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APPLICATION NUMBER:

22-402

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross Discipline Team Leader Review
 NDA 22-402
 Ellen Fields, M.D., M.P.H.

Cross-Discipline Team Leader Review

Date	July 15, 2009
From	Ellen Fields, M.D., M.P.H.
Subject	Cross-Discipline Team Leader Review
NDA#	22-402 505(b)(2) application
Applicant	Roxane
Date of Submission	July 2, 2008
PDUFA Goal Date	August 2, 2009
Proprietary Name / Established (USAN) names	Codeine Sulfate tablets
Dosage forms / Strength	Immediate-Release Tablets/ 15mg, 30mg, 60mg
Proposed Indication(s)	Treatment of mild to moderately severe acute pain in adults
Recommended:	Approval

Material Reviewed/Consulted OND Action Package, including:	
Primary Medical Officer Review	Carolyn Yancey, M.D.
Statistical Reviews	N/A
Pharmacology Toxicology Reviews	Elizabeth Bolan, Ph.D. Dan Mellon Ph.D.
Biopharmaceutics Reviewers	Sheetal Agarwal, Ph.D. Suresh Doddapaneni, Ph.D.
CMC Reviews	Eugenia Nashed, Ph.D. Ali Al Hakim, Ph.D.
DDMAC	Mathilda Fienkeng Sangeeta Vaswani
DSI	Jacqueline A. O'Shaughnessy, Ph.D. Gopa Biswas, Ph.D.
CSS	James Hunter, R.Ph., M.P.H Silvia Calderon, Ph.D. Michael Klein, Ph.D.

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1. Introduction

There are numerous unapproved narcotic analgesics marketed under the mistaken belief that as very old products the applications were not subject to review under the Drug Efficacy Study Implementation in support of continued marketing. This NDA is for marketed, but unapproved Codeine Sulfate oral tablets. Although there are many approved combination products containing codeine indicated for the treatment of pain, there is no single-entity approved codeine product. Codeine sulfate is marketed world-wide.

In response to the FDA 2006 guidance entitled "Marketed Unapproved Drugs - Compliance Policy Guide," Roxane has filed an NDA for their codeine sulfate product. The Applicant has submitted a 505(b)(2) application that relies on published literature in support of efficacy, and references the Agency's previous findings of safety for Tylenol with Codeine #3 (ANDA 85-055) in support of the safety of single-entity codeine sulfate. The Applicant has also relied on published literature to support the non-clinical aspects of this submission. No new clinical efficacy or safety studies and no new non-clinical studies were performed in support of this NDA. Five Phase 1 pharmacokinetic studies were carried out by the Applicant in order to establish adequate bridging between the codeine phosphate component of Tylenol with Codeine #3 and codeine sulfate, dose proportionality of the proposed dosage strengths, food effect, steady state pharmacokinetics, and dosage form proportionality.

The Applicant submitted a review of the published literature related to the efficacy of oral codeine based on a PubMed literature search for articles published from 1960 to 2007. Because of the decades of use of codeine as an analgesic in combination products, a literature review was determined to be adequate to support efficacy of single-entity codeine sulfate for the treatment of acute pain in adults.

The original PDUFA date for this application was May 2, 2009. Due to multiple CMC deficiencies in the application and the submission of a major amendment on DATE, the review clock was extended three months to August 2, 2009. Details regarding the CMC issues are discussed in Section 2.

1. Background

A Pre IND meeting was held on January 24, 2007 at which time the Division agreed to a regulatory path forward via a 505(b)(2) application that would rely on the Agency's previous findings of safety and efficacy for codeine-containing products, and upon the published literature on codeine. The Division further stated that that Tylenol® with Codeine No. 3 may be an acceptable reference to support safety as long as 1) the codeine doses used in the combination product are the same or higher than those used in the proposed codeine sulfate oral tablets, and 2) the pharmacokinetics of codeine in the reference product are similar to those of the Applicant's product. During the meeting, the Division also agreed to conduct a preliminary evaluation of the selected clinical and non-clinical literature to determine their adequacy.

A literature review alone was not deemed sufficient to address the requirements of PREA in terms of pediatric dosing, safety and efficacy. To address these requirements the Sponsor was told that they must perform single- and multiple-dose pharmacokinetic trials in children, as well as sufficient data on safety and analgesic efficacy.

From a biopharmaceutics perspective, the following information would be required to support the NDA application:

1. Dose linearity information using 1x15 mg vs. 1x30 mg vs. 1x60 mg
2. Food effect from 60-mg strength tablet
3. Multiple dose from 15-mg strength tablet Q4h
4. Relative BA information using the listed drug(s) the Sponsor plans to rely upon for the Agency's finding of safety and/or effectiveness in support of the 505(b)(2) application.

In terms of preclinical data, the Sponsor planned to submit literature articles to support the application. It was determined that there were no required data unique to this application that could not be found via reference to the published literature. _____

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_____ The Division informed the Sponsor that reliance on literature alone was adequate to support the application from a non clinical pharmacology/toxicology perspective. _____

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The NDA application, which was submitted on July 1, 2008, was comprised of literature supportive of the preclinical and efficacy portions of the NDA, five pharmacokinetic studies, and a Chemistry, Manufacturing and Controls (CMC) section with supportive data. Although the submission was deemed acceptable for filing it lacked an Integrated Summary of Efficacy and required CMC data. Additionally, a full pediatric plan was not included in the original application. All required components were ultimately submitted to the NDA, however the review clock was extended three months due to additional time required to review the numerous CMC amendments that were submitted late in the review cycle.

Indication

The proposed indication for codeine sulfate tablets is the treatment of mild to moderately-severe acute pain in adults.

2. CMC/Device

The primary CMC review was conducted by Eugenia Nashed, Ph.D. with secondary concurrence by Ali Al-Hakim, Ph.D. The following is a summary of Dr. Nashed's review.

The drug substance codeine sulfate trihydrate is a derivative of codeine alkaloid, which belongs to the Morphinan-6 α -ol group of opioids occurring naturally in the opium poppy plant. It is manufactured by _____ in _____ from the _____
_____ The manufacturing and controls are supported by two DMFs _____ and

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Both DMFs have adequate status to support the application, and the [redacted] has acceptable EER recommendation from the Office of Compliance.

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The drug product consists of white [redacted] (15 mg and 30 mg) or [redacted] (60 mg), biconvex un-coated tablets. The tablets are scored and debossed with strength-designation number on one side, and debossed with numbers on the other side.

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Each tablet contains 15 mg, or 30 mg, or 60 mg of codeine sulfate, in addition to standard NF/USP grade excipients, which include microcrystalline cellulose [redacted], pregelatinized starch [redacted], colloidal silicon dioxide [redacted], and stearic acid. In addition, [redacted] was used in 15 mg tablets, but it is absent in the registration and commercial drug product batches. The dosage strengths are not compositionally proportional and contain [redacted] API by weight for 15 mg tablets, and [redacted] API by weight for the 30 mg and 60 mg tablets. However, Dr. Sheetal Agarwal's review found the submitted bioequivalence studies adequate to support the NDA application.

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The commercial drug product tablets are packaged in [redacted] bottles (100 tablets), or in [redacted] blister cards (4 cards of 25 tablets per pack).

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The release and stability controls for the drug product were revised significantly during the review process. Based on the 12 months of incomplete stability data submitted, and considering the recent changes in formulation and manufacturing, the expiry period for drug product is limited to 18 months, when stored at [redacted].

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The manufacturing is carried by the Boehringer Ingelheim Raxane, Inc in Columbus, Ohio, with an additional distribution center in Reno, Nevada. No issues have arisen regarding the manufacturing site.

Please refer to the Pharmacology/Toxicology section of this review for information regarding impurities.

The original NDA application was incomplete in terms of CMC data in that it lacked testing for the moisture content, hardness, friability and adequate method for dissolution testing of the tablets. In response to comments sent in multiple information request letters, the Applicant has implemented testing for the above attributes and proposed interim acceptance criteria due to the limited data available. Please see Dr. Nashed's review for details regarding the interim acceptance criteria.

An agreement was reached with the Applicant to collect additional data within the first 2.5 years of manufacturing, to be submitted in a prior approval supplement by July 1, 2012, in order to improve the interim acceptance criteria for dissolution, hardness and friability. Also, the drug product expiry period was limited to 18 months (from the originally proposed [redacted] [redacted], due to the lack of representative stability data.

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The following are the post marketing agreements made with the Applicant (from Dr. Nashed's review):

1. You agree to submit dissolution profile data generated for a minimum of 20 production batches (first 10 batches for the 15 mg tablets and first 5 batches for each of the 30 mg and 60 mg tablets) during release and stability testing of commercial drug product. The dissolution profiles will include adequate number of data points to allow for comparison of the profiles, e.g., 10 min, 15 min, 30 min and 45 min. A statistical evaluation of batch to batch variability, between different drug product strengths and within the same batch during stability storage, sorted by the type of container closure, will be provided.
2. You agree to submit available data for hardness and friability generated during release and stability testing of commercial drug product tablets. A statistical evaluation of batch to batch variability, between different drug product strengths and within the same batch during stability storage, sorted by the type of container closure will be provided.

We remind you of the agreement that any extension of drug product expiry period beyond 24 months may be accomplished only *via* a prior approval supplement with adequate supporting data. The currently approved expiry period for drug product is 18 months, starting from the first use of drug substance in the drug product manufacturing process. The drug product expiry period may be extended to 24 months based on acceptable stability data collected according to the approved stability protocol, in accord with 21 CFR 314.70.

This NDA application is recommended for approval from the CMC perspective, based on extensive agreements with the Applicant to perform post marketing studies.

3. Nonclinical Pharmacology/Toxicology

Marcus Delatte, Ph.D., with supervisory concurrence from Dan Mellon, Ph.D., performed the nonclinical pharmacology and toxicology review for this NDA. The following is a summary of Dr. Delatte's review.

No new nonclinical pharmacology studies were conducted in support of this application. The proposed formulation for codeine sulfate includes excipients at levels that are less than or equal to amounts provided in FDA-approved products.

Drug substance specifications for impurities were proposed by the Applicant that included _____ codeinone, and codeine methyl ether (CME). Individually, these impurities were proposed to be in accordance with ICH Q3A Qualification level of $\leq 0.15\%$ NMT, except for CME, which exceeds ICH Q3A standards at _____ CME has been reported to be a known impurity of codeine; however, the Applicant did not provide adequate safety qualification for this impurity. Therefore, the Applicant should either reduce the specification to NMT 0.15% or 1 mg, whichever is lower, or submit the following studies:

- Minimal genetic toxicology screen (two *in vitro* genetic toxicology studies, e.g., one point mutation assay and one chromosome aberration assay) with the isolated impurity, tested up to the limit dose for the assay.

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- Repeat dose toxicology of 90-days duration to support the proposed indication.

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Given the presumed clinical experience with codeine and the existing marketing experience with this unapproved marketed product, Dr. Delatte concluded that the above qualification studies for codeine methyl ether may be conducted post-approval.

DMF — for codeine was referenced by the Applicant in support of this NDA, and initially was thought to contain inadequate characterization of the cytogenetic potential of codeinone, a drug substance impurity that contains a structural alert for mutagenicity. Codeinone tested negative in the Ames bacterial reverse mutation assay and although the results of the *in vitro* chromosomal aberration assay were negative, the assay was deemed to be inconclusive by the review team due to excessive chromosomal condensation at higher concentrations. Following further discussion between Drs. Mellon and Delatte, and Dr. David Jacobson-Kram, Associate Director of Pharmacology Toxicology (OND CDER), the excessive chromosomal condensation was deemed evidence of toxicity and therefore, the highest concentrations tested in the already completed assay were deemed to be the maximum feasible concentrations. As such, Dr. Jacobson-Kram deemed these studies valid. Therefore, the Agency considers codeinone to have been adequately tested and deemed negative in a minimal genetic toxicology screen. In terms of genotoxic potential, this impurity can be considered as a non-genotoxic impurity and regulated as per ICH Q3A.

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From the nonclinical pharmacology and toxicology perspective, the NDA may be approved pending agreement on the labeling and with the post marketing requirements stated above.

4. Clinical Pharmacology/Biopharmaceutics

The primary Clinical Pharmacology review was performed by Sheetal Agarwal, Ph.D. with concurrence of her Team Leader, Suresh Doddapaneni, Ph.D. The information that follows is a summary of Dr. Agarwal's review.

The Applicant is relying on the Agency's previous findings of safety of codeine in Tylenol #3 with codeine (ANDA 85-055) which contains 30mg of codeine phosphate. A bioequivalence study linking the codeine sulfate tablets and codeine phosphate in Tylenol #3 was conducted. In addition, data from four other Clinical Pharmacology studies assessing dose proportionality, dosage form proportionality, steadystate pharmacokinetics and food effect were submitted. Several related published articles were also submitted. No new information related to special populations such as hepatic and renal impairment was submitted. Instead, the Applicant is relying on the existing language in the package insert of Tylenol® with codeine # 3 for all other Clinical Pharmacology aspects not specifically acquired for this product.

The individual studies are summarized below:

Study ~~CODE-T15-30-60-PVFS-1~~ examined the dose linearity of 15 mg, 30 mg, and 60 mg codeine sulfate tablets under fasted conditions. Mean plasma concentrations of codeine after administration of codeine as 1 x 15 mg, 1 x 30 mg, and 1 x 60 mg tablets increased in

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proportion to the increase in dose. Mean values for C_{max}, AUC(0-t) and AUC(inf) also increased in proportion to dose. The associated 90% confidence intervals for all comparisons among tablet strengths were within the 80% to 125% equivalence window demonstrating dose proportionality among the three tablet strengths with respect to codeine.

Table X from Dr. Agarwal's review summarizes the pharmacokinetic parameters of the three doses tested.

Parameter ¹	1 x 15 mg	1 x 30 mg	1 x 60 mg
C _{max} (ng/mL)	38.5 ± 14.5 (33)	81.2 ± 27.3 (34)	167 ± 46.9 (34)
T _{max} (h)	1.25 (33) [0.50 - 2.00]	1.01 (34) [0.50 - 2.50]	1.00 (34) [0.50 - 1.50]
AUC(0-t) (h·ng/mL)	149 ± 44.9 (33)	308 ± 93.3 (34)	653 ± 172 (34)
AUC(inf) (h·ng/mL)	154 ± 45.1 (33)	313 ± 95.3 (33)	654 ± 156 (32)
λ _z (h ⁻¹)	0.2761 ± 0.0369 (33)	0.2580 ± 0.0329 (33)	0.2041 ± 0.0634 (32)
t _{1/2} (h)	2.55 ± 0.34 (33)	2.73 ± 0.40 (33)	3.76 ± 1.26 (32)
Ln(C _{max})	3.59 ± 0.34 (33)	4.34 ± 0.34 (34)	5.08 ± 0.29 (34)
Ln[AUC(0-t)]	4.96 ± 0.30 (33)	5.69 ± 0.30 (34)	6.45 ± 0.26 (34)
Ln[AUC(inf)]	5.00 ± 0.29 (33)	5.70 ± 0.30 (33)	6.45 ± 0.24 (32)

¹Arithmetic mean ± standard deviation (N) except for T_{max} for which the median (N) [Range] is reported.

Study CODE- T60-PVFS/FD-1 assessed the effect of food on the absorption of codeine from a 60 mg codeine sulfate tablet employing the Agency recommended high-fat breakfast. Mean plasma concentrations of codeine after administration of Roxane Laboratories' Codeine Sulfate 60 mg tablet were comparable after administration under fed and fasted conditions. There was a 50% increase in the median T_{max}, from 1.00 h to 1.54 h, and an 11% decrease in C_{max}, suggesting a slight decrease in the rate of absorption under fed conditions. However, the 90% confidence intervals for C_{max}, AUC(0-t), and AUC(inf) were within the 80% to 125% equivalence window, demonstrating no effect of food on the bioavailability with respect to codeine.

Table X from Dr. Agarwal's review summarizes the pharmacokinetic parameters for codeine sulfate 60mg after oral administration to healthy volunteers under fasted and fed conditions.

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Parameter ¹	Fasted	Fed
C _{max} (ng/mL)	167 ± 54.0 (36)	149 ± 49.2 (36)
T _{max} (h)	1.00 (36) [0.50 – 2.50]	1.54 (36) [0.25 – 4.00]
AUC(0-t) (h×ng/mL)	629 ± 175 (36)	711 ± 211 (36)
AUC(inf) (h×ng/mL)	639 ± 175 (36)	720 ± 212 (36)
λ _z (h ⁻¹)	0.2163 ± 0.0490 (36)	0.2174 ± 0.0436 (36)
t _{1/2} (h)	3.41 ± 0.93 (36)	3.33 ± 0.75 (36)
Ln(C _{max})	5.06 ± 0.35 (36)	4.95 ± 0.36 (36)
Ln[AUC(0-t)]	6.41 ± 0.28 (36)	6.52 ± 0.32 (36)
Ln[AUC(inf)]	6.42 ± 0.27 (36)	6.53 ± 0.31 (36)

¹Arithmetic mean ± standard deviation (N) except for T_{max} for which the median (N) [Range] is reported.

Study CODE-T15-PVFS-1 characterized the steady-state pharmacokinetics of codeine and its metabolites morphine, M3G, and M6G after oral administration of codeine sulfate tablets administered at a dose of 15 mg Q4H x 5 days. Steady state was achieved by Day 3 of dosing. The mean plasma concentration profiles for all four moieties measured were relatively consistent across the six doses administered on Day 5. Codeine comprised the largest portion of circulating material (~55%) followed by M3G (~36%), M6G (~6%), and morphine (~2%) respectively.

The details of the pharmacokinetic measures may be found in Dr. Agrawal's review.

Study CODE-T30-PVFS-1 assessed relative bioavailability of codeine from codeine sulfate 30 mg tablets to reference product Tylenol® #3 under fasted conditions. Although Roxane Laboratories' Codeine Sulfate 30mg tablet contains _____ of codeine base, and the 30mg codeine phosphate in Tylenol #3 contains _____ of codeine base (approximately _____ difference), the mean plasma concentrations after administration of the two codeine preparations were essentially superimposable. A summary of the PK parameters for Roxane's codeine sulfate and Tylenol #3 (codeine phosphate) is shown in the following table from Dr. Agrawal's review.

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Parameter ¹	Roxane 30 mg	Tylenol #3
C _{max} (ng/mL)	71.2 ± 23.9 (34)	70.1 ± 21.9 (36)
T _{max} (h)	1.25 (34) [0.50 – 2.50]	1.25 (36) [0.50 – 3.00]
AUC(0-t) (h·ng/mL)	282 ± 98.0 (34)	272 ± 84.8 (36)
AUC(inf) (h·ng/mL)	289 ± 98.6 (34)	279 ± 86.3 (36)
λ _z (h ⁻¹)	0.2580 ± 0.0448 (34)	0.2620 ± 0.0419 (36)
t _{1/2} (h)	2.77 ± 0.51 (34)	2.71 ± 0.43 (36)
Ln(C _{max})	4.21 ± 0.34 (34)	4.20 ± 0.31 (36)
Ln[AUC(0-t)]	5.58 ± 0.35 (34)	5.56 ± 0.31 (36)
Ln[AUC(inf)]	5.61 ± 0.34 (34)	5.59 ± 0.30 (36)

¹Arithmetic mean ± standard deviation (N) except for T_{max} for which the median (N) [Range] is reported.

Mean values for all pharmacokinetic parameters were comparable for both formulations with geometric mean ratios for C_{max}, AUC(0-t), and AUC(inf) of approximately 100%. All of the associated 90% confidence intervals were within the 80% to 125% equivalence window, demonstrating bioequivalence between products with respect to codeine.

Study CODE-T60-PLFS-1 assessed the comparative bioavailability of Roxane Laboratories' codeine sulfate tablets after oral administration of 60 mg doses as 1 x 60 mg, 2 x 30 mg and 4 x 15 mg under fasted conditions. Mean plasma concentrations of codeine after administration of 60 mg of codeine as 1 x 60 mg, 2 x 30 mg, and 4 x 15 mg tablets were essentially super imposable. Mean values for all pharmacokinetic parameters were comparable for all three treatments with geometric mean ratios for C_{max}, AUC(0-t), and AUC(inf) of approximately 100% for all comparisons. All of the associated 90% confidence intervals were well within the 80% to 125% equivalence window, demonstrating bioequivalence among the three tablet strengths with respect to codeine.

A summary of the PK parameters after oral administration of 60 mg doses of Roxane Laboratories' codeine tablets as 1 x 60 mg, 2 x 30 mg, and 4 x 15 mg tablets to healthy volunteers under fasted conditions is shown in the following table from Dr. Agrawal's review.

Parameter ¹	1 x 60 mg	2 x 30 mg	4 x 15 mg
C _{max} (ng/mL)	169 ± 46.5 (18)	157 ± 37.9 (18)	159 ± 41.5 (18)
T _{max} (h)	1.13 (18) [0.25 – 1.50]	1.00 (18) [0.50 – 2.00]	1.00 (18) [0.50 – 2.00]
AUC(0-t) (h×ng/mL)	614 ± 146 (18)	624 ± 136 (18)	626 ± 140 (18)
AUC(inf) (h×ng/mL)	623 ± 146 (18)	633 ± 136 (18)	634 ± 141 (18)
λ _z (h ⁻¹)	0.2358 ± 0.0376 (18)	0.2287 ± 0.0391 (18)	0.2162 ± 0.0442 (18)
t _{1/2} (h)	3.01 ± 0.49 (18)	3.11 ± 0.52 (18)	3.34 ± 0.71 (18)
Ln(C _{max})	5.09 ± 0.29 (18)	5.03 ± 0.23 (18)	5.03 ± 0.26 (18)
Ln[AUC(0-t)]	6.39 ± 0.26 (18)	6.41 ± 0.21 (18)	6.42 ± 0.23 (18)
Ln[AUC(inf)]	6.41 ± 0.26 (18)	6.43 ± 0.21 (18)	6.43 ± 0.23 (18)

¹Arithmetic mean ± standard deviation (N) except for T_{max} for which the median (N) [Range] is reported.

In summary, review of the submitted Clinical Pharmacology studies showed the following:

- The extent and rate of exposure of codeine was dose proportional after oral administration of 1 x 15 mg, 1 x 30 mg, and 1 x 60 mg doses of Codeine Sulfate Tablets.
- Oral administration of Codeine Sulfate Tablet 60 mg under fed conditions resulted in no clinically significant change in the rate or extent of absorption of codeine when compared to fasted conditions.
- Oral administration of Codeine Sulfate Tablet 15 mg Q4H x 5 days resulted in steady-state plasma concentrations of codeine within 48 hours. Mean plasma concentrations and mean values for C_{max} and AUC(0-4) for codeine were consistent across the six individual doses on Day 5. Codeine comprised the largest portion of circulating material (~55%) followed by M3G (~36%), M6G (~6%), and morphine (~2%) respectively.
- Codeine Sulfate Tablet 30 mg was bioequivalent to reference product Tylenol® #3 (Codeine Phosphate 30 mg) with respect to codeine.
- After oral administration at a total dose of 60 mg, the 15 mg, 30 mg, and 60 mg codeine sulfate tablets demonstrated formulation bioequivalence with respect to codeine.

From the clinical pharmacology perspective, this NDA may be approved.

5. Clinical Microbiology

This section is not applicable to this submission.

6. Clinical/Statistical- Efficacy

The efficacy of codeine has been established in combination products, and it has been used for decades both in combination with other drugs and as an unapproved single entity product to treat mild-to-moderate pain. In order to meet the requirements for approval for single-entity codeine, the efficacy of codeine sulfate oral tablets in this NDA submission is based on published literature. No new clinical efficacy studies were performed in support of this

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application. The Agency agreed to accept a literature-based submission at the Pre IND meeting held in January of 2004, given the long history of codeine use in the United States, and the large amount of published literature available regarding the efficacy of oral codeine.

The Applicant's initial proposal was to submit relevant literature published between 2003 and 2007; however the Division requested that the literature search include articles published since 1960. The Applicant was encouraged to submit literature that represented the Agency's standards for adequate and well-controlled clinical trials, that is, randomized, double-blind, controlled, superiority trials with appropriate statistical analyses.

Prior to the NDA submission, the Division reviewed 159 literature articles submitted by the Applicant in order to assess their adequacy for support of efficacy of codeine sulfate. Drs. Yasmine Choudhry and Mwango Kashoki completed this review on July 10, 2007, and found that the submitted literature appeared adequate to support the NDA application.

The primary review of efficacy for this NDA was completed by Dr. Carolyn Yancey. Of the 159 articles submitted in support of the efficacy of codeine, the routes of administration and formulations studied included oral immediate-release codeine (145 references), oral controlled-release codeine (6), rectal codeine (1), and intramuscular codeine (7). The studies included multiple pain models, including post-operative pain, dental pain, chronic pain, postpartum episiotomy pain and a number of others. Single-entity codeine was compared to placebo and active comparators, including codeine combination products. The references included assessments of single and multiple-dose codeine administration.

The interpretation of the results presented in all of the reviewed literature articles is limited by the absence of information regarding details of the study protocols, protocol deviations and violations, the lack of raw data and subsequent unknown reliability and integrity of the data, and lack of information regarding the specific methods of statistical analysis utilized, including but not limited to the handling of missing data. The table below describes the articles reviewed by Dr. Yancey that were supportive of the efficacy of oral codeine for treatment of acute pain in adults, and is followed by a brief summary of each study, its findings, and specific limitations. For a more detailed review of the articles please refer to Dr. Yancey's review. The full citation for each article may be found at the end of this review.

Study Design	Population	Treatments	Duration	Pain Measures	Results
DB, R, PC Ref#20	N=137 Post-episiotomy pain	Codeine/APAP Codeine (30mg) APAP Placebo	single-dose	Pain severity 0-5 Pain relief 1-5	All superior to placebo:
DB, R, PC Ref#69	N=120 Dental pain	Codeine/APAP Codeine (60mg) APAP Placebo	single-dose	Pain intensity 0-10 Pain relief 0-4	All superior to placebo

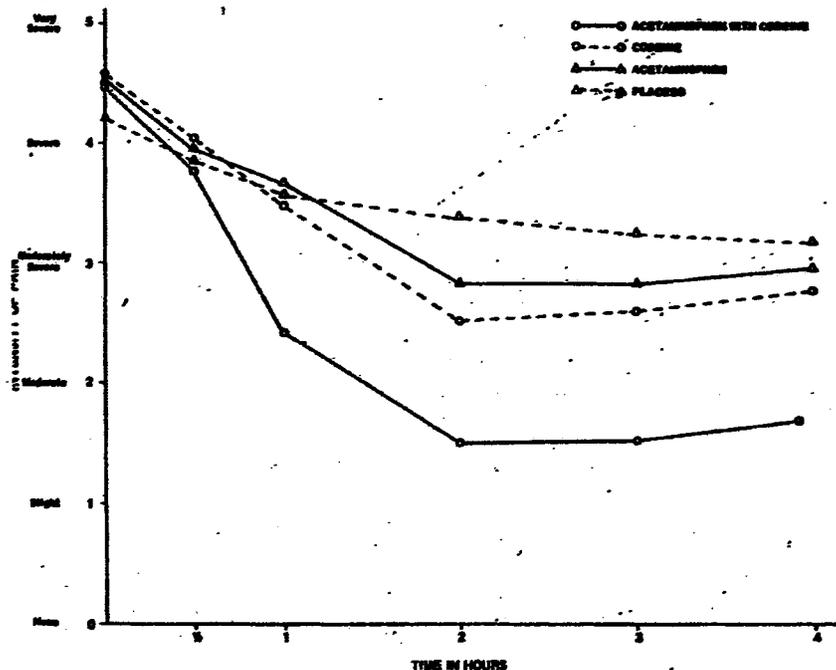
DB, R, PC Ref#56	N=501 Dental pain	Dextropropoxyphene NME (Ro-4-1778/1) Codeine (60mg) Placebo	multiple-dose 48 hours	Pain relief	Codeine more effective than DXP or placebo
DB, R, PC, XO Ref #78	N= 44/60 chronic pain	Z.424 Codeine 60mg Placebo	single and multiple-dose (3 days)	Pain intensity 0- 3	All superior to placebo
DB, R, PC Ref #24	N=127 episiotomy pain	butorphanol codeine 60mg placebo	multiple-dose 24 hours	Pain severity 0-4	All superior to placebo
DB, R, PC, XO Ref #40	N=94 post orthopedic surgery	codeine phosphate 65mg Dextropropoxyphene 100mg Meperidine 100mg Placebo	multiple dose (3 days)	Pain relief	All superior to placebo

Summaries of individual references

Study 20 was a double-blind, randomized, placebo controlled, single-dose study of patients with moderate-to-severe post-episiotomy pain that demonstrated the efficacy of codeine over placebo. One hundred thirty-seven post-partum patients were randomized in a 1:1:1:1 ratio to receive a single dose of APAP 600mg/codeine 30mg, APAP 600mg, codeine 30mg, or placebo when the complaint of moderately-severe to severe episiotomy pain was made. Pain intensity was measured using a six point scale, where 0 = no pain, and 5 = very severe pain. Pain relief was also measured using a five point scale, where 1 = worse pain, and 5 = pain completely gone. Following treatment with study medication, pain intensity and relief were measured at ½, 1, 2, 3, and 4 hours after dosing. Any patient who received rescue medication during the four hours post-treatment was considered a treatment failure. The pain intensity recorded prior to rescue medication administration was used in the statistical analysis for these subjects. The results of the study were statistically analyzed using the Mantel and Haenzel method of pairwise comparisons of all treatments. The Chi Square statistic was used to test for association between treatment and response.

The results of the study showed that a dose of APAP 600mg/codeine 30mg was superior to 600mg APAP alone, 30mg codeine alone, and placebo in decreasing pain intensity and improving pain relief. In addition, codeine alone was statistically superior to APAP alone at a $p < 0.01$ level, and both were superior to placebo ($p < 0.01$) for both pain intensity and relief. The figure below (excerpted from the reference) illustrates the change in pain severity for each treatment group over four hours.

Figure 1 Comparison of the Change in Severity of Pain



While onset of pain relief was not measured using currently accepted methodology (double-stop watch), all active treatments appeared to show a decrease in pain intensity at one to two hours. In terms of duration of action, again not measured using current standards, the decrease in pain intensity from codeine alone appears to wane by the four hour time point. These findings support the commonly used dosing interval of four hours.

The authors completed a responder analysis of sorts, and measured the subjects' pain relief over time in terms of percentage of pain relief. Approximately 40% of patients who received codeine alone reported at least a 50% pain relief at two hours and approximately 50% of the patients reported at least a 50% pain relief at four hours. In contrast, the patients who received the APAP/codeine combination reported approximately 90% pain relief at 3 hours following treatment.

The study, as reported, demonstrated that codeine 30mg was statistically superior to placebo in the treatment of moderate-to-severe post episiotomy pain. The waning of pain relief by four hours is consistent with the commonly used dosing interval of four hours. Limitations regarding interpretation of the results in addition to those discussed at the beginning of the efficacy section of this review include the following: The authors did not designate a primary endpoint, and carried out analyses of changes in pain intensity and pain relief without correction for multiple endpoints and multiple comparisons between treatments. The true onset and duration of pain relief as measured in this study is informative, however does not meet current standards in terms of measurement.

Study 69 was a double-blind, randomized, placebo-controlled trial that supports findings of efficacy of a single dose of 60mg of codeine over placebo, and the combination of codeine and acetaminophen over each agent alone using a dental pain model (removal of impacted tooth). Patients (n=128) were randomized to a single dose of APAP with codeine, APAP alone, codeine alone, or placebo in a 2:2:1:1 allocation, and were instructed to take their study medication when they could no longer tolerate the pain post operatively. Pain intensity and relief were measured by subjects using numerical rating scales (0-9 pain intensity, and 0-5 pain relief) hourly for five hours post-treatment. Subjects were allowed rescue medication (APAP/codeine), and if administered prior to five hours post-treatment, the pain intensity and relief scores obtained immediately prior to rescue were carried forward for analysis.

The authors calculated the following measures: hourly pain intensity differences from baseline (PID), sum of PIDs (SPID), total pain relief (TOTPAR), largest pain intensity difference (PEAKPID), largest pain relief (PEAKREL), and time to remediation. The study was analyzed using the "2 x 2 factorial design" appropriate for testing the combination of two constituent compounds in a combination drug. Tables from Dr. Yancey's review summarizing the efficacy measures and statistical significance as determined by the authors follow:

Table X Summary of Efficacy Measures

Summary of Efficacy Measures - Literature Reference # 69				
Treatment	No. of Patients	Mean (standard deviation)		
		SPID	TOTPAR	Median time to remediation
1000 mg APAP/ 60 mg Codeine	41	9.71 (10.49)	11.45 (5.01)	4.17
1000 mg APAP	41	6.17	8.68 (5.25)	3.25
60 mg Codeine	21	4.33 (11.80)	7.48 (5.58)	2
PBO	17	-2	4.94 (6.13)	1.47

Abbreviations: PBO = placebo; APAP = acetaminophen; mg = milligrams; SPID = sum pain intensity difference score; TOTPAR = total pain relief score

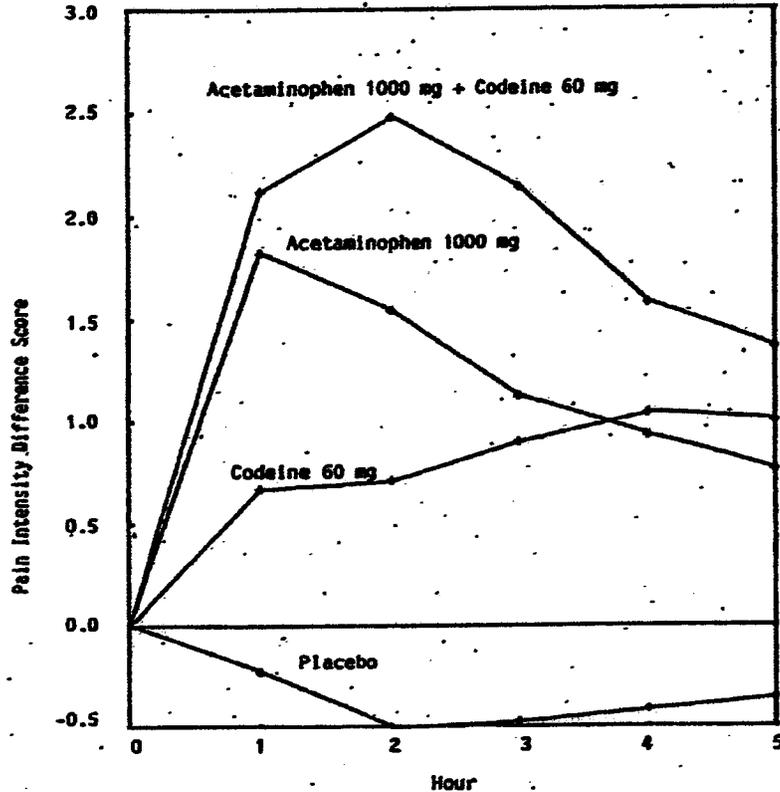
Table X: Significance levels (one-tailed)

	Acetaminophen 1000 mg	Codeine 60 mg
Contribution to the analgesic effect of the combination		
SPID	0.0014	0.0246
PEAKPID	0.0002	0.032
TOTPAR	0.0001	0.0012
PEAKREL	0.0001	0.012
Duration of analgesia combination versus	0.0047	0.0021

The authors reported that both acetaminophen and codeine effects were statistically significant according to their one-tailed statistical analysis.

The figure below extracted from the literature reference illustrates the mean PID scores over time. Codeine is shown to be numerically superior to placebo. There was no statistical analysis. A similar result was reported regarding pain relief, in that codeine was numerically superior to placebo, and acetaminophen alone and the combination of codeine and acetaminophen were each superior to codeine alone and placebo.

Figure X: Mean PID Scores versus Time



The median time to remedication for codeine alone was two hours, compared to three hours for APAP alone, 4 hours for APAP/codeine and 1.47 hours for placebo.

The results of this study show that codeine 60mg appears superior to placebo in the treatment of pain resulting from dental extractions. The dental pain model is appropriate for analgesic trials of acute pain, however lack of details regarding the baseline pain scores and the comparability of the treatment groups make the data difficult to interpret.

Study 56 was also a double-blind, randomized, placebo-controlled trial in patients with dental pain that demonstrated the efficacy of 60mg of codeine over placebo. In this study, codeine alone was compared to dextropropoxyphene 65mg, a new molecular entity (Ro4-1778/1), and placebo in subjects who underwent dental extractions. Approximately 500 subjects were randomized equally into the four treatment groups, and instructed to take one capsule every 4 hours as needed for pain. Subjects returned 48 hours following their procedure to obtain assessments of pain relief obtained from the first dose of study medication and multiple doses of study medication. All assessments were based on the subject's recall of the prior 48 hours. The results showed that codeine 60mg was statistically superior to placebo and dextropropoxyphene at the $p < .01$ level for both single and multiple doses.

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The interpretation of the results of this study is limited by the methodology used to obtain pain relief data. The subjects were asked to recall their pain relief over a 48 hour period, which is known to lead to inaccuracies in reporting and is not the current standard for the collection of patient reported pain outcomes. The authors attempted to minimize this by assessing an "all or none" effect on analgesia which would not take into account different degrees of analgesia. Limitations related to multiple endpoints and lack of information regarding data integrity and reliability also apply to this study report. With these limitations in mind, it appears that codeine 60mg was superior to placebo for the treatment of post-extraction dental pain during the first 48 hours.

Study 78 was a randomized, double-blind, placebo-controlled crossover trial that assessed the analgesic efficacy single and multiple doses of 60mg of codeine in hospitalized patients with chronic pain. Comparators included a new molecular entity and placebo. The single-dose aspect of the study was designed so that each subject received one dose of each medication over three days (not necessarily consecutive) in a randomized order. Medication was administered when a subject complained of moderate or severe pain. Pain intensity was reported by the subject prior to drug administration and hourly for five hours following using a four-point scale where zero equaled no pain and three equaled severe pain.

The second part of the study assessed multiple doses of each medication. Each subject received each of the three treatments for one day on a TID schedule, apparently regardless of pain intensity prior to dosing. The treatment days may or may not have been consecutive. Pain intensity scores were obtained from the subjects at the time of dosing and two hours after each dose.

For analysis of single dose efficacy, the authors calculated hourly PIDs, and the SPID at 5 hours (SPID5). Analysis of variance was used to statistically show that codeine 60mg was superior to placebo for single dose efficacy based on the SPID5. Similar analyses were performed for the multiple-dose efficacy assessment, and again, codeine was statistically superior to placebo at the $p < 0.05$ level. It appears the difference between the total pain intensity scores between treatment groups were used in the statistical calculations.

The results of this study appear to show superiority of codeine 60mg over placebo for single and multiple doses in a chronic pain model. Although the study population did not represent the group of patients targeted by the proposed indication of acute pain, chronic pain patients have been included in trials of analgesics for acute pain, and may be acceptable. A specific limitation regarding the interpretation of these results relates to lack of washout between study drugs. In both periods of the study, subjects received each study drug after uncontrolled periods of time, most likely without adequate washout time between drugs, leading to a lack interpretability of the pain scores. Additionally, for acute pain trials, a SPID at 5 hours is not currently accepted as an adequate primary endpoint as it does not measure the durability of analgesia over an adequate time period. The current standard is the SPID over two to five days for the primary endpoint in analgesic trials of acute pain. Other limitations include those already mentioned as common to all of the literature based reports.

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Study 24 was a randomized, double-blind, placebo-controlled, multiple-dose efficacy trial comparing butorphanol tartrate 8 and 16 mg, codeine phosphate 60mg and placebo for the treatment of moderate to severe post-episiotomy pain. One-hundred-twenty-seven women were randomized in a 1:1:1 ratio to receive one of the study drugs every six hours for a total of four doses. They were to have pain severity of at least moderate to severe prior to the first dose. Pain severity was measured by an observer using a five point scale where zero equaled no pain and four equaled very severe pain. Pain severity was measured prior to dosing and at the following intervals after the first dose: 0.5 hrs, 1 hr, 2, 3, 4, 5, 6, 8, 12, 18, 20, and 24 hours.

According to the authors, subjects in all treatment groups had similar initial mean pain severity scores (~3). All active treatments, including codeine, were superior to placebo at 1, 2, and 3 hours post initial dose ($p < 0.05$). Codeine was not significantly better than placebo at 5 and 6 hours following the first dose, or at 6 hours following the second and third doses. It was however superior at 6 hours following the fourth dose. The authors also performed an analysis of the pain intensities summed at 2, 4, 6, 12, 18, and 24 hours. All showed codeine to be significantly superior to placebo at the $p < 0.05$ level. Pain relief was also assessed and was significantly better for codeine compared to placebo at all time points.

The results as presented by the authors appear to support the efficacy of multiple-dose codeine 60mg compared to placebo. The lack of superiority of codeine over placebo at time points after three hours is consistent with the usual dosing of codeine on a Q4 hours basis. Again, there are multiple limitations, including that an observer rated the subjects' pain, and there was no correction for the analysis of multiple endpoints. Information related to data integrity and reliability are also absent in this published article. However, given the apparent conduct of the study, these results appear to support the analgesic efficacy of multiple doses of codeine 60mg.

Study 40 is not summarized here, as it did not add additional support for the efficacy of codeine. The study design was similar to Study 78 (above) in that subjects received each study drug over a three day period without any washout between drugs. Details regarding this study may be found in Dr. Yancey's review.

In conclusion, the five references summarized above appear to be supportive of the efficacy of codeine 30mg and 60mg given as single and multiple doses for acute pain. Although caution must be exercised in the interpretation of the study results due to the numerous limitations inherent in the use of literature references (absence of information regarding the study protocol, deviations and violations; the lack of raw data and subsequent unknown reliability and integrity of the data; the lack of information regarding the specific methods of statistical analysis utilized, including but not limited to the handling of missing data), these references in combination with the decades of use of codeine for pain relief in already approved combination products provide adequate evidence of the efficacy of codeine for the treatment of acute pain.

None of the referenced articles above provided support for the efficacy of codeine 15mg. As with other opioid analgesics, the lower doses are often used in a stepwise fashion to titrate the

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patient to an adequate level of analgesia. The absence of data to support the efficacy of codeine 15mg does not preclude its approval.

Although dosing intervals for codeine were not assessed in accordance with current standards, the results of the reviewed studies generally support a dosing interval of every four hours.

7. Safety

Safety for single-entity codeine sulfate is supported by the Agency's prior findings of safety for the reference product Tylenol with Codeine #3 (acetaminophen 500mg/codeine phosphate 30mg). Tylenol with Codeine #3 is an oral combination product approved for the relief of mild to moderately severe pain. The applicant has provided support for the use of the referenced product through a relative bioavailability study (See Section 4).

Common adverse events associated with codeine are similar to those of other opioids and include lightheadedness, dizziness, sedation, nausea, vomiting, abdominal pain and constipation. Serious adverse events include overdose, severe respiratory depression, coma and death.

Codeine sulfate is a Schedule II controlled substance and like all opioids, its' use can result in abuse, misuse, psychological and or physical dependence, and tolerance.

A safety issue unique to codeine relates to its' use in nursing mothers. On August 17, 2007, an FDA Alert was issued regarding a very rare, but serious side effect in nursing infants whose mothers are taking codeine and are ultra-rapid metabolizers of codeine. Evidence suggests that individuals who are ultra-rapid metabolizers (those with a specific CYP2D6 genotype) may convert codeine to its active metabolite, morphine, more rapidly and completely than other people. In nursing mothers, this metabolism can result in higher than expected serum and breast milk morphine levels. One published case report of an infant death raised concern that nursing babies may be at increased risk of morphine overdose if their mothers are taking codeine and are ultra-rapid metabolizers of the drug.

Even at labeled dosage regimens, individuals who are ultra-rapid metabolizers may experience overdose symptoms. Signs of morphine overdose in infants include increased sleepiness, difficulty breastfeeding or breathing, or decreased tone. Nursing mothers may also experience overdose symptoms such as extreme sleepiness, confusion, shallow breathing or severe constipation.

The prevalence of this CYP2D6 phenotype varies widely and has been estimated at 0.5 to 1% in Chinese and Japanese, 0.5% to 1% in Hispanics, 1 to 10% in Caucasians, 3% in African Americans, and 16 to 28% in North Africans, Ethiopians, and Arabs. Data are not available for other ethnic groups.

As a result of this phenomenon, appropriate language has been added to the labels of all products containing codeine regarding ultra-rapid metabolizers and the prescribing of codeine to nursing mothers.

8. Advisory Committee Meeting

No Advisory Committee meeting was held regarding this application.

9. Pediatrics

Currently, the only approved analgesic that contains codeine and has dosing recommendations for the pediatric age group is acetaminophen/codeine oral solution (120mg/12mg/5ml), which has dosing instructions for ages 3 years and above. However, codeine is used commonly throughout the entire pediatric age range for the treatment of acute pain.

There is minimal data available from controlled studies evaluating the efficacy of codeine for pain in children, and also very little information in the literature regarding pharmacokinetics and safe and effective dosing in children.

The pediatric plan initially submitted by the Sponsor for this NDA was inadequate. The proposal was _____

b(4)

_____ A deferral for the initiation of all studies was requested until after the adult indication is approved. _____

b(4)

A deferral of pediatric studies is acceptable since the application is ready for approval in adults. It is not acceptable _____

b(4)

_____ In consultation with the Clinical Pharmacology team, it was determined that the metabolic pathways for codeine (predominantly CYP2D6) are consistently mature at age 1 month. Therefore, studies will be deferred for age 1 month to _____, of age, and waived below one month of age.

b(4)

The Division communicated to the Sponsor on 22 January 2009 via email regarding the inadequacies of their pediatric plan, including 1) _____

b(4)

_____ 2) _____ and 3) that PK, safety and efficacy studies must be conducted from age 1 month to _____

b(4)

_____ Study of patients below the age of one month will be waived based on the maturation of the metabolic enzymes necessary for the metabolism of codeine.

A revised pediatric plan was submitted to the Division on 29 January 2009 which is summarized as follows:

1. Objective: to evaluate the efficacy, safety, and pharmacokinetics (after single and multiple-doses) of immediate-release codeine sulfate in a pediatric population with

- _____ An age-appropriate formulation will be used for the younger pediatric subjects. b(4)
2. Three (3) studies will be conducted with subjects divided into the following age groups: 1 month – 2 years, 2 years – 12 years and 12 years – 17 years.
 3. Efficacy studies will be designed as superiority trials
 4. A deferral for these studies was requested until after approval of codeine for the adult indication.
 5. The estimated timeline is as follows:

Study Number	Protocol Submission	Study Initiation	Final Report Submission
Study #1 (12-17 years)	November 2009	April 2010	October 2011
Study #2 (2-12 years)	January 2010	June 2010	December 2011
Study #3(1 month-2 years)	May 2010	October 2010	April 2012

The Division presented the agreed upon Pediatric Plan to PeRC on March 11. Concurrence was obtained from the committee at that time.

10. Other Relevant Regulatory Issues

There are no outstanding regulatory issues. The regulatory requirements to support this 505(b)(2) application have been adequately addressed.

The Controlled Substance Staff is in agreement that Codeine sulfate tablets should remain subject to the controls imposed by Schedule II of the Controlled Substances Act, as proposed by the Applicant.

11. Labeling

The label was submitted in PLR format and is under review at this time. No proprietary name was proposed for this product.

DDMAC and DMETS have reviewed the label and provided comments regarding the removal of promotional and unclear language.

The Controlled Substance Staff is in agreement with the proposed drug abuse and dependence section of the label.

12. Recommendations/Risk Benefit Assessment

- Recommended Regulatory Action – Approval
- Risk Benefit Assessment - The overall benefit associated with immediate-release oral codeine sulfate tablets outweighs the risks associated its use.

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- Recommendation for Postmarketing Risk Management Activities - Codeine sulfate is an immediate-release Schedule II opioid analgesic and carries similar risks as other opioid analgesics in this category. The current practice of the Division is that risks associated with these products can be managed with appropriate labeling and routine pharmacovigilance. No Risk Evaluation and Minimization Strategy is recommended at this time.

- Recommendation for other Postmarketing Study Requirements
 - Studies to fulfill the PREA requirements to assess pharmacokinetics, safety, and efficacy in pediatric patients ages 1 month to 12 years, and 12 years to 17 years. b(4)

 - Preclinical post-marketing requirements:
 - Minimal genetic toxicology screen (two *in vitro* genetic toxicology studies, e.g., one point mutation assay and one chromosome aberration assay) with the isolated impurity, tested up to the limit dose for the assay.
 - Repeat dose toxicology of 90-days duration to support the proposed indication. b(4)

 - CMC post-marketing agreements
 - Submit dissolution profile data generated for a minimum of 20 production batches (first 10 batches for the 15 mg tablets and first 5 batches for each of the 30 mg and 60 mg tablets) during release and stability testing of commercial drug product. The dissolution profiles will include adequate number of data points to allow for comparison of the profiles, e.g., 10 min, 15 min, 30 min and 45 min. A statistical evaluation of batch to batch variability, between different drug product strengths and within the same batch during stability storage, sorted by the type of container closure, will be provided.

 - Submit available data for hardness and friability generated during release and stability testing of commercial drug product tablets. A statistical evaluation of batch to batch variability, between different drug product strengths and within the same batch during stability storage, sorted by the type of container closure will be provided.

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Literature References in Support of Efficacy

Study 20: Levin HM, Bare WW, Berry FN, Miller JM. Acetaminophen with codeine for the relief of severe pain in postpartum patients. *Current Therapeutic Research*, Vol. 16, No. 9, September 1974: 921-927.

Study # 24

Levin HM. Double-blind oral analgesic study of butorphanol in episiotomy pain: a comparison with codeine and placebo. *J Int Med Res*. 1978; 6:24-33.

Study # 40

Van Bergen WS, North WC, Karp M. Effect of dextro propoxyphene, meperidine and codeine on postoperative pain. *JAMA*, 1960; 172:1372-5.

Study # 56

Chilton NW, Lewandowski A, Cameron JR. Double-blind evaluation of a new analgesic agent in post-extraction pain. *Am J Med Sci*. 1961; 242:702-6.

Study # 69

Bently KC, Head TW. The additive analgesic efficacy of acetaminophen, 1000 mg, codeine, 60 mg, in dental pain. *Clin Pharmacol ther*. 1987;42:634-40.

Study #78

Martinetti L, Lodola E, Monafò V, Ferrari V. Clinical evaluation of an oral analgesic, Z.424, in patients with chronic pain. *J.Clin Pharmacol J New Drugs*, 1970; 10:390-9.

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/s/

Ellen Fields
7/15/2009 11:45:29 AM
MEDICAL OFFICER