

CLINICAL PHARMACOLOGY REVIEW

<i>NDA</i>	22-450	<i>Submission Dates</i>	05/13/2009
<i>Brand Name</i>	-		
<i>Generic Name</i>	IV acetaminophen		
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<i>OCP Division</i>	Division of Clinical Pharmacology-II		
<i>OND Division</i>	Division of Anesthesia, Analgesia, and Rheumatology Products		
<i>Sponsor</i>	Cadence Pharmaceuticals, Inc.		
<i>Relevant IND(s)</i>	58,362		
<i>Submission Type; Code</i>	505 (b) (2)	P	
<i>Formulation; Strength(s)</i>	Sterile solution for intravenous infusion, 1000 mg/vial		
<i>Indication</i>	Treatment of acute pain and fever		
<i>Proposed Dosing Regimen</i>	Single or repeated dose via a 15-minute intravenous infusion. The dose administered varied depending on age and body weight.		

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# **1. EXECUTIVE SUMMARY**

## **1.1. Recommendations**

The submission is acceptable from a Clinical Pharmacology and Biopharmaceutics perspective provided that a mutually satisfactory agreement can be reached between the sponsor and the Agency regarding the language in the package insert.

## **1.2. Phase IV Commitments**

None.

### **1.2.1. Summary of Clinical Pharmacology and Biopharmaceutics Findings**

#### **Background**

Acetaminophen Injection for Intravenous Use (ACETAVANCE™), subject of NDA22450, was developed by Cadence Pharmaceuticals, Inc. for the treatment of acute pain and fever in adults and pediatric patients. Although orally administered acetaminophen is extensively used as an effective antipyretic and analgesic agent, there is currently no parenterally administered antipyretic approved drug product for these indications in the US. An IV formulation of acetaminophen was first approved in 2001 for use in France and marketed as Perfalgan® by Bristol-Myers Squibb (BMS) starting in 2002. Currently, Perfalgan® is approved in approximately 80 countries. In 2006, Cadence licensed North American development and commercialization rights to IV acetaminophen from BMS and undertook its US development. ACETAVANCE provides the availability of an intravenous formulation with a rapid onset of action to address a longstanding and significant unmet medical need for patients who cannot use oral acetaminophen. As such, priority review is granted to this submission.

The clinical development program focused on establishing safety, efficacy, and PK characteristics of the product in patients with pain and fever (b) (4)

Two studies (CPI-APA-102 and Study EHRC #26095) in pediatric patients utilized population methods for PK assessment. (b) (4)

(b) (4). The (b) (4) phase 3 studies were designed to investigate the safety and efficacy (pain and/or fever) of IV acetaminophen in (b) (4) pediatrics (n=3).

The proposed dosing regimen for IV acetaminophen is as follows:

Adults and adolescents weighing 50 kg and over:

- 650 to 1000 mg every 4 to 6 hours e.g. 1000 mg q6h or 650 mg q4h to a maximum of 4000 mg in 24 hours. Minimum dosing interval of 4 hours.

Adults and adolescents weighing under 50 kg and all children:

- 12.5 to 15 mg/kg every 4 to 6 hours e.g. 15 mg/kg q6h or 12.5 mg/kg q4h to a maximum of 75 mg/kg in 24 hours. Minimum dosing interval of 4 hours.

Infants and Neonates:

- Infants 1 to 2 years old: 50 to 60 mg/kg in 24 hours e.g. 12.5 mg/kg q6h or 10 mg/kg q4h. Minimum dosing interval of 4 hours.
- Infants 29 days to 1 year old: 40 to 50 mg/kg in 24 hours e.g. 10 mg/kg q6h or 12.5 mg/kg q6h. Minimum dosing interval of 6 hours.
- Full-Term Neonates: 22.5 to 30 mg/kg in 24 hours e.g. 7.5 mg/kg q8h or 7.5 mg/kg q6h. Minimum dosing interval of 6 hours.
- Premature Neonates (postmenstrual age 32 – 36 weeks): 22.5 mg/kg in 24 hours e.g. 7.5 mg/kg q8h. Minimum dosing interval of 8 hours.

### **Mechanism of Action**

Although the exact site and mechanism of action of acetaminophen are not clearly defined, its effectiveness as an antipyretic agent has been attributed to its effect on the hypothalamic heat-regulating center, while its analgesic effect is due to raising the pain threshold.

### **Clinical Pharmacology**

(b) (4)

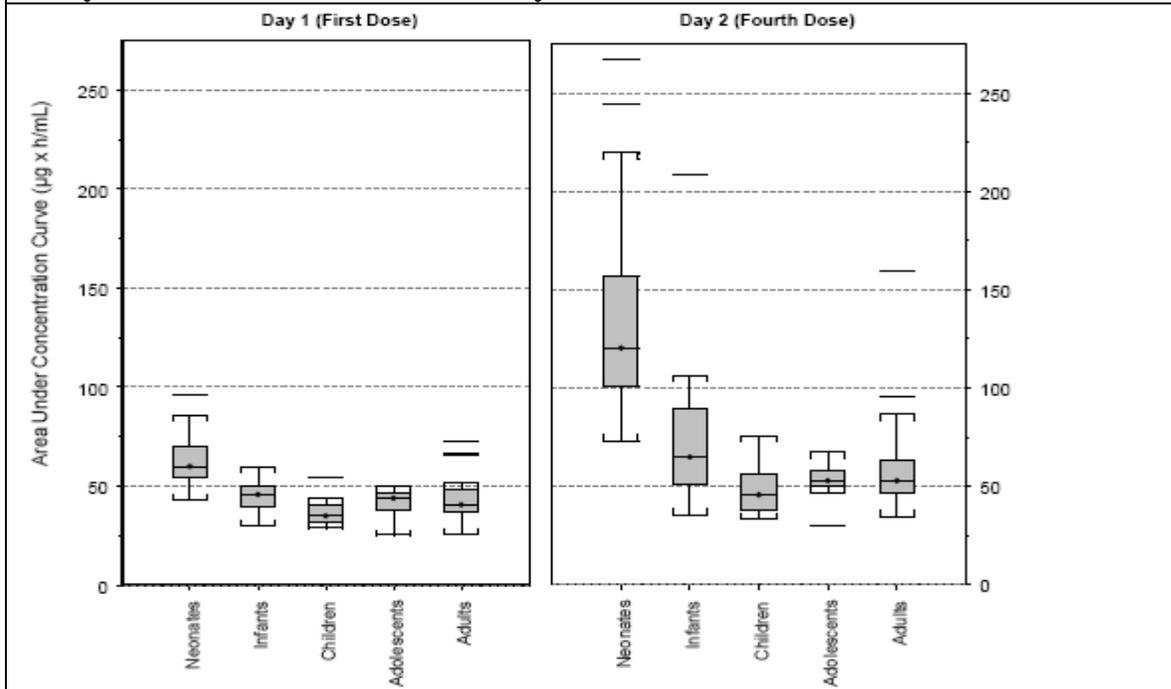
(b) (4)



Neonates, infants, children and adolescents The PK profile for IV acetaminophen for pediatric patients, ranging from premature neonates to adolescents, was evaluated in Study CPI-APA-102 and the Palmer Study. Following body weight normalized dosing

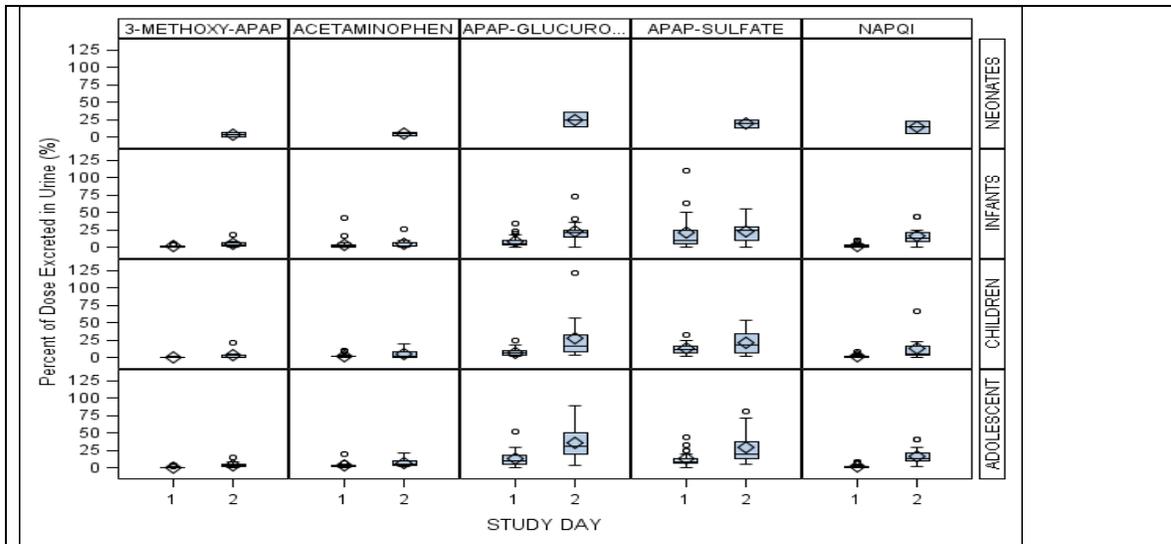
regimen, population PK model predicted acetaminophen  $AU_T$  values were consistent across age groups, with the exception of neonates, who displayed higher exposure values following both single and repeated treatments (i.e., Day 2, 4th dose).

**Figure 3. Relationships between age and acetaminophen AUC values for pediatric and adult populations receiving intravenous acetaminophen (15 mg q6h regimen) Study CPI-APA-102 and Palmer Study.**



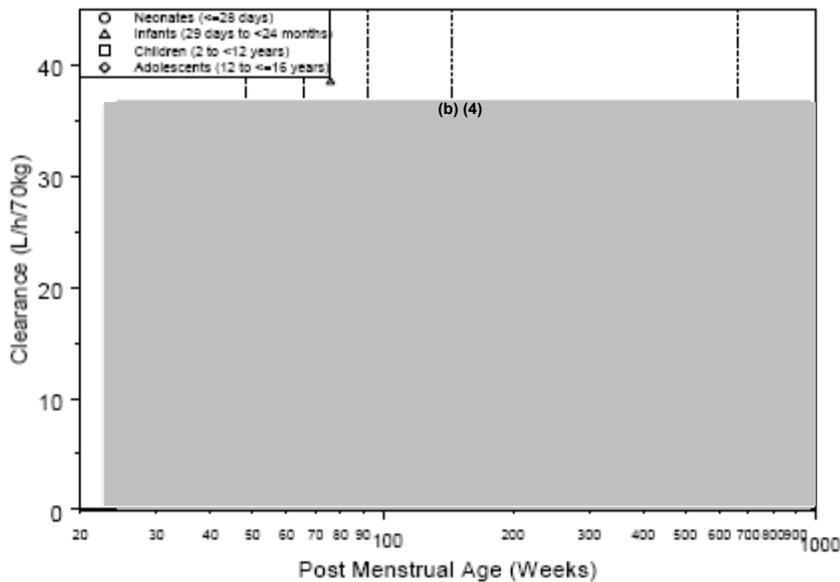
The percent of dose excreted in the urine in pediatric patients for NAPQI appeared to be comparable among different age groups (Study CPI-APA-102) and also comparable to the adults.

**Figure 4. Percent of individual metabolites eliminated after 12.5 mg/kg or 15 mg/kg was administered to pediatric patients (Study CPI-APA-102).**



A population PK analysis was conducted based on data from the two pediatric studies (Studies CPI-APA-102 and ERHC#26095). A two-compartment model with linear elimination was found to best fit the plasma concentration time profiles. Age and body weight were identified as significant covariates for PK parameter clearance (CL). Body weight was also a significant covariate for central volume of distribution (Vc), inter-compartmental clearance (Q) and peripheral volume of distribution (Vp).

**Figure 5: Maturation of standardized clearance versus post-menstrual age (Study CPI-APA-102 and the Palmer Study)**



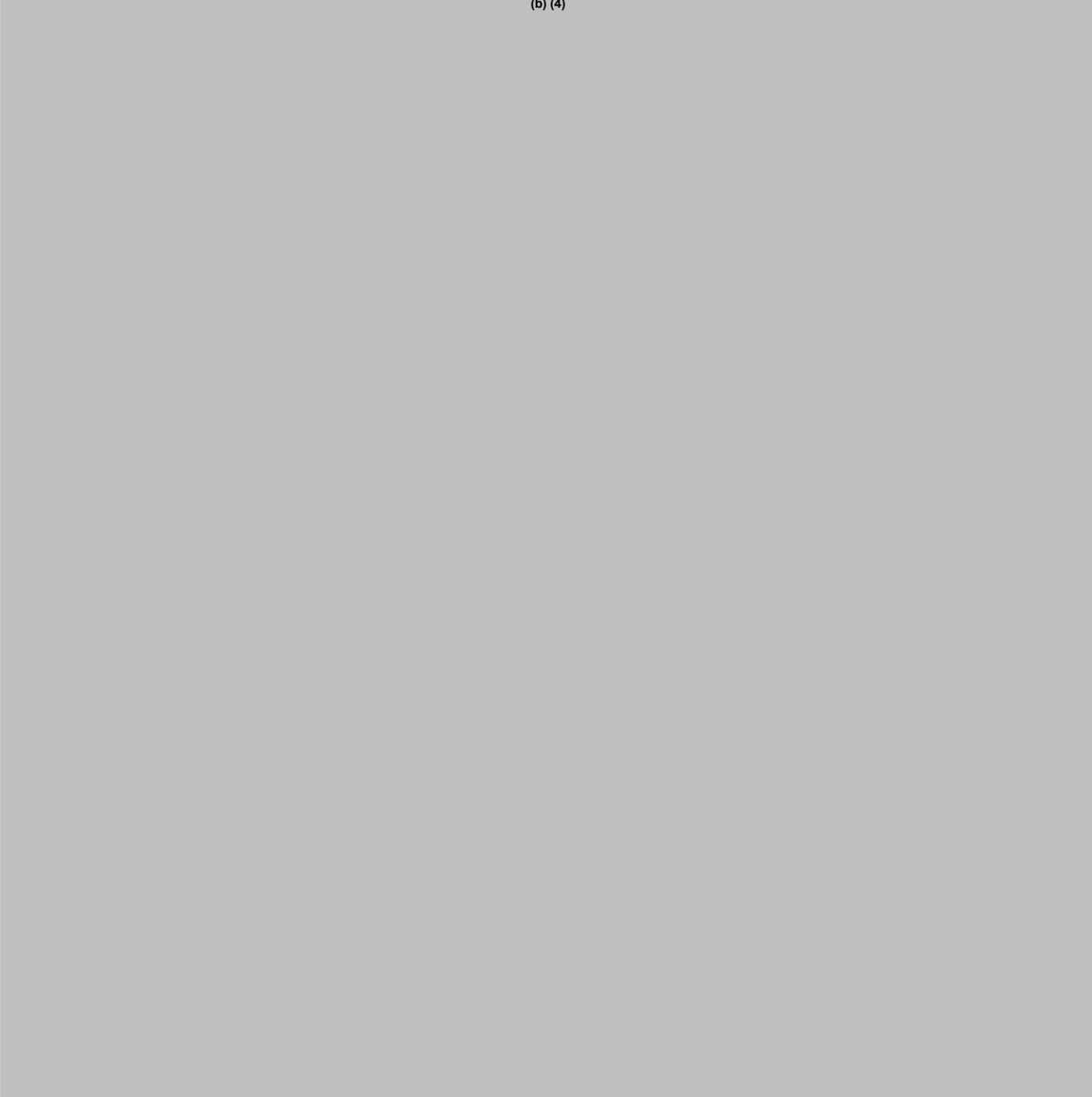
Note: Individual data points represent the standardized post hoc individual clearances from the final model. The y-axis on the right represents the ratio of the standardized CL over 18.3 L/h/70 kg.

\* Age represents PNA assuming a gestational period of 40 weeks.

Full line represents the equation of standardized clearance:  $CL(L/h/70\text{ kg}) = 18.3 \times \left[ 1 - 0.796 \times \exp\left(-\frac{(PMA - 40) \times \ln(2)}{32.6}\right) \right]$

Source: CADE-RAS-003 [Figure 6.3:7](#).

(b) (4)



## 2. QUESTION-BASED REVIEW

### 2.1. General Attributes

#### 2.1.1. What pertinent regulatory background or history contributes to the current assessment of the clinical pharmacology of this drug?

Acetaminophen Injection for Intravenous Use (ACETAVANCE™), subject of NDA22450, was developed by Cadence Pharmaceuticals, Inc for the treatment of acute pain and fever in adults and pediatric patients. Although orally administered acetaminophen is extensively used as an effective antipyretic and analgesic agent, there is currently no parenterally administered antipyretic approved for this indication in US. An IV formulation of acetaminophen was first approved in 2001 for use in France and marketed as Perfalgan® by Bristol-Myers Squibb (BMS) starting in 2002. Currently, Perfalgan® is approved in approximately 80 countries. In 2006, Cadence licensed North American development and commercialization rights to IV acetaminophen from BMS and undertook its US development. ACETAVANCE provides the availability of an intravenous formulation with a rapid onset of action to address a longstanding and significant unmet medical need. As such, priority review is granted to this submission.

The clinical development program focused on establishing safety, efficacy, and PK characteristics of the product in patients with pain and fever (b) (4)

Two studies (CPI-APA-102 and Study EHRC #26095) in pediatric patients utilized population methods for PK assessment. (b) (4)

The (b) (4) phase 3 studies were designed to investigate the safety and efficacy (pain and/or fever) of IV acetaminophen in (b) (4) pediatrics (n=3).

**2.1.2. What are the highlights of the chemistry and physical-chemical properties of the drug substance, and the formulation of the drug product as they relate to clinical pharmacology and biopharmaceutics review?**

ACETAVANCE is a sterile, clear, colorless, non pyrogenic, preservative free, isotonic formulation of acetaminophen intended for intravenous infusion. Each ready-to-use 100 mL glass vial contains 1000 mg acetaminophen (10 mg/mL).

**2.1.3. What are the proposed mechanism of action and therapeutic indication(s)?**

Although the exact site and mechanism of action of acetaminophen are not clearly defined, its effectiveness as an antipyretic agent has been attributed to its effect on the hypothalamic heat-regulating center, while its analgesic effect is due to raising the pain threshold.

**2.1.4. What are the proposed dosage(s) and route(s) of administration?**

The proposed dosing regimen for IV acetaminophen is to be given as a single or repeated dose as a 15-minute intravenous infusion by age and weight strata.

**Adults and adolescents weighing 50 kg and over:**

- 650 to 1000 mg every 4 to 6 hours e.g. 1000 mg q6h or 650 mg q4h to a maximum of 4000 mg in 24 hours. Minimum dosing interval of 4 hours.

**Adults and adolescents weighing under 50 kg and all children:**

- 12.5 to 15 mg/kg every 4 to 6 hours e.g. 15 mg/kg q6h or 12.5 mg/kg q4h to a maximum of 75 mg/kg in 24 hours. Minimum dosing interval of 4 hours.

**Infants and Neonates**

- Infants 1 to 2 years old: 50 to 60 mg/kg in 24 hours e.g. 12.5 mg/kg q6h or 10 mg/kg q4h. Minimum dosing interval of 4 hours.
- Infants 29 days to 1 year old: 40 to 50 mg/kg in 24 hours e.g. 10 mg/kg q6h or 12.5 mg/kg q6h. Minimum dosing interval of 6 hours.
- Full-Term Neonates: 22.5 to 30 mg/kg in 24 hours e.g. 7.5 mg/kg q8h or 7.5 mg/kg q6h. Minimum dosing interval of 6 hours.
- Premature Neonates (postmenstrual age 32 – 36 weeks): 22.5 mg/kg in 24 hours e.g. 7.5 mg/kg q8h. Minimum dosing interval of 8 hours.

## 2.2. General Clinical Pharmacology

### 2.2.1. What are the design features of the clinical pharmacology and clinical studies used to support dosing or claims?

The clinical development program focused on establishing safety, efficacy, and PK characteristics of the product in patients with pain and fever (b) (4)



Two studies (CPI-APA-102 and Study EHRC #26095) in pediatric patients utilized population methods for PK assessment. (b) (4)

The (b) (4) phase 3 studies were designed to investigate the safety and efficacy (pain and/or fever) of IV acetaminophen in (b) (4) pediatrics (n=3).

**Table 3. Tabular listing of all clinical studies in adult subjects.** (b) (4)



**Table 4. Tabular listing of all clinical studies of IV acetaminophen in pediatric patients.**

Study	Objectives	Dosing Regimen Used in the Study
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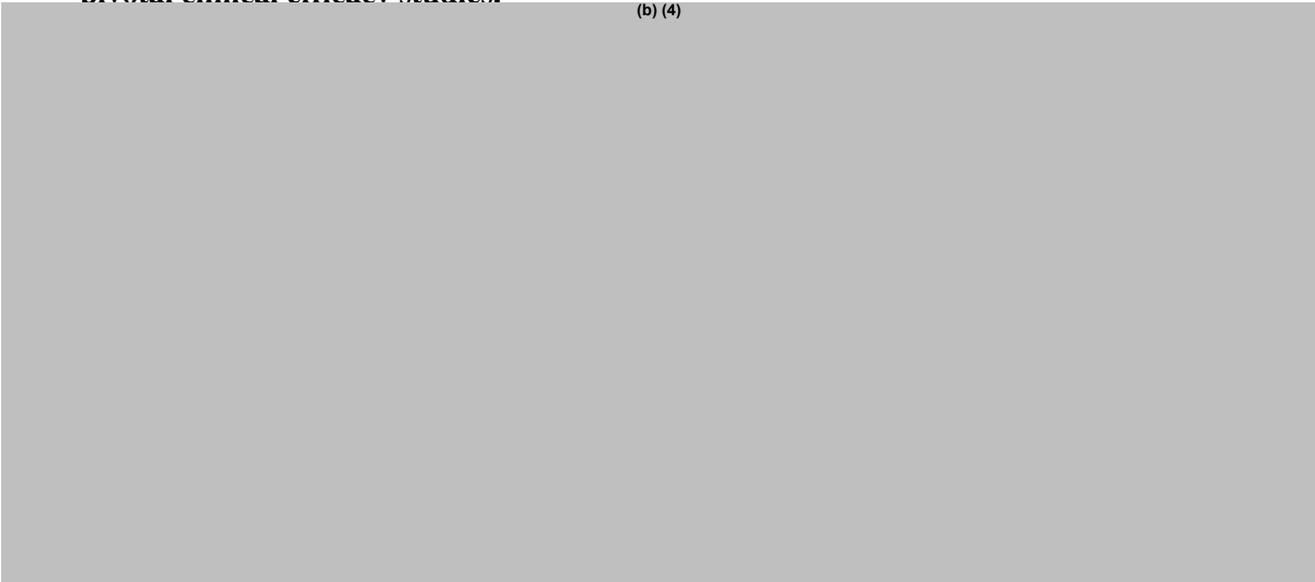
CPI-APA-102	Phase 1 PK and safety	R, OL, 48-h Full-Term Neonates: 12.5 mg/kg q6h, 15 mg/kg q8h (maximum daily dose of 50 mg/kg) Infants, children, and adolescents: 15 mg/kg q6h (maximum of 660 mg/dose) 12.5 mg/kg q4h (maximum of 1 g/dose) (maximum daily dose of 75 mg/kg or 4 g)
26095 (Palmer et al.)	Phase 1 PK and safety	28-<32 weeks PMA: 10 mg/kg q6h 32-<36 weeks PMA: 12.5 mg/kg q6h >=36 weeks PMA: 15 mg/kg q6h
RC210 3 006 (BMS)	Phase 3 safety and efficacy No PK	R, DB, SD, active-controlled, 2-parallel group 15 mg/kg SD APAP (n=95) 30 mg/kg SD PPA (n=88) (propacetamol)
CN145-001 (BMS)	Antipyretic efficacy and safety (acute fever) No PK	15 mg/kg SD APAP (n=35) (0.1-11.7 yrs) 30 mg/kg SD PPA (n=32) (0.2-9.5 yrs)
CPI-APA-352 (Cadence)	Safety and efficacy No PK	OL, MD, R, 29 days to <6 mths: 10-15 mg/kg q6h (n=1) 6 to <12 mths: 10-15 mg/kg q6h (n=1) 12 to <24 mths: 6.7-12.5 mg/kg q4h (n=1) 2-11 yrs: 6.7-12.5 mg/kg q4h (n=7) and 10-15 mg/kg q6h (n=33) 12-16 yrs: 6.7-12.5 mg/kg q4h (n=9) and 10-15 mg/kg q6h (n=42)

**2.2.2. What is the basis for selecting the response endpoints, i.e., clinical or surrogate endpoints, or biomarkers (also called pharmacodynamics, PD) and how are they measured in clinical pharmacology and clinical studies?**

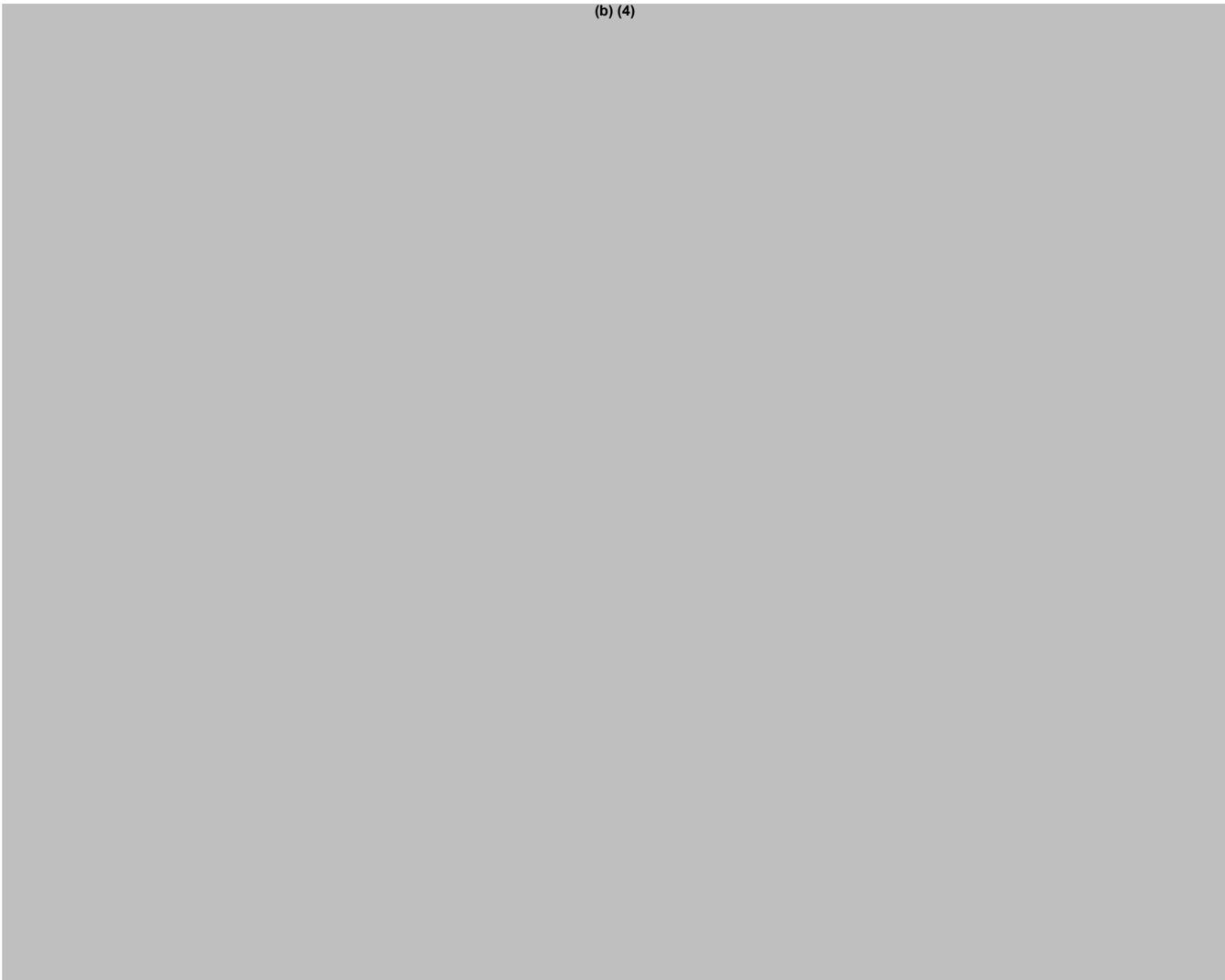
The primary and secondary efficacy/pharmacodynamic endpoints in the pivotal clinical studies are listed in the Table 5 below.

**Table 5. Efficacy/pharmacodynamic primary and secondary endpoints of the pivotal clinical efficacy studies.**

(b) (4)



(b) (4)



**2.2.3. Are the active moieties in the plasma (or other biological fluid) appropriately identified and measured to assess pharmacokinetic parameters and exposure response relationships?**

*Yes. Please refer to the analytical section for details.*

**2.2.4. Exposure-response**

**2.2.4.1. What are the characteristics of the exposure-response relationships (dose-response, concentration-response) for efficacy? If relevant, indicate the time to the onset and offset of the pharmacological response or clinical**

(b) (4)

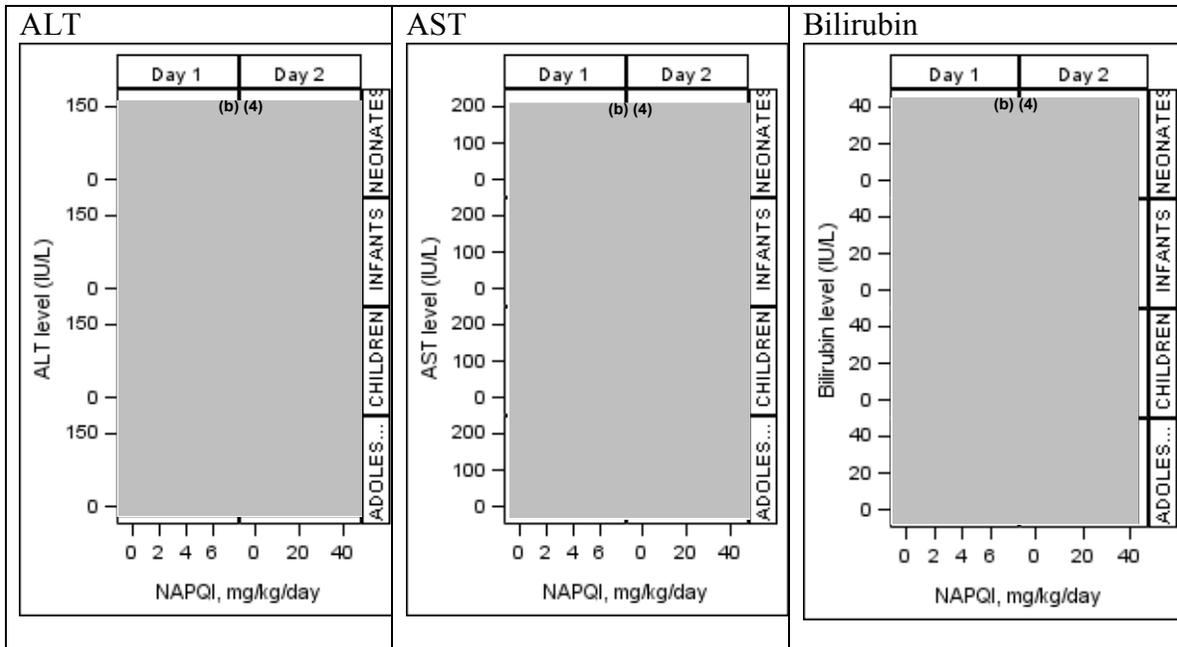


(b) (4)

**2.2.4.2. What are the characteristics of the exposure-response relationships (dose-response, concentration-response) for safety?**

(b) (4)

**Figure 8. Scatter plots of markers of liver function (AST, ALT, and Bilirubin) versus amount excreted as NAPQI conjugates (Study CPI-APA-102).**



**2.2.4.3. Does this drug prolong the QT or QTc interval?**

*No QT study was conducted in this submission.*

**2.2.5. What are the PK characteristics of the drug and its major metabolite?**

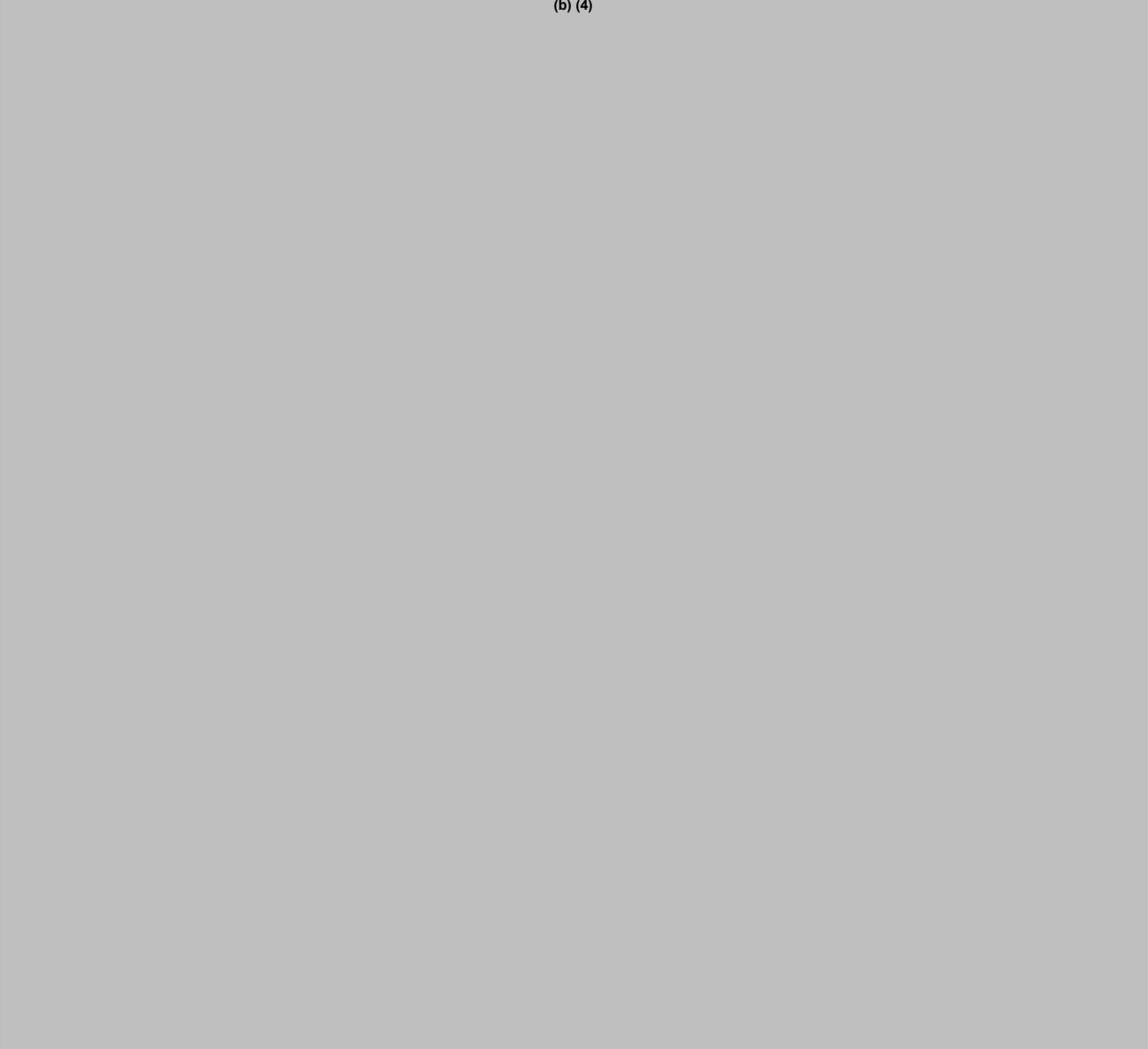
**2.2.5.1. What are the single dose and multiple dose PK parameters?**

(b) (4)

(b) (4)



(b) (4)



(b) (4)

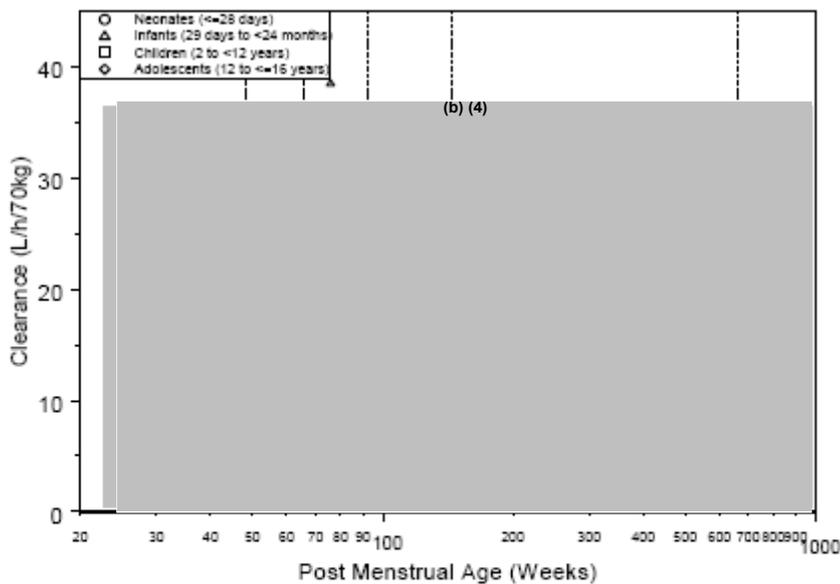
- 2.3.2. Based upon what is known about exposure-response relationships and their variability, and the groups studied (volunteers vs. patients); what dosage regimen adjustments, if any, are recommended for each of these subgroups (examples shown below)? If dosage regimen adjustments are not based upon exposure-response relationships, describe the alternative basis for the recommendation?**

a) pediatric patients

Based on population PK analysis, age and body weight were found to be significant PK covariates in the pediatric patients. Therefore, the body weight and age adjusted dosing regimen was proposed for the pediatric patients.

The meta-analysis based on combined datasets from study CPI-APA-102 and the palmer study showed that the body weight normalized clearance was a function of age as shown in the figure below.

**Figure 12. Maturation of standardized clearance versus post-menstrual age (Study CPI-APA-102 and the Palmer Study).**



Note: Individual data points represent the standardized post hoc individual clearances from the final model  
The y-axis on the right represents the ratio of the standardized CL over 18.3 L/h/70 kg

\* Age represents PNA assuming a gestational period of 40 weeks

Full line represents the equation of standardized clearance:  $CL(L/h/70\text{ kg})=18.3 \times \left[ 1 - 0.796 \times \exp\left(-\frac{(PMA - 40) \times \ln(2)}{32.6}\right) \right]$

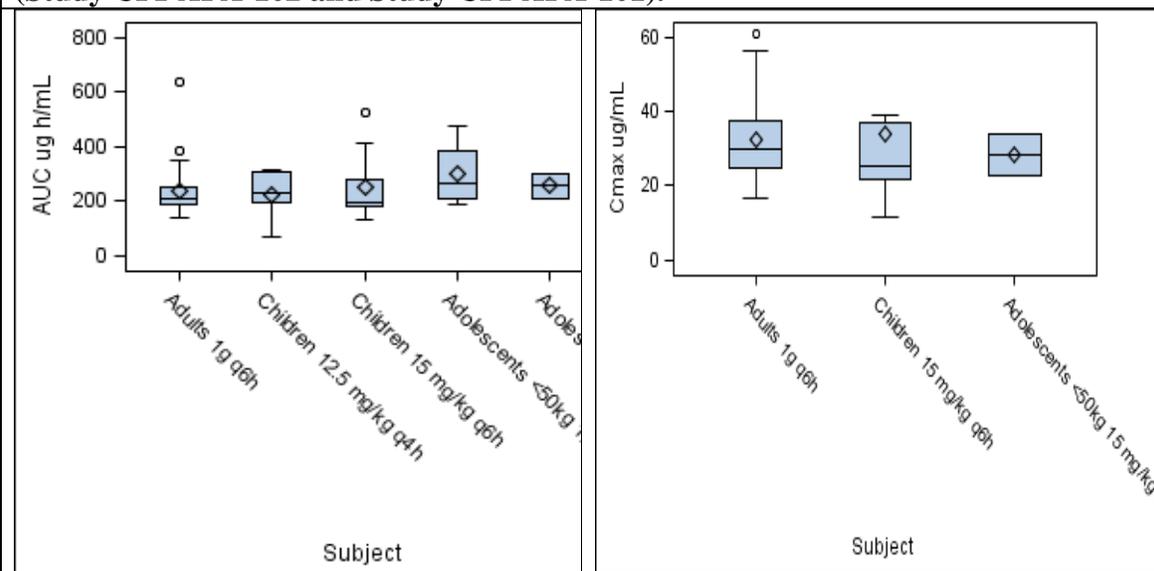
Source: CADE-RAS-003 [Figure 6.3:7](#).

Based on the agreement at the end-of-phase 2 (EOP2) meeting between the Agency and sponsor, the basis of approval of IV acetaminophen for pediatric indications of pain and fever was bridging adult efficacy data with the pediatric PK and safety data.

The proposed dosing regimen of adolescents weighing less than 50 kg and children is 15 mg/kg q6h or 12.5 mg/kg q4h for adolescents weighing less than 50 kg and all children and 1000 mg q6h or 650 mg q4h for adolescents weighing more than 50 kg. At the proposed dosing regimen, the exposure in children and adolescents were comparable to that in adults given 1 g q6h. Therefore, the proposed dosing regimen is appropriate in children and adolescents.

Acetaminophen exposure (AUC) in all children and adolescents <50 kg given 12.5 mg/kg q4h, 15 mg/kg q6h, and adolescents >50 kg given 1 g was comparable to AUC in adults given 1 g q6h.

**Figure 13. Acetaminophen daily exposure (AUC) in children and adolescents (2-16 year) (15 mg/kg q6h, 1 g q6h, or 12.5 mg/kg q4h) as compared to adults (1 g q6h) (Study CPI-APA-102 and Study CPI-APA-101).**



Note: 1) AUC was calculated based on noncompartmental analysis from Day 2 data.  
 2)  $AUC = AUCTAU * 4$  (if q4h) or  $AUC = AUCTAU * 6$  (if q6h).  
 3) Adults: N=38; Children 12.5 mg/kg q4h: N=6; Children 15 mg/kg q6h: N=15; Adolescents <50kg 12.5 mg/kg q4h: N=4, Adolescents <50 kg 15 mg/kg q6h: N=2; Adolescents  $\geq 50$  kg: N=11 (predicted).

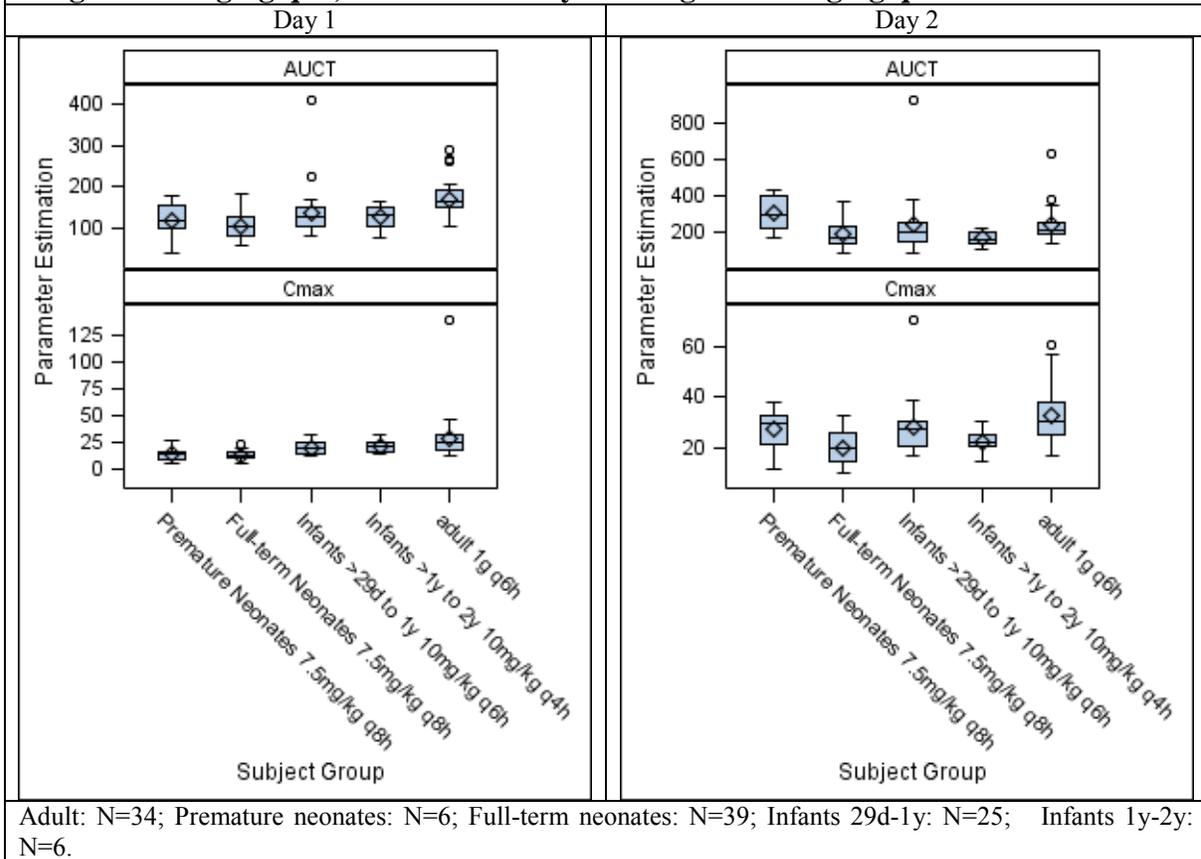
The proposed dosing regimen in neonates and infants are as follows:

- Infants 1 to 2 years old: 50 to 60 mg/kg in 24 hours e.g. 12.5 mg/kg q6h or 10 mg/kg q4h. Minimum dosing interval of 4 hours.
- Infants 29 days to 1 year old: 40 to 50 mg/kg in 24 hours e.g. 10 mg/kg q6h or 12.5 mg/kg q6h. Minimum dosing interval of 6 hours.
- Full-Term Neonates: 22.5 to 30 mg/kg in 24 hours e.g. 7.5 mg/kg q8h or 7.5 mg/kg q6h. Minimum dosing interval of 6 hours.
- Premature Neonates (postmenstrual age 32 – 36 weeks): 22.5 mg/kg in 24 hours e.g. 7.5 mg/kg q8h. Minimum dosing interval of 8 hours.

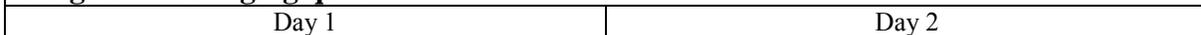
The above proposed dosing regimens were selected from a dose of 7.5, 10, 12.5 and 15 mg/kg given every 4, 6, 8, or 12 hours at a variety of combination using trial simulation by sponsor to reach optimal concentration range, which was prespecified based on adult and adolescent concentration data. The optimal dosing regimen was chosen such that the mean Cmax after the first dose was in the range of 10 to 20  $\mu\text{g/mL}$ , the mean Cmax after the repeated doses was in the range of <30  $\mu\text{g/mL}$ , and the drug exposure duration within 10 and 30  $\mu\text{g}$  was maximized whereas the exposure duration below 10  $\mu\text{g/mL}$  or above 30  $\mu\text{g/mL}$  was minimized (*details in Appendix 4.3*).

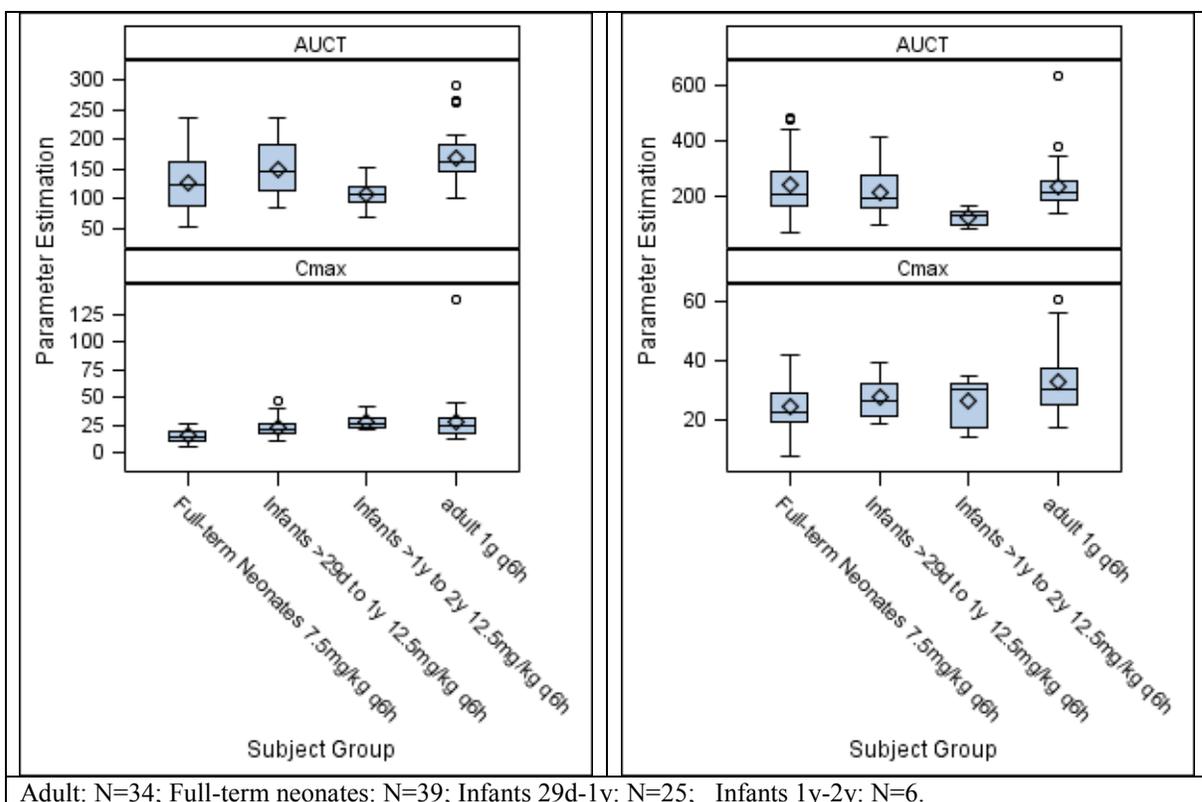
At the selected dosing regimens as shown in Figures 14 and 15, model predicted exposure in neonates and infants was comparable to the observed exposure in adults given 1g every 6 hours after both first dose and repeated doses.

**Figure 14. Exposure comparison with adults given 1 g q6h, for premature neonates given 7.5 mg/kg q8h, full-term neonates given 7.5 mg/kg q8h, infants 29-day to 1-year old given 10 mg/kg q6h, and infants 1-2 year old given 10 mg/kg q4 h.**



**Figure 15. Exposure comparison with adults given 1 g q6h for full-term neonates given 7.5 mg/kg q6h, infants 29-day to 1-year old given 12.5 mg/kg q6h, and infants 1-2 year old given 12.5 mg/kg q6h.**



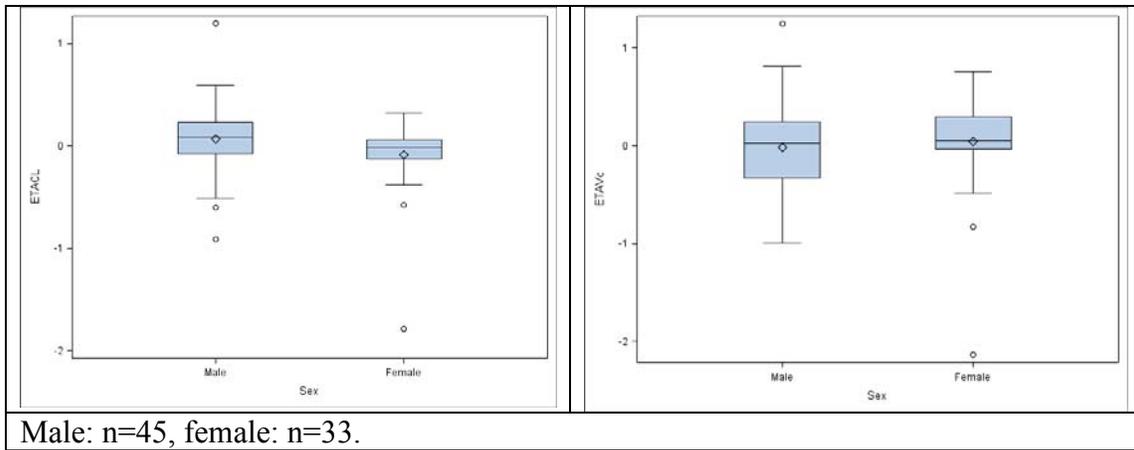


b) Gender

*Gender effect in adult population could not be evaluated due to few numbers of females in the study. Gender appeared not affecting the PK of IV acetaminophen in pediatric patients.*

In phase 1 clinical studies, only 3 out of 84 adult subjects were female. The few numbers of female subjects prevented rigorous comparison of acetaminophen PK between men and women. In study CPI-APA-102, the effects of gender on the PK profile of IV acetaminophen in pediatrics (N = 44 male and N = 31 female subjects) were evaluated in the population PK modeling. Gender was not a PK covariate.

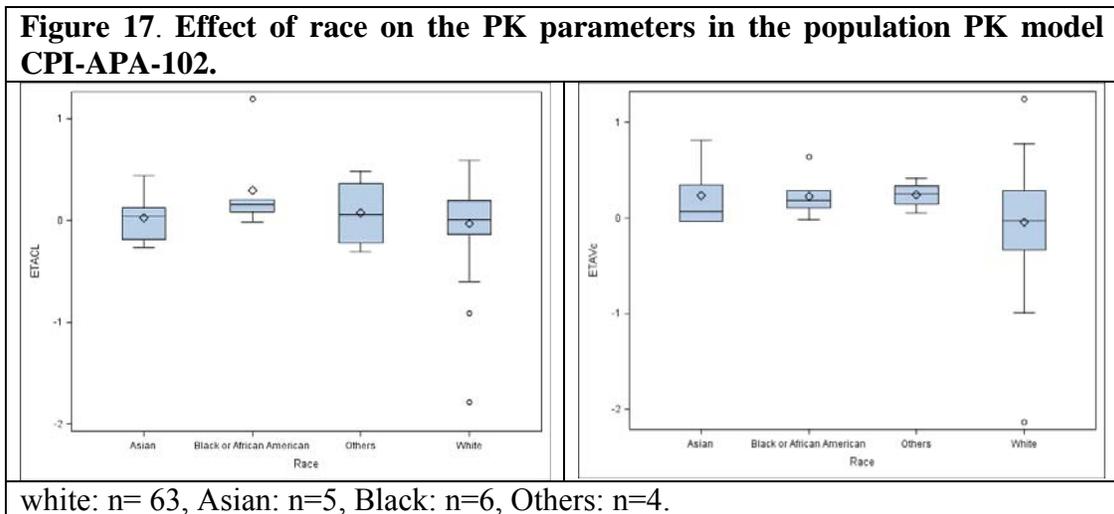
**Figure 16. Effect of sex on the PK parameters in the population PK model CPI-APA-102.**



c) race

*Race appeared not to affect the PK of IV acetaminophen.*

In Study 116-01-03, the PK parameters for single doses of IV acetaminophen 1000 mg were similar for 9 Caucasian and 10 African American subjects; mean (SD)  $AUC_{0-\infty}$  values were 71.5 (23.0) and 75.7 (21.7)  $\mu\text{g}\cdot\text{h}/\text{mL}$ , respectively and mean (SD)  $C_{\text{max}}$  values were 26.5 (6.9) and 30.2 (5.7)  $\mu\text{g}/\text{mL}$ , respectively. Race was not a PK covariate in the population PK analysis in pediatric studies.



d) Hepatic impairment

*The effect of hepatic impairment was not evaluated in this submission. Instead, sponsor relied on information from public domain.*

e) Renal impairment

*The effect of renal impairment was not evaluated in this submission. Instead, sponsor relied on information from public domain.*

## 2.4. Extrinsic Factors

### 2.4.1 What extrinsic factors (drugs, herbal products, diet, smoking, and alcohol use) influence exposure and/or response and what is the impact of any differences in exposure on pharmacodynamics?

*Pharmacokinetics of IV acetaminophen was not studied with regard to interactions with drugs, herbal products, diet, smoking in this submission. Instead, sponsor relied upon literature information to address the interactions with other drugs, smoking, and alcohol. In general, acetaminophen exhibited limited potential for drug-drug interactions.*

Summarized below are the results from the drug-drug interaction studies published in the literature.

Table 9. Literature summary of potential drug-drug interaction with acetaminophen.

Drug	Interaction Mechanism	Interaction potential
Alcohol	Alcohol induce CYP2E1 and a substrate of CYP2E1	In theory, acetaminophen overdoses during the window of sudden alcohol abstinence may produce a risk of acetaminophen-induced hepatotoxicity. However, based upon the literature it appears that therapeutic acetaminophen dosing is safe in general.
Anticonvulsions (carbamazepine, phenobarbital, phenytoin, diphenylhydantoin)	Nonspecific liver inducers	Literature summary from long term studies failed to show the anticonvulsions induced liver toxicity partly due to increased metabolism through non-toxic elimination pathway.
Caffeine	Substrate of CYP1A2	Enhance early exposure of oral acetaminophen. Not expect to affect IV acetaminophen.
Cimetidine	Inhibitor of CYP2E1	May not affect NAPQI formation at therapeutic doses. However, in case of acetaminophen overdose, cimetidine can be used in conjunction of N-acetylcysteine administration.
Difunisal		Increase acetaminophen level by 50%. Clinical significance not known.
Isoniazid	CYP 2E1 substrate and induce CYP2E1.	Increased risk of acetaminophen liver toxicity only in the short period of isoniazid treatment termination
Serotin-3-antagonists	PD interaction	Suspect to block analgesic effect of acetaminophen, however, it is not confirmed.
Warfarin	PD interaction	Acetaminophen may increase INR in patients taken warfarin

Source: page 79-81 in the summary-clin-pharm.pdf.

## 2.5. General Biopharmaceutics

### 2.7.1 What is the in vivo relationship of the proposed to-be-marketed formulation to the pivotal clinical trial formulation in terms of comparative exposure?

Bioequivalence was established between the to-be-marketed formulation and the pivotal clinical trial formulation for IV acetaminophen.

Three formulations of IV acetaminophen (referred to as the initial, current, and proposed commercial formulations) were used in the development program. A summary of the formulations of IV acetaminophen used in the clinical studies and the formulation proposed for commercial use in presented in Table 9.

**Table 9: Summary of IV acetaminophen formulations and dosages used in clinical trials.**

Study Number	Sponsor, Type of Study	IV APAP Dosage (b) (4)	Manufacturer	Batch/Lot Number
<b>Current Formulation</b>				
RC 210 3 006 <sup>2</sup> CN145-001 <sup>2</sup>	BMS: S/E, fever, pediatric S/E, fever, pediatric	1000 mg	BMS Delmas Laboratories <sup>1</sup>	FD 00007
(b) (4)				
CPI-APA-102 <sup>2</sup> (b) (4)	Cadence: PK, pediatrics	1000 mg	BMS (Anagni, Italy)	6H11817
CPI-APA-352 <sup>2</sup> (b) (4)	S/E, fever, pediatric			
<b>Proposed Commercial Formulation</b>				
(b) (4)				
Definitions: APAP = acetaminophen; BE = bioequivalence; BMS = Bristol-Myers Squibb; IV = intravenous; PK = pharmacokinetic; S/E = safety and efficacy <sup>1</sup> BMS Delmas Laboratories in Chambray Les Tours, France. <sup>2</sup> In the pediatric studies, patients were dosed on a mg/kg basis. <sup>3</sup> Lot 6F18792 was a non US Commercial, US clinical lot that was manufactured as a routine production lot in Anagni, Italy. <sup>4</sup> A 650 mg dose also was administered, but not assessed for bioequivalence between manufacturing sites. Source: Module 3, Section 3.2.P.2.2.1.2 (Formulation Development)				

(b) (4)

(b) (4)



## 2.6. Analytical Section

### 2.6.1. How are the active moieties identified and measured in the plasma and urine in the clinical pharmacology studies?

HPLC-MS/MS was the bioanalytical method used to analyze plasma samples for acetaminophen and the urine samples for acetaminophen and its metabolites.

### 2.7.2 How was the assay performed for the analytes?

The analytical assay for all the analytes for studies (b) (4), CPI-APA-102, (b) (4) appears adequate and validated.

**Table 11. A brief validation summary of the bioanalytical assay in human plasma.**

Validation Report Number	(b) (4)	VAL-RPT-810
Species/Sample Matrix		Human plasma
Analyte		Acetaminophen
Method Utilized		HPLC-MS/MS
Calibration Range		50 – 30,000 ng/mL
LLOQ (Accuracy)		50 ng/mL (98.5%)
Standard Curve Precision (ie, assay recovery)		68 to 86%
Specificity		No interference noted.
Inter-assay Precision (CV)		2.1 to 5.0%
Inter-assay Accuracy		95.9 to 102.3%
Intra-assay Precision (CV)		0.2 to 6.0%
Intra-assay Accuracy		97.7 to 102.3%
Testing Facility		4)
Clinical Study		CPI-APA-102

Definitions: CV = coefficient of variation; HPLC-MS/MS = high performance liquid chromatography separation with tandem mass spectrometer detection; LLOQ = lower limit of quantitation

**Table 12. A brief validation summary of the bioanalytical assay in human urine.**

Analyte	Acetaminophen	Acetaminophen sulfate	Acetaminophen glucuronide	3-methoxy acetaminophen
Calibration Range (µg/mL)	0.05-5	0.25-10	0.25-10	0.1-5
Precision (%CV)	7.1-27.8	3.9-33.2	8.5-28	6.7-9.7
Accuracy (%)	90-93	97.3-99.4	92.4-104.3	90.5-100.7
LLOQ (ug/mL)	0.05	0.25	0.25	0.1
Analyte	3-cysteiny acetaminophen	Acetaminophen mercapturate	Methylthioacetaminophen	
Calibration Range (µg/mL)	0.25-5	0.1-5	0.1-5	
Precision (%CV)	5.4-9.8	4.1-10.9	9.5-11.8	

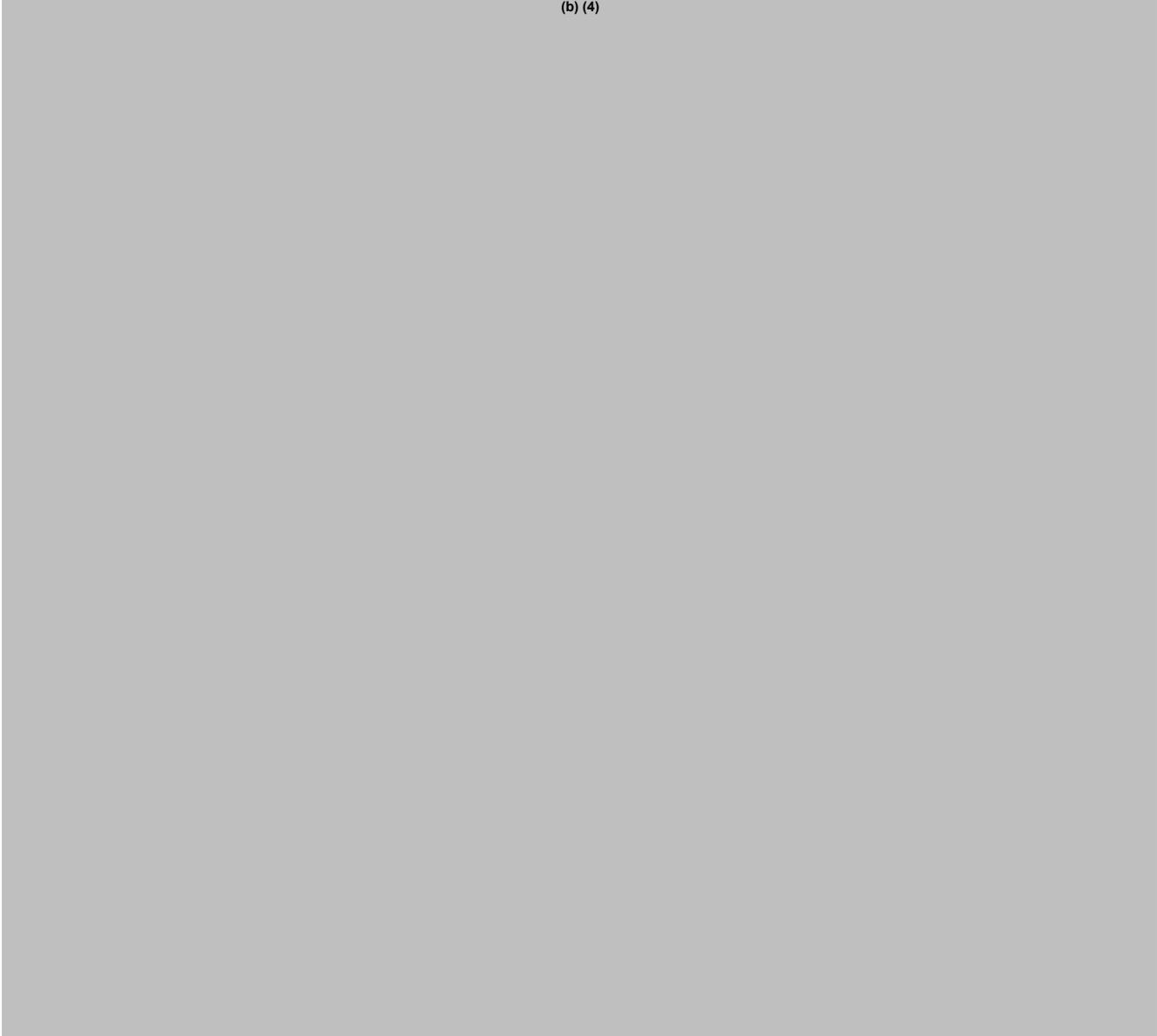
Accuracy (%)	97.3-98.5	96.7-98	91.5-98	
LLOQ (ug/mL)	0.25	0.10	0.10	

Source: m2007-28-voll.pdf

### 3. DETAILED LABELING RECOMMENDATIONS

(Reviewer suggested changes: ~~Strikeout text~~ should be removed from labeling and underlined text should be added to labeling)

(b) (4)



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U.S. PATENT NUMBERS: 6,028,222; 6,992,218

## 4.2. Individual Study Review

(b) (4)



**Cadence Study CPI-APA-102**

**Study Title:** A Prospective, Multi-Center, Randomized, Open-Label, Single and Repeated Dose, 48-Hour Study of Intravenous Acetaminophen in Pediatric Inpatients to Determine Pharmacokinetics and Safety in Acute Pain and Fever

**Objectives:** The primary objectives of this study were to define the single dose and multiple dose PK of IV acetaminophen given at various dosing regimens in pediatric inpatient populations [12.5 mg/kg q6h or 15 mg/kg every 8 hours (q8h) in neonates and

12.5 mg/kg q4h or 15 mg/kg q6h in infants, children, and adolescents], and to assess the safety of repeated doses of IV acetaminophen given under various dosing regimens in pediatric inpatients. Secondary objectives were to examine the PK differences resulting from various IV acetaminophen dosing regimens; to examine the exposure – safety relationship; and to compare the data obtained from this study to historical PK data of IV acetaminophen and IV PPA in pediatrics, as well as data from recently completed PK studies in adults.

**Study Design:** This was a multi-center, randomized, open-label study in infants, children, and adolescents requiring analgesic or antipyretic therapy. Subjects were randomized to one of two dosing regimens within each age strata: 12.5 mg/kg q6h or 15 mg/kg q8h in neonates and 12.5 mg/kg q4h or 15 mg/kg q6h in infants, children, and adolescents. The duration of treatment was 2 days (48 hours). Blood samples were taken for assay of acetaminophen following the first and last dose of IV acetaminophen, and at several time points in between (usually predose). Due to improvements in analytical assays, smaller sample volumes were required, and a less sparse sampling schedule was possible, resulting in a richer dataset of concentration values. Blood was collected for clinical laboratory tests and LFTs. Urine samples were collected for assay of acetaminophen and metabolites, as well as for urinalysis.

**Study Population:** The subjects enrolled in the study: 3 neonates ( $\leq 28$  days), 25 infants (29 days to  $< 24$  months), 25 children (2 to  $< 12$  years), and 22 adolescents (12 to  $\leq 16$  years). The majority of subjects in each age stratum were White/Caucasian, and there was a total of 44 males and 31 female patients enrolled in the study

**Bioanalytical Analysis:** Validated HPLC-MS/MS was used to analyze plasma samples for acetaminophen and the urine samples for acetaminophen and its metabolites.

**Data Analysis:** Both compartmental and non-compartmental analyses were used to analyze the plasma acetaminophen concentration-time profiles. Noncompartmental methods were used to analyze the urinary excretion of the free or primary methods.

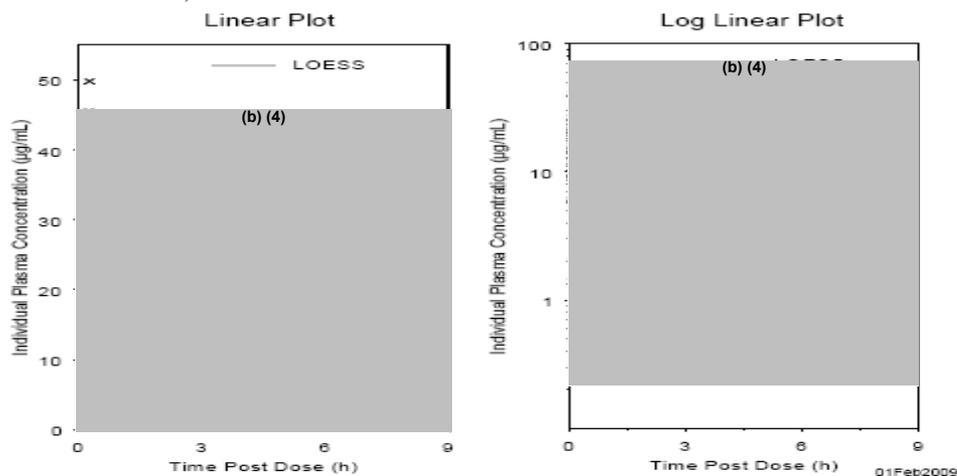
**Pharmacokinetic Results:** Noncompartmental analysis of the PK parameters is presented in the Table below:

**Table:** Summary statistics of noncompartmental analysis of the PK parameters of IV acetaminophen in study CPI-APA-102.

Treatment (Dosage Form, Dose, Route)	Mean (N, SD) Pharmacokinetic Parameters <sup>1</sup>			
	C <sub>max</sub> (µg/mL)	T <sub>max</sub> <sup>2</sup> (h)	AUC <sub>0-t</sub> (µg·h/mL)	t <sub>1/2</sub> (h)
IV acetaminophen: <u>12.5 mg/kg</u>	Dose 1 <u>12.5 mg/kg</u>	Dose 1 <u>12.5 mg/kg</u>	Dose 1 <u>12.5 mg/kg</u>	Dose 1 <u>12.5 mg/kg</u>
Neonates (≤ 28d) q6h	40.1 (2, 34.3)	0.450 (2, 0.0707)	70.3 (2, 39.8)	NA
Infants (29 d to < 24 mo) q4h	17.5 (13, 3.14)	0.232 (13, 0.1390)	31.6 (13, 7.69)	0.899 (1, NC)
Children (2 to < 12y) q4h	19.3 (9, 4.89)	0.211 (9, 0.0862)	32.4 (9, 10.7)	1.37 (3, 0.113)
Adolescents (12 to ≤ 16 y) q4h	17.4 (12, 5.63)	0.210 (12, 0.0764)	30.1 (12, 7.62)	1.79 (5, 0.147)
<u>15 mg/kg</u>	<u>15 mg/kg</u>	<u>15 mg/kg</u>	<u>15 mg/kg</u>	<u>15 mg/kg</u>
Neonates (≤ 28d) q8h	20.1 (1, NC)	0.333 (1, NC)	73.2 (1, NC)	NA
Infants (29 d to < 24 mo) q6h	20.3 (12, 3.05)	0.326 (12, 0.192)	51.1 (12, 6.53)	NA
Children (2 to < 12y) q6h	25.5 (16, 11.7)	0.235 (16, 0.105)	48.9 (16, 13.9)	2.37 (16, 0.601)
Adolescents (12 to ≤ 16 y) q6h	27.8 (10, 12.3)	0.240 (10, 0.104)	55.5 (10, 15.5)	2.86 (10, 0.464)
	Last Dose <u>12.5 mg/kg</u>	Last Dose <u>12.5 mg/kg</u>	Last Dose <u>12.5 mg/kg</u>	Last Dose <u>12.5 mg/kg</u>
	19.9 (2, 0.90)	0.455 (2, 0.177)	65.6 (2, 13.9)	3.88 (1, NC)
	19.9 (12, 5.88)	0.393 (12, 0.319)	42.8 (12, 17.87)	2.22 (8, 0.537)
	21.8 (6, 10.7)	0.168 (6, 0.100)	37.2 (6, 15.1)	3.11 (3, 1.19)
	33.2 (12, 26.8)	0.264 (12, 0.133)	56.0 (12, 31.6)	3.40(10, 0.521)
	<u>15 mg/kg</u>	<u>15 mg/kg</u>	<u>15 mg/kg</u>	<u>15 mg/kg</u>
	32.2 (1, NC)	0.250 (1, NC)	105 (1, NC)	NA
	36.0 (9, 43.2)	0.263 (9, 0.126)	78.7 (9, 52.2)	3.03 (9, 1.03)
	33.9 (15, 25.1)	0.293 (15, 0.186)	61.9 (15, 26.7)	3.19 (14, 0.922)
	26.7 (6, 9.15)	0.260 (6, 0.0155)	61.6 (6, 19.7)	3.84 (6, 0.686)

A scatter plot of individual plasma concentration-time profiles of acetaminophen in all the subjects are shown in the figure below:

**Figure:** Individual Plasma Concentration-Time Profiles of Acetaminophen in All Subjects/All Age Strata following the First Intravenous Acetaminophen Administration (Study CPI-APA-102).



LOESS = locally-weighted scatterplot smoothing  
Source: Study CPI-APA-102, Figure 1

A 2-compartment structural model with linear elimination and size effects on the PK parameters (CL), inter-compartment flow rate (Q), volume of distribution of the central compartment (V<sub>c</sub>), and volume of distribution of the peripheral compartment (V<sub>p</sub>) (*ie*, an allometric scaling model) was used to fit the plasma concentration versus time profiles of acetaminophen. A summary of population PK parameters of IV acetaminophen derived from the final population PK model including post natal age as a maturation function is displayed below:

**Table:** Primary Population Pharmacokinetic Parameters of Intravenous Acetaminophen – Final Population Pharmacokinetic Model (Study CPI-APA-102)

Population PK Parameters	Geometric Mean	Between Subject Variability
CL (L/h)	$18.4 \times \left( \frac{\text{Weight (kg)}}{70} \right)^{0.75} \times \left( 1 - 0.678 \times \exp \left( -\text{PNA (weeks)} \times \frac{\ln(2)}{41} \right) \right)$	37.4%
V <sub>c</sub> (L)	$16.0 \times \left( \frac{\text{Weight (kg)}}{70} \right)$	61.6%
Q (L/h)	$97.8 \times \left( \frac{\text{Weight (kg)}}{70} \right)^{0.75}$	19.6%
V <sub>p</sub> (L)	$59.5 \times \left( \frac{\text{Weight (kg)}}{70} \right)$	39.8%

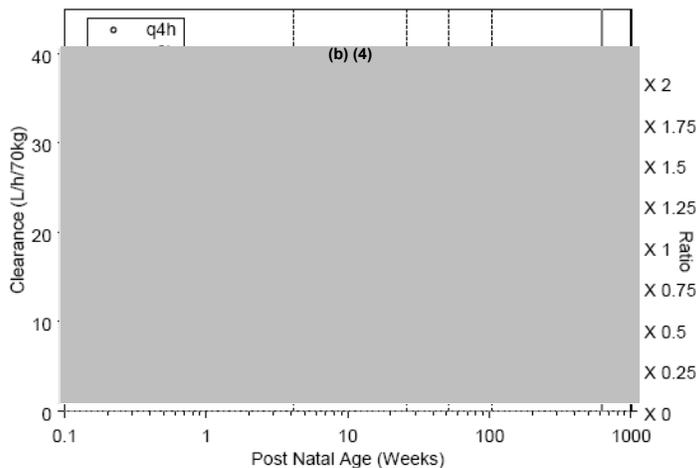
Definitions: See [List of Abbreviations](#)

Note: Correlation between CL and V<sub>c</sub> was 0.546 and correlation between Q and V<sub>p</sub> was 1.

Source: CADE-RAS-002, [Table 6.4:4](#)

The relationship between age maturation and the post hoc standardized CL values of acetaminophen for the 75 pediatric subjects included in the population PK analysis are presented in the figure below:

**Figure:** Maturation of Standardized Acetaminophen Clearance versus Post-natal Age – Final Population Pharmacokinetic Model (Study CPI-APA-102)



Source: Study CPI-APA-102, [Figure 6](#)

A sigmoidal pattern between CL and PNA, with a plateau of 18.4 L/h/70 kg

observed beginning at approximately 2 years of age.

A descriptive statistics for primary fitted PK parameters expressed per kg body weight are presented in the table below:

**Table:** Summary of Population Pharmacokinetic Primary Parameters following Intravenous Acetaminophen in Pediatric Patients (Study CPI-APA-102)

Dose (mg/kg)	Subpopulation (Age Strata)	Dosing Frequency	Mean (n, SD)	
			CL (L/h/kg)	V <sub>c</sub> (L/kg)
12.5	Neonates (≤ 28 days)	q6h	0.205 (2, 0.00982)	0.259 (2, 0.0256)
	Infants (29 days to < 24 mo)	q4h	0.364 (13, 0.179)	0.296 (13, 0.094)
	Children (2 to < 12 y)	q4h	0.371 (9, 0.121)	0.260 (9, 0.121)
	Adolescents (12 to ≤ 16 y)	q4h	0.293 (12, 0.0971)	0.244 (12, 0.186)
15	Neonates (≤ 28 days)	q8h	0.176 (1, NC)	0.231 (1, NC)
	Infants (29 days to < 24 mo)	q4h	0.268 (12, 0.106)	0.261 (12, 0.091)
	Children (2 to < 12 y)	q4h	0.328 (16, 0.0841)	0.221 (16, 0.107)
	Adolescents (12 to ≤ 16 y)	q4h	0.284 (10, 0.0461)	0.261 (10, 0.118)

Definitions: See [List of Abbreviations](#)

Source: Study CPI-APA-102, [Table 19](#)

The mean CL/kg for acetaminophen in neonate subjects (0.176 to 0.205 L/h/kg) was lower than mean values observed in infants (0.268 to 0.364 L/h/kg), children (0.328 to 0.371 L/h/kg), and adolescents (0.284 L/h/kg to 0.293 L/h/kg). The mean CL/kg values in infants, children, and adolescents were comparable. The V<sub>c</sub>/kg for acetaminophen was consistent across all populations.

**Table:** Summary of Population Pharmacokinetic Secondary Parameters following Intravenous Acetaminophen in Pediatric Patients (Study CPI-APA-102)

Dose (mg/kg)	Subpopulation (Age Strata)	Dosing Frequency	Mean (n, SD)		
			Last Dose		
			t <sub>½</sub> (h)	AUC <sub>0-τ</sub> (μg•h/mL)	C <sub>max</sub> (μg/mL)
12.5	Neonates	q6h	3.89 (2, 0.631)	61.2 (2, 2.94)	25.3 (2, 0.103)
	Infants	q4h	2.45 (13, 0.61)	38.7 (13, 10.9)	25.0 (13, 4.72)
	Children		2.93 (9, 1.13)	36.6 (9, 13.2)	26.2 (9, 6.89)
	Adolescents		3.67 (12, 2.88)	40.9 (12, 23.1)	28.4 (12, 9.25)
15	Neonates	q8h	4.19 (1, NC)	85.1 (1, NC)	30.3 (1, NC)
	Infants	q6h	3.18 (12, 1.28)	80.2 (12, 84.8)	37.9 (12, 34.7)
	Children		2.98 (16, 1.54)	49.0 (16, 14.2)	32.3 (16, 7.04)
	Adolescents		2.91 (10, 0.685)	53.1 (10, 10.1)	34.8 (10, 8.18)

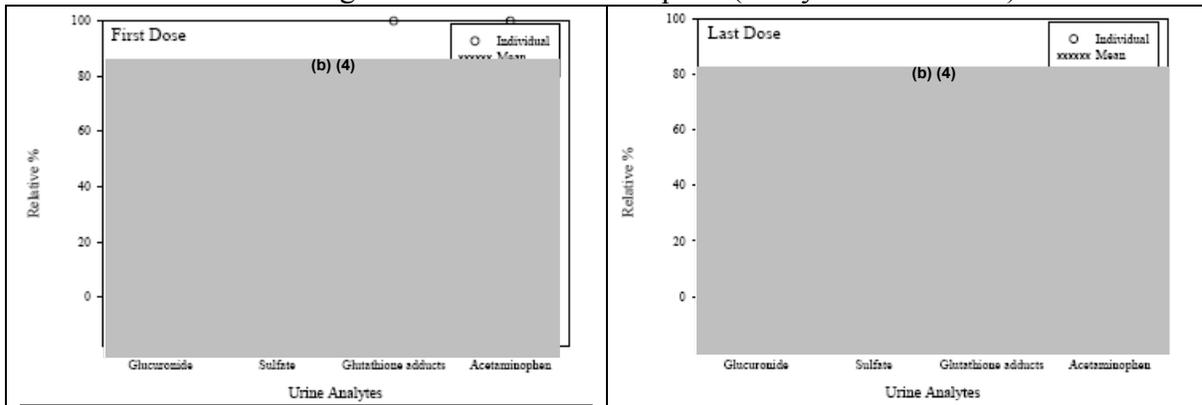
Definitions: See [List of Abbreviations](#)

Source: Study CPI-APA-102 [Table 20](#)

Mean terminal elimination half-life from the 2-compartment PK model (t<sub>½β</sub>) values in neonates (3.89 and 4.19 h, respectively, for the 12.5 and 15 mg/kg dose levels) were

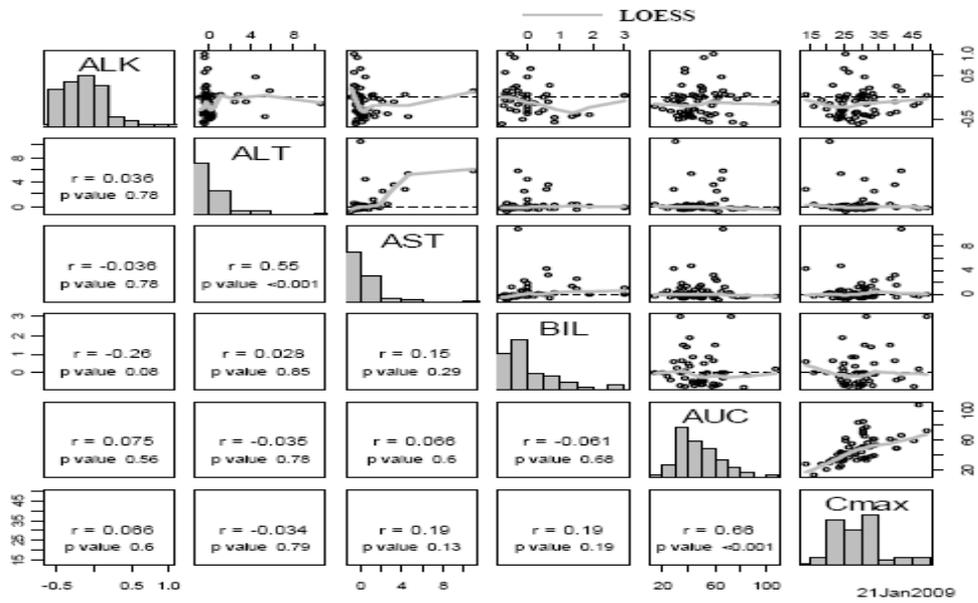
longer than those observed in infants, children, and adolescents (range in mean values of 2.45 to 3.18 h). Mean  $t_{1/2}$  values were comparable across the infant, child, and adolescent age strata. As expected based upon the  $t_{1/2}$  values, mean neonate  $AUC_{0-\tau}$  values (61.2 to 85.1  $\mu\text{g}\cdot\text{h}/\text{mL}$ , respectively, for the 12.5 and 15 mg/kg dose levels) were 46 to 86% higher than those observed in infants (38.7 to 80.2  $\mu\text{g}\cdot\text{h}/\text{mL}$ ), children (36.6 to 49.0  $\mu\text{g}\cdot\text{h}/\text{mL}$ ), or adolescents (36.6 to 53.1  $\mu\text{g}\cdot\text{h}/\text{mL}$ ). Differences in median IV acetaminophen  $C_{\text{max}}$  values across each age stratum for a given dose were negligible. Mean  $C_{\text{max}}$  values appeared to increase in a dose proportional manner.

**Figure:** Individual and Mean Percentage of Acetaminophen and Metabolites in Urine for Each Collection following Intravenous Acetaminophen (Study CPI-APA-102)



The following figure lists a summary of the relationships between individual exposure values of acetaminophen ( $AUC$  and  $C_{\text{max}}$ ) derived from the population PK model and percent changes from baseline in markers of hepatic function (LFTs): bilirubin (BIL), alanine aminotransferase (ALT), aspartate aminotransferase (AST), and alkaline phosphatase (ALK).

**Figure:** Relationships Between Population Pharmacokinetic Parameters of Acetaminophen and Percent Changes from Baseline of Markers of liver Function (Study CPI-APA-102)



No trends were observed between PK parameters of acetaminophen and markers of hepatic injury.

**Conclusions:** The allometric model allowed the comparison of PK parameters of acetaminophen in full-term neonates with those from other pediatric age groups. Overall, a sigmoidal pattern between CL and PNA was observed, with a CL plateau of 18.4 L/h/70 kg observed approximately at age 2 years and older. Therefore, it is expected that children and adolescents would display an acetaminophen CL value similar to that of adults. Based upon the results from the final population PK model, and consistent with published literature on PO acetaminophen, neonates and younger infants display a reduced acetaminophen CL relative to children, adolescents, and adults. No trend was observed between individual exposure values of acetaminophen ( $AUC_{0-\tau}$  and  $C_{max}$ ) and percent change from baseline in LFTs or between individual values for urinary excretion of glutathione adducts and LFT values.

### 4.3. Pharmacometrics Report

#### OFFICE OF CLINICAL PHARMACOLOGY: PHARMACOMETRIC REVIEW

<b>Application Number</b>	NDA22450
<b>Submission Number (Date)</b>	0000 (May 12, 2009)
<b>Clinical Division</b>	Division of Anesthesia, Analgesia, and Rheumatology
<b>Primary PM Reviewers</b>	Ping Ji, Ph.D.
<b>Team Leader</b>	Yaning Wang, Ph.D.

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## Summary of Findings

The key pharmacometric findings from IV acetaminophen NDA22450 submission are:

- The two-compartment model with linear elimination and size effect on PK parameters fitted the concentration-time profiles of acetaminophen in the pediatric populations.
- A sigmoidal pattern between body-weight normalized CL and post-natal age was observed, with a plateau value observed in children and adolescents.
- The proposed dosing regimens for adults and pediatric patients appeared to be appropriate.
- The level of liver function markers (AST, ALT, and Bilirubin) was independent of percent (or amount) excreted as NAPQI conjugates in both adults and pediatric patients.

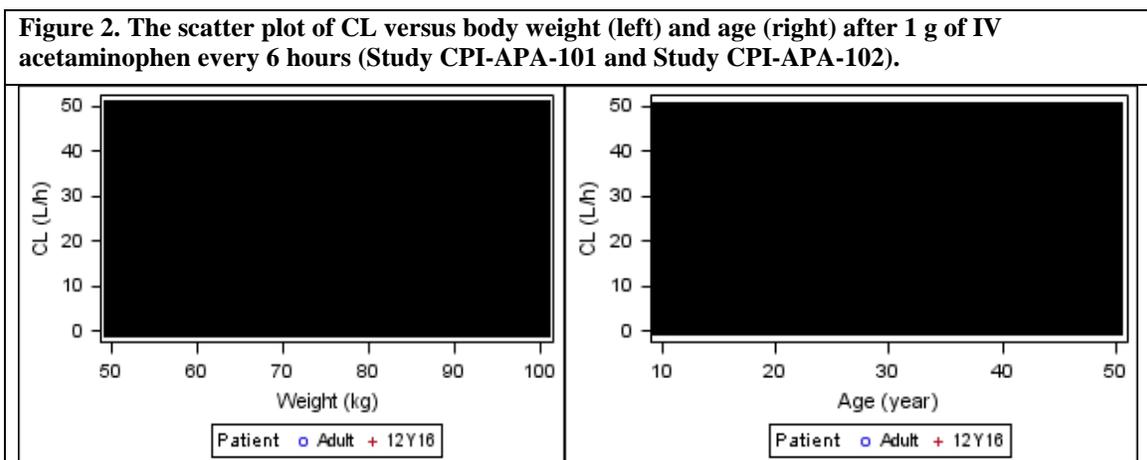
## Key Review Questions

The purpose of the pharmacometrics review is to address the following key questions.

Is the proposed dosing regimen in adults and adolescents >50 kg appropriate?

*Yes, the proposed dosing regimen in adults is appropriate.*

The proposed dosing regimen in adults and adolescents >50 kg is 650 to 1000 mg every 4 to 6 hours, e.g. 1000 mg q6h or 650 mg q4h to a maximum of 4000 mg in 24 hours. The scatter plot of CL versus body weight or age showed that exposure appeared to be independent of WT or age in the range studied.



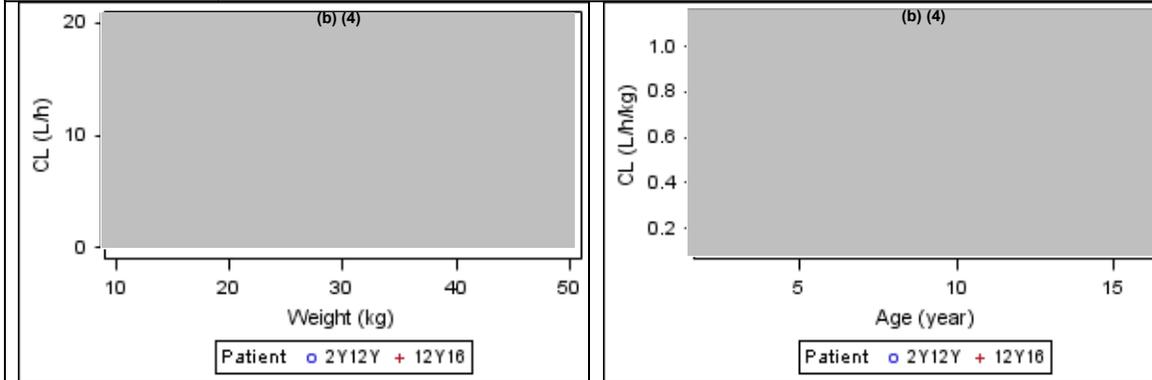
Is the proposed dosing regimen in adolescents and all children appropriate?

*Yes, the proposed dosing regimen in adolescents and children is appropriate.*

The proposed dosing regimen in adolescents and children are as follows: 15 mg/kg q6h or 12.5 mg/kg q4h for adolescents weighing less than 50 kg and all children and 1000 mg q6h or 650 mg q4h for adolescents weighing more than 50 kg.

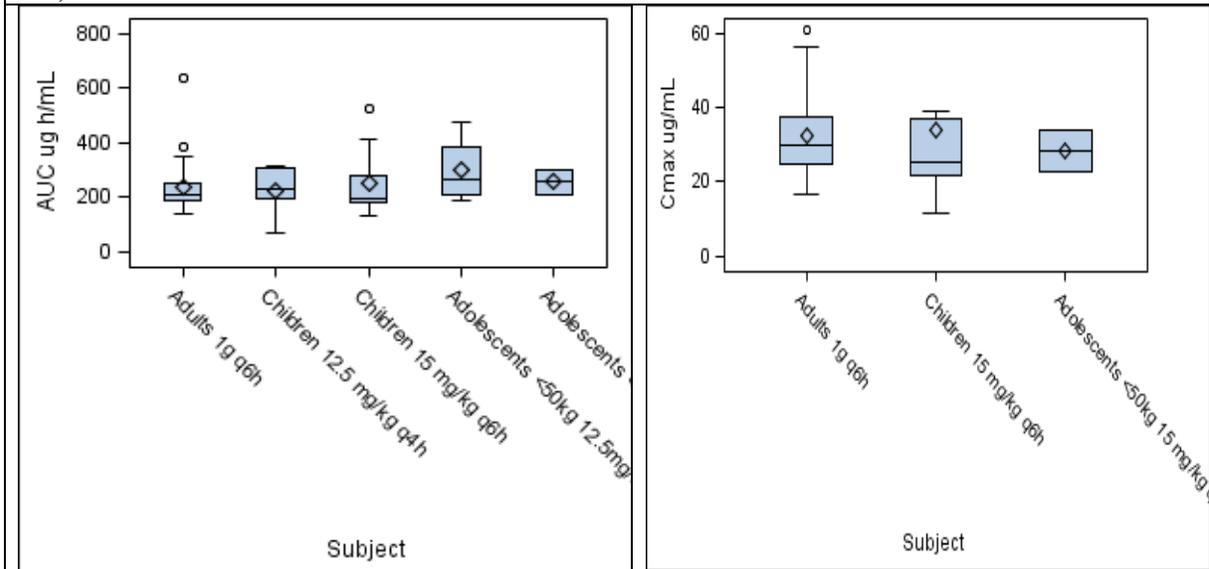
The CL appears to be positively correlated with body weight and body-weight normalized CL appears to be independent of age (Figure 2).

**Figure 2. The scatter plot of CL versus body weight (Left) and age (Right) in children and adolescents (Study CPI-APA-102).**



Acetaminophen exposure (AUC) in all children and adolescents <50 kg given 12.5 mg/kg q4h, 15 mg/kg q6h, and adolescents >50 kg given 1 g was comparable to AUC in adults given 1 g q6h.

**Figure 3. Acetaminophen daily exposure (AUC) in children and adolescents (2-16 year) (15 mg/kg q6h, 1 g q6h, or 12.5 mg/kg q4h) as compared to adults (1 g q6h) (Study CPI-APA-102 and Study CPI-APA-101).**



Note: 1) AUC was calculated based on noncompartmental analysis from Day 2 data.

2)  $AUC = AUCTAU * 4$  (if q4h) or  $AUC = AUCTAU * 6$  (if q6h).

3) Adults: N=38; Children 12.5 mg/kg q4h: N=6; Children 15 mg/kg q6h: N=15; Adolescents <50kg 12.5 mg/kg q4h: N=4, Adolescents <50 kg 15 mg/kg q6h: N=2.

Based on the agreement at the end-of-phase 2 (EOP2) meeting between agency and industry, the basis of approval of IV acetaminophen for pediatric indications of pain and fever was bridging adult efficacy data with the pediatric PK and safety data. As indicated above, at the proposed dosing regimen, the exposure in children and adolescents were comparable to that in adults given 1 g q6h. Therefore, the proposed dosing regimen is appropriate in children and adolescents.

Is the proposed dosing regimen in neonates and infants appropriate?

*Yes, the proposed dosing regimen in neonates is appropriate in neonates and infants.*

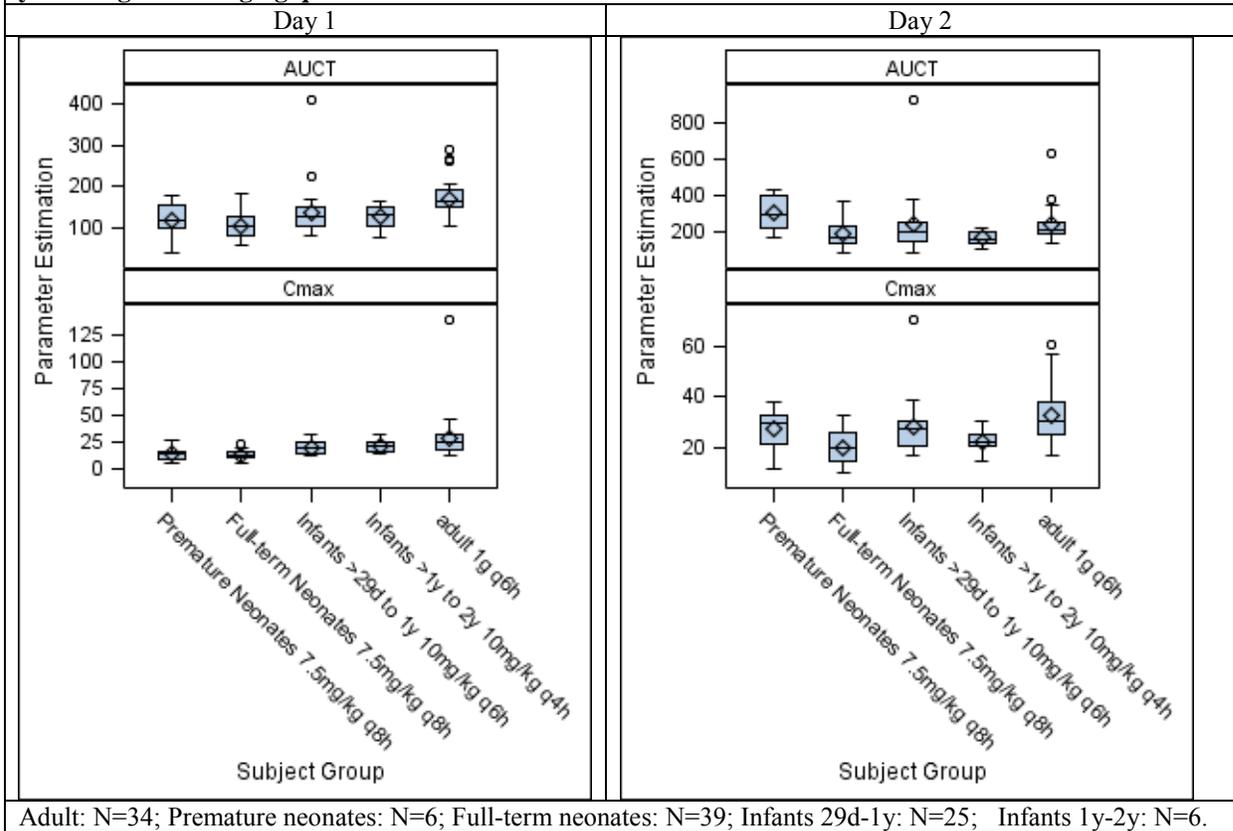
The proposed dosing regimen in neonates and infants are listed below:

- Infants 1 to 2 years old: 50 to 60 mg/kg in 24 hours e.g. 12.5 mg/kg q6h or 10 mg/kg q4h. Minimum dosing interval of 4 hours.
- Infants 29 days to 1 year old: 40 to 50 mg/kg in 24 hours e.g. 10 mg/kg q6h or 12.5 mg/kg q6h. Minimum dosing interval of 6 hours.
- Full-Term Neonates: 22.5 to 30 mg/kg in 24 hours e.g. 7.5 mg/kg q8h or 7.5 mg/kg q6h. Minimum dosing interval of 6 hours.
- Premature Neonates (postmenstrual age 32 – 36 weeks): 22.5 mg/kg in 24 hours e.g. 7.5 mg/kg q8h. Minimum dosing interval of 8 hours.

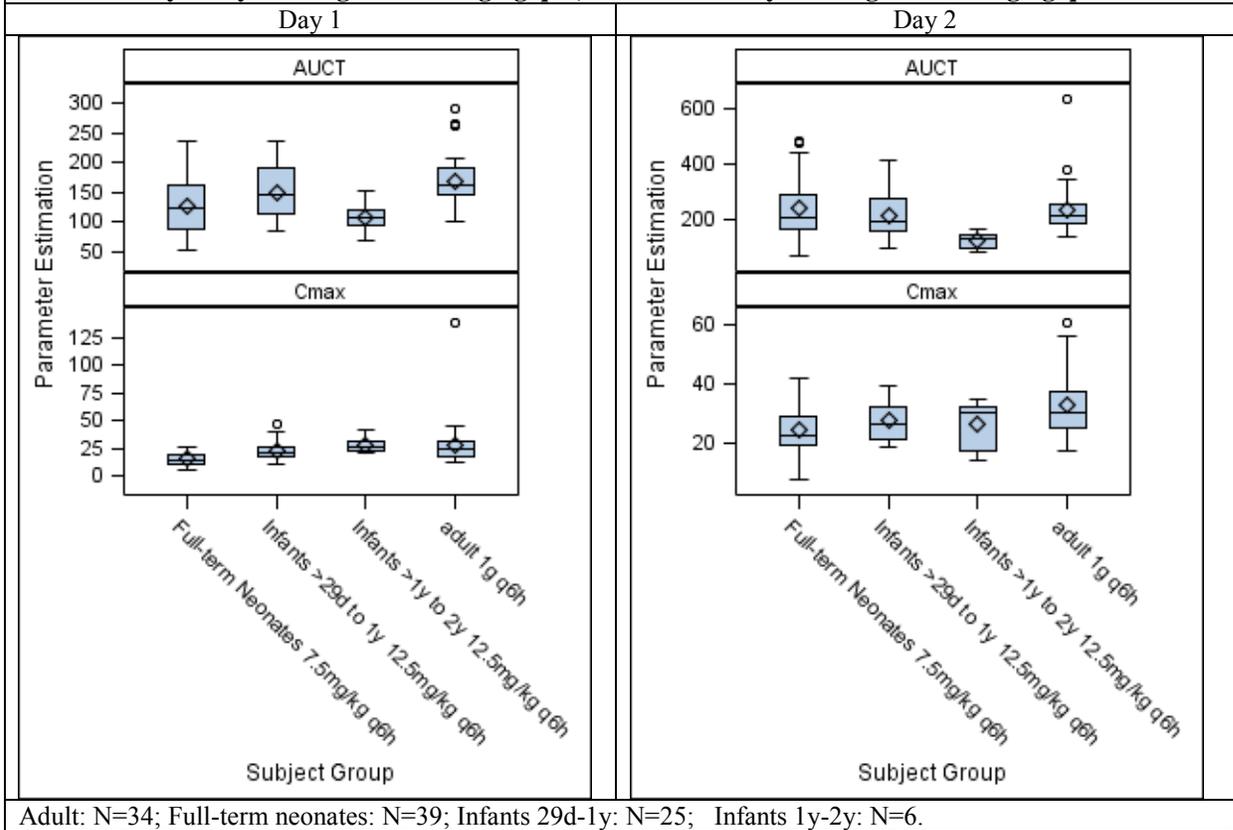
The above proposed dosing regimens were selected from a dose of 7.5, 10, 12.5 and 15 mg/kg given every 4, 6, 8, or 12 hours at variety of combination using trial simulation by sponsor to reach optimal concentration range, which was prespecified based on adult and adolescent concentration data. The optimal dosing regimen was chosen such that the mean C<sub>max</sub> after the first dose was in the range of 10 to 20 µg/mL, the mean C<sub>max</sub> after the repeated doses was in the range of <30 µg/mL, and the drug exposure duration within 10 and 30 µg was maximized whereas the exposure duration below 10 µg/mL or above 30 µg/mL was minimized (*see details in sponsor's analysis Section 3*).

At the selected dosing regimens as shown in Figures 4 and 5, model predicted exposure in neonates and infants was comparable to the observed exposure in adults given 1g every 6 hours after both first dose and repeated doses.

**Figure 4. Exposure comparison with adults given 1 g q6h for premature neonates given 7.5 mg/kg q8h, full-term neonates given 7.5 mg/kg q8h, infants 29-day to 1-year old given 10 mg/kg q6h, and infants 1-2 year old given 10 mg/kg q4 h.**



**Figure 5. Exposure comparison with adults given 1 g q6h for full-term neonates given 7.5 mg/kg q6h, infants 29-day to 1-year old given 12.5 mg/kg q6h, and infants 1-2 year old given 12.5 mg/kg q6h.**



The proposed dosing regimen in pre-term neonates was 7.5 mg/kg q8h only. The model predicted geometric mean AUCTAU after first dose (Day 1) and repeated doses (Day 2) was 106 and 286 ug h/mL, respectively. Therefore, the proposed dosing regimen is appropriate in neonates and infants.

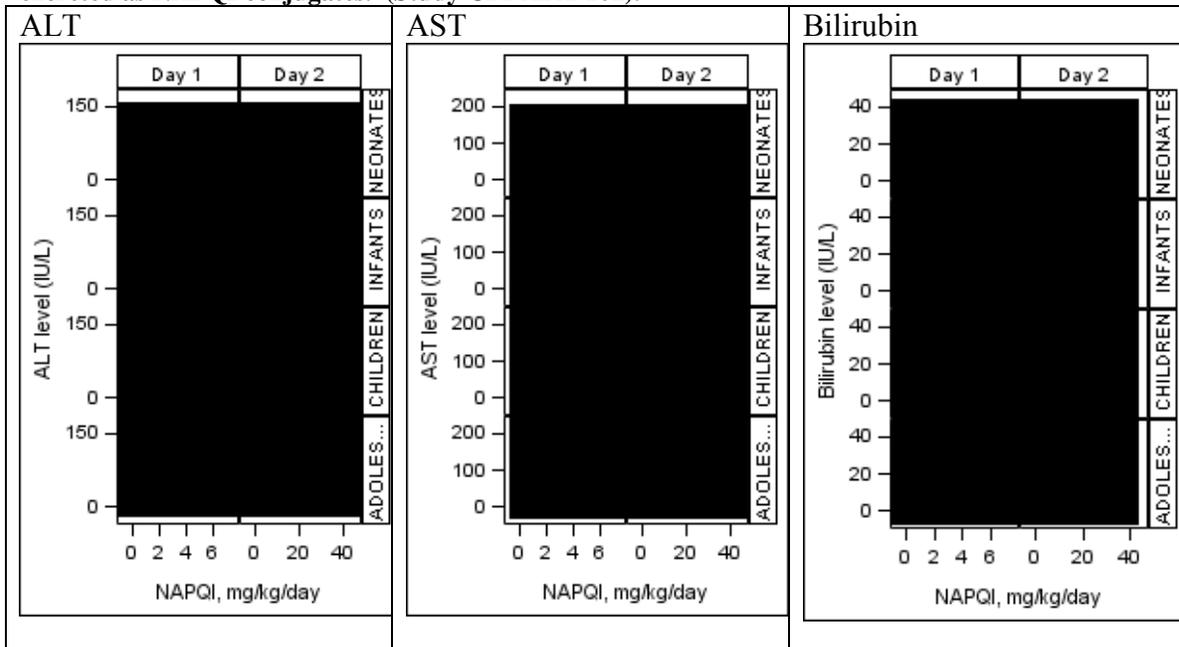
What is the exposure response relationship in terms of safety?

*Corelation of liver function markers with NAPQI production was assessed. The level of liver function markers (AST, ALT, and Bilirubin) was independent of percent (amount) excreted as NAPQI production (acetaminophen mercapturate, 3'-[S-cysteinyl] acetaminophen, and 3'-S-methylacetaminophen).*

(b) (4)

The level of liver function markers (AST, ALT, and Bilirubin) was independent of amount excreted as NAPQI production in pediatric patients given as 12.5 mg/kg or 15 mg/kg every 4 or 6 hours intravenously.

**Figure 7. Scatter plots of markers of liver function (AST, ALT, and Bilirubin) versus amount excreted as NAPQI conjugates. (Study CPI-APA-102).**



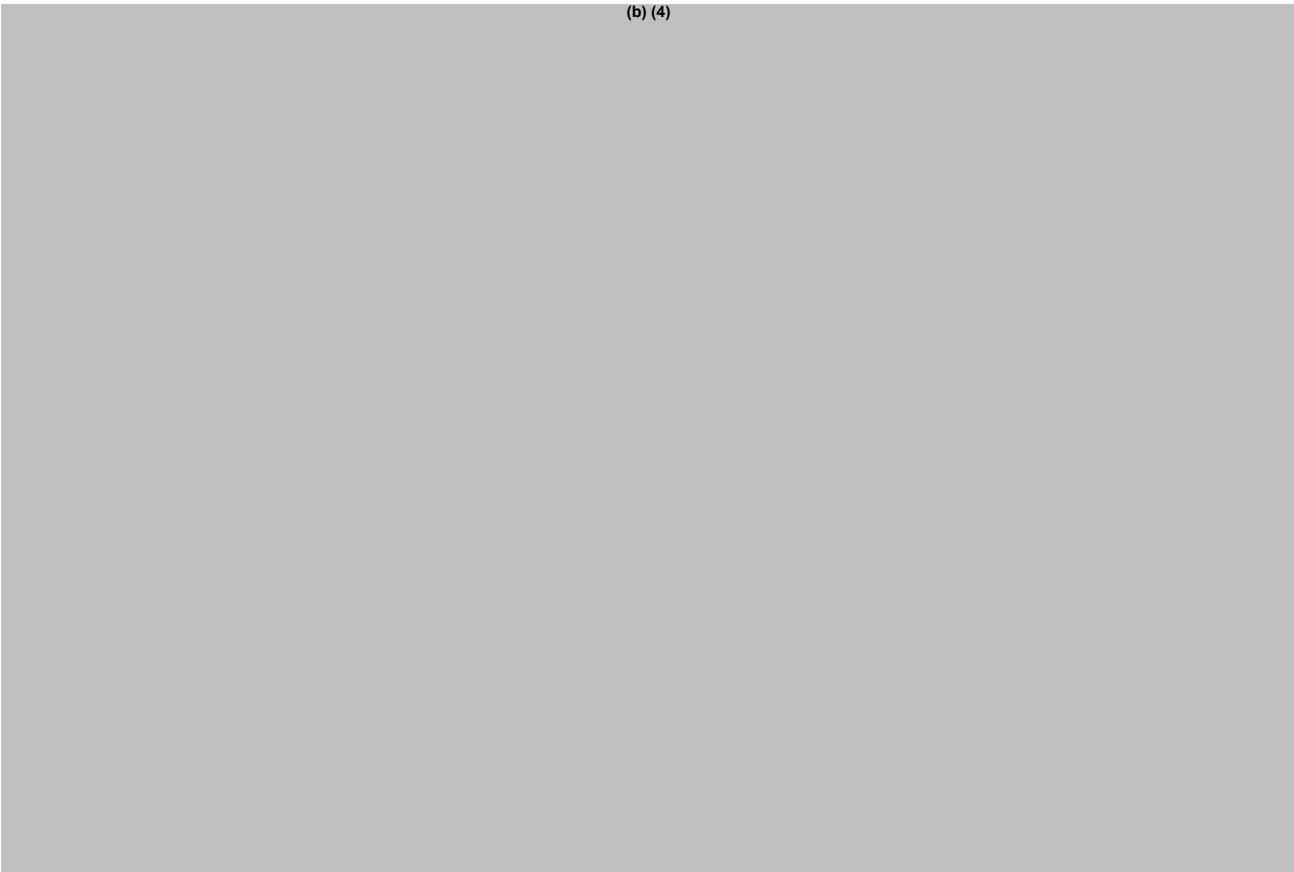
## Recommendations

None.

### 1.3 Labeling Statements

Labeling statements to be removed are shown in ~~red strikethrough font~~ and suggested labeling to be included is shown in underline blue font.

(b) (4)



#### **Pertinent regulatory background**

Acetaminophen Injection for Intravenous Use (ACETAVANCE™) is proposed for the treatment of acute pain and fever in adults and pediatric patients. Although orally administered acetaminophen is extensively used as an effective antipyretic agent, there is currently no parenterally administered antipyretic approved for this indication in US. An IV formulation of acetaminophen was first approved in 2001 for use in France and marketed as Perfalgan® by Bristol-Myers Squibb (BMS) starting in 2002. Currently, Perfalgan® is approved in approximately 80 countries. In 2006, Cadence licensed North American development and commercialization rights to IV acetaminophen from BMS and undertook its US development. ACETAVANCE provides the availability of an intravenous formulation with a rapid onset of action to address a longstanding and significant unmet medical need. As such, priority review is granted to this submission.

A total of (b) (4) 5 clinical studies in pediatric patients (Table 2) are included in this submission.

**Table 8. Overview of clinical studies and key study features with IV acetaminophen in adults.**

Objectives	study	Subjects	Dosing Regimen Used in the Study	Proposed Dosing Regimen
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(b) (4)

**Table 9. Overview of clinical studies and key study features with IV acetaminophen in pediatric patients.**

Study	Objectives	Dosing Regimen Used in the Study	Proposed Dosing Regimen
CPI-APA-102	Phase 1 PK and safety	R, OL, 48-h Full-Term Neonates: 12.5 mg/kg q6h, 15 mg/kg q8h (maximum daily dose of 50 mg/kg) Infants, children, and adolescents: 15 mg/kg q6h (maximum of 660 mg/dose) 12.5 mg/kg q4h (maximum of 1 g/dose) (maximum daily dose of 75 mg/kg or 4 g)	Full-term neonates: 7.5 mg/kg q8h or 7.5 mg/kg q6h. Premature neonates: 7.5 mg/kg q8h. Minimum dosing interval of 8 hours
26095 (Palmer et al.)	Phase 1 PK and safety	28-<32 weeks PMA: 10 mg/kg q6h 32-<36 weeks PMA: 12.5 mg/kg q6h >=36 weeks PMA: 15 mg/kg q6h	Infants (29 days to 1 years old): 10 mg/kg q6h or 12.5 mg/kg q6h
RC210 3006 (BMS)	Phase 3 safety and efficacy No PK	R, DB, SD, active-controlled, 2-parallel group 15 mg/kg SD APAP (n=95) 30 mg/kg SD PPA (n=88) (propacetamol)	Infants (1 to 2 years old): 12.5 mg/kg q4h or 10 mg/kg q4h Adolescents weighing less than 50 kg and all children: 15 mg/kg q6h or 12.5 mg/kg q4h Adolescents weighing more than 50 kg:
CN145-001 (BMS)	Antipyretic efficacy and safety (acute fever) No PK	15 mg/kg SD APAP (n=35) (0.1-11.7 yrs) 30 mg/kg SD PPA (n=32) (0.2-9.5 yrs)	1000 mg q6h or 650 mg q4h
CPI-APA-352 (Cadence)	Safety and efficacy No PK	OL, MD, R, 29 days to <6 mths: 10-15 mg/kg q6h (n=1) 6 to <12 mths: 10-15 mg/kg q6h (n=1) 12 to <24 mths: 6.7-12.5 mg/kg q4h (n=1)	

		2-11 yrs: 6.7-12.5 mg/kg q4h (n=7) and 10-15 mg/kg q6h (n=33) 12-16 yrs: 6.7-12.5 mg/kg q4h (n=9) and 10-15 mg/kg q6h (n=42)	
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### Results of Sponsor's Analysis

In this submission, sponsor conducted a population PK analysis from the phase 1 study CPI-APA-102 (A Prospective, Multi-Center, Randomized, Open-Label, Single and Repeated Dose, 48-Hour Study of Intravenous Acetaminophen in Pediatric Inpatients to Determine Pharmacokinetics and Safety in Acute Pain and Fever). The primary objectives of this study were to characterize PK and to assess the safety of repeated doses of IV acetaminophen under various dosing regimen in pediatric patients. Intravenous acetaminophen was administered q4h, q6h, or q8h over a 48-hour treatment period according to age strata.

Full-term neonates were randomized to one of two groups:

1. IV acetaminophen 12.5 mg/kg body weight q6h around the clock
2. IV acetaminophen 15 mg/kg body weight q8h around the clock

The maximum daily dose for neonates was 50 mg/kg.

Infants, children, and adolescents were randomized to one of two groups:

1. IV acetaminophen 12.5 mg/kg body weight q4h around the clock (maximum of 660 mg/dose)
2. IV acetaminophen 15 mg/kg body weight q6h around the clock (maximum of 1 g/dose)

The maximum daily dose for infants, children, and adolescents was 75 mg/kg or 4 g, whichever was less.

A total of 81 patients were randomized including 3 neonates, 27 infants, 28 children, and 23 adolescents.

The key findings from this population PK analysis are listed below:

- Individual concentrations of acetaminophen were well fitted with a 2-compartment model including an allometric scaling component on all PK parameters and a maturation function on CL.
- A sigmoidal pattern between CL and post-natal age was observed, with a plateau value observed in children and adolescents.
- Children and adolescents are expected to have a CL value (L/h/70 kg) of acetaminophen similar to the matured value in adult patients.
- Full-term neonates and infants have lower CL values. Median terminal elimination half-life ( $T_{1/2\beta}$ ) of acetaminophen in neonate patients for the 12.5 and

15 mg/kg dose levels (3.89 and 4.19 h, respectively), were longer than those observed in infants, children and adolescents (median range: 2.24 to 3.34 h).

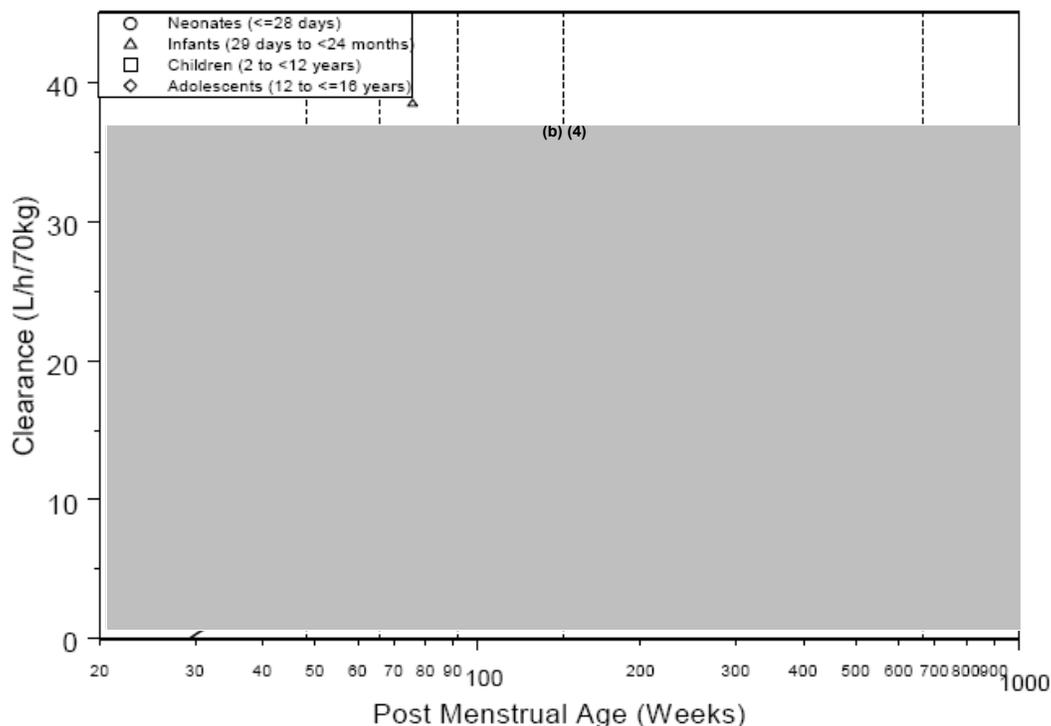
- The median AUC<sub>0-τ</sub> values of acetaminophen in neonates for the 12.5 and 15 mg/kg dose levels were between 1.6- and 1.9-fold higher than those observed in children and adolescents.
- Differences in median C<sub>max</sub> values of acetaminophen across each age strata for a given dose were negligible and C<sub>max</sub> appeared to increase in a dose proportional manner.

Reviewer's comments: *Sponsor's population PK analysis is generally adequate and the results were reproduced by the reviewer (see Reviewer's analysis).*

Results from the population PK model of acetaminophen developed in Study CPI-APA-102 was used for the meta-analysis of the combined data from Study CPI-APA-102 and the Palmer Study, resulting in 125 pediatric subjects with 1260 acetaminophen concentration values for inclusion in the meta analysis (report #cade-ras-003). In the meta-analysis, the subjects include 46 neonates, 32 infants, 25 children and 22 adolescents.

- A two-compartment model with linear elimination, size effect on PK parameters and effect of post-menstrual age (PMA) on systemic clearance (CL) fitted the plasma/serum concentration-time profiles of acetaminophen adequately in a pediatric population.
- A sigmoid pattern between acetaminophen CL and PMA was observed, with a rapid increase in CL in neonate and infants leveling off to a plateau value of 18.3 L/h/70 kg starting at approximately 2 years.

**Figure 6.3:7 Maturation of Standardized Clearance versus Post-Menstrual Age (Studies 102 and Palmer Combined)**



Note: Individual data points represent the standardized post hoc individual clearances from the final model

The y-axis on the right represents the ratio of the standardized CL over 18.3 L/h/70 kg

\* Age represents PNA assuming a gestational period of 40 weeks

Full line represents the equation of standardized clearance:  $CL(L/h/70\text{ kg})=18.3 \times \left[ 1 - 0.796 \times \exp\left(-\frac{(PMA - 40) \times \ln(2)}{32.6}\right) \right]$

Source: p31 in report #cade-ras-003-ped-pk-report.pdf

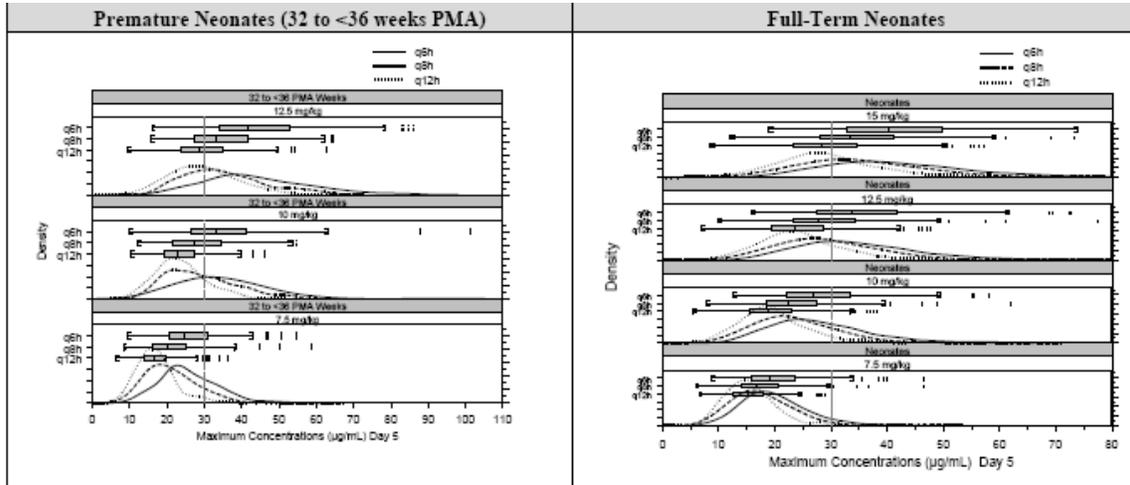
- The volume of distribution of acetaminophen at steady-state ( $V_{ss}$ ) adjusted for body weight was consistent across all subpopulations (i.e., median values: 1.07, 1.10, 1.16 and 1.08 L/kg, respectively for neonates, infants, children and adolescents).
- The mean elimination half-life of acetaminophen in neonate patients ( $\leq 28$  days) of 7.0 (2.66) hours appeared to be longer than that observed in infants, children and adolescents whose mean (SD) values were 4.2 (2.90), 3.0 (1.53), and 2.9 (0.69) hours, respectively.

*Reviewer's comments: Sponsor's population PK analysis is generally adequate and the results were reproduced by the reviewer. The examination of the diagnostic plots per age group strata showed that the model fits data well and there appeared no systemic bias in the prediction (see Reviewer's analysis).*

Sponsor thereafter utilized the results from the population meta-analysis to perform a trial simulation in neonates and infants to support the development of optimum IV acetaminophen dosing recommendations in neonates and infants (report #cade-ras-005-peds-dosing-sim-report.pdf). In the trial simulation, the target exposure was 10-20  $\mu\text{g/mL}$  for mean  $C_{max}$  after the first dose and  $<30 \mu\text{g/mL}$  for mean  $C_{max}$  after the repeated dose, with median  $AUC_{\tau}$  less than 51.4  $\mu\text{g} \cdot \text{h/mL}$  (median adolescent values). A total of randomly generated 250 neonate and

infant patients were used in the simulation based on a resampling procedure from the dataset of the meta-analysis. The predicted maximum acetaminophen concentration ( $C_{max}$ ) curves at steady state for premature neonates (32 to <36 weeks PMA; N=3) and all neonates (N=40) for each of the 12 regimens are presented in Figure 10.

**Figure 8. Predicted Steady State Acetaminophen  $C_{max}$  in Neonates: IV acetaminophen Dosing Simulations**



Definitions:  $C_{max}$ =maximum concentrations; IQR=interquartile range;  $Q1=1^{st}$  quartile,  $Q3=3^{rd}$  quartile  
 Note: The distribution of  $C_{max}$  values for each dose regimen was based on the 250 concentration-time profiles resampled randomly from the neonates in Study CPI-APA-102 and EHR/C#26095.

The frequency distribution plots represent the distribution of  $C_{max}$  around central values. The horizontal “box-and-whisker” plot above the  $C_{max}$  distribution curve was programmed as follows: the median value is reflected by the vertical solid line in the middle of the gray rectangle; the rectangle represents the middle two quartiles ( $Q1$  and  $Q3$ : 25 to 75 % percentile values); and the horizontal lines (whisker) on either side of the rectangle represents the boundary values for the outliers. Values higher than  $Q3+1.5 \times IQR$  or lower than  $Q1-1.5 \times IQR$  were considered as outliers and were represented by dotted vertical lines. The y-axis indicates the density that a given concentration resulted from the simulations. The x-axis indicates the acetaminophen at  $C_{max}$  in  $\mu\text{g/mL}$ . The vertical dashed gray line is set to 30  $\mu\text{g/mL}$  to reflect the prespecified safety threshold.

Source: Report # CADE-RA5-005, Figures 5.2.1:1 and 5.2.1:2.

Based upon the  $C_{max}$  analysis, in premature neonates (32 to <36 weeks PMA) regimens of 7.5 mg/kg q8h and 10 mg/kg q12h appear to meet the prespecified PK parameters. For full-term neonates it appears that regimens of 7.5 mg/kg q6h and 10 mg/kg q8h met the prespecified parameters. Higher doses or more frequent administrations produce  $C_{max}$  values at steady state that exceed the target values in a substantial portion of the simulated cases.

Exposure duration was also simulated for each dosing regimen to predict the amount of time during a 24-hour period that acetaminophen plasma concentrations would exceed 30  $\mu\text{g/mL}$ , the time it would remain between 10 to 30  $\mu\text{g/mL}$ , and the time it would fall below 10  $\mu\text{g/mL}$ . The calculated steady state exposure duration values predicted for adolescents receiving IV acetaminophen 15 mg/kg q6h were used as the simulation targets. Figure 11 presents the predicted exposure durations at steady state in premature neonates (32 to <36 weeks PMA) relative to the targets derived from adolescent data. Figure 12 presents the predicted exposure durations at steady state for full-term neonates relative to the targets derived from adolescent data.

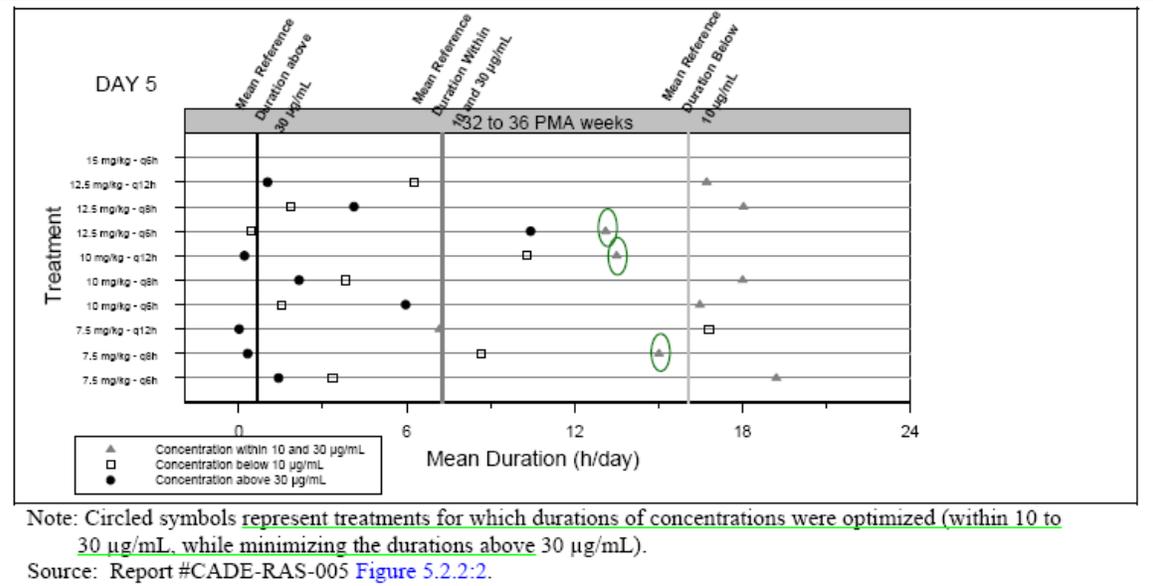
The solid black vertical line at 0.63 h represents the mean duration that adolescent predicted concentrations would exceed 30  $\mu\text{g/mL}$ , based upon an IV acetaminophen regimen of 15 mg/kg q6h. The two vertical gray lines at approximately 7 and 16 hours represents the mean durations at steady state that adolescent predicted concentrations

would be between 10 to 30 µg/mL and below 10 µg/mL, respectively, based upon an IV acetaminophen regimen of 15 mg/kg q6h.

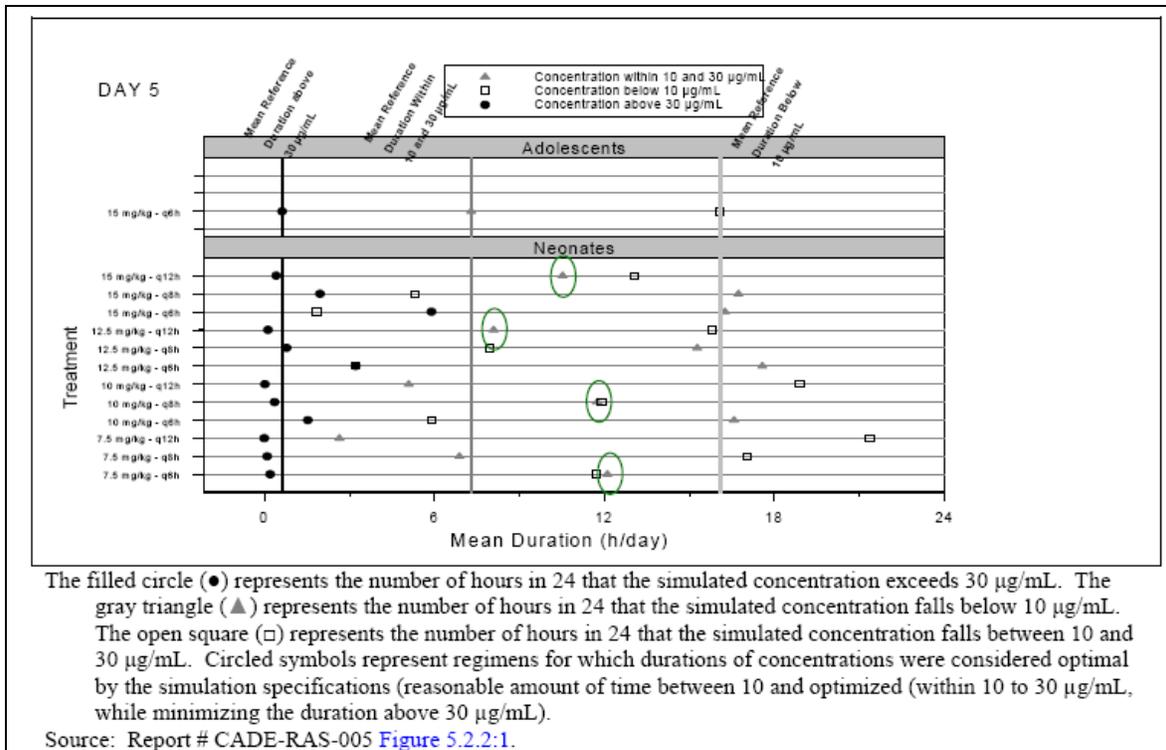
Based upon the prespecified simulation targets, the following should occur for a viable dosing regimen:

- The solid circle (predicted mean time durations with concentrations are above 30 µg/mL) should stay near or to the left of the solid vertical black line near 0.63 h, the predicted mean time duration for adolescents (to optimize safety by reducing exposure to outliers);
- The gray triangle (predicted mean time durations with concentrations between 10 to 30 µg/mL) should remain at or to the right of the middle solid vertical grey line (adolescent value) or in other words, the duration of time that exposure levels remain between 10 to 30 µg/mL should be at least 7.3 h, the predicted mean time duration for adolescents (to optimize efficacy);
- The open square (predicted mean time durations with concentrations below 10 µg/mL) should stay to the left of the solid vertical grey line (adolescent value) or in other words, the duration of time that exposure levels remain below 10 µg/mL should be no greater than 16 h, the predicted mean time duration for adolescents (to optimize efficacy).

**Figure 9. Mean Steady State Acetaminophen Exposure Durations in Premature (32 to <36 weeks PMA) Neonates Relative to Adolescents**



**Figure 10. Mean Steady State Acetaminophen Exposure Durations in Full-Term Neonates Relative to Adolescents**



Based upon the exposure duration analysis, appropriate neonate dosing regimens meeting the prespecified targets are identified by the ovals around the solid gray triangles in [Figure 11](#) and [Figure 12](#). Appropriate regimens for premature neonates (32 to <36 weeks PMA) include 7.5 mg/kg q8h, 7.5 q12h, and 10 mg/kg q12h. Appropriate regimens for full-term neonates include 7.5 mg/kg q6h, 10 mg/kg q8h, 12.5 q12h, and 15 mg/kg q12h. The 7.5 mg/kg q8h dose may also be considered, as it is close to an optimal dose regimen. The 15 mg/kg dose exceeds the prespecified  $AUC_T$  target (median predicted  $AUC_T$  of 51.4 µg h/mL in adolescents versus median predicted  $AUC_T$  from 114.5 to 127.8 µg h/mL in neonates). The 12.5 mg/kg q12h dose could be acceptable, but as some outliers may also exceed the  $AUC_T$  target, this dose regimen will not be recommended.

The key findings from the simulations are listed as follows:

- Neonates: recommended IV acetaminophen dose should be a maximum of 30 mg/kg/day administered as 7.5 mg/kg q6h or 10 mg/kg q8h. The 12.5 mg/kg q12h dose is also acceptable. The recommended daily dose range for full-term neonates is 25-30 mg/kg/day.
- Premature neonates: (PMA 32 to <36 weeks) a maximum dose range of 20 to 22.5 mg/kg/day administered either as a 10 mg/kg q12h dose or a 7.5 mg/kg q8h dose is recommended
- Infants: Acceptable dose regimens for younger infants (29 days to <6 months) include: 7.5 mg/kg q4h (45 mg/kg/day), 10 mg/kg q6h (40 mg/kg/day, and 12.5 mg/kg q6h or q8h (37.5 to 50 mg/kg/day), or a daily maximum dose range of 37.5

to 50 mg/kg. For older infants (12 to <24 months), dose regimens of 10 mg/kg q4h (60 mg/kg/day) or 12.5 mg/kg q6h (50 mg/kg/day) are preferred.

*Reviewer's comments: In the trial simulation, sponsor used adolescents' exposure as reference. Although the exposure were generally comparable between adolescents and adults (sponsor's report: CADE-RAS-003a-PK-comparability-report.pdf), to avoid data creep, reviewer reexamined the sponsor's proposed dosing regimen with the data from adults only (see reviewer's analysis).*

## Reviewer's Analysis

### Objective

The aim of the analysis was:

- To evaluate the proposed dosing regimen by age strata.
- To assess the exposure response (safety) relationship.

### Methods

#### Data Sets

Data sets used are summarized in Table 3.

**Table 10. Analysis Data Set**

Study Number	Name	Link to EDR
CPI-APA-101	Dm.xpt, vs.xpt, lb.xpt	<a href="\\Cdsub1\evsprod\NDA022450\0000\m5\datasets\cpi-apa-101\tabulations\dm.xpt, vs.xpt, lb.xpt">\\Cdsub1\evsprod\NDA022450\0000\m5\datasets\cpi-apa-101\tabulations\dm.xpt, vs.xpt, lb.xpt</a>
CPI-APA-101	Pkparm.xpt	<a href="\\Cdsub1\evsprod\NDA022450\0000\m5\datasets\cpi-apa-101\analysis\pkparm.xpt">\\Cdsub1\evsprod\NDA022450\0000\m5\datasets\cpi-apa-101\analysis\pkparm.xpt</a>
CPI-APA-102	pp.xpt, dm.xpt, vs.xpt	<a href="\\Cdsub1\evsprod\NDA022450\0000\m5\datasets\cpi-apa-102\tabulations\pp.xpt, dm.xpt, vs.xpt">\\Cdsub1\evsprod\NDA022450\0000\m5\datasets\cpi-apa-102\tabulations\pp.xpt, dm.xpt, vs.xpt</a>
CADE-RAS-003	Palm102.xpt	<a href="\\Cdsub1\evsprod\NDA022450\0000\m5\datasets\cade-ras-003\analysis\palm102.xpt">\\Cdsub1\evsprod\NDA022450\0000\m5\datasets\cade-ras-003\analysis\palm102.xpt</a>
CADE-RAS-003	Posthoc.xpt	<a href="\\Cdsub1\evsprod\NDA022450\0000\m5\datasets\cade-ras-003\analysis\posthoc.xpt">\\Cdsub1\evsprod\NDA022450\0000\m5\datasets\cade-ras-003\analysis\posthoc.xpt</a>

#### Software

SAS9.2 and NONMEM VI were used for the reviewer's analyses.

## Results

- The two-compartment model with linear elimination and size effect on PK parameters fitted the concentration-time profiles of acetaminophen in the pediatric populations (Table 3, Table 4, and Figure 8)
- (b) (4)
- The CL appears to be positively correlated with body weight and body-weight normalized CL appears to be independent of age (Study CPI-APA-102) (Figure 2).
- Acetaminophen exposure (AUC and C<sub>max</sub>) in all children and adolescents <50 kg given 12.5 mg/kg q4h, 15 mg/kg q6h, and adolescents >50 kg given 1 g was comparable to that in adults given 1 g q6h (Figure 3).
- At the selected dosing regimens as shown in Figures 4 and 5, model predicted exposure in neonates and infants was comparable to the observed exposure in adults given 1g every 6 hours after both first dose and repeated doses
- Percent of individual metabolites eliminated was comparable between IV and Oral in adults and also comparable to pediatric patients (Figures 8 and 9).
- The level of liver function markers (AST, ALT, and Bilirubin) was independent of percent (or amount) excreted as NAPQI conjugates (Figures 6 and 7).

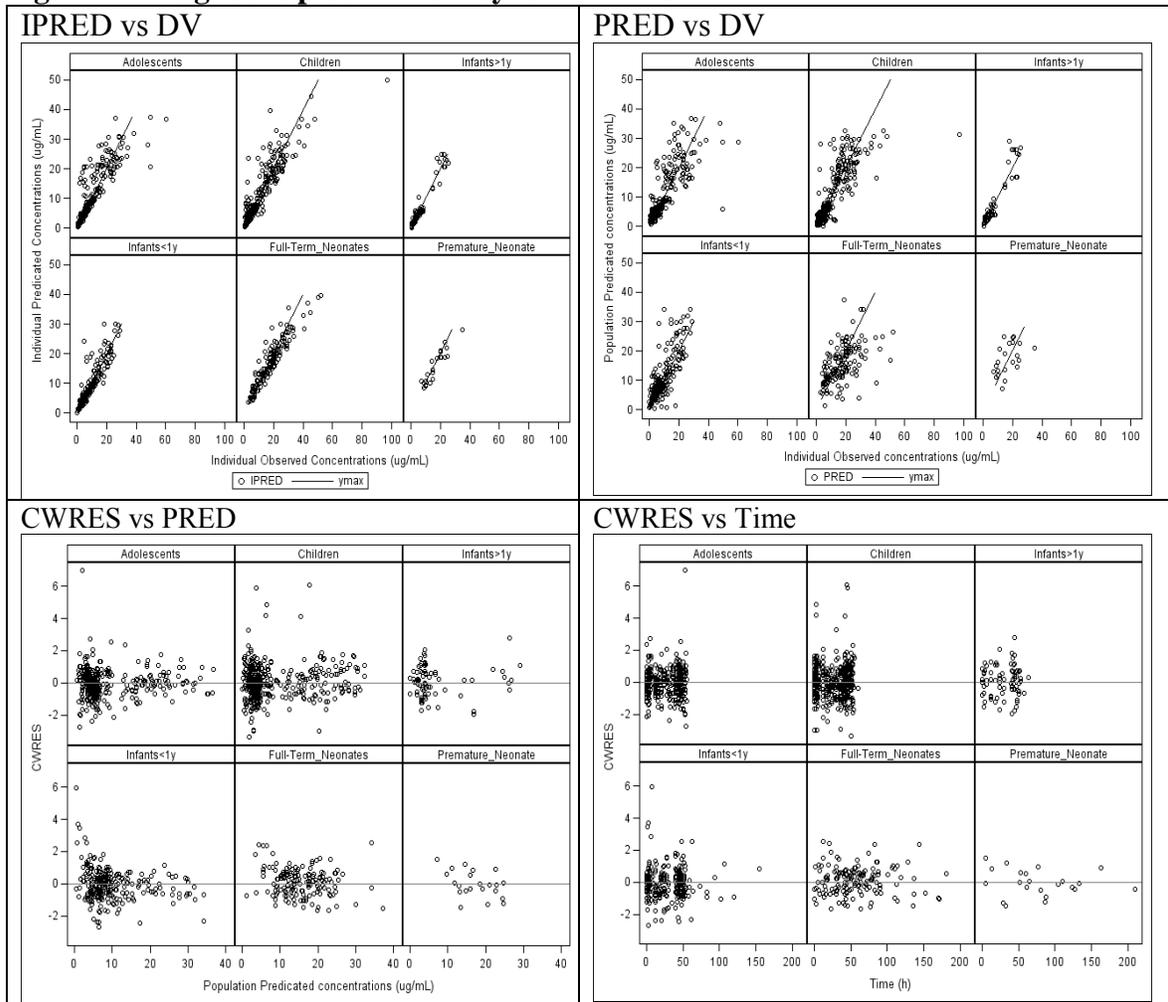
**Table 3: Population Pharmacokinetic Analysis from study CPI-APA-102.**

Parameters	Units	Typical Value (RSE%)	Between Subject Variability (RSE)%
Clearance (CL)	L/h	18.4 (4.9)	37.4 (41.7)
Central Volume (V <sub>c</sub> )	L	16 (8.8)	61.6 (33.4)
Intercompartmental Clearance (Q)	L/h	97.8 (7.0)	19.6 (39.2)
Peripheral Volume (V <sub>2</sub> )	L	59.5 (7.1)	—
Slope CL	—	-0.678 (5.7)	—
TCL	—	41 (51.5)	—
Reta V <sub>2</sub>	—	2.03 (17.8)	—
Residual Variability:			
Additive	—	168.2 (44.5)	
Proportional	—	0.28 (16.8)	

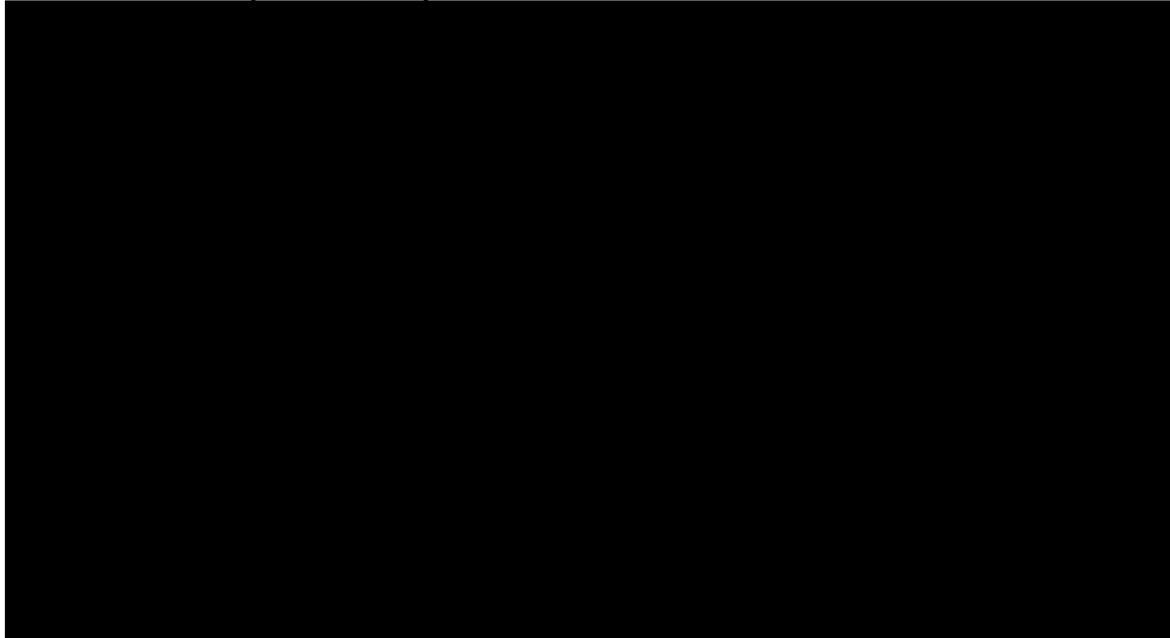
**Table 4: Population Pharmacokinetic Analysis from study CADE-RAS-103.**

<b>Parameters</b>	<b>Units</b>	<b>Typical Value (RSE%)</b>	<b>Between Subject Variability (RSE)%</b>
Clearance (CL)	L/h	18.3 (4.3)	39.2 (24.4)
Central Volume (Vc)	L	16 (12.4)	62.3 (28.4)
Intercompartmental Clearance (Q)	L/h	97.9 (18.2)	20.5 (83.4)
Peripheral Volume (V2)	L	59.5 (8.5)	—
Slope CL	—	-0.796 (1.9)	—
TCL	—	32.6 (19.3)	—
Reta V2	—	1.96 (39.4)	—
Residual Variability:			
Additive	—	171.8 (42.0)	
Proportional	—	0.27 (16.2)	

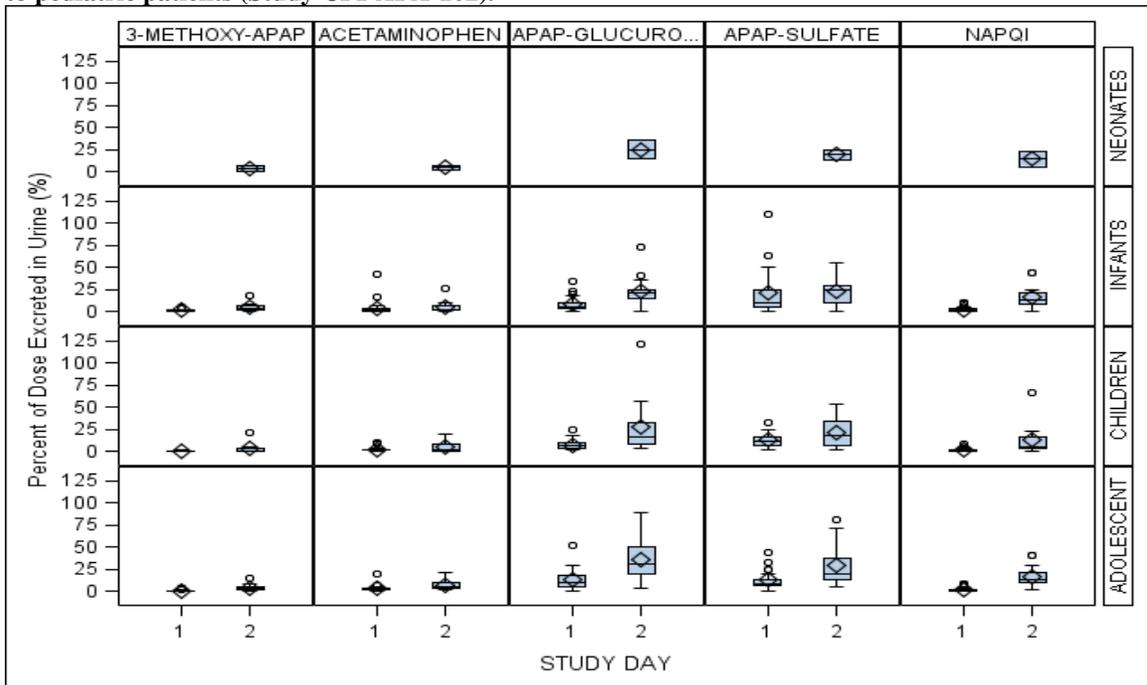
**Figure 8: Diagnostic plot from study CADE-RAS-103.**



**Figure 9. Percent of individual metabolites eliminated after 1 g of acetaminophen was administered to adults IV or oral every 6 hours (Study CPI-APA-101).**



**Figure 10. Percent of individual metabolites eliminated after 12.5 mg/kg or 15 mg/kg was administered to pediatric patients (Study CPI-APA-102).**



4.4. Clinical Pharmacology and Biopharmaceutics filing form/checklist for  
NDA 22-450

Office of Clinical Pharmacology <i>New Drug Application Filing and Review Form</i>				
<u>General Information About the Submission</u>				
	Information		Information	
NDA/BLA Number	022450		Brand Name	TBD
OCP Division (I, II, III, IV, V)	II		Generic Name	Acetaminophen
Medical Division	DAARP		Drug Class	
OCP Reviewer	Ping Ji		Indication(s)	Acute pain and fever
OCP Team Leader	Doddapaneni, Suresh		Dosage Form	Sterile solution for IV infusion
Pharmacometrics Reviewer	Ping Ji		Dosing Regimen	Single dose or repeated dose as a 15 minute infusion
Date of Submission	May 12, 2009		Route of Administration	IV infusion
Estimated Due Date of OCP Review	Oct 6, 2009		Sponsor	Cadence Pharmaceuticals
Medical Division Due Date	Oct 12, 2009		Priority Classification	P
PDUFA Due Date	Nov 13, 2009			
Clin. Pharm. and Biopharm. Information				
	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE	x			
Table of Contents present and sufficient to locate reports, tables, data, etc.	x			
Tabular Listing of All Human Studies	x			
HPK Summary	x			
Labeling	x			
Reference Bioanalytical and Analytical Methods	x	2	2	
I. Clinical Pharmacology				
Mass balance:				

<b>Isozyme characterization:</b>				
<b>Blood/plasma ratio:</b>				
<b>Plasma protein binding:</b>				
<b>Pharmacokinetics (e.g., Phase I) -</b>				
<i>Healthy Volunteers-</i>				
single dose:	x	3	3	
multiple dose:				
<b>Patients-</b>				
single dose:	x			
multiple dose:				
<b>Dose proportionality -</b>	x	1	1	
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
<b>Drug-drug interaction studies -</b>				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
<b>Subpopulation studies -</b>				
ethnicity:				
gender:				
pediatrics:	x	2	2	
geriatrics:				
renal impairment:				
hepatic impairment:				
<b>PD -</b>				
Phase 2:				
Phase 3:	x	14		
<b>PK/PD -</b>				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
<b>Population Analyses -</b>				
Data rich:	x	1	1	
Data sparse:	x	1	1	
<b>II. Biopharmaceutics</b>				
<b>Absolute bioavailability</b>				
<b>Relative bioavailability -</b>				
solution as reference:				
alternate formulation as reference:				
<b>Bioequivalence studies -</b>				

traditional design; single / multi dose:		<b>1</b>	<b>1</b>	
replicate design; single / multi dose:				
<b>Food-drug interaction studies</b>				
<b>Bio-waiver request based on BCS</b>				
<b>BCS class</b>				
<b>Dissolution study to evaluate alcohol induced dose-dumping</b>				
<b>III. Other CPB Studies</b>				
<b>Genotype/phenotype studies</b>				
<b>Chronopharmacokinetics</b>				
<b>Pediatric development plan</b>				
<b>Literature References</b>				
<b>Total Number of Studies</b>		<b>20</b>	<b>11</b>	

On **initial** review of the NDA/BLA application for filing:

	<b>Content Parameter</b>	<b>Yes</b>	<b>No</b>	<b>N/A</b>	<b>Comment</b>
<b>Criteria for Refusal to File (RTF)</b>					
1	Has the applicant submitted bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?	x			
2	Has the applicant provided metabolism and drug-drug interaction information?	x			
3	Has the sponsor submitted bioavailability data satisfying the CFR requirements?	x			
4	Did the sponsor submit data to allow the evaluation of the validity of the analytical assay?	x			
5	Has a rationale for dose selection been submitted?	x			
6	Is the clinical pharmacology and biopharmaceutics section of the NDA organized, indexed and paginated in a manner to allow substantive review to begin?	x			
7	Is the clinical pharmacology and biopharmaceutics section of the NDA legible so that a substantive review can begin?	x			
8	Is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work?	x			
<b>Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality)</b>					

<b>Data</b>					
9	Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?			x	
10	If applicable, are the pharmacogenomic data sets submitted in the appropriate format?			x	
<b>Studies and Analyses</b>					
11	Is the appropriate pharmacokinetic information submitted?	x			
12	Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?	x			
13	Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?	x			
14	Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?	x			
15	Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?				
16	Did the applicant submit all the pediatric exclusivity data, as described in the WR?	x			
17	Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the label?	x			
<b>General</b>					
18	Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	x			
19	Was the translation (of study reports or other study information) from another language needed and provided in this submission?			x	

IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE? y\_\_\_\_\_

If the NDA/BLA is not fileable from the clinical pharmacology perspective, state the reasons and provide comments to be sent to the Applicant.

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

None

<u>Ping Ji</u>	<u>June 02, 2009</u>
Reviewing Clinical Pharmacologist	Date

<u>Doddapaneni Suresh</u>	<u>Oct 01, 2009</u>
Team Leader/Supervisor	Date

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22450	ORIG-1	CADENCE PHARMACEUTICA LS INC	Ofirmev (acetaminophen for injection)

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

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/s/  
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Ping Ji  
04/08/2010

The review was originally signed off on Nov 15, 2009. However, that review contained a watermark and this review without the watermark replaces that. Otherwise, both reviews are identical.

YANING WANG  
04/08/2010

SURESH DODDAPANENI  
04/08/2010