (b) (4) exceeds the ICH Q3B threshold of NMT 0.2%, the Applicant submitted a Letter of Authorization to cross-reference safety findings for this impurity from NDA 22324 (REMOXY; oxycodone HCl), which the Applicant owns.

The Pharmacology/Toxicology review team recommended Approval for this product. A review of the preclinical development of Tradename has been performed by Dr. Jay Chang, and those interested in further detail are referred to that review.

4.4 Clinical Pharmacology

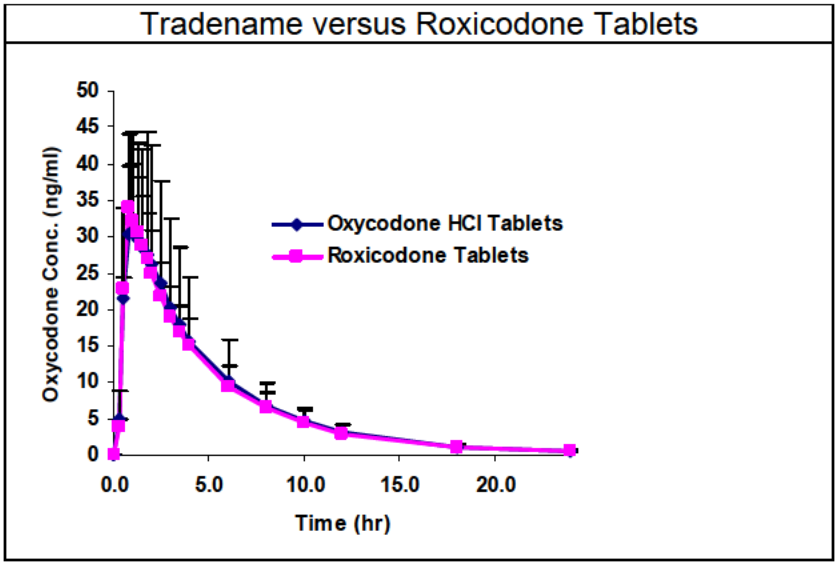
Please refer to the Clinical Pharmacology review by Dr. Suresh Naraharisetti for detailed discussion of the clinical pharmacokinetics of Tradename.

The following two pharmacokinetic studies were submitted with this NDA:

1. **AP-ADD-100:** This study served as the pivotal bioequivalence pharmacokinetic study with the referenced drug (Roxicodone) in healthy volunteers (see Table 2 below). This three-period, three-treatment crossover study design compared the PK of Tradename (2 x 7.5 mg) with Roxicodone Tablets (15 mg) and of Tradename (2 x 7.5 mg) with Acurox tablets (oxycodone/niacin, 2 x 7.5 mg/30 mg) (N22451).

   This study demonstrated bioequivalence between Tradename and Roxicodone tablets (Figure 1), with the ratios of geometric means and the 90% confidence intervals for C_{max} and systemic exposure (AUC_{last} and AUC_{inf}) within the accepted 80% to 125% limits.

Figure 1: Mean oxycodone concentration-time profiles after administration of Tradename and Roxicodone Tablets



Source: Modified from Dr. Suresh Naraharisetti's Clinical Pharmacology Review, Figure 2.5.1a, p.11 of 56.

2. **K234-10-1001:** This study assessed the dose-proportionality and food-effect of Tradename in healthy volunteers (see Table 2 below). The study design included a 5-period, 5-way crossover design that evaluated dose-proportionality between

5, 10 and 15 mg Tradename; the food effect on Tradename; and the food effect comparison between Tradename and Roxicodone tablets under fed conditions.

Administration of Tradename with a high-fat meal increased the AUC by 21%, decreased the C_{max} by 14% and delayed the T_{max} from 1.25 hours to 3.0 hours . A similar food effect was also observed with Acurox, and previously reported with oxycodone solution. Compared to Roxicodone, Tradename resulted in similar AUCs, a 17% decrease in C_{max} and a delayed T_{max} (3 hours versus 1.3 hours) under fed conditions. The Clinical Pharmacology review team felt that the observed food effect for Tradename does not warrant any dosing adjustments.

The Clinical Pharmacology review team felt that NDA 202080 is acceptable provided that the DSI inspection finds the data from pivotal bioequivalence study (AP-ADD-100) are acceptable and agreement can be reached between the Applicant and the Agency regarding the language in the package insert.

4.4.1 Mechanism of Action

Oxycodone HCl is a semi-synthetic narcotic analgesic with multiple actions qualitatively similar to those of morphine. The most prominent of these pharmacologic properties involve the central nervous system and organs composed of smooth muscle. Although it can interact with other opioid receptors at higher doses, oxycodone is a pure opioid agonist with relative selectivity for the mu receptor. The principal therapeutic action of oxycodone is analgesia. As with all pure opioid agonists, there is no ceiling effect to analgesia, such as is seen with partial agonists or non-opioid analgesics.

4.4.2 Pharmacodynamics

As a 505(b)(2) application, pharmacodynamic studies were not required.

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

A listing of the Phase 1 biopharmaceutics and pharmacology clinical studies submitted with this application are shown in Table 2 and
Table 3 below, respectively.

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Table 2: Summary of Biopharmaceutics Studies

Study ID	Study Objectives	Study Design/Regimen	Treatments[a]	Mean Parameters (±SD)					Subjects (enrolled/completed) Subjects (gender M/F) Mean age (range) Race
Single-dose Pharmacokinetic Studies in Healthy Subjects				C_{max} (ng/mL)	T_{max} (h)[b] Median (range)	AUC_{last} (ng/mL x h)	AUC_{inf} (ng/mL x h)	$T_{½}$ (h)	
AP-ADD-100 Amendment 1 Amendment 2 (additional analysis)	**Pivotal bioequivalence**: Compare the PK characteristics of oxycodone in the test product, Acurox® (oxycodone HCl, USP) Tablets, with 2 reference products, Acurox® with Niacin Tablets and Roxicodone® (Oxycodone HCl Tablets USP)	Single-dose, open-label, randomized, 3-period, 3-treatment crossover study in 40 healthy adult subjects 3 separate single-dose administrations of study drug separated by 7-day washout periods	2 x 7.5 mg Acurox® Tablets	34.5 ± 7.83	1.18 ± 0.57 1.00 (0.50-2.50)	165.8 ± 36.46	168.9 ± 37.53	3.94±0.63	40/37 40 (26/14) 36 years (19-55)
			1 x 15 mg Roxicodone®	36.5 ± 8.78	0.98 ± 0.40 0.75 (0.50-2.00)	160.3 ± 40.85	163.4 ± 42.08	3.99±0.79	22 White 14 Black 3 American Indian/Alaska Native 1 Native Hawaiian or other Pacific Islander
K234-10-1001	**Dose proportionality and food effect:** Determine the dose proportionality and the effects of food on the bioavailability of oxycodone in Acurox® Tablets; assess the relative bioavailability of Acurox® and Roxicodone® in the fed state	Single-dose, open-label, randomized, 5-period, 5-treatment crossover study in 35 healthy adult subjects 5 separate single-dose administrations of study drug separated by 7-day washout periods	1 x 5 mg Acurox® Tablet	10.0 ± 3.08	1.40 ± 0.67 1.25 (0.75-3.50)	45.38 ± 12.65	47.40 ± 13.07	3.24±0.61	35/28 35 (19/16) 33 years (18-55)
			2 x 5 mg Acurox® Tablets	19.9 ± 5.64	1.21 ± 0.37 1.25 (0.50-2.03)	93.19 ± 25.46	95.50 ± 25.64	3.38±0.60	24 White 9 Black 1 American Indian/Alaska Native 1 Asian
			2 x 7.5 mg Acurox® Tablets	32.9 ± 9.09	1.23 ± 0.58 1.25 (0.50-3.00)	152.9 ± 41.11	155.4 ± 41.57	3.57±0.58	
			2 x 7.5 mg Acurox® Tablets (fed)	28.5 ± 7.37	3.04 ± 1.14 3.00 (1.25-6.00)	178.8 ± 44.58	184.1 ± 45.02	3.71±0.55	
			1 x 15 mg Roxicodone® (fed)	37.7 ± 11.3	1.33 ± 0.89 1.00 (0.50-4.00)	186.3 ± 50.13	189.2 ± 51.23	3.74±0.59	

Source: 2.7.1 Summary of Biopharmaceutic Studies & Associated Analytical Methods, Table 2, p.10 of 22.
Note: Acurox was the previous proposed proprietary Name.

Table 3: Summary of the Abuse Liability Study

Study ID	Number of Study Centers Location(s)	Study Start Enrollment Status, Date, Total Enrollment/ Enrollment Goal	Design Control Type	Study & Control Drugs Dose, Route & Regimen	Study Objectives	Number of Subjects by Arm Entered/ Completed	Gender (M/F) Median Age (Range)	Diagnosis Inclusion Criteria	Primary Endpoints
K234-10-1002	1 Toronto, Ontario, Canada	13 Sep 2010 30 Sep 2010 40 subjects randomized to Treatment Phase	Phase 1, randomized, double-blind, single-dose, active-controlled, 2-way crossover study	Drug Discrimination: Single dose (3 × 5 mg = 15 mg) of crushed and intranasally administered Roxicodone® (Oxycodone Hydrochloride Tablets USP) and equivalent volume of placebo powder. Treatment Phase: Single dose (2 × 7.5 mg = 15 mg) of crushed and intranasally administered Acurox® Tablets vs. single dose (3 × 5 mg = 15 mg) of crushed and intranasally administered Roxicodone® Tablets.	Relative abuse liability and safety	Treatment Phase: 40/40	32/8 33.5 years (19-55 years)	Recreational opioid users not dependent on opioids (≥10 uses in last 12 months and ≥1 use in last 12 weeks) Experience with intranasal opioid drug use (≥3 × in last 12 months)	Drug Liking assessed by 100-point, bipolar VAS Take Drug Again (VAS) Global Assessment of Overall Drug Liking (VAS)

Source: 2.7.2 Summary of Clinical Pharmacology Studies, Table 1, p.7 of 16

5.2 Review Strategy

For this 505(b)(2) application, the Applicant is relying on the Agency's prior findings of safety and efficacy using pharmacokinetic data (a pivotal bioequivalence study and a dose-proportionality/food effect study) as a bridge, published, peer-reviewed literature (ten efficacy trials with oxycodone HCl.)

5.3 Discussion of Individual Studies/Clinical Trials

The Applicant did not submit any new clinical studies with the current NDA submission.

6 Review of Efficacy

Efficacy Summary

For the previous formulation (Acurox with Niacin; NDA 22451), the Applicant submitted a single adequate and well-controlled study (Study AP-ADF-105) in support of their 505(b)(2) application for "the relief of moderate to severe pain where the use of an immediate-release, orally administered, opioid analgesic tablet is appropriate." Please (b) (4)

No new adequate and well-controlled studies were conducted in support of the current application. Instead, the Applicant cites pharmacokinetic data, published, peer-reviewed literature, and the Agency's previous findings of efficacy for Roxicodone. For immediate-release oxycodone hydrochloride products there is clear evidence of efficacy based on the Agency's prior findings from other products.

6.1 Indication

For this immediate-release oral formulation of oxycodone HCl, the applicant seeks an indication of "the management of moderate to severe pain where the use of an (b) (4) opioid analgesic is appropriate." They propose to rely on the pharmacokinetic data, published, peer-reviewed literature, and the Agency's previous findings of efficacy for Roxicodone in support of this application.

6.1.1 Methods

This section is not applicable.

6.1.2 Demographics

This section is not applicable.

6.1.3 Subject Disposition

This section is not applicable.

6.1.4 Analysis of Primary Endpoint(s)

This section is not applicable.

6.1.5 Analysis of Secondary Endpoints(s)

This section is not applicable.

6.1.6 Other Endpoints

This section is not applicable.

6.1.7 Subpopulations

This section is not applicable.

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

This section is not applicable.

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

This section is not applicable.

6.1.10 Additional Efficacy Issues/Analyses

This section is not applicable.

7 Review of Safety

Safety Summary

For the safety evaluation plan of Tradename, the Applicant cites pharmacokinetic data (for establishing reliance on referenced drug, Roxicodone), published, peer-reviewed literature, and the Agency's previous findings of safety for Roxicodone. Additionally, the Applicant evaluated the relative abuse potential and safety of the product by intranasal administration, and assessed the safety of excipients contained in the formulation at doses up to 16 tablets per day. As with efficacy there is clear evidence of safety for immediate-release oxycodone HCl products based on the Agency's prior findings from other products.

7.1 Methods

This section is not applicable.

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

No new clinical studies were conducted in support of the safety of the current application.

7.1.2 Categorization of Adverse Events

This section is not applicable.

7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

This section is not applicable.

7.2 Adequacy of Safety Assessments

There is clear evidence of safety for immediate-release oxycodone HCl products based on the Agency's prior findings from other products.

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

The extent of exposure to at least one dose of Tradename consists of 114 of 115 enrolled subjects, including 75 healthy volunteers enrolled in the two biopharmaceutics studies (AP-ADD-100 and K234-10-1001) and 40 recreational adult opioid users recruited for the abuse liability study (K234-10-1002). In the biopharmaceutics studies, subjects received three to five separate single doses of 5 to 15 mg of oxycodone HCl while naltrexone blocked, and for the abuse liability study, subjects received 15 mg of oxycodone HCl by insufflation on three separate occasions.

7.2.2 Explorations for Dose Response

This section is not applicable.

7.2.3 Special Animal and/or In Vitro Testing

There was no special animal or in vitro testing performed.

7.2.4 Routine Clinical Testing

This section is not applicable.

7.2.5 Metabolic, Clearance, and Interaction Workup

This section is not applicable.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

This section is not applicable.

7.3 Major Safety Results

Since subjects were administered single oxycodone HCl doses (up to 15 mg on separate occasions) while naltrexone blocked in the pharmacokinetic studies, the data from these studies is not infomative about the safety of oxycodone. There were no novel or unexpected adverse events in the abuse liabilty studies that enrolled opioid experienced subjects.

7.3.1 Deaths

There were no deaths reported with this submission.

7.3.2 Nonfatal Serious Adverse Events

There were no nonfatal serious adverse events reported with this submission.

7.3.3 Dropouts and/or Discontinuations

A total of ten (8.7%) of 115 subjects enrolled in the Phase 1 Clinical Development program discontinued for any reason from study (Table 4), with vomiting (n=5) and protocol non-compliance (n=2) as the most common reason for withdrawal.

Table 4: Disposition of Subjects in Phase 1 Studies

Study	Enrolled	Discontinued	Reasons
AP-ADD-100	40	3	Viral syndrome (n=1) Vomiting (n=1) Positive urine drug screen (n=1)
K234-10-1001	35	7	Vomiting (n=4) Protocol non-compliance (n=2) Withdrew consent (n=1)
K234-10-1002 (Treatment Phase)	40	0	Not applicable

Source: 2.7.4 Summary of Clinical Safety, Table 3, p.22 of 59.

7.3.4 Significant Adverse Events

This section is not applicable.

7.3.5 Submission Specific Primary Safety Concerns

The Applicant submitted a Phase 1 Abuse Liability study (K234-10-1002) to assess the relative abuse potential of crushed and intranasally administered Tradename (2 x 7.5 mg) compared with crushed and intranasally administered Roxicodone tablets (3 x 5 mg) in non-dependent recreational opioid users (see 7.7 Additional Submissions/Safety Issues). As anticipated (b) (4) treatment-emergent adverse events related to nasal irritation (nasal congestion, dryness, and/or discomfort, rhinorrhoea, throat irritation and lacrimation) were more common with Tradename than with Roxicodone (see Table 5). Since subjects had only one exposure to the Applicant's product, possible long-term complications (e.g., ulceration or septal perforation) could not be assessed related to this off-label use. For detailed discussion regarding Study K234-10-1002, please refer to the Controlled Substance Staff (CSS) Reviews by Drs. Ling Chen and Jovita Randall-Thompson

Table 5: Treatment-Emergent Adverse Events (Study K234-10-1002)

MedDRA® System Organ Class/Preferred Term	Crushed Acurox® Tablets N=40	Crushed Roxicodone® Tablets N=40
Any System Organ Class, Any Event	**39 (98)**	**34 (85)**
Eye disorders	**17 (43)**	**3 (8)**
Blepharospasm	1 (3)	0
Eye pain	1 (3)	0
Lacrimation increased	14 (35)	2 (5)
Ocular hyperaemia	1 (3)	0
Vision blurred	0	1 (3)
Gastrointestinal disorders	**2 (5)**	**2 (5)**
Abdominal discomfort	0	1 (3)
Nausea	1 (3)	0
Salivary hypersecretion	1 (3)	0
Vomiting	1 (3)	1 (3)
General disorders and administration site conditions	**12 (30)**	**6 (15)**
Facial pain	7 (18)	1 (3)
Fatigue	1 (3)	1 (3)
Feeling cold	1 (3)	1 (3)
Feeling hot	3 (8)	3 (8)
Infections and infestations	**1 (3)**	**0**
Upper respiratory tract infection	1 (3)	0
Investigations	**1 (3)**	**0**
Oxygen saturation decreased	1 (3)	0
Nervous system disorders	**9 (23)**	**10 (25)**
Dizziness	1 (3)	3 (8)
Dysgeusia	1 (3)	0
Headache	4 (10)	2 (5)
Somnolence	2 (5)	6 (15)
Sinus headache	2 (5)	1 (3)
Psychiatric disorders	**21 (53)**	**31 (78)**
Agitation	1 (3)	0
Euphoric mood	21 (53)	31 (78)
Respiratory, thoracic and mediastinal disorders	**38 (95)**	**18 (45)**
Dyspnoea	1 (3)	0
Dry throat	0	1 (3)
Nasal congestion	32 (80)	11 (28)
Nasal dryness	0	1 (3)
Nasal discomfort	29 (73)	12 (30)
Rhinorrhoea	32 (80)	5 (13)
Throat irritation	19 (48)	3 (8)
Skin and subcutaneous tissue disorders	**2 (5)**	**11 (28)**
Hyperhidrosis	0	1 (3)
Pruritus generalised	2 (5)	4 (10)
Pruritus	0	6 (15)
Vascular disorders	**1 (3)**	**2 (5)**
Flushing	1 (3)	0
Hypotension	0	2 (5)

Source: 2.7.4 Summary of Clinical Safety, Table 10, p.34 of 59

7.4 Supportive Safety Results

This section is not applicable.

7.4.1 Common Adverse Events

This section is not applicable.

7.4.2 Laboratory Findings

This section is not applicable.

7.4.3 Vital Signs

This section is not applicable.

7.4.4 Electrocardiograms (ECGs)

The Applicant did not submit any ECG data with the current submission.

7.4.5 Special Safety Studies/Clinical Trials

The Applicant did not submit any special safety study, clinical study or trial data with the current submission.

7.4.6 Immunogenicity

This section is not applicable.

7.5 Other Safety Explorations

This section is not applicable.

7.5.1 Dose Dependency for Adverse Events

This section is not applicable.

7.5.2 Time Dependency for Adverse Events

This section is not applicable.

7.5.3 Drug-Demographic Interactions

This section is not applicable.

7.5.4 Drug-Disease Interactions

This section is not applicable.

7.5.5 Drug-Drug Interactions

The applicant is relying on the findings for Roxicodone.

7.6 Additional Safety Evaluations

This section is not applicable.

7.6.1 Human Carcinogenicity

There was no data on human carcinogenicity submitted with this application.

7.6.2 Human Reproduction and Pregnancy Data

There was no data on human reproduction and pregnancy submitted with this application.

7.6.3 Pediatrics and Assessment of Effects on Growth

There was no assessment for the effect of Tradename on growth.

No pediatric exposure was reported in the current submission.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

There were no reported incidents of accidental or intentional overdose in the safety data for this submission.

7.7 Additional Submissions/Safety Issues

Study K234-10-1002 was a randomized, double-blind, active-controlled, single-dose, 2-way crossover study assessing the relative abuse potential of crushed and intranasally administered Tradename (see Table 3). In this study, intranasal administration of crushed Tradename (2 x 7.5 mg) was compared with crushed immediate-release oxycodone HCl (Roxicodone) tablets (3 x 5 mg) in non-dependent recreational opioid users (n=40). Eligible subjects were required to be able to distinguish crushed Roxicodone tablets (positive control) from crushed placebo. The primary endpoint for this study was drug liking, measured up to eight hours post dosing using a visual analogue scale (VAS) during the study sessions ("at the moment" Drug Liking VAS) and at the end of the sessions (Overall Drug Liking VAS). Overall Drug Liking and Take Drug Again were secondary outcomes measured at eight hours post-dose (E_{8h}). Least square mean differences were estimated from a linear mixed-effect ANOVA with treatment sequence, period, and treatment as fixed effects, and subject within treatment sequence as a random effect.

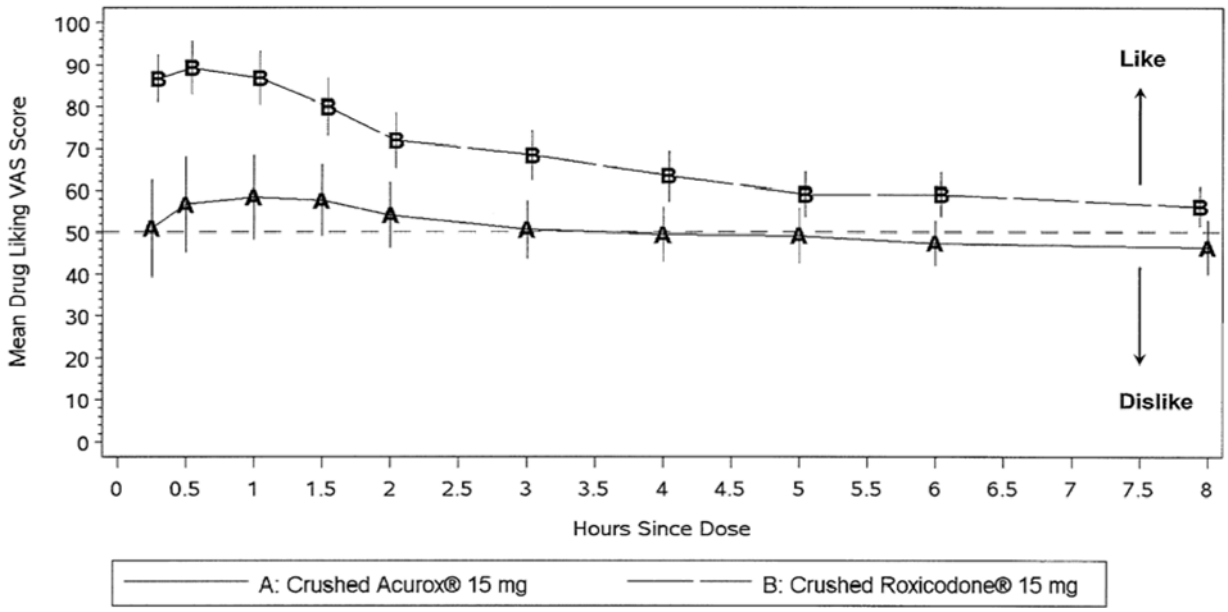
The Applicant reported that nasal administration of crushed Tradename resulted in lower drug liking (Table 6; Figure 2) and greater nasal irritation (see Table 5) compared with crushed oxycodone HCl tablets, with considerable individual variability observed (ranging from 4% and 100%). The clinical significance of the degree of reduction in drug liking in this study has not been established.

Table 6: Summary of Primary Analyses: Tradename Compared with Roxicodone Tablets

	Least Square Mean Difference[a] (SE)	95% CI	P-value
Drug Liking VAS E_{max}	-22.6 (4.67)	-32.0, -13.3	<0.0001
Overall Drug Liking VAS E_{8h}	-39.5 (6.25)	-52.0, -27.1	<0.0001[b]
Take Drug Again VAS E_{8h}	-45.4 (7.28)	-59.9, -30.9	<0.0001[b]

Source: Clinical Overview, Table 1, p.10 of 31.
Abbreviations: E_{8h}, effect at 8 hours; E_{max}, maximum peak effect; SE, standard error; VAS, visual analogue scale.

Figure 2: Mean (± 95% CI) Drug Liking VAS Scores Over Time



Source: Clinical Overview, Figure 2, p.9 of 31.

Dr. Ling Chen, the mathematical statistician for the Controlled Substance Staff (CSS), was consulted to evaluate Study K234-10-1002. Please refer to her review for a detailed description of the statistical concerns related to the design and conduct of this study. Overall, the study design of this Abuse Liability Study was considered inadequate. The primary deficiency in the study design was the potential for unblinding due to a greater than three-fold mg weight difference between crushed Tradename and crushed

Roxicodone. Within the allotted five minutes of scheduled time, 21 subjects (53%) were unable to completely insufflate Tradename. However, the average percent of the Tradename dose insufflated was similar, regardless of sequence, whether it was administered before (84.7%) or after (82.6%) Roxicodone administration (p=NS). The most common reason for incomplete insufflation or Tradename was nasal passages blocked with material from the crushed tablet(reported by 18 subjects). Four subjects had low insufflation percentages for crushed Tradename, but had drug liking VAS scores higher than 90 mm. All patients were able to completely insufflate the entire dose of crushed Roxicodone tablets. Further, a sequence effect was observed in which 17 out of 20 subjects (85%) reported a Drug Liking VAS E_{max} score >60 mm versus 10 out of 20 subjects when Tradename were administered before and after Roxicodone, respectively. Mean differences in Drug Liking VAS E_{max} scores between Tradename and Roxicodone tablets were approximately -15 mm and -30 mm when Tradename was administered first versus second, respectively (All $p<0.05$). Since adjustments for the sequence effects were not possible, only first treatment comparisons were considered acceptable. Based on these data, no statistically significant differences (Wilcoxon-Mann-Witney test) in median responses between treatment groups were observed for the primary (p=0.2261) and secondary outcomes (p>0.0609).

Dr. Chen concluded that the study did not demonstrate that Tradename had a lower abuse potential than Roxicodone tablets when crushed and administered intranasally to non-dependent recreational opioid users. Consultation with Dr. Jovita Randall-Thompson, the CSS pharmacologist reviewer, was pending at the time of this review.

However, while drug liking scores did not separate statistically, the difficulty snorting the crushed Tradename relative to Roxicodone, and the increased reports of nasal blocking and irritation suggest that the Tradename formulation is less attractive for a nasal route of abuse than conventional formulations.

8 Postmarket Experience

At the time of this review, Tradename is not approved in any other country.

9 Appendices

9.1 Literature Review/References

Literature is appropriately referenced throughout the review. Ten published clinical trials that evaluated the efficacy and safety of oxycodone HCl for various pain conditions were also included in this submission to further support findings of efficacy and safety of oxycodone HCl.

9.2 Proprietary Name

The Division of Medication Error Prevention and Analysis (DMEPA) from the Office of Surveillance and Epidemiology (OSE) found the original proposed tradename "Acurox" unacceptable (b) (4)

The Applicant has subsequently proposed OXECTA as an alternative proprietary name for assessment by the Agency. The acceptability of OXECTA as the proposed tradename is under review at this time. The Brand Institute and Drug Safety Institute Safety Research review determined that this trade name was acceptable based on risks for sound-alike and/or look-alike similarity, product profile overlaps, prescription misinterpretations, severity of outcome, probability of detection, promotional issues, linguistic concerns, USAN/INN issues, and misinterpretations in handwritten inpatient prescriptions, handwritten outpatient orders, or in verbal prescription interpretation.

9.3 Labeling Recommendations

The Applicant's originally proposed labeling was based on the label of the referenced drug, Roxicodone (NDA 021011), which is owned by the Applicant.

In terms of pharmacokinetics, efficacy and/or safety, Tradename does not offer any advantages or disadvantages over existing oxycodone products. However, the Applicant proposes to include in the label a (b) (4)

(b) (4)

DMEPA also reviewed the proposed carton and container labels and recommended that the Applicant make the following revisions:

1. The established name presentation be in accordance with 21 CFR 201.10(g)(2)
2. Different colors on the principal display panel of the label be used to ensure adequate differentiation between the two proposed dose strengths (5 mg and 7.5 mg)
3. Revise and relocate to the principal display panel the language to state that “tablets are to be swallowed whole and are not to be administered via nasogastric or any other feeding tubes.”
4. Unbold the text of the Rx Only and container size statements.
5. Reduce the size of the graphic above the proprietary name so that it does not compete with its prominence

The labeling review is still ongoing within the Division.

9.4 Advisory Committee Meeting

No advisory committee meeting is planned for this application.

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

/s/

FRANK PUCINO
05/24/2011

SHARON H HERTZ
05/24/2011
I concur.

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

NDA/BLA Number: 202-080 **Applicant: King Pharmaceuticals** **Stamp Date: 17 December 2010**

Drug Name: Acurox (oxycodone HCl) **NDA/BLA Type:**

On initial overview of the NDA/BLA application for filing:

	Content Parameter	Yes	No	NA	Comment
FORMAT/ORGANIZATION/LEGIBILITY					
1.	Identify the general format that has been used for this application, e.g. electronic CTD.	√			
2.	On its face, is the clinical section organized in a manner to allow substantive review to begin?	√			
3.	Is the clinical section indexed (using a table of contents) and paginated in a manner to allow substantive review to begin?	√			
4.	For an electronic submission, is it possible to navigate the application in order to allow a substantive review to begin (*e.g.*, are the bookmarks adequate)?	√			
5.	Are all documents submitted in English or are English translations provided when necessary?	√			
6.	Is the clinical section legible so that substantive review can begin?	√			
LABELING					
7.	Has the applicant submitted the design of the development package and draft labeling in electronic format consistent with current regulation, divisional, and Center policies?	√			
SUMMARIES					
8.	Has the applicant submitted all the required discipline summaries (*i.e.*, Module 2 summaries)?	√			
9.	Has the applicant submitted the integrated summary of safety (ISS)?			√	
10.	Has the applicant submitted the integrated summary of efficacy (ISE)?			√	
11.	Has the applicant submitted a benefit-risk analysis for the product?	√			
12.	Indicate if the Application is a 505(b)(1) or a 505(b)(2). If Application is a 505(b)(2) and if appropriate, what is the reference drug?	√			Roxicodone (NDA 021-011)
DOSE					
13.	If needed, has the applicant made an appropriate attempt to determine the correct dosage and schedule for this product (*i.e.*, appropriately designed dose-ranging studies)? Study Number: Study Title: Sample Size: Arms: Location in submission:			√	
EFFICACY					
14.	Do there appear to be the requisite number of adequate and well-controlled studies in the application? Pivotal Study #1 Indication:			√	

File name: 5_Clinical Filing Checklist for NDA_BLA or Supplement 010908

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
	Pivotal Study #2 Indication:			√	
15.	Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?			√	
16.	Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints.			√	
17.	Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission?			√	
SAFETY					
18.	Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division?	√			
19.	Has the applicant submitted adequate information to assess the arythmogenic potential of the product (*e.g.*, QT interval studies, if needed)?			√	
20.	Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product?	√			
21.	For chronically administered drugs, have an adequate number of patients (based on ICH guidelines for exposure[1]) been exposed at the dose (or dose range) believed to be efficacious?			√	
22.	For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division?	√			
23.	Has the applicant submitted the coding dictionary[2] used for mapping investigator verbatim terms to preferred terms?	√			
24.	Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs?	√			
25.	Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)?			√	

[1] For chronically administered drugs, the ICH guidelines recommend 1500 patients overall, 300-600 patients for six months, and 100 patients for one year. These exposures MUST occur at the dose or dose range believed to be efficacious.

[2] The "coding dictionary" consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
OTHER STUDIES					
26.	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?	√			
27.	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (*e.g.*, label comprehension, self selection and/or actual use)?			√	
PEDIATRIC USE					
28.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?	√			
ABUSE LIABILITY					
29.	If relevant, has the applicant submitted information to assess the abuse liability of the product?	√			
FOREIGN STUDIES					
30.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?			√	
DATASETS					
31.	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?	√			
32.	Has the applicant submitted datasets in the format agreed to previously by the Division?	√			
33.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?			√	
34.	Are all datasets to support the critical safety analyses available and complete?	√			
35.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?			√	
CASE REPORT FORMS					
36.	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?	√			
37.	Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?	√			
FINANCIAL DISCLOSURE					
38.	Has the applicant submitted the required Financial Disclosure information?	√			
GOOD CLINICAL PRACTICE					
39.	Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?	√			

IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE? YES

If the Application is not fileable from the clinical perspective, state the reasons and provide comments to be sent to the Applicant.

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

[signature]	01-31-11
Reviewing Medical Officer	Date
[signature]	Ok-31-11
Clinical Team Leader	Date

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

/s/

FRANK PUCINO
02/02/2011

ROBERT B SHIBUYA
02/03/2011