CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

022450Orig1s000

SUMMARY REVIEW

Summary Review for Regulatory Action

Date	(electronic stamp)
From	Sharon Hertz, M.D.
Subject	Deputy Division Director Summary Review
NDA/BLA #	22-450/000
Applicant Name	Cadence Pharmaceuticals, Inc.
Date of Submission	May 4, 2010
PDUFA Goal Date	November 4, 2010
Proprietary Name / Established (USAN) Name	Tradename/ Acetaminophen Injection for Intravenous Use
Dosage Forms / Strength	Intravenous/ 10 mg per 1 mL solution
Proposed Indication(s)	Acute pain and fever in adult and pediatric patients
Action/Recommended Action:	Approval

Material Reviewed/Consulted OND Action Package, including:	
CMC Review/OBP Review	Martin Haber, Ph.D., Ali Al Hakim, Ph.D.
DSI	Susan Leibenhaut, M.D., Jean Mulinde, M.D.
OSE/DMEPA	Richard Abate, RPh, Melina Griffis, RPh, Carol Holquist, RPh
Other	

OND=Office of New Drugs
DDMAC=Division of Drug Marketing, Advertising and Communication
OSE= Office of Surveillance and Epidemiology
DMEPA=Division of Medication Errors Prevention
DSI=Division of Scientific Investigations
CDTL=Cross-Discipline Team Leader

Signatory Authority Review Template

1. Introduction

The product is a parenteral formulation of acetaminophen intended for intravenous use for pain and fever in adults and children. The applicant has submitted a 505(b)(2) application referencing the Agency's previous findings of efficacy and safety for Tylenol (NDA 19-872) and scientific literature. The product is a sterile, clear, colorless, preservative-free, isotonic formulation of acetaminophen. Each 100 mL glass vial contains 1000 mg acetaminophen (10 mg/mL).

This submission is in response to a complete response (CR) action taken on February 10, 2010. The deficiency from that action was a result of problems with the manufacturing process, and the language from the CR letter is reproduced here:

1. Control procedures are not established which validate the performance of those manufacturing process that may be responsible for causing variability in the characteristics of in-process material and the drug product.
2. Records are not kept for the maintenance and inspection of equipment.
3. Acceptance criteria for the sampling and testing conducted by the quality control unit is not adequate to assure that batches of drug products meet each appropriate specification as a condition for their approval and release.
4. Products that do not conform to specifications are not adequately controlled.

2. Background

Development of this product occurred under IND 58,362. Although the applicant had not initially wanted to seek an indication for pain, the Division of Analgesic, Anti-Inflammatory and Ophthalmic Drug Products asked the applicant to conduct trials in pain as it was likely the product would be used for that purpose.

3. CMC/Device

During the first review cycle, an amendment was received on January 13, 2010, which contained updated drug product stability data for 12 months for three primary batches and a shelf life of 18 months for the drug product is requested. The amendment was not reviewed during the first cycle because it was received so close to the PDUFA due date (February 2010). The 4-aminophenol impurity level has been considered critical to establishment of the shelf-life. Dr. Haber has reviewed this material and found that the [redacted] (b) (4) shelf-life has been projected taking into account the tighter limits for pH and 4-aminophenol that were set in the September 14, 2009 amendment. The updated stability data for the 4-aminophenol impurity show that [redacted] (b) (4) at 18 months. These values are within the tightened specification

limit (b) (4) agreed to by the firm in the last review cycle. Therefore, (b) (4) the shelf-life to 18 months is acceptable.

During the first review cycle, an inspection of the drug manufacturer, Baxter Healthcare Corporation (Cleveland, MS), was conducted by the Office of Compliance from January 15, 2010 to February 5, 2010. Particulates were again found in the drug product, including fibers and what appeared to be skin cells. A number of cGMP problems were identified by the office of Compliance inspectors that were part of the written 483 issued to the site manager and are listed below.

1. Control procedures are not established which validate the performance of those manufacturing process that may be responsible for causing variability in the characteristics of in-process material and the drug product as evidenced by variability in the lots produced, including fill volumes, presence of particulates and foreign matter.
2. A change of procedures relative to the processing of rubber stoppers was submitted to the Sponsor but was not included in the Sponsor's submission to FDA
3. Records are not kept for the maintenance and inspection of equipment.
4. Acceptance criteria for the sampling and testing conducted by the quality control unit is not adequate to assure that batches of drug products meet each appropriate specification as a condition for their approval and release.
5. Products that do not conform to specifications are not adequately controlled.

Based on the above findings, the Office of Compliance had recommended an overall withhold status for the application.

A reinspection of the drug manufacturer has found sufficient correction of the deficiencies and an overall recommendation of acceptable was made on October 26, 2010, for all manufacturing sites.

I concur with the CMC reviewer that there are no outstanding CMC issues for this application.

4. Nonclinical Pharmacology/Toxicology

There were no new nonclinical data.

5. Clinical Pharmacology/Biopharmaceutics

There were no new clinical pharmacology data.

6. Clinical Microbiology

There were no new microbiology data.

7. Clinical/Statistical-Efficacy

There were no new efficacy data.

8. Safety

There were no new safety data.

9. Advisory Committee Meeting

This application was not brought to an advisory committee. Acetaminophen is a well known drug substance and there were no novel concerns raised in this application that required an advisory committee.

10. Pediatrics

The pediatric study requirements for the NDA included cross-study comparison of relative bioavailability between pediatric and adult populations, the use of relative pharmacokinetic profiles to bridge adult efficacy to the pediatric population, in addition to pediatric safety data as basis of approval for pediatric indications. A Pediatric Written Request was issued to the Applicant on August 24, 2007. The studies submitted adequately support the dosing instructions in the following table.

Table 2 Pediatric dosing recommendations.

Age group	Dose given every 4 hours	Dose given every 6 hours	Maximum Single dose	Maximum total daily dose of Acetaminophen
Adults and adolescents (13 years and older) weighing ≥ 50 kg	650 mg	1000 mg	1000 mg	4000 mg in 24 hours
Adults and adolescents (13 years and older) weighing < 50 kg	12.5 mg/kg	15 mg/kg	15 mg/kg (up to 750 mg)	75 mg /kg in 24 hours (up to 3750 mg)

Age group	Dose	Frequency of use	Maximum Single dose*	Maximum total daily dose of Acetaminophen
Children ≥ 2 to 12 years of age	12.5 mg/kg	every 4 hours	15 mg/kg	75 mg /kg per day
	15 mg/kg	every 6 hours		

Dosing below the age of 2 must be confirmed with efficacy studies. Although thought to be acceptable during the first cycle, there is no efficacy data to support efficacy in pediatric patients under the age of 2. The applicant has a written request in place that describes a pharmacokinetic/ pharmacodynamic study to be conducted which will also provide evidence of efficacy. [redacted] (b) (4)

11. Relevant Regulatory Issues

DSI inspections of clinical sites did not reveal any concerns that would impact the overall data reliability.

Reinspection of the drug manufacturing site found adequate resolution of prior deficiencies.

12. Labeling

A re-evaluation of the proposed proprietary name, Ofirmev, did not identify any vulnerabilities that would result in medication errors with the additional names noted in this review. Thus, the Division of Medication Error Prevention and Analysis (DMEPA) has no objection to the proprietary name, Ofirmev, for this product at this time.

The applicant had sought to include a statement Section 14.1 (Clinical Studies) [redacted] (b) (4) After internal discussion, it was decided that the following language would be permitted:

> The efficacy of OFIRMEV in the treatment of acute pain in adults was evaluated in two randomized, double-blind, placebo-controlled clinical trials in patients with postoperative pain. **Pain Study 1** evaluated the analgesic efficacy of repeated doses of OFIRMEV l000 mg vs. placebo every 6 hours for 24 hours in 101 patients with

moderate to severe pain following total hip or knee replacement. OFIRMEV was statistically superior to placebo for reduction in pain intensity over 24 hours. There was an attendant decrease in opioid consumption, the clinical benefit of which was not demonstrated.

13. Decision/Action/Risk Benefit Assessment

- Approval

- Risk Benefit Assessment

Overall the risk and benefit balance favorable for this parenteral acetaminophen product.

- Recommendation for Postmarketing Risk Management Activities

None.

- Recommendation for other Postmarketing Study Requirements

A randomized, double-blind, placebo controlled study of efficacy, pharmacokinetics and pharmacodynamics of IV APAP for the treatment of acute pain in pediatric patients from 0 to 2 years of age.

Final Protocol Submission: 10/2011
Study/Trial Completion: 10/2014
Final Report Submission: 10/2015

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/s/

SHARON H HERTZ
11/02/2010