

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**022450Orig1s000**

**CLINICAL PHARMACOLOGY AND  
BIOPHARMACEUTICS REVIEW(S)**

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   |                         |            |
| <i>Reviewer</i>                 | Ping Ji, Ph.D.   |                         |            |
| <i>Team Leader</i>              | Suresh Doddapaneni, Ph.D.  |                         |            |
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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 and is supported by twenty studies including five Phase 1 clinical pharmacology studies, one bioequivalence study and fourteen Phase 3 studies. The five Phase 1 clinical pharmacology studies were designed to establish PK and safety in adults (Study CPI-APA-101, Study 116-01-03, and Study 98051C-CIS) and in pediatric patients (Study CPI-APA-102 and Study EHRC #26095). Study CPI-APA-101 compared repeated doses of IV acetaminophen 1000 mg administered every four hours (q4h) and every six hours (q6h) to PO acetaminophen 1000 mg administered q4h and q6h, respectively. Study 116-01-03 compared the single dose PK of IV and PO acetaminophen 1000 mg. Study 98051C-CIS compared the single dose PK of IV acetaminophen 1000 mg and 500 mg with 2000 mg of IV propacetamol (PPA), a prodrug that is converted to acetaminophen in the blood (2000 mg to 1000 mg). Two studies (CPI-APA-102 and Study EHRC #26095) in pediatric patients utilized population methods for PK assessment. The bioequivalence study (Study CPI-APA-103) was conducted to determine the bioequivalence of the clinical formulation to the

proposed commercial formulation. The fourteen phase 3 studies were designed to investigate the safety and efficacy (pain and/or fever) of IV acetaminophen in adults (n=11) and 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.

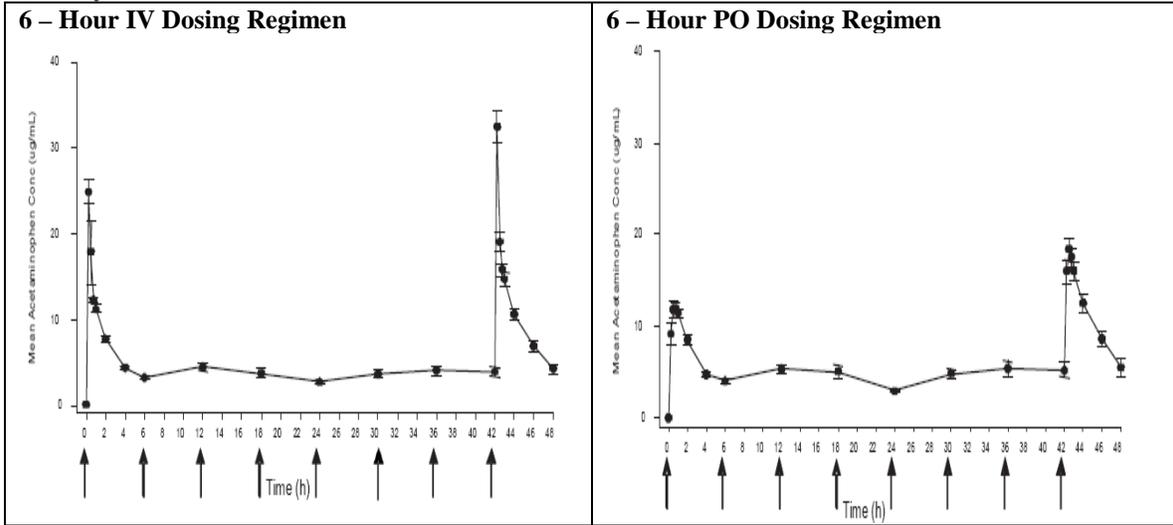
## **Mechanism of Action**

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**

**Pharmacokinetic Findings** Adults After single dose administration of IV acetaminophen, the mean maximum plasma concentration was approximately 70% higher than that following single dose PO dosing at 1000 mg. Mean Tmax values for the IV acetaminophen 1000 mg were approximately 30 minutes faster compared with the PO acetaminophen 1000 mg. Mean AUC values at steady state were comparable between IV and PO acetaminophen, with the oral bioavailability greater than 90% (Study CPI-APA-101).

**Figure 1. Mean acetaminophen concentrations over time profiles for 6-Hour dosing (Study CPI-APA-101).**



**Table 1. Mean (SD) pharmacokinetic parameters following single and multiple doses of intravenous and oral acetaminophen 1000 mg (Study CPI-APA-101).**

| Day<br>Parameter                     | IV<br>Acetaminophen<br>1000 mg q4h<br>(N = 32) | IV<br>Acetaminophen<br>1000 mg q6h<br>(N = 34) | PO<br>Acetaminophen<br>1000 mg q4h<br>(N = 35) | PO<br>Acetaminophen<br>1000 mg q6h<br>(N = 33) |
|--------------------------------------|--|--|--|--|
| Day 1, Dose 1                        |  |  |  |  |
| AUC (µg·h/mL)                        | 34.6 (7.98)                                    | 42.3 (10.58)                                   | 32.6 (7.22)                                    | 39.4 (9.57)                                    |
| C <sub>1,max</sub> (µg/mL)           | 26.0 (7.67)                                    | 28.4 (21.17)                                   | 15.1 (5.36)                                    | 15.1 (4.37)                                    |
| T <sub>max</sub> (h)                 | 0.25 (0.00)                                    | 0.28 (0.10)                                    | 0.84 (0.58)                                    | 0.72 (0.42)                                    |
| t <sub>1/2</sub> (h)                 | 2.28 (0.52)                                    | 2.39 (0.57)                                    | 2.91 (0.98)                                    | 2.66 (0.68)                                    |
| Day 2, Dose 4 (8 <sup>th</sup> Dose) |  |  |  |  |
| AUC (µg·h/mL)                        | 53.0 (20.83)                                   | 59.2 (22.73)                                   | 55.3 (23.45)                                   | 64.5 (31.20)                                   |
| C <sub>4,max</sub> (µg/mL)           | 36.2 (7.31)                                    | 32.4 (10.81)                                   | 18.4 (6.25)                                    | 21.2 (6.86)                                    |
| T <sub>max</sub> (h)                 | 0.25 (0.00)                                    | 0.26 (0.02)                                    | 0.84 (0.58)                                    | 0.66 (0.42)                                    |
| t <sub>1/2</sub> (h)                 | 2.7 (1.10)                                     | 2.8 (1.03)                                     | 3.2 (0.91)                                     | 3.1 (0.80)                                     |
| CL (L/h)                             | 21.1 (7.30)                                    | 18.5 (4.73)                                    | 20.3 (5.89)                                    | 17.7 (5.37)                                    |
| V <sub>ss</sub> (L)                  | 29.5 (9.2)                                     | 37.2 (8.92)                                    | 37.3 (10.8)                                    | 42.2 (11.9)                                    |

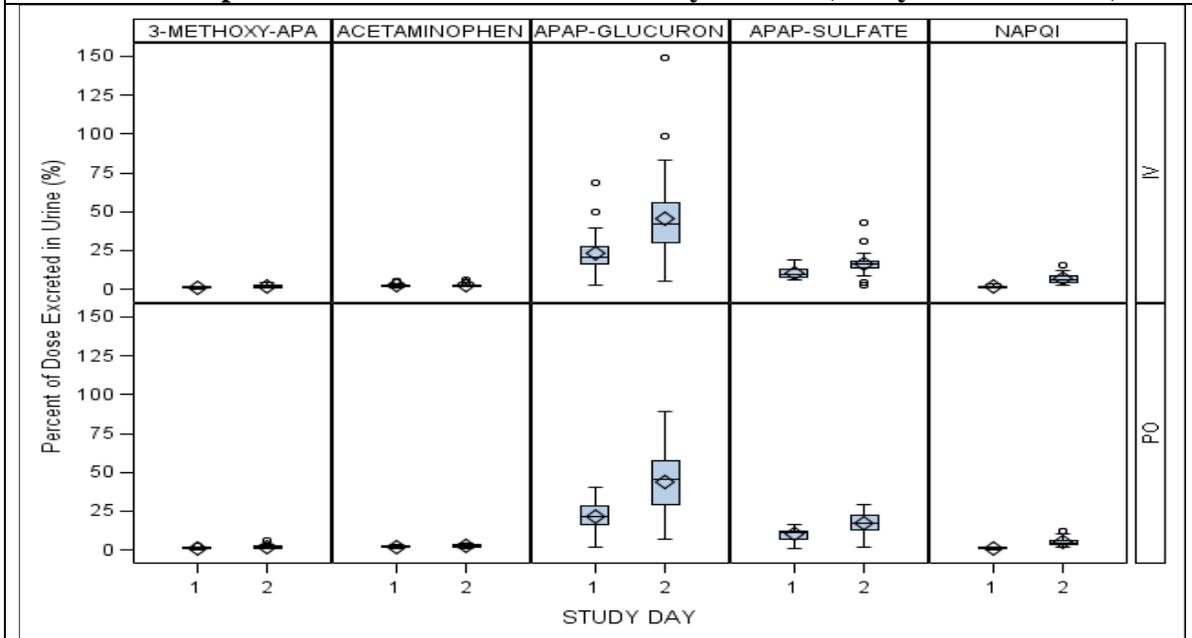
Dose proportionality was established between 500 mg and 1000 mg after IV administration (Study 98051C-CIS).

**Table 2. Mean pharmacokinetic parameters following a single dose of intravenous and orally administered acetaminophen (500 mg and 1000 mg) and propacetamol (2000 mg) in healthy adults (Study 98051C-CIS).**

| Parameter                | Mean (SD)                        |                                   |                         |
|--------------------------|----------------------------------|-----------------------------------|-------------------------|
|                          | IV acetaminophen 500 mg (N = 24) | IV acetaminophen 1000 mg (N = 24) | IV PPA 2000 mg (N = 24) |
| AUC (µg·h/mL)            | 27.0 (4.9)                       | 57.6 (10.4)                       | 51.0 (9.1)              |
| C <sub>max</sub> (µg/mL) | 14.4 (4.2)                       | 29.9 (8.3)                        | 24.7 (6.0)              |
| T <sub>max</sub> (h)     | 0.26 (0.04)                      | 0.25 (0.02)                       | 0.26 (0.02)             |
| t <sub>1/2</sub> (h)     | 2.7 (0.4)                        | 2.7 (0.4)                         | 2.8 (0.4)               |
| CL (L/h)                 | 19.2 (4.1)                       | 17.9 (3.4)                        | 20.3 (4.1)              |

The metabolites of acetaminophen include: acetaminophen glucuronide, acetaminophen sulfate, 3'-methoxyacetaminophen, and N-acetyl-p-benzoquinone imine (NAPQI) production (3'-S-Methyl-acetaminophen, 3'-(S-cysteinyl) acetaminophen, and acetaminophen mercapturate). The route of administration did not appear to have a clinically significant impact on fractional excretion in urine of free or unconjugated acetaminophen or the various acetaminophen metabolites assessed. Specifically, the appearance of NAPQI metabolites in urine was comparable for IV q6h vs. PO q6h.

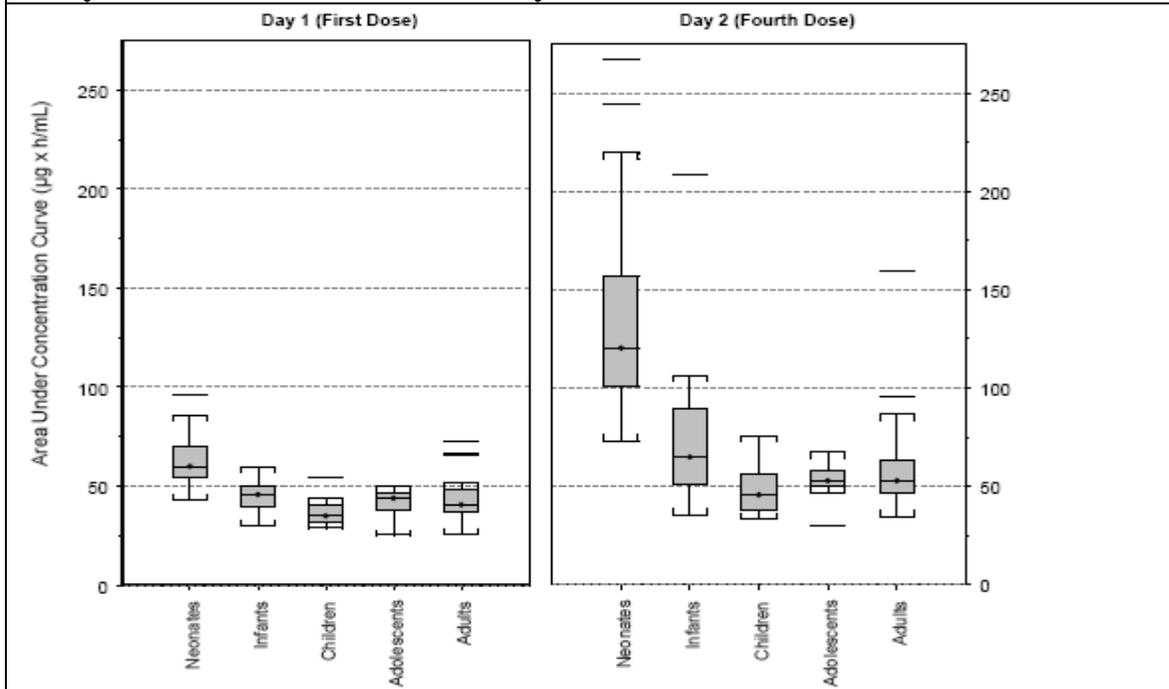
**Figure 2. Percent of individual metabolites excreted in the urine following 1 g IV or oral acetaminophen administration to adults every 6 hours (Study CPI-APA-101).**



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

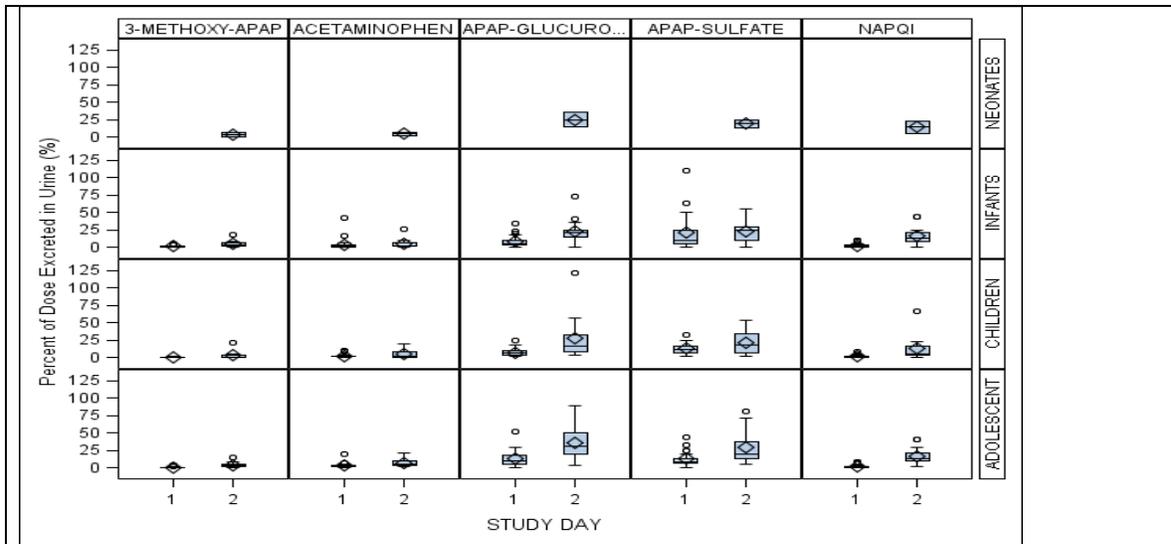
regimen, population PK model predicted acetaminophen  $AUC_{\tau}$  values were consistent across age groups, with the exception of neonates, who displayed higher exposure values following both single and repeated treatments (i.e., Day 2, 4th dose).

**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.**



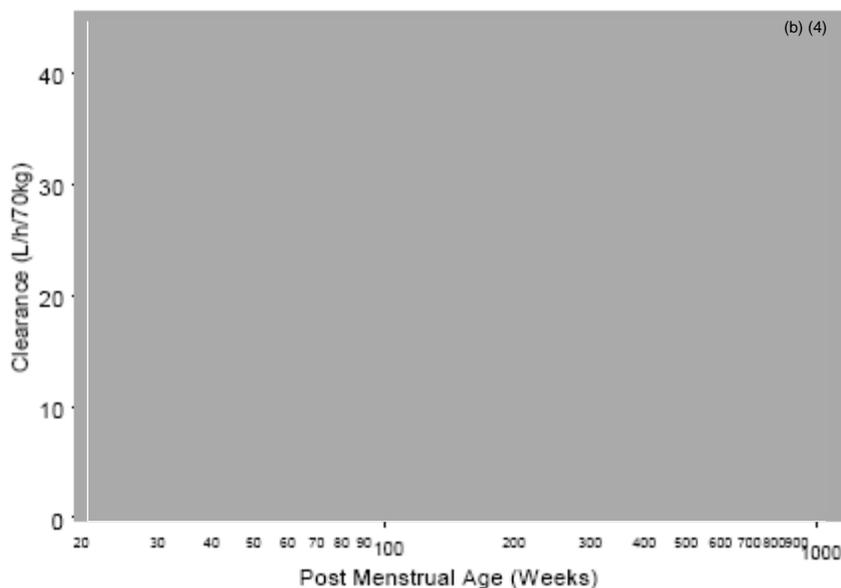
The percent of dose excreted in the urine in pediatric patients for NAPQI appeared to be comparable among different age groups (Study CPI-APA-102) and also comparable to the adults.

**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.

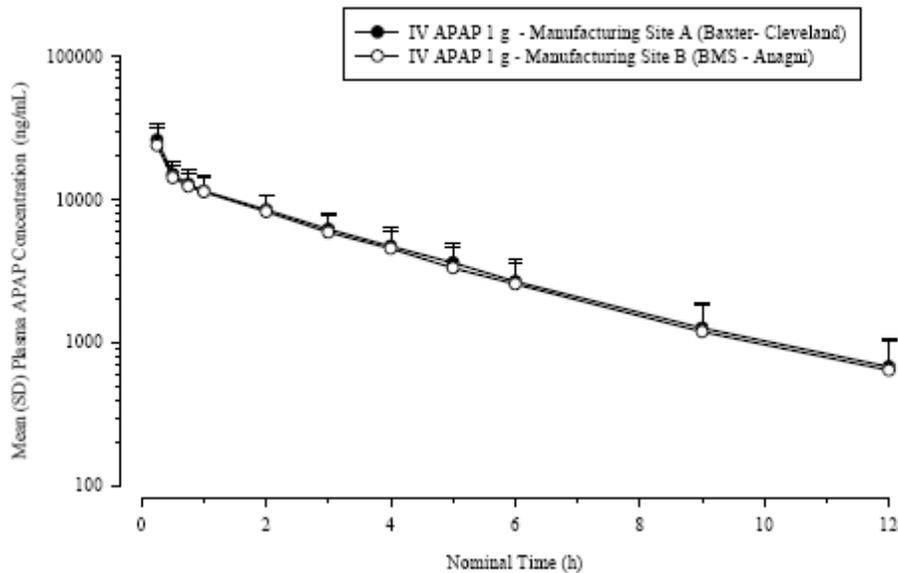
Full line represents the equation of standardized clearance:  $CL(L/h/70\text{ kg}) = 18.3 \times \left[ 1 - 0.796 \times \exp\left(-\frac{(PMA - 40) \times \ln(2)}{32.6}\right) \right]$

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

**Exposure (dose) response (efficacy and safety) relationship** Both 1 g q6h (4 g/day) and 650 mg q4h (4 g/day) IV acetaminophen have been shown to significantly reduce pain after abdominal laparoscopic surgery in a randomized double-blind study CPI-APA-304. A statistically significant reduction in temperature was also observed for IV 1 g acetaminophen subjects compared to placebo (Study CPI-APF-302). Correlation of liver function markers with NAPQI production was also assessed. The levels of liver function markers (AST, ALT, and Bilirubin) was independent of percent (amount) excreted as NAPQI production (acetaminophen mercapturate, 3'-[S-cysteiny] acetaminophen, and 3'-S-methylacetaminophen).

**Biopharmaceutics** Three formulations of IV acetaminophen (referred to as the initial, current, and proposed commercial formulations) were used in the development program. The two pivotal efficacy trials (Studies CPI-APF-302 and CPI-APA-304) used the current formulation. Bioequivalence of the current formulation manufactured by BMS in Anagni, Italy and used in the Cadence-sponsored clinical trials to the proposed commercial formulation manufactured by Baxter in Cleveland, Mississippi was established in Study CPI-APA-103.

**Figure 6. Mean plasma acetaminophen concentrations for intravenous acetaminophen from two manufacturing sites (Study CPI-APA-103)**



## **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 and is supported by twenty studies including five Phase 1 clinical pharmacology studies, one bioequivalence study and fourteen Phase 3 studies. The five Phase 1 clinical pharmacology studies were designed to establish PK and safety in adults (Study CPI-APA-101, Study 116-01-03, and Study 98051C-CIS) and in pediatric patients (Study CPI-APA-102 and Study EHRC #26095). Study CPI-APA-101 compared repeated doses of IV acetaminophen 1000 mg administered every four hours (q4h) and every six hours (q6h) to PO acetaminophen 1000 mg administered q4h and q6h, respectively. Study 116-01-03 compared the single dose PK of IV and PO acetaminophen 1000 mg. Study 98051C-CIS compared the single dose PK of IV acetaminophen 1000 mg and 500 mg with 2000 mg of IV propacetamol (PPA), a prodrug that is converted to acetaminophen in the blood (2000 mg to 1000 mg). Two studies (CPI-APA-102 and Study EHRC #26095) in pediatric patients utilized population methods for PK assessment. The bioequivalence study (Study CPI-APA-103) was conducted to determine the bioequivalence of the clinical formulation to the proposed commercial formulation. The fourteen phase 3 studies were designed to investigate the safety and efficacy (pain and/or fever) of IV acetaminophen in adults (n=11) and 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 and is supported by twenty studies including five Phase 1 clinical pharmacology studies, one bioequivalence study and fourteen Phase 3 studies. The five Phase 1 clinical pharmacology studies were designed to establish PK and safety in adults (Study CPI-APA-101, Study 116-01-03, and Study 98051C-CIS) and in pediatric patients (Study CPI-APA-102 and Study EHRC #26095). Study CPI-APA-101 compared repeated doses of IV acetaminophen 1000 mg administered every four hours (q4h) and every six hours (q6h) to PO acetaminophen 1000 mg administered q4h and q6h, respectively. Study 116-01-03 compared the single dose PK of IV and PO acetaminophen 1000 mg. Study 98051C-CIS compared the single dose PK of IV acetaminophen 1000 mg and 500 mg with 2000 mg of IV propacetamol (PPA), a prodrug that is converted to acetaminophen in the blood (2000 mg to 1000 mg). Two studies (CPI-APA-102 and Study EHRC #26095) in pediatric patients utilized population methods for PK assessment. The bioequivalence study (Study CPI-APA-103) was conducted to determine the bioequivalence of the clinical formulation to the proposed commercial formulation. The fourteen phase 3 studies were designed to investigate the safety and efficacy (pain and/or fever) of IV acetaminophen in adults (n=11) and pediatrics (n=3).

**Table 3. Tabular listing of all clinical studies in adult subjects.**

| Objectives            | study                 | Subjects                  | Dosing Regimen Used in the Study        |
|-----------------------|-----------------------|---------------------------|---|
| Phase 1 PK and safety | CPI-APA-101           | n=32, 34 (>50 kg)         | 1 g q4h, 1 g q6h                        |
|                       | 116-01-03             | n=21 (137-248 lb)         | 1 g IV                                  |
|                       | 98051C-CIS            | N=24, 24 (60-83 kg)       | 500 mg, 1 g                             |
|                       | CPI-APA-103           | N= 26 (132-229 lb)        | 1 g                                     |
| Fever                 | CPI-APF-302 (pivotal) | N=31 healthy (126-232 lb) | 1 g SD                                  |
|                       | CPI-APF-303           | n=54 healthy (126-273 lb) | 1 g SD                                  |
| Pain                  | RC210 3 002 (pivotal) | N=49 (61-111 kg)          | 1 g                                     |
|                       | CPI-APA-301           | N=166 (98-275 lb)         | 1 g                                     |
|                       | CPI-APA-304           | N=134 (103-256 lb)        | 1 g q6h, 650 mg q4h                     |
|                       | RC210 3 001           | N=51 (40-97 kg)           | 1 g SD                                  |
|                       | CN145-004             | N=264 (50-95 kg)          | 1 g SD                                  |
|                       | 136-01-03             | N=35 (129-293 lb)         | 1 g SD                                  |
|                       | 136-02-03             | N=30 (61-76 kg)           | 1 g repeat dose, 24 h                   |
|                       | 136-03-03             | N=23 (108-238 lb)         | 1 g repeat dose, 24 h                   |
|                       | CPI-APA-351           | N=183 (43-235 kg)         | 1 g or 650 mg, repeat dose up to 5 days |

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

| Study | Objectives | Dosing Regimen Used in the Study |
|-------|------------|----------------------------------|
|-------|------------|----------------------------------|

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

| Study                       | Primary Endpoint   | Secondary Endpoints   |
|-----------------------------|--|---|
| CPI-APF-302 fever (pivotal) | WSTD6  | WSTD3<br>Maximum temperature reduction during the period from T0 to T360 minutes<br>The percentage of subjects with temperature < 38 °C (100.4 °F) at any time point from T0 to T360 minutes<br>Change in temperature at each assessment time point (T5 to T360)<br>Time to a reduction in temperature of 1.5 °C (2.7 °F) |
| RC210 3 002 pain (pivotal)  | <u>Original single dose endpoint:</u> mean PR scores at each assessment through 6 h T-CARE<br><u>single dose endpoint from reanalysis:</u> SPID24 (WOCF) | <u>Single dose:</u> PID and PRID at each assessment time from 0.25 to 6h, TOTPAR4/6, SPID4/6, SPRID4/6, time to first rescue, number and percentage of patients requiring rescue in the first 6h, patient's global evaluation at 6h<br><u>Repeat dose:</u> mean PI over 24 h, number of requests                          |

| Study                         | Primary Endpoint  | Secondary Endpoints  |
|-------------------------------|---|--|
|                               | <u>Original repeated dose endpoint:</u><br>Mean PI over 24 h adjusted for rescue medication consumption | for and actual administrations of rescue medication, rescue medication consumption, number and percentage of patients requiring rescue, patient's global evaluation at 24h<br>T-CARE: SPID24 using other imputation methods; SPI24 |
| CPI-APA-304<br>Pain (pivotal) | SPID24 (VAS)  | SPID24 (VAS) (all other comparisons and imputation methods), patient's global evaluation at 24 h, time to first rescue, rescue consumption over 24 h, TOTPAR24   |

The therapeutic effect of IV acetaminophen is due to its ability to reduce pain and fever. Therefore, quantifying fever and pain relief are meaningful clinical endpoints in a clinical trial. The primary endpoint in pain studies was SPID24 (weighted sum of pain intensity difference from baseline at time 0 to 24 hours). The primary endpoint in fever study was WSTD6 (weighted sum of temperature differences from the temperature at each assessment timepoint through 6 hours compared with the temperature at time 0, weighted by the time elapsed between each two consecutive timepoints) In addition, the following related secondary clinical endpoints in the phase 3 trial were also assessed for fever: maximum temperature reduction during the period from T0 to T360 minutes, the percentage of subjects with temperature < 38 °C (100.4 °F) at any time point from T0 to T360 minutes, change in temperature at each assessment time point (T5 to T360), time to a reduction in temperature of 1.5 °C (2.7 °F). For pain: pain intensity difference (PID), total pain relief (TOTPAR), pain intensity difference from baseline (SPRID), time to first rescue, number and percentage of patients requiring rescue in the first 6h, patient's global evaluation at 6h, mean pain intensity (PI) over 24 h, number of requests for and actual administrations of rescue medication, rescue medication consumption, number and percentage of patients requiring rescue, patient's global evaluation at 24h T-CARE.

**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 endpoint.**

*The exposure-response relationships were not explored in this submission. However, both 1 g q6h and 650 mg q4h IV acetaminophen have been shown to significantly reduce pain after abdominal laparoscopic surgery in a randomized double-blind study CPI-APA-304. In addition, a statistically significant reduction in temperature was also*

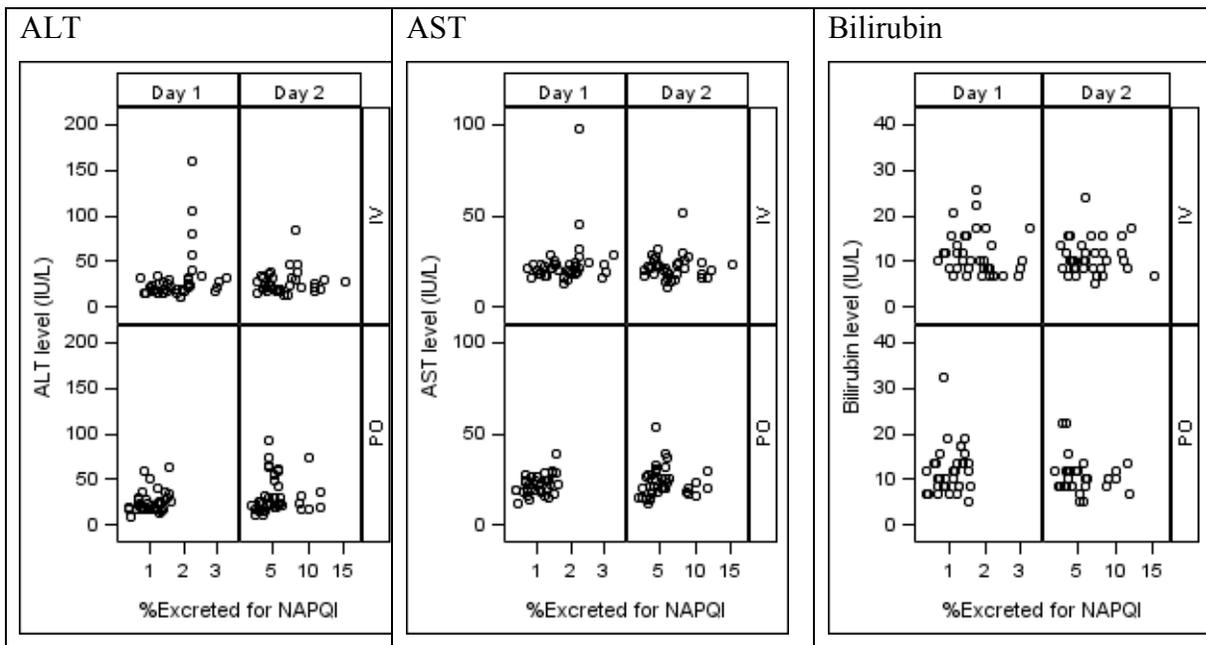
observed for IV 1 g acetaminophen subjects compared to placebo (Study CPI-APF-302). For details, please refer to clinical and Biostatistics review.

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

Correlation of liver function markers with NAPQI production was assessed. The levels 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).

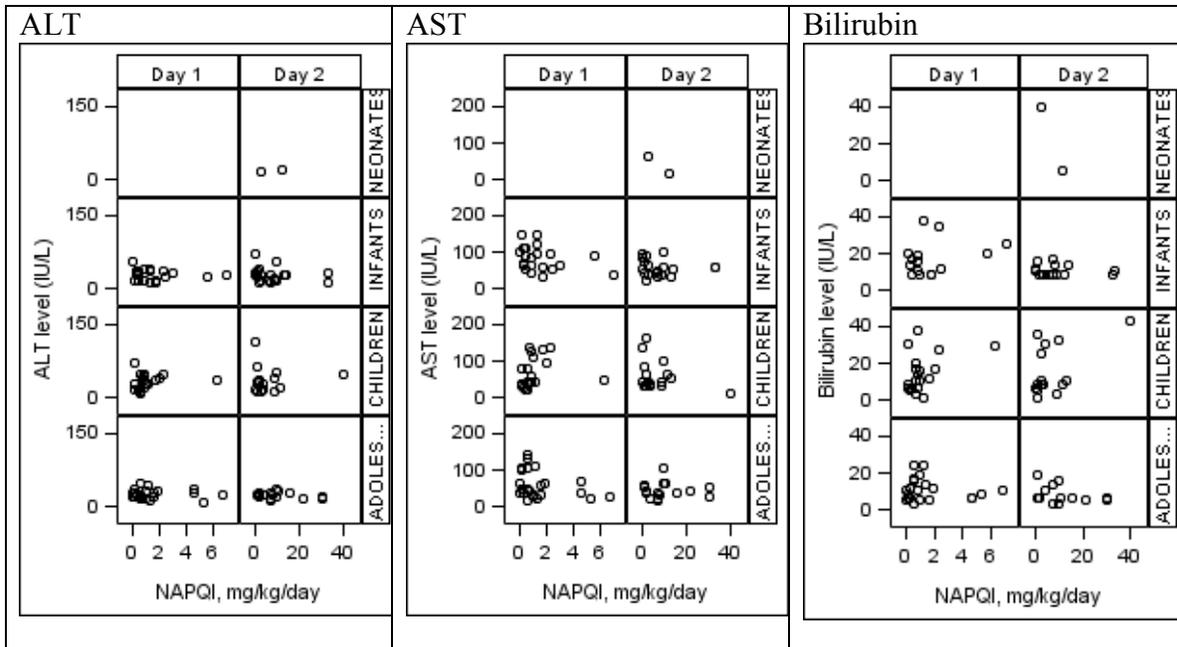
The levels of liver function markers (AST, ALT, and Bilirubin) were independent of percent excreted as NAPQI production in adults given as 1 g every 6 hours intravenously.

**Figure 7. Scatter plots of markers of liver function (AST, ALT, and Bilirubin) versus percent excreted as NAPQI conjugates. (Study CPI-APA-101).**



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 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.*

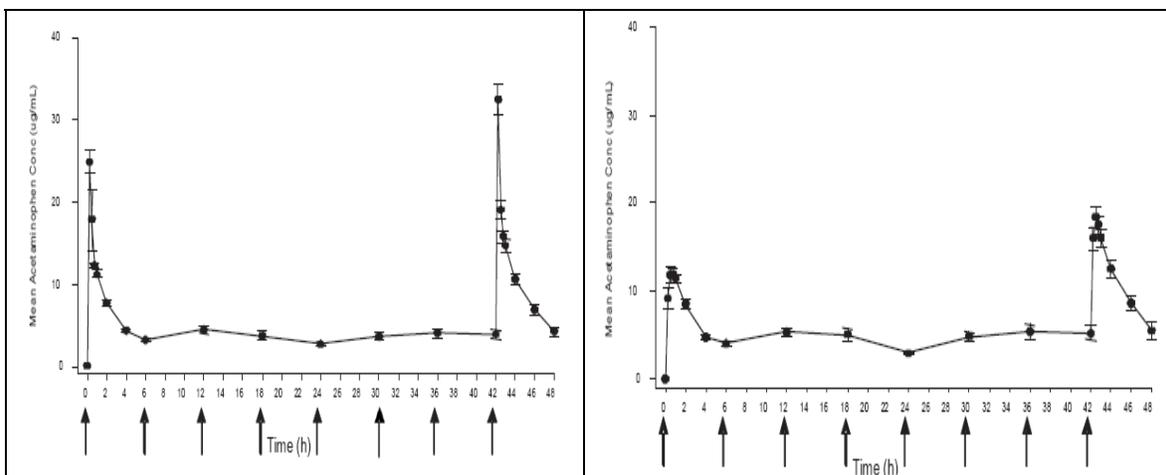
**2.2.5. What are the PK characteristics of the drug and its major metabolite?**

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

In the open-label, 4-period, randomized crossover study designed to compare the PK of 1000 mg IV and PO acetaminophen administered q4h and q6h over a 2-day treatment period (Study C0402), IV acetaminophen produced a mean maximum plasma concentration for the first dose ( $C_{1,max}$ ) that was approximately 70% higher than that following PO dosing. Mean  $T_{max}$  values for the IV acetaminophen 1000 mg q4h and q6h treatment groups (Day 1 and Day 2 median values = 0.25 h for each IV treatment group) were approximately 30 minutes faster compared with the PO acetaminophen 1000 mg q4h and q6h groups. Mean AUC values at steady state were comparable between the treatment groups, with the oral bioavailability greater than 90%.

**Figure 9. Mean Acetaminophen Concentrations Over Time Profiles for 6-Hour Dosing (Study CPI-APA-101)**

|  |  |
|--|--|
| 6 – Hour IV Dosing Regimen (Treatment B) | 6 – Hour PO Dosing Regimen (Treatment D) |
|--|--|



**Table 6. Mean (SD) Pharmacokinetic Parameters following Single and Multiple Doses of Intravenous and Oral Acetaminophen 1000 mg (Study CPI-APA-001).**

| Day<br>Parameter                     | IV<br>Acetaminophen<br>1000 mg q4h<br>(N = 32) | IV<br>Acetaminophen<br>1000 mg q6h<br>(N = 34) | PO<br>Acetaminophen<br>1000 mg q4h<br>(N = 35) | PO<br>Acetaminophen<br>1000 mg q6h<br>(N = 33) |
|--------------------------------------|--|--|--|--|
| Day 1, Dose 1                        |  |  |  |  |
| AUC (µg·h/mL)                        | 34.6 (7.98)                                    | 42.3 (10.58)                                   | 32.6 (7.22)                                    | 39.4 (9.57)                                    |
| C <sub>1,max</sub> (µg/mL)           | 26.0 (7.67)                                    | 28.4 (21.17)                                   | 15.1 (5.36)                                    | 15.1 (4.37)                                    |
| T <sub>max</sub> (h)                 | 0.25 (0.00)                                    | 0.28 (0.10)                                    | 0.84 (0.58)                                    | 0.72 (0.42)                                    |
| t <sub>1/2</sub> (h)                 | 2.28 (0.52)                                    | 2.39 (0.57)                                    | 2.91 (0.98)                                    | 2.66 (0.68)                                    |
| Day 2, Dose 4 (8 <sup>th</sup> Dose) |  |  |  |  |
| AUC (µg·h/mL)                        | 53.0 (20.83)                                   | 59.2 (22.73)                                   | 55.3 (23.45)                                   | 64.5 (31.20)                                   |
| C <sub>4,max</sub> (µg/mL)           | 36.2 (7.31)                                    | 32.4 (10.81)                                   | 18.4 (6.25)                                    | 21.2 (6.86)                                    |
| T <sub>max</sub> (h)                 | 0.25 (0.00)                                    | 0.26 (0.02)                                    | 0.84 (0.58)                                    | 0.66 (0.42)                                    |
| t <sub>1/2</sub> (h)                 | 2.7 (1.10)                                     | 2.8 (1.03)                                     | 3.2 (0.91)                                     | 3.1 (0.80)                                     |
| CL (L/h)                             | 21.1 (7.30)                                    | 18.5 (4.73)                                    | 20.3 (5.89)                                    | 17.7 (5.37)                                    |
| V <sub>SS</sub> (L)                  | 29.5 (9.2)                                     | 37.2 (8.92)                                    | 37.3 (10.8)                                    | 42.2 (11.9)                                    |

**2.2.5.2. How does the PK of the drug in healthy volunteers compare to that in patients?**

*The PK of acetaminophen was comparable between healthy subjects and pain patients.*

In healthy subjects given 1 g IV acetaminophen every 6 hours, the mean C<sub>max</sub> after the first dose and AUC at steady state were 28.4 µg/mL and 59.2 µg h/mL, respectively (study CPI-APA-101). In pain patients given 1 g IV acetaminophen single dose, the mean C<sub>max</sub> and AUC were 25.02 µg/mL and 61.08 µg h/mL, respectively (Study 136-01-03).

**Table 72: Arithmetic (±SD) and geometric mean of 1g single dose acetaminophen injection pharmacokinetic properties in patients following primary total hip arthroplasty (N = 11) (Study 136-01-03)**

| Parameter (unit) | Arithmetic Mean | Geometric Mean |
|------------------|-----------------|----------------|
|------------------|-----------------|----------------|

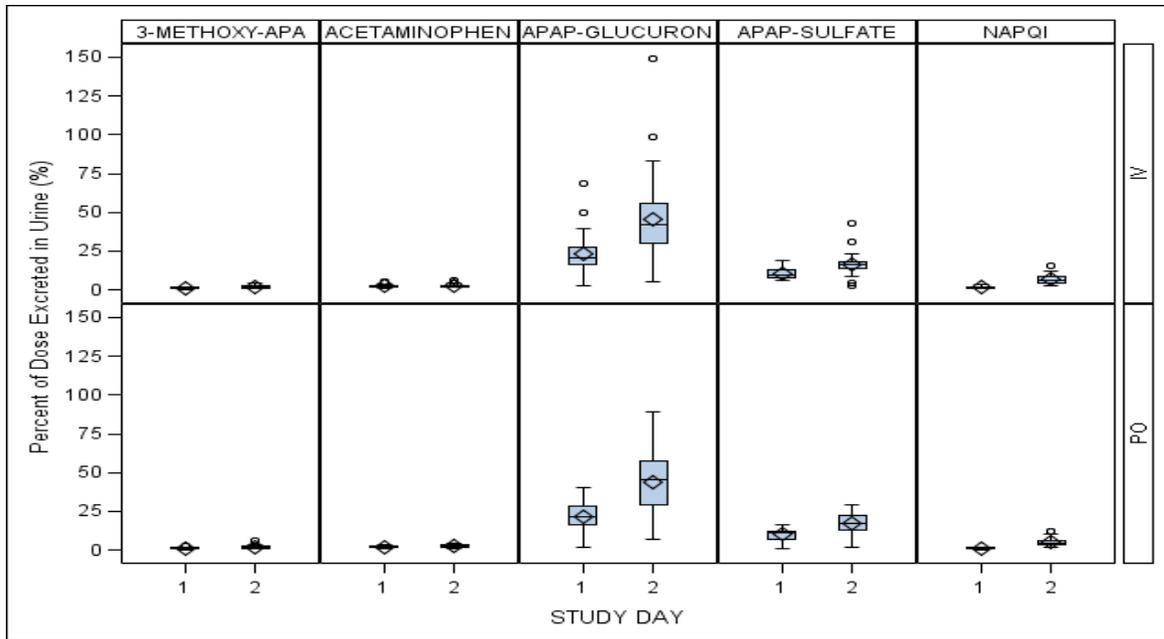
|                   |               |       |
|-------------------|---------------|-------|
| AUC0-24 (hr*mg/L) | 59.69 (26.60) | 54.78 |
| AUC0-∞ (hr*mg/L)  | 61.08 (28.76) | 55.61 |
| t1/2 (hr)         | 3.62 (2.12)   | -     |
| Cmax (mg/L)       | 25.02 (9.29)  | 23.46 |
| Tmax (hr)         | 0.25 (0.0)    | -     |

### 2.2.5.3. What are the characteristics of drug metabolism?

*Acetaminophen is metabolized by the liver via glucuronidation, sulfation, and oxidation pathways. Additionally, hydroxylation to form 3-hydroxyacetaminophen and methoxylation to form 3-methoxyacetaminophen, along with excretion of free or unconjugated acetaminophen in the urine typically represent minor clearance pathways.*

Comparisons of acetaminophen metabolism between IV and PO dosing in adult subjects were based on measurements of acetaminophen metabolites in the urine of subjects participating in three studies in adults (CPI-APA-101, 116-01-03, and 136-01 03). Urine was collected and analyzed for presence of free acetaminophen and the most significant acetaminophen metabolites. Urine metabolite evaluations included: acetaminophen glucuronide, acetaminophen sulfate, 3'-methoxyacetaminophen, and NAPQI metabolites (3'-S-Methyl-acetaminophen, 3'-(S-cysteinyl) acetaminophen, and acetaminophen mercapturate). The route of administration did not appear to have a clinically significant impact on fractional excretion in urine of free or unconjugated acetaminophen or the various acetaminophen metabolites assessed. Specifically, the appearance of NAPQI metabolites in urine (12-hour collections after the 8th dose) was comparable for IV q6h vs. PO q6h.

**Figure 10. Percent of individual metabolites excreted in the urine following 1 g IV or oral acetaminophen administration to adults every 6 hours (Study CPI-APA-101).**



**2.2.5.4. Based on PK parameters, what is the degree of linearity or nonlinearity in the dose-concentration relationship?**

*Dose proportionality was established between 500 mg and 1000 mg after IV administration.*

Dose proportionality was investigated in study 98051C-CIS over the IV acetaminophen dose range of 500 mg and 1000 mg. The C<sub>max</sub> and AUC after 500 mg IV acetaminophen was 14.4 µg/mL and 27 µg h/mL, respectively. The C<sub>max</sub> and AUC after 1000 mg IV acetaminophen was 29.9 µg/mL and 57.6 µg h/mL, respectively.

**Table 8. Mean pharmacokinetic parameters following a single dose of intravenous and orally administered acetaminophen (500 mg and 1000 mg) and propacetamol (2000 mg) in healthy adults (Study 98051C-CIS).**

| Parameter                | Mean (SD)                              |   |                               |
|--------------------------|--|---|-------------------------------|
|                          | IV acetaminophen<br>500 mg<br>(N = 24) | IV acetaminophen<br>1000 mg<br>(N = 24) | IV PPA<br>2000 mg<br>(N = 24) |
| AUC (µg·h/mL)            | 27.0 (4.9)                             | 57.6 (10.4)                             | 51.0 (9.1)                    |
| C <sub>max</sub> (µg/mL) | 14.4 (4.2)                             | 29.9 (8.3)                              | 24.7 (6.0)                    |
| T <sub>max</sub> (h)     | 0.26 (0.04)                            | 0.25 (0.02)                             | 0.26 (0.02)                   |
| t <sub>1/2</sub> (h)     | 2.7 (0.4)                              | 2.7 (0.4)                               | 2.8 (0.4)                     |
| CL (L/h)                 | 19.2 (4.1)                             | 17.9 (3.4)                              | 20.3 (4.1)                    |

**2.2.5.5. What are the major causes of variability in the PK parameters?**

The plasma concentration time profiles of IV acetaminophen were best characterized as a two-compartment model with linear elimination. The following parameters were allometrically scaled on the basis of body weight: linear clearance (CL), central volume of distribution (Vc), intercompartmental clearance (Q), and peripheral volume of distribution (Vp). In addition, age was also identified as a covariate of CL. After adjusting these covariates, the inter-subject variability (%CV) of CL and Vc was 39 and 62, respectively.

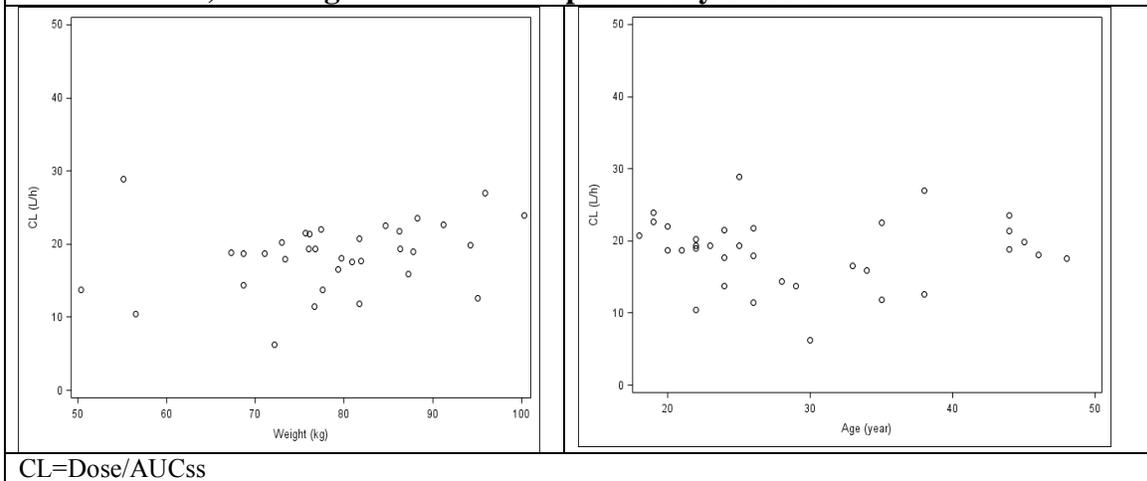
## 2.3. Intrinsic Factors

### 2.3.1. What intrinsic factors (age, gender, weight, etc.) influence exposure and/or response and what is the impact of any differences in exposure on the pharmacodynamics?

*No specific studies were conducted with regard to intrinsic factors. The noncompartmental analysis showed that CL was independent of body weight and age in the range studied in adult population.*

The scatter plot of CL versus body weight (50-100 kg) or age (18-48 y) showed that CL appeared to be independent of WT and age in the range studied (Study CPI-APA-101).

**Figure 11. The scatter plot of CL versus body weight (left) and age (right) (Study CPI-APA-101) after 1 g of IV acetaminophen every 6 hours.**



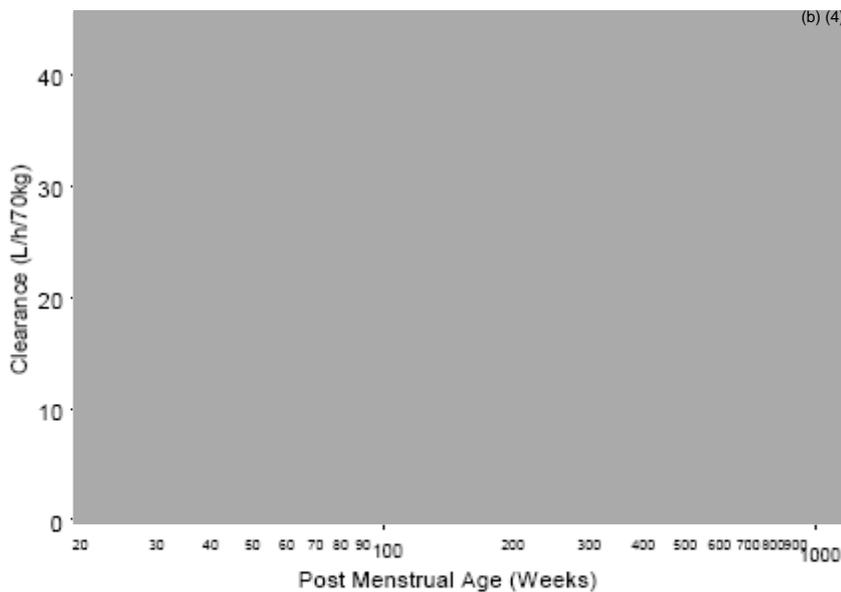
### 2.3.2. Based upon what is known about exposure-response relationships and their variability, and the groups studied (volunteers vs. patients); what dosage regimen adjustments, if any, are recommended for each of these subgroups (examples shown below)? If dosage regimen adjustments are not based upon 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:  $CL(L/h/70\text{ kg})=18.3 \times \left[ 1 - 0.796 \times \exp\left(-\frac{(PMA - 40) \times \ln(2)}{32.6}\right) \right]$

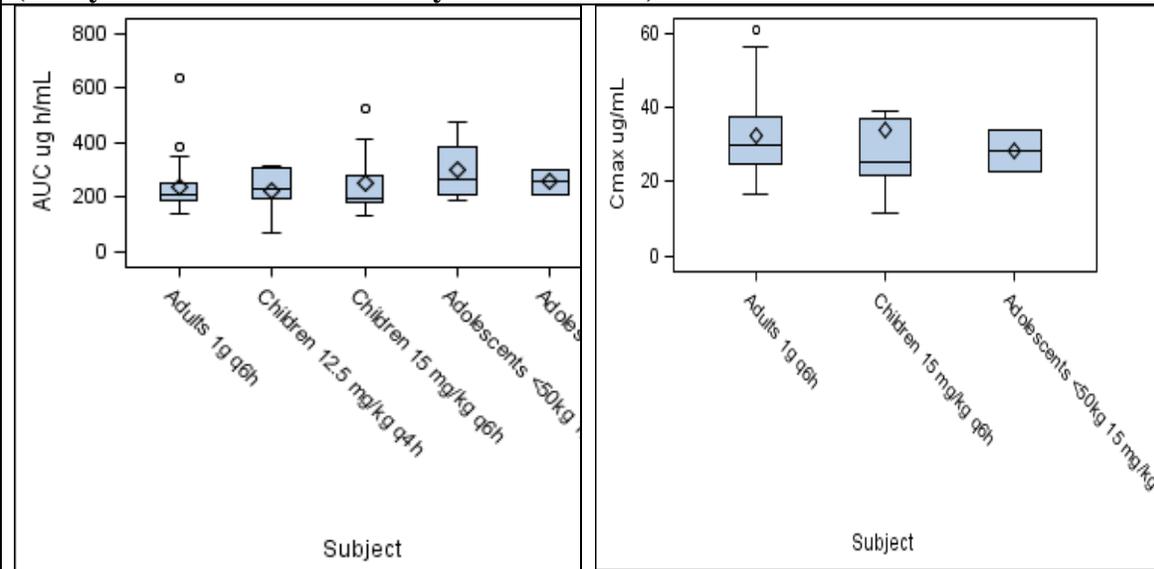
Source: CADE-RAS-003 [Figure 6.3:7](#).

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).

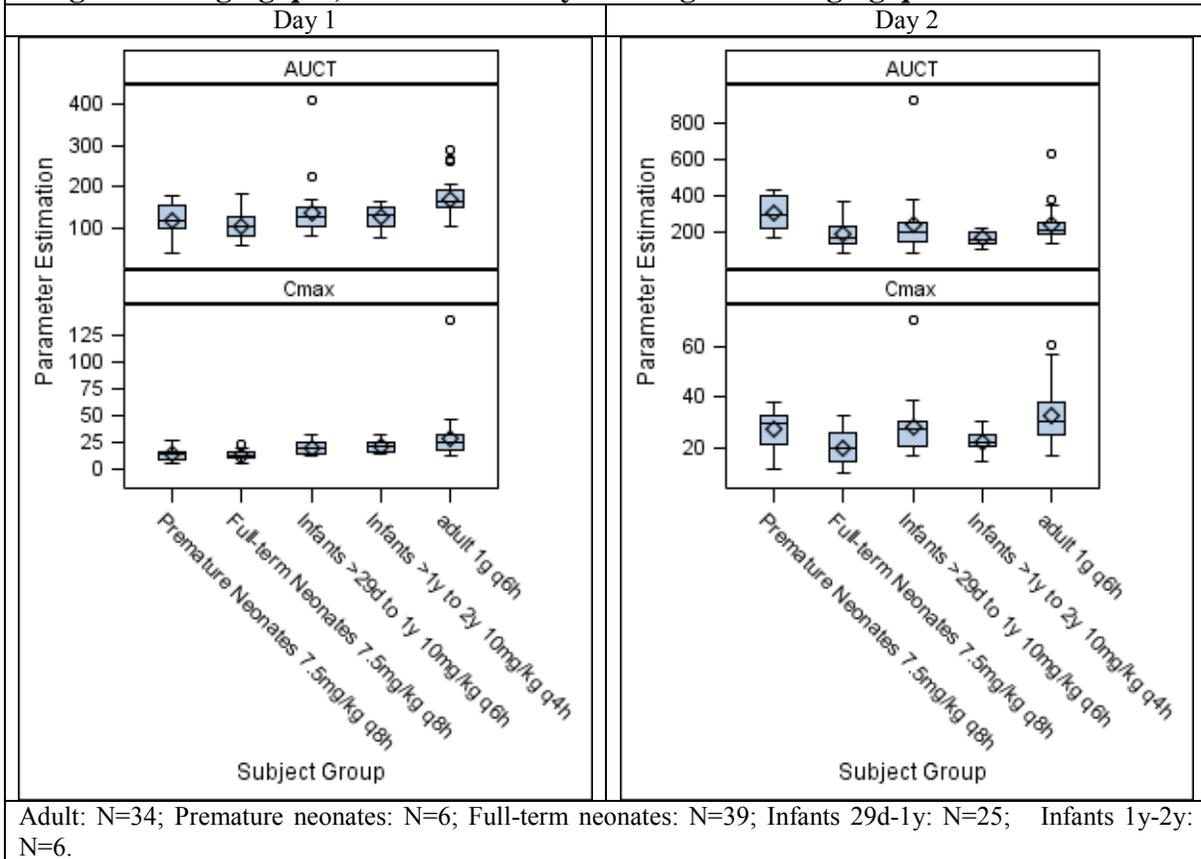
The proposed dosing regimen in neonates and infants are as follows:

- 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.

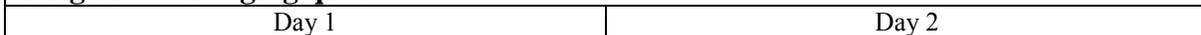
The above proposed dosing regimens were selected from a dose of 7.5, 10, 12.5 and 15 mg/kg given every 4, 6, 8, or 12 hours at a variety of combination using trial simulation by sponsor to reach optimal concentration range, which was prespecified based on adult and adolescent concentration data. The 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*).

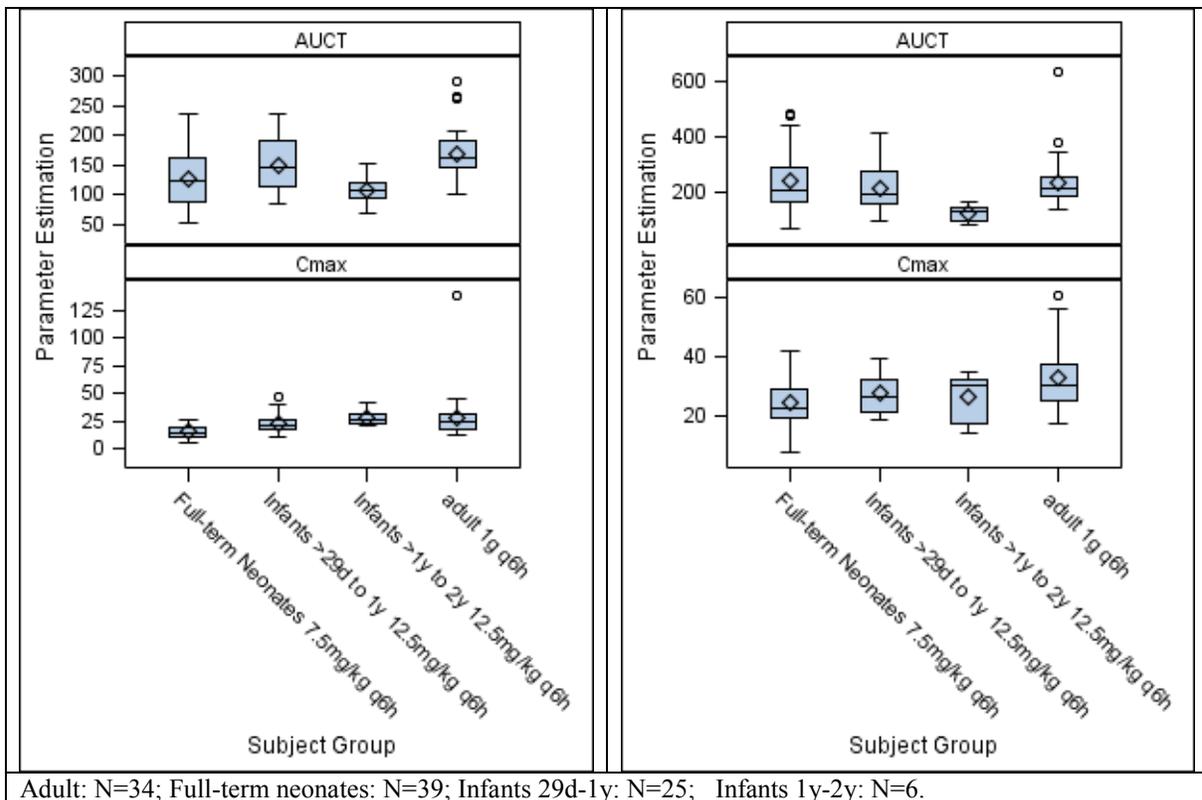
At the selected dosing regimens as shown in Figures 14 and 15, model predicted exposure in neonates and infants was comparable to the observed exposure in adults given 1g every 6 hours after both first dose and repeated doses.

**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.**



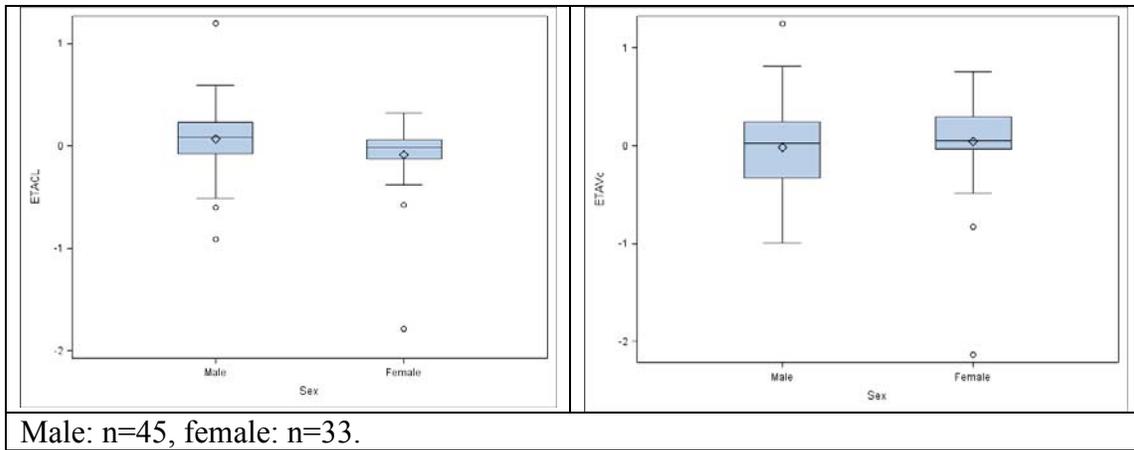


#### b) Gender

*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.

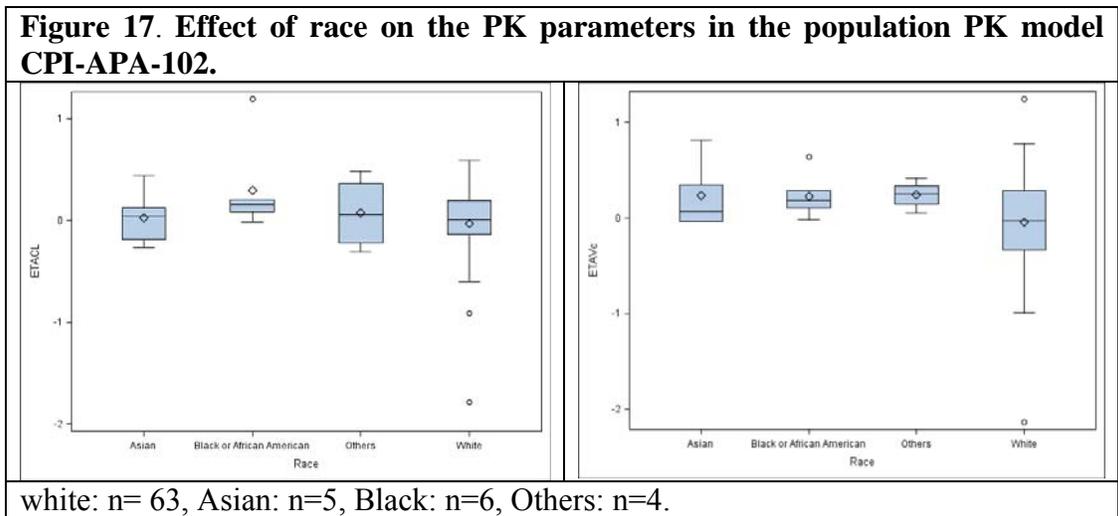
**Figure 16. Effect of sex on the PK parameters in the population PK model CPI-APA-102.**



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       | Manufacturer                         | Batch/Lot Number     |
|--|---|----------------------|--------------------------------------|----------------------|
| <b>Initial Formulation</b>   |   |                      |                                      |                      |
| <a href="#">RC 210 3 001</a>   | BMS: S/E, pain, adults  | 1000 mg              | BMS Delmas Laboratories <sup>1</sup> | PE 97030             |
| <a href="#">RC 210 3 002</a>   | BMS: S/E, pain, adults  | 1000 mg              | BMS Delmas Laboratories <sup>1</sup> | FD 99037             |
| <a href="#">98051C-CIS</a>   | BMS: PK, healthy adults   | 500 mg<br>1000 mg    | BMS Delmas Laboratories <sup>1</sup> | 1198/A<br>8083/A     |
| <b>Current Formulation</b>   |   |                      |                                      |                      |
| <a href="#">RC 210 3 006</a> <sup>2</sup><br><a href="#">CN145-001</a> <sup>2</sup>  | BMS:<br>S/E, fever, pediatric<br>S/E, fever, pediatric  | 1000 mg              | BMS Delmas Laboratories <sup>1</sup> | FD 00007             |
| <a href="#">CN145-004</a>  | BMS: S/E, pain adults   | 1000 mg              | BMS (Anagni, Italy)                  | 3A60230              |
| <a href="#">116-01-03</a><br><a href="#">136-01-03</a><br><a href="#">136-02-03</a><br><a href="#">136-03-03</a>   | BMS:<br>PK, healthy adults<br>S/E, PK, pain, adults<br>S/E, pain, adults<br>S/E, pain, adults   | 1000 mg              | BMS (Anagni, Italy)                  | 3C69720              |
| <a href="#">CPI-APA-101</a>  | Cadence: PK, healthy adults   | 1000 mg              | BMS (Anagni, Italy)                  | 6F18792 <sup>3</sup> |
| <a href="#">CPI-APA-102</a> <sup>2</sup><br><a href="#">CPI-APA-301</a><br><a href="#">CPI-APF-302</a><br><a href="#">CPI-APF-303</a><br><a href="#">CPI-APA-304</a><br><a href="#">CPI-APA-351</a><br><a href="#">CPI-APA-352</a> <sup>2</sup><br><a href="#">CPI-APA-103</a> | Cadence:<br>PK, pediatrics<br>S/E, pain, adults<br>S/E, fever, adults<br>S/E, fever, adults<br>S/E, pain, adults<br>S/E, fever, adults<br>S/E, fever, pediatric<br>BE, healthy adults | 1000 mg              | BMS (Anagni, Italy)                  | 6H11817              |
| <b>Proposed Commercial Formulation</b>   |   |                      |                                      |                      |
| <a href="#">CPI-APA-103</a>  | Cadence: BE, healthy adults   | 1000 mg <sup>4</sup> | Baxter (Cleveland, Mississippi)      | V337108              |

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.

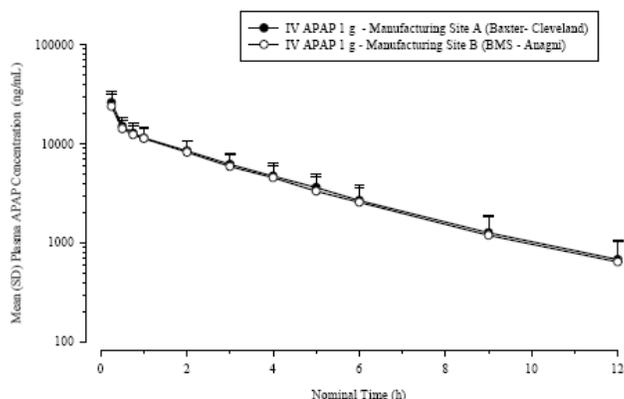
<sup>4</sup> A 650 mg dose also was administered, but not assessed for bioequivalence between manufacturing sites.

Source: Module 3, [Section 3.2.P.2.2.1.2](#) (Formulation Development)

A bioequivalence study with IV acetaminophen ([Study CPI-APA-103](#)) was conducted to determine the bioequivalence of the current formulation manufactured by BMS in Anagni, Italy and used in the Cadence-sponsored clinical trials to the proposed

commercial formulation manufactured by Baxter in Cleveland, Mississippi. Plasma acetaminophen PK profiles were similar between the 1000 mg IV acetaminophen manufactured at Site A (Baxter –Cleveland, Mississippi) and Site B (BMS – Anagni, Italy).

**Figure 18. Mean plasma acetaminophen concentrations for intravenous acetaminophen from two manufacturing sites (Study CPI-APA-103).**



Results of statistical comparisons of IV acetaminophen are summarized in Table 10.

**Table 10. Statistical comparison of pharmacokinetic parameters (Study CPI-APA-103).**

| PK Parameters                                       | Geometric Least-Squares Means |        | Ratio A/B% | 90% CI           | p-value | Intra-Subject (CV%) |
|---|-------------------------------|--------|------------|------------------|---------|---------------------|
|   | A                             | B      |            |                  |         |                     |
|   | N = 26                        | N = 26 |            |                  |         |                     |
| $C_{max}$ ( $\mu\text{g/mL}$ )                      | 24.8                          | 22.5   | 110.04     | (97.67, 123.97)  | 0.1822  | 25.4                |
| $AUC_{0-t}$ ( $\mu\text{g}\cdot\text{hr/mL}$ )      | 51.9                          | 49.4   | 105.03     | (102.62, 107.49) | 0.0014  | 4.9                 |
| $AUC_{0-\infty}$ ( $\mu\text{g}\cdot\text{hr/mL}$ ) | 54.6                          | 52.0   | 105.05     | (102.55, 107.62) | 0.0019  | 5.1                 |

Definitions are provided in the [List of Abbreviations](#).

Treatment A = Manufacturing Site A (Baxter – Cleveland, Mississippi)

Treatment B = Manufacturing Site B (BMS – Anagni, Italy)

Source: CPI-APA-103 Bioequivalence Report [Table 9.2.1](#)

As shown in Table 10, the 90% CIs for the ratios of the geometric least-squares (LS) means between the IV acetaminophen manufactured at Baxter in Cleveland, Mississippi (Manufacturing Site A) and the IV acetaminophen manufactured at BMS in Anagni, Italy (Manufacturing Site B) were completely contained within the equivalence limits of 80% to 125% for  $AUC_{0-t}$  (102.62, 107.49),  $AUC_{0-\infty}$  (102.55, 107.62), and  $C_{max}$  (97.67, 123.97). Therefore, the IV acetaminophen from the two manufacturing facilities was bioequivalent.

## 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 CPI-APA-101, CPI-APA-102, and CPI-APA-103 appears adequate and validated.*

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

| Validation Report Number                      | VAL-RPT-718              | VAL-RPT-810            |
|---|--------------------------|------------------------|
| Species/Sample Matrix                         | Human plasma             | Human plasma           |
| Analyte                                       | Acetaminophen            | Acetaminophen          |
| Method Utilized                               | HPLC-MS/MS               | HPLC-MS/MS             |
| Calibration Range                             | 50 – 10,000 ng/mL        | 50 – 30,000 ng/mL      |
| LLOQ (Accuracy)                               | 50 ng/mL (102.4%)        | 50 ng/mL (98.5%)       |
| Standard Curve Precision (ie, assay recovery) | 93.6 to 96.9%            | 68 to 86%              |
| Specificity                                   | No interference noted.   | No interference noted. |
| Inter-assay Precision (CV)                    | 2.9 to 3.4%              | 2.1 to 5.0%            |
| Inter-assay Accuracy                          | 98.4 to 105.1%           | 95.9 to 102.3%         |
| Intra-assay Precision (CV)                    | 1.9 to 3.6%              | 0.2 to 6.0%            |
| Intra-assay Accuracy                          | 101.4 to 105.1%          | 97.7 to 102.3%         |
| Testing Facility                              | (b) (4)                  |                        |
| Clinical Study                                | CPI-APA-101; CPI-APA-103 | 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                  |                         |

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|              |           |         |         |  |
|--------------|-----------|---------|---------|--|
| 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

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### 3. DETAILED LABELING RECOMMENDATIONS

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

18 Pages Draft Labeling Withheld in Full as B4 (CCI/TS) Immediately Following This Page

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

## 4.2. Individual Study Review

### CPI-APA-101

**Study Title:** Open-label, Four-period, Randomized Crossover Study to Determine the Comparative Pharmacokinetics of Oral and Intravenous Acetaminophen Administration in Healthy Male Volunteers

**Objectives:** The primary objective of this study was to determine the comparative exposure of IV and PO acetaminophen administration in healthy male volunteers. The secondary objectives were to measure plasma PK and concentrations of urine metabolites, and to assess clinical safety.

**Study Design:** This was an open-label, 4-period, randomized crossover study designed to compare the PK of 1000 mg IV and PO acetaminophen (elixir formulation) administered q4h to a maximum of 4 g/day and q6h over a 2-day treatment period (eight doses were administered on each schedule). Subjects were randomized to one of four treatment sequence groups on a 1:1:1:1 basis, each of which consisted of a unique sequence of four treatments, with each treatment consisting of four IV or PO acetaminophen doses each day on either a q4h or q6h regimen. There was a minimum washout period of 3 days between treatments.

**Study Population:** A total of 38 male subjects were enrolled in the study. The subjects ranged in age from 18 to 48 years with a mean of 29.2 years; 63% of subjects were Caucasian. Mean body mass index (BMI) was 24.3 kg/m<sup>2</sup> and ranged from 18 to 31 kg/m<sup>2</sup>.

**Data Analysis:** The values for the PK variables were determined with a non-compartmental method.

**Sample Analysis:** HPLC-MS/MS was the bioanalytical method used to analyze plasma samples for acetaminophen and the urine samples for acetaminophen and its metabolites. The performance of sample analysis is provided below:

| Analyte               | Biological Media | Standard curve range (µg/mL) | LLO Q (µg/mL) | QC samples (µg/mL)         | Precision (%) | Accuracy (%) |
|-----------------------|------------------|------------------------------|---------------|----------------------------|---------------|--------------|
| Acetaminophen         | plasma           | 0.05-30                      |               | 0.15, 10, and 20           | 5.7-13.8      | 94.6-101.1   |
| Acetaminophen         | urine            | 0.05-5.00                    | 0.05          | 0.15, 0.40, 4.0, and 40.00 | 3.9-28        | 90-105       |
| Acetaminophen sulfate | urine            | 0.25-10.00                   | 0.25          | 0.75, 1, 8, 250, 1000      | 3.9-33.2      | 96-102.5     |
| Acetaminophen         | urine            | 0.25-10.00                   | 0.25          | 0.75, 2.0, 8.0, 250,       | 8.5-28        | 92.4-104     |

| Analyte                    | Biological Media | Standard curve range (µg/mL) | LLO Q (µg/mL) | QC samples (µg/mL)       | Precision (%) | Accuracy (%) |
|----------------------------|------------------|------------------------------|---------------|--------------------------|---------------|--------------|
| glucuronide                |                  |                              |               | 1000                     |               |              |
| 3-Methoxy acetaminophen    | urine            | 0.10-5.00                    | 0.10          | 0.30, 1.50, 4.0, 40.0    | 21.9-41.2     | 82-91.3      |
| 3-Cysteinylacetaminophen   | urine            | 0.25-5.00                    | 0.25          | 0.75, 2.0, 4.0, and 40.0 | 5.4-9.8       | 97.3-98.5    |
| Acetaminophen mercapturate | urine            | 0.10-5.00                    | 0.10          | 0.3, 1.5, 4.0, 40        | 4.1-10.9      | 96.7-98      |
| Methylthioacetaminophen    | urine            | 0.10-5.00                    | 0.10          | 0.3, 1.50, 4.0, 40.00    | 9.5-11.5      | 91.5-98      |

**Pharmacokinetic Results:** Summary statistics of pharmacokinetic parameters after single and multiple dose of IV acetaminophen are shown the table below:

Table: Mean (SD) Pharmacokinetic Parameters following Single and Multiple Doses of Intravenous and Oral Acetaminophen 1000 mg, Study CPI-APA-101 (PK Population)

| Day<br>Parameter                     | IV<br>Acetaminophen<br>1000 mg q4h<br>(N = 32) | IV<br>Acetaminophen<br>1000 mg q6h<br>(N = 34) | PO<br>Acetaminophen<br>1000 mg q4h<br>(N = 35) | PO<br>Acetaminophen<br>1000 mg q6h<br>(N = 33) |
|--------------------------------------|--|--|--|--|
| Day 1, Dose 1                        |  |  |  |  |
| AUC (µg·h/mL)                        | 34.6 (7.98)                                    | 42.3 (10.58)                                   | 32.6 (7.22)                                    | 39.4 (9.57)                                    |
| C <sub>1,max</sub> (µg/mL)           | 26.0 (7.67)                                    | 28.4 (21.17)                                   | 15.1 (5.36)                                    | 15.1 (4.37)                                    |
| T <sub>max</sub> (h)                 | 0.25 (0.00)                                    | 0.28 (0.10)                                    | 0.84 (0.58)                                    | 0.72 (0.42)                                    |
| t <sub>1/2</sub> (h)                 | 2.28 (0.52)                                    | 2.39 (0.57)                                    | 2.91 (0.98)                                    | 2.66 (0.68)                                    |
| Day 2, Dose 4 (8 <sup>th</sup> Dose) |  |  |  |  |
| AUC (µg·h/mL)                        | 53.0 (20.83)                                   | 59.2 (22.73)                                   | 55.3 (23.45)                                   | 64.5 (31.20)                                   |
| C <sub>4,max</sub> (µg/mL)           | 36.2 (7.31)                                    | 32.4 (10.81)                                   | 18.4 (6.25)                                    | 21.2 (6.86)                                    |
| T <sub>max</sub> (h)                 | 0.25 (0.00)                                    | 0.26 (0.02)                                    | 0.84 (0.58)                                    | 0.66 (0.42)                                    |
| t <sub>1/2</sub> (h)                 | 2.7 (1.10)                                     | 2.8 (1.03)                                     | 3.2 (0.91)                                     | 3.1 (0.80)                                     |
| CL (L/h)                             | 21.1 (7.30)                                    | 18.5 (4.73)                                    | 20.3 (5.89)                                    | 17.7 (5.37)                                    |
| V <sub>SS</sub> (L)                  | 29.5 (9.2)                                     | 37.2 (8.92)                                    | 37.3 (10.8)                                    | 42.2 (11.9)                                    |

Definitions: See [List of Abbreviations](#)

Source: Study CPI-APA-101 [Table 5](#) and [Table 14.2.2.2](#).

Mean T<sub>max</sub> values (Table 4) for the IV acetaminophen 1000 mg q4h and q6h treatment groups (Day 1 and Day 2 median values = 0.25 h for each IV treatment group) were approximately 30 minutes faster compared with the PO acetaminophen 1000 mg q4h and q6h groups (Day 1 median values = 0.75 h Day 1 for both groups, and Day 2 median values = 0.75 and 0.5 h, respectively). Note that the mean (and median) T<sub>max</sub> values for the IV group occurred at the end of the 15-minute infusion. The t<sub>1/2</sub> was comparable across treatment groups at 2.7 to 3.2 h.

Mean AUC values at steady state (AUC, calculated after Day 2, Dose 4 [last or 8th dose]) were comparable between the treatment groups (Table 4). The differences between mean AUC values for the q4h IV vs. PO groups and the q6h IV vs. PO groups were within 2.3% and 6.5%, respectively. Mean  $V_{ss}$  values for Dose 4 for the IV acetaminophen treatments were similar to those for the PO groups.

IV acetaminophen produced a mean maximum plasma concentration for the first dose ( $C_{1,max}$ ) that was approximately 70% higher ( $p < 0.0001$ ) than that following PO dosing. The  $C_{1,max}$  for IV acetaminophen was 23% higher than the  $C_{max}$  observed after the 8th dose (4th dose on day 2) of 1000 mg PO acetaminophen given q6h.

A statistical comparison of acetaminophen PK parameters are shown in the table below:

Table: Statistical Comparisons of Acetaminophen Pharmacokinetic Parameters for Intravenous and Oral Acetaminophen Dosed q4h or q6h (Study CPI-APA-101).

| Parameter   | Geometric Means (N) | Treatment Comparisons <sup>1</sup> | Ratio (%) | 90% CI       |
|---|---------------------|------------------------------------|-----------|--------------|
| <b>Day 1, Dose 1</b>                                |                     |                                    |           |              |
| $C_{1,max}$<br>( $\mu\text{g/mL}$ )                 | A = 24.87 (32)      | A (IV) vs. C (PO)                  | 173.2     | 154.2, 194.6 |
|   | B = 24.97 (34)      | B (IV) vs. D (PO)                  | 170.7     | 152.0, 191.8 |
|   | C = 14.37 (35)      | A (q4h) vs. B (q6h)                | 100.3     | 89.2, 112.7  |
|   | D = 14.52 (33)      | C (q4h) vs. D (q6h)                | 101.7     | 90.6, 114.2  |
| $AUC_{1,\tau}$<br>( $\mu\text{g}\cdot\text{h/mL}$ ) | A = 33.65 (32)      | A (IV) vs. C (PO)                  | 106.8     | 99.9, 114.2  |
|   | B = 41.09 (34)      | B (IV) vs. D (PO)                  | 106.6     | 99.7, 113.9  |
|   | C = 31.82 (35)      | A (q4h) vs. B (q6h)                | 122.5     | 114.5, 130.9 |
|   | D = 38.34 (33)      | C (q4h) vs. D (q6h)                | 122.7     | 114.8, 131.2 |
| <b>Day 2, Dose 4 (8<sup>th</sup> Dose)</b>          |                     |                                    |           |              |
| $C_{4,max}$<br>( $\mu\text{g/mL}$ )                 | A = 35.41 (32)      | A (IV) vs. C (PO)                  | 202.3     | 180.0, 227.4 |
|   | B = 30.80 (34)      | B (IV) vs. D (PO)                  | 151.8     | 135.1, 170.5 |
|   | C = 17.57 (34)      | A (q4h) vs. B (q6h)                | 86.9      | 77.3, 97.7   |
|   | D = 20.15 (33)      | C (q4h) vs. D (q6h)                | 115.8     | 103.1, 130.1 |
| $AUC_{4,\tau}$<br>( $\mu\text{g}\cdot\text{h/mL}$ ) | A = 50.00 (32)      | A (IV) vs. C (PO)                  | 97.7      | 91.4, 104.5  |
|   | B = 56.28 (34)      | B (IV) vs. D (PO)                  | 93.5      | 87.5, 100.0  |
|   | C = 51.85 (34)      | A (q4h) vs. B (q6h)                | 112.9     | 105.6, 120.7 |
|   | D = 59.84 (33)      | C (q4h) vs. D (q6h)                | 117.9     | 110.3, 126.0 |

Definitions: See [List of Abbreviations](#)

<sup>1</sup> Acetaminophen dose and route of administration: A = 1000 mg IV q4h; B = 1000 mg IV q6h; C = 1000 mg PO q4h; D = 1000 mg PO q6h

<sup>2</sup> p-value corresponds to two-sided hypothesis test that ratio = 100%

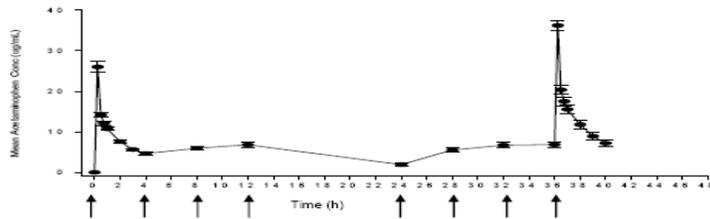
Note: Analysis based on a linear mixed-effect model for each parameter with fixed effects for treatment, day, treatment  $\times$  day, period, and sequence, a random effect for subject within sequence and day as a repeated effect  
Source: Study CPI-APA-101 [Table 6](#)

Mean  $AUC_{4,\tau}$  values for Day 2/Dose 4 (8th Dose) demonstrated that oral bioavailability (compared to IV) was approximately 97.7% (Treatment C vs. A) or 93.5% (Treatment D vs. B). The mean  $AUC_{4,\tau}$  values for PO acetaminophen were similar to those for IV acetaminophen and the 90% confidence intervals (CI) (for A vs. C and B vs. D treatments) were within the acceptable range of 80 - 125%.

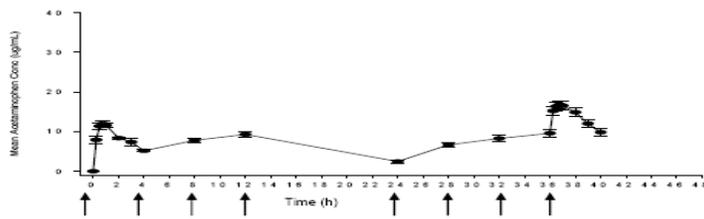
An assessment of the mean trough plasma acetaminophen concentrations showed that there was minimal accumulation after every 4- or 6-hour dosing for both IV and oral regimens.

Figure: Mean Acetaminophen Concentrations Over Time Profiles for 4-Hour Dosing

**4-Hour IV Dosing Regimen (Treatment A)**



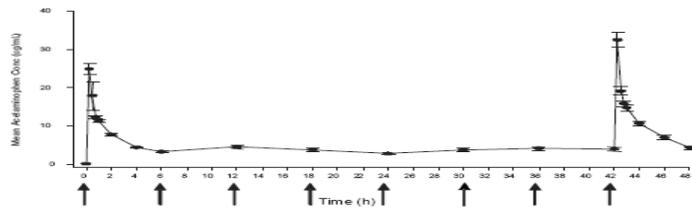
**4-Hour PO Dosing Regimen (Treatment C)**



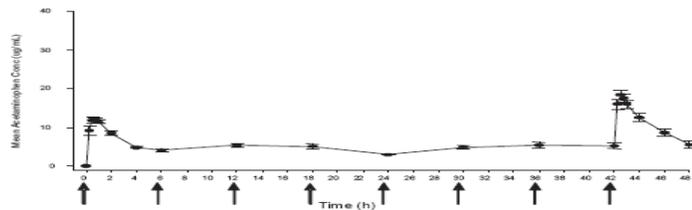
Note: Arrows indicate dosing time (hours): T0, T4, T8, T12, T24, T28, T32, and T36, error bar (standard error), solid dot, and line (arithmetic mean acetaminophen concentration). All concentrations between 4 and 36 hours, inclusive, represent trough (predose) acetaminophen concentrations.  
Source: Study CPI-APA-101, Figure 2

Figure: Mean Acetaminophen Concentrations Over Time Profiles for 6-Hour Dosing

**6-Hour IV Dosing Regimen (Treatment B)**



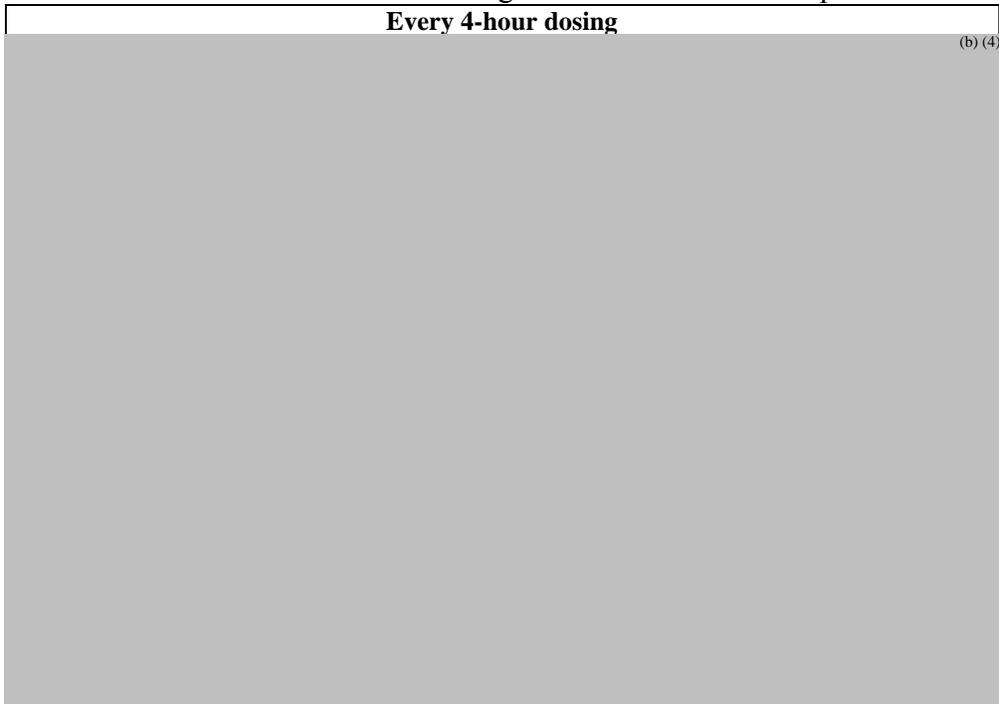
**6-Hour PO Dosing Regimen (Treatment D)**



Note: Arrows indicate dosing time (hours): T0, T6, T12, T18, T24, T30, T36, and T42, error bar (standard error), solid dot, and line (arithmetic mean acetaminophen concentration). All concentrations between 6 and 42 hours, inclusive, represent trough (predose) acetaminophen concentrations.  
Source: Study CPI-APA-101, Figure 3

Urine was collected and analyzed for the presence of free acetaminophen and significant acetaminophen metabolites. Urine metabolite evaluations included: acetaminophen glucuronide, acetaminophen sulfate, glutathione adducts (3'-(*S*-cysteinyl) acetaminophen, acetaminophen mercapturate, and 3'-(*S*-methylacetaminophen), and 3'-methoxyacetaminophen. Results for urinary excretion of acetaminophen and metabolites following IV acetaminophen and PO acetaminophen are presented in Figure below:

Figure: Individual and Mean Relative Percentage of Acetaminophen and metabolites in Urine for Each Collection following Intravenous Acetaminophen



The summary statistics of acetaminophen and its metabolites in the urine are displayed in the table below:

Table: Mean Concentrations (mg) of Acetaminophen and Metabolites in Urine by Collection Period for Intravenous and Oral Acetaminophen (Study CPI-APA-101)

| Collection  |        | Mean (SD)                          |                                    |                                    |                                    |
|---|--------|------------------------------------|------------------------------------|------------------------------------|------------------------------------|
|   |        | IV APAP<br>1000 mg q4h<br>(N = 32) | IV APAP<br>1000 mg q6h<br>(N = 34) | PO APAP<br>1000 mg q4h<br>(N = 35) | PO APAP<br>1000 mg q6h<br>(N = 33) |
| Day, Dose   | Period |                                    |                                    |                                    |                                    |
| <b>Acetaminophen Glucuronide</b>                  |        |                                    |                                    |                                    |                                    |
| Day 1, Dose 1                                     | 0-4 h  | 461.4 (193.1)                      | 500.4 (271.2)                      | 435.3 (190.6)                      | 461.1 (210.9)                      |
| Day 2, Dose 4                                     | 0-4 h  | 1393 (599)                         | 985.8 (578.1)                      | 1246 (500)                         | 946.2 (422.2)                      |
|   | 0-12 h | 2421 (858)                         | 2011 (767)                         | 2596 (765)                         | 2099 (603)                         |
| <b>Acetaminophen Sulfate</b>                      |        |                                    |                                    |                                    |                                    |
| Day 1, Dose 1                                     | 0-4 h  | 160 (52.9)                         | 158.5 (50.3)                       | 161.3 (59.7)                       | 152.7 (57)                         |
| Day 2, Dose 4                                     | 0-4 h  | 331.8 (129.5)                      | 251.8 (108.9)                      | 315.7 (103.3)                      | 258 (109.4)                        |
|   | 0-12 h | 563.5 (183.4)                      | 477.5 (148)                        | 602.5 (143.5)                      | 516.8 (158.6)                      |
| <b>Acetaminophen Mercapturate<sup>1</sup></b>     |        |                                    |                                    |                                    |                                    |
| Day 1, Dose 1                                     | 0-4 h  | 23.38 (8.72)                       | 21.71 (9.01)                       | 13.1 (5.92)                        | 12.72 (5.06)                       |
| Day 2, Dose 4                                     | 0-4 h  | 93 (47.4)                          | 73.45 (34.72)                      | 71.01 (39.92)                      | 68.32 (37.17)                      |
|   | 0-12 h | 211.3 (104.8)                      | 181.4 (83.1)                       | 174.6 (89.8)                       | 180.5 (82.7)                       |
| <b>3'-(S-cysteinyl) Acetaminophen<sup>1</sup></b> |        |                                    |                                    |                                    |                                    |
| Day 1, Dose 1                                     | 0-4 h  | 11.62 (3.8)                        | 11.71 (4.47)                       | 6.765 (2.439)                      | 6.466 (2.53)                       |
| Day 2, Dose 4                                     | 0-4 h  | 60.99 (39.49)                      | 43.52 (24.14)                      | 41.29 (20.49)                      | 31.58 (16.58)                      |
|   | 0-12 h | 128.1 (66.7)                       | 104.3 (42.4)                       | 97.05 (43.95)                      | 96.34 (38.77)                      |
| <b>Acetaminophen</b>                              |        |                                    |                                    |                                    |                                    |
| Day 1, Dose 1                                     | 0-4 h  | 24.37 (5.98)                       | 24.27 (9.3)                        | 22.01 (8.04)                       | 19.1 (6.22)                        |
| Day 2, Dose 4                                     | 0-4 h  | 62.95 (57.1)                       | 27.37 (10.57)                      | 47.62 (22.81)                      | 26.38 (9.95)                       |
|   | 0-12 h | 81.11 (62.97)                      | 48.02 (23.02)                      | 70.38 (34.74)                      | 52.8 (42.44)                       |
| <b>3'-Methoxyacetaminophen</b>                    |        |                                    |                                    |                                    |                                    |
| Day 1, Dose 1                                     | 0-4 h  | 12.48 (5.23)                       | 11.67 (5.54)                       | 11.42 (7.62)                       | 10.97 (6.14)                       |
| Day 2, Dose 4                                     | 0-4 h  | 31.63 (15.55)                      | 22.86 (10.77)                      | 25.42 (13.37)                      | 22.69 (12.71)                      |
|   | 0-12 h | 60.99 (37.69)                      | 50.37 (22.57)                      | 52.85 (25.98)                      | 49.63 (26.46)                      |
| <b>3'-S-Methyl-acetaminophen<sup>1</sup></b>      |        |                                    |                                    |                                    |                                    |
| Day 1, Dose 1                                     | 0-4 h  | 0.5572 (0.3171)                    | 0.4977 (0.2771)                    | 0.333 (0.21)                       | 0.3806 (0.217)                     |
| Day 2, Dose 4                                     | 0-4 h  | 10.83 (7.61)                       | 8.58 (5.373)                       | 5.639 (3.552)                      | 6.068 (4.602)                      |
|   | 0-12 h | 27.99 (17.83)                      | 29.22 (16.31)                      | 16.34 (11.88)                      | 18.85 (12.82)                      |

Definitions: See [List of Abbreviations](#)

<sup>1</sup>Note that the 3-cysteinyl, mercapturate, and 3-S-methyl metabolites are all NAPQI glutathione conjugates

Source: Study CPI-APA-101 [Table 8](#), [Table 9](#), [Table 10](#), and [Table 11](#).

The route of administration or dosing interval assessed in this study did not appear to have a clinically significant impact on fractional excretion in urine of free or unconjugated acetaminophen or the various acetaminophen metabolites assessed. Specifically, the appearance of NAPQI-glutathione conjugates (3'-S-Methyl-acetaminophen, 3'-(S-cysteinyl) acetaminophen, and acetaminophen mercapturate) in urine (12-hour collections after the 8th dose) was comparable across the treatment groups. For the IV and PO q4h groups and q6h groups, the differences between the mean values (IV minus PO) of NAPQI-glutathione conjugates were within 26.3% and 6.5% of the IV mean values, respectively.

**Conclusions:** Acetaminophen mean C<sub>max</sub> was statistically significantly higher (by approximately 70%) and the T<sub>max</sub> was 30 minutes earlier for IV acetaminophen administered as a 15-minute IV infusion compared with PO administration. The area under the concentration versus time curve and V<sub>d</sub> values were comparable across treatment groups. Minimum drug accumulation with repeated IV dosing once steady state

was achieved (by 12 hours or the 3<sup>rd</sup> dose). Elimination half-life, CL, and metabolism were comparable between the IV and PO acetaminophen groups. The route of administration or dosing interval assessed in this study showed comparable fractional excretion in urine of free or unconjugated acetaminophen or the various acetaminophen metabolites assessed.

### **CPI-APA-103**

**Study Title:** A Double-blind, Randomized, Two-Way, Crossover Study in Healthy Adults to Determine the Bioequivalence of Intravenous Acetaminophen Manufactured at Two Sites

**Objectives:** The primary objective was to determine whether IV acetaminophen product from Manufacturing Site A (Baxter – Cleveland, Mississippi) was bioequivalent to IV acetaminophen product from Manufacturing Site B (BMS – Anagni, Italy). A third arm of the study assessed the PK parameter estimates and dose linearity for a 650 mg dose of IV acetaminophen from Manufacturing Site A.

**Study Design:** This was a Phase I, single-center, double-blind, randomized, two-period crossover study comparing IV acetaminophen from Manufacturing Site A (Baxter – Cleveland, Mississippi) to IV acetaminophen from Manufacturing Site B (BMS – Anagni, Italy).

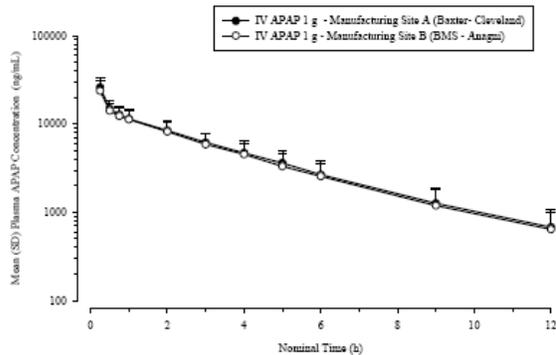
**Study Population:** Twenty-six subjects (10 male and 16 female) were enrolled. All 26 subjects completed the bioequivalence portion of the study (treatment periods 1 and 2). Overall, the mean age of the subjects was 29.7 years (range: 18.2 – 47.4 years).

**Bioanalytical Analysis:** Validated HPLC-MS/MS was used to analyze plasma samples for acetaminophen.

**Data Analysis:** Noncompartmental PK methods were used to determine the acetaminophen PK parameter estimates. Statistical methods for testing bioequivalence were based on confidence intervals (CI) and ratios for comparing PK parameter estimates for test versus reference treatments.

**Pharmacokinetic Results:** Mean plasma concentration-time profiles of IV acetaminophen for the two treatments are displayed on semi-log scales in [the figure below](#):

Figure: Mean Plasma Concentration-Time Profiles of Acetaminophen from Two Manufacturing Sites (Study CPI-APA-103)



Plasma acetaminophen PK profiles were similar between the 1000 mg IV acetaminophen manufactured at Site A (Baxter –Cleveland, Mississippi) and Site B (BMS – Anagni, Italy). Descriptive statistics of the PK parameters for the 1000 mg dose groups from both manufacturing sites are presented below in the Table below.

Table: Descriptive Statistics of Pharmacokinetic Parameters (Study CPI-APA-103)

| PK Parameter                      | Treatments<br>Mean (±SD)   |  |   |
|-----------------------------------|--|--|---|
|                                   | Manufacturing Site A<br>(Baxter, Cleveland)<br>IV APAP 1000 mg<br>(N = 26) | Manufacturing Site B<br>(BMS, Anagni)<br>IV APAP 1000 mg<br>(N = 26) | Manufacturing Site A<br>(Baxter, Cleveland)<br>IV APAP 650 mg<br>(N = 12) |
| AUC <sub>0-4</sub> (µg•h/mL)      | 37.6 (9.02)  | 36.0 (9.00)  | 22.6 (6.05)   |
| AUC <sub>0-6</sub> (µg•h/mL)      | 44.9 (11.4)  | 42.9 (11.1)  | 27.1 (7.78)   |
| AUC <sub>0-1</sub> (µg•h/mL)      | 53.8 (14.8)  | 51.3 (14.4)  | 32.8 (10.5)   |
| AUC <sub>0-∞</sub> (µg•h/mL)      | 56.8 (16.5)  | 54.1 (15.9)  | 35.6 (12.1)   |
| C <sub>max</sub> (µg/mL)          | 26.0 (8.04)  | 23.8 (7.46)  | 14.5 (4.52)   |
| T <sub>max</sub> (h) <sup>1</sup> | 0.25   | 0.25   | 0.25  |
| t <sub>1/2</sub> (h)              | 2.90 (0.476)   | 2.88 (0.470)   | 3.29 (0.654)  |
| CL (L/h)                          | 19.1 (5.47)  | 20.0 (5.70)  | 20.2 (6.28)   |
| Vd (L)                            | 65.9 (16.7)  | 69.3 (18.6)  | 74.9 (15.3)   |

<sup>1</sup> Median value for T<sub>max</sub>

Definitions: See [List of Abbreviations](#)

NA = not applicable

Source: Study CPI-APA-103 [Table 16.2.6.3](#), [Table 16.2.6.4](#), and [Table 16.2.6.5](#)

The median time to reach maximum concentration (T<sub>max</sub>) observed for the IV acetaminophen 1000 mg from Manufacturing Site A (Baxter – Cleveland, Mississippi) and Site B (BMS – Anagni, Italy) was 0.25 hours (at the end of the 15-minute infusion) for both groups. The mean terminal elimination half-life (t<sub>1/2</sub>) for IV acetaminophen 1000 mg was approximately 2.9 hours for both groups. Administration of 1000 mg of IV acetaminophen from Manufacturing Site A (Baxter – Cleveland, Mississippi) and

Manufacturing Site B (BMS – Anagni, Italy) resulted in a similar area under the concentration versus time curve (AUC) from time 0 to 4 hours (AUC<sub>0-4</sub>; 37.6 vs. 36.0 µg·h/mL, respectively) and from time 0 to 6 hours (AUC<sub>0-6</sub>; 44.9 vs. 42.9 µg·h/mL, respectively) for both groups.

A statistical comparison of the PK parameters are shown in the table below:

Table: Statistical Comparison of Pharmacokinetic Parameters (Study CPI-APA-103)

| PK Parameters                 | Geometric Least-Squares Means |        | Ratio A/B% | 90% CI           | p-value | Intra-Subject (CV%) |
|-------------------------------|-------------------------------|--------|------------|------------------|---------|---------------------|
|                               | A                             | B      |            |                  |         |                     |
|                               | N = 26                        | N = 26 |            |                  |         |                     |
| C <sub>max</sub> (µg/mL)      | 24.8                          | 22.5   | 110.04     | (97.67, 123.97)  | 0.1822  | 25.4                |
| AUC <sub>0-t</sub> (µg·hr/mL) | 51.9                          | 49.4   | 105.03     | (102.62, 107.49) | 0.0014  | 4.9                 |
| AUC <sub>0-∞</sub> (µg·hr/mL) | 54.6                          | 52.0   | 105.05     | (102.55, 107.62) | 0.0019  | 5.1                 |

Definitions are provided in the [List of Abbreviations](#).

Treatment A = Manufacturing Site A (Baxter – Cleveland, Mississippi)

Treatment B = Manufacturing Site B (BMS – Anagni, Italy)

Source: CPI-APA-103 Bioequivalence Report [Table 9.2.1](#)

The 90% CIs for the ratios of the geometric least-squares (LS) means between the IV acetaminophen manufactured at Baxter in Cleveland, Mississippi (Manufacturing Site A) and the IV acetaminophen manufactured at BMS in Anagni, Italy (Manufacturing Site B) were completely contained within the equivalence limits of 80% to 125% for AUC<sub>0-t</sub> (102.62, 107.49), AUC<sub>0-∞</sub> (102.55, 107.62), and C<sub>max</sub> (97.67, 123.97). Therefore, the IV acetaminophen from the two manufacturing facilities was bioequivalent.

**Conclusions:** The rate and extent of exposure to IV acetaminophen 1000 mg manufactured at Baxter in Cleveland, Mississippi, USA can be considered to be bioequivalent to that of IV acetaminophen 1000 mg manufactured at a BMS manufacturing site in Anagni, Italy. The IV acetaminophen 650 mg dose was dose-proportional to the IV acetaminophen 1000 mg dose.

### BMS Study 116-01-03

**Study Title:** Open-label, Crossover, Two-period, Single-dose Study of the Pharmacokinetics and Safety of Acetaminophen after Intravenous Administration of Acetaminophen Injection 1000 mg, and Oral Administration of Acetaminophen 1000 mg in Healthy Subjects

**Objectives:** To determine and compare the urinary metabolite and PK profile of acetaminophen after a single 15-minute IV infusion of IV acetaminophen 1000 mg and PO immediate-release acetaminophen 1000 mg in healthy male and female subjects and to evaluate and compare the safety of IV acetaminophen 1000 mg and PO acetaminophen 1000 mg in healthy subjects.

**Study Design:** This is an open-label, 2-period, randomized, crossover study designed to compare the PK of single doses of 1000 mg IV and PO acetaminophen. Subjects were randomized to one of two treatment sequence groups, each of which consisted of a single dose of IV or PO acetaminophen. There was a washout period of 7 days between treatments.

**Study Population:** A total of 22 subjects were randomized in the study, including 19 males and three females. One subject received only the oral formulation prior to discontinuation from the study. The subjects ranged in age from 19 to 60 years; nine subjects were Caucasian, 10 were Black/African American, and three were Hispanic. Mean BMI values were 26.2 and 29.3 kg/m<sup>2</sup>, in the two treatment sequence groups, respectively, and ranged from 18 to 40 kg/m<sup>2</sup>

**Bioanalytical Analysis:** No validation report for the bioanalytical analysis is available for this study.

**Data Analysis:** Noncompartmental PK methods were used to determine the acetaminophen PK parameter estimates.

**Pharmacokinetic Results:** Summary statistics of plasma PK parameters are provided in the table below:

**Table:** Mean Pharmacokinetic Parameters following a Single Dose of Intravenous and Oral acetaminophen 1000 mg (Study 116-01-03)

| Parameter                    | Mean (SD)                    |                              |
|------------------------------|------------------------------|------------------------------|
|                              | IV acetaminophen<br>(N = 21) | PO acetaminophen<br>(N = 22) |
| AUC <sub>0-∞</sub> (μg·h/L)  | 71.8 (20.6)                  | 64.1 (17.7)                  |
| AUC <sub>0-τ</sub> (h*μg/mL) | 69.92 (20.4)                 | 61.72 (16.7)                 |
| C <sub>max</sub> (μg/mL)     | 28.7 (7.2)                   | 16.5 (4.5)                   |
| T <sub>max</sub> (h)         | 0.3 (0.02)                   | 0.7 (0.4)                    |
| t <sub>1/2</sub> (h)         | 3.8 (1.1)                    | 3.8 (1.0)                    |
| CL (L/h)                     | 15.0 (4.2)                   | 17.0 (5.4)                   |
| V <sub>d</sub> (L)           | 80.0 (32.8)                  | 92.6 (43.7)                  |

Definitions: See [List of Abbreviations](#)

Source: Study 116-01-03 [Table 11.1.1](#)

IV acetaminophen produced a mean C<sub>max</sub> that was approximately 70% higher than the mean C<sub>max</sub> for PO acetaminophen, and the mean T<sub>max</sub> for the IV group was approximately 30 minutes faster compared with the PO group. The mean T<sub>max</sub> for the IV group occurred just after the end of the 15-minute infusion. The mean t<sub>1/2</sub> values for both treatment groups were 3.8 hours. The oral bioavailability of acetaminophen was estimated to be 89.9%, based on AUC<sub>0-τ</sub> values for PO relative to IV acetaminophen.

Urinary clearance values for acetaminophen and important metabolites are presented in the table below:

**Table:** Mean Fractional Renal Clearance for Acetaminophen and Mean Formation Clearance of Acetaminophen Metabolites in Urine after a Single Dose of 1000 mg (Study 116-01-03)

| Analyte                                 | Parameter             | Mean (SD)                 |                           |
|---|-----------------------|---------------------------|---------------------------|
|   |                       | IV acetaminophen (N = 21) | PO acetaminophen (N = 21) |
| Acetaminophen Glucuronide               | CL <sub>f</sub> (L/h) | 7.811 (3.2766)            | 8.048 (3.5506)            |
| Acetaminophen Sulfate                   | CL <sub>f</sub> (L/h) | 5.329 (1.9999)            | 5.364 (2.0168)            |
| 3'-Glutathione conjugate <sup>1</sup>   | CL <sub>f</sub> (L/h) | 1.124 (0.6595)            | 1.167 (0.7855)            |
| 3-Cysteinyll acetaminophen <sup>1</sup> | CL <sub>f</sub> (L/h) | 0.592 (0.3182)            | 0.629 (0.4198)            |
| Acetaminophen                           | CL <sub>f</sub> (L/h) | 0.481 (0.1914)            | 0.413 (0.2052)            |
| 3-Mercapturic Acid <sup>1</sup>         | CL <sub>f</sub> (L/h) | 0.460 (0.2759)            | 0.986 (0.8501)            |
| Methoxyacetaminophen                    | CL <sub>f</sub> (L/h) | 0.281 (0.1996)            | 0.287 (0.1737)            |

Definitions: See [List of Abbreviations](#)

<sup>1</sup> The 3'-glutathione conjugate, 3-cysteinyll, and 3-mercapturic acid metabolites are all NAPQI glutathione conjugates.

Source: Study 116-01-03, [Table 14.2.1.2](#).

The renal clearance (CL<sub>f</sub>) of acetaminophen after single-dose administration of IV acetaminophen was  $0.48 \pm 0.19$  L/h compared with  $0.41 \pm 0.20$  L/h after single-dose administration of PO acetaminophen. The route of administration did not alter the fractional metabolism of acetaminophen to glutathione conjugates or other metabolites. For acetaminophen glucuronide, the formation clearance (CL<sub>f</sub>) following IV acetaminophen ( $7.8 \pm 3.3$  L/h) and PO acetaminophen ( $8.0 \pm 3.5$  L/h) was not significantly different. Mean fractional clearances to the sulfate metabolite following IV and PO acetaminophen were  $5.3 \pm 2.0$  L/h and  $5.3 \pm 2.0$  L/h, respectively. The mean CL<sub>f</sub> values of the total glutathione conjugates were not significantly different between IV acetaminophen ( $1.12 \pm 0.66$  L/h) and PO acetaminophen ( $1.17 \pm 0.78$  L/h), as well as for methoxyacetaminophen ( $0.28 \pm 0.20$  vs.  $0.29 \pm 0.17$  L/h, respectively).

**Conclusions:** Pharmacokinetic parameters following IV and PO acetaminophen were similar to previously published values. Single-dose administration of IV acetaminophen 1000 mg in healthy subjects did not result in an increased formation of reactive metabolites when compared to a single dose administration of PO acetaminophen.

### BMS Study 98051C-CIS

**Study Title:** Phase I, Open-label, Cross-over, Three-period Study of the Pharmacokinetics and Safety of Paracetamol after a Single Intravenous Administration of Paracetamol Solution 500 mg and 1000 mg and after a Single Intravenous Administration

of Propacetamol Hydrochloride 2000 mg (Pro-Dafalgan®) in Twenty-four Healthy Subjects

**Objectives:** To determine and compare the serum PK profile of paracetamol (IV acetaminophen) after a single 15-minute IV infusion of acetaminophen solution (500 mg and 1000 mg) and after a single 15-minute IV infusion of propacetamol hydrochloride (2000 mg).

**Study Design:** Study 98051C-CIS was an open-label, 3-period, randomized, crossover study designed to compare the PK of single doses of IV acetaminophen 1000 mg, IV acetaminophen 500 mg, and IV PPA 2000 mg. Subjects were randomized to one of three treatment sequence groups, each of which consisted of a single dose of IV acetaminophen 1000 mg, IV acetaminophen 500 mg, or the active comparator, IV PPA 2000 mg. There was a washout period of 7 days between treatments.

**Study Population:** A total of 24 male subjects completed all three treatments and were included in the PK analysis. Mean age was 27.0 years and ranged from 19 to 37 years. Mean weight and height were 70.9 kg and 177 cm, respectively

**Bioanalytical Analysis:** Plasma levels of paracetamol is determined by HPLC with UV detection after liquid/liquid Plasma levels of paracetamol is determined by HPLC with UV detection.

**The assay performance for the quality control samples is listed below:**

| PARACETAMOL Concentrations (mg/l) | 0.02   | 0.80  | 8.00 | 20.0  |
|-----------------------------------|--------|-------|------|-------|
| mean                              | 0.0205 | 0.818 | 8.18 | 20.74 |
| sd                                | 0.0017 | 0.025 | 0.25 | 0.81  |
| precision CV (%)                  | 8.39   | 3.08  | 3.05 | 3.89  |
| accuracy (%)                      | 2.53   | 2.22  | 2.23 | 3.69  |
| n                                 | 67     | 80    | 76   | 80    |

**Data Analysis:** Pharmacokinetic exposure was analyzed by a non-compartmental analysis approach.

**Pharmacokinetic Results:** Summary statistics of plasma PK parameters are provided in the table below:

**Table:** Mean Pharmacokinetic Parameters following a Single Dose of Intravenous and Orally Administered Acetaminophen (500 mg and 1000 mg) and Propacetamol (2000 mg) in Healthy Adults (Study 98051C-CIS)

| Parameter                | Mean (SD)                              |   |                               |
|--------------------------|--|---|-------------------------------|
|                          | IV acetaminophen<br>500 mg<br>(N = 24) | IV acetaminophen<br>1000 mg<br>(N = 24) | IV PPA<br>2000 mg<br>(N = 24) |
| AUC (µg·h/mL)            | 27.0 (4.9)                             | 57.6 (10.4)                             | 51.0 (9.1)                    |
| C <sub>max</sub> (µg/mL) | 14.4 (4.2)                             | 29.9 (8.3)                              | 24.7 (6.0)                    |
| T <sub>max</sub> (h)     | 0.26 (0.04)                            | 0.25 (0.02)                             | 0.26 (0.02)                   |
| t <sub>1/2</sub> (h)     | 2.7 (0.4)                              | 2.7 (0.4)                               | 2.8 (0.4)                     |
| CL (L/h)                 | 19.2 (4.1)                             | 17.9 (3.4)                              | 20.3 (4.1)                    |
| V <sub>ss</sub> (L)      | 74.5 (10.2)                            | 69.2 (8.6)                              | 80.3 (11.3)                   |
| MRT (h)                  | 3.94 (0.66)                            | 3.97 (0.64)                             | 4.02 (0.65)                   |

Definitions: See [List of Abbreviations](#)

Source: Study 98051C-CIS, [Table 11.4.2.3:1](#)

Mean exposure to IV acetaminophen 500 mg and 1000 mg, as assessed by AUC and C<sub>max</sub>, demonstrated dose proportionality, which also was demonstrated by the ratio of dose-normalized values of  $0.98 \pm 0.24$  for C<sub>max</sub> and  $0.94 \pm 0.08$  for AUC, with 90% CI within the acceptable range of 80 to 125%. This was also confirmed with the two-one sided t-test (Schuirmann test) that showed that the dose-normalized values for the two treatments were equivalent. The same results were observed for the total CL and V<sub>ss</sub>. The mean residence times (MRT) did not differ statistically between treatment groups, and meant that acetaminophen resides in the body on an average of approximately 4 h following dosing of IV acetaminophen 500 mg and 1000 mg (3.94 and 3.97 h, respectively). Median T<sub>max</sub> for IV acetaminophen occurred by the end of the 15-minute infusion. The t<sub>1/2</sub> was approximately 3 h and not statistically different across treatments. Comparison of dose normalized C<sub>max</sub> and AUC values for the two IV acetaminophen doses (500 mg and 1000 mg) with PPA 2000 mg showed a C<sub>max</sub> ratio of  $1.19 \pm 0.34$  and  $1.23 \pm 0.27$ , respectively, and an AUC ratio of  $1.06 \pm 0.10$  and  $1.13 \pm 0.09$ , respectively. The 90% CI for C<sub>max</sub> and AUC for IV acetaminophen were within the acceptable range of 80 to 125% of corresponding values for PPA 2000 mg.

**Conclusions:** The acetaminophen serum concentrations for IV acetaminophen 500 mg and 1000 mg were dose proportional. The IV acetaminophen 1000 mg was bioequivalent to PPA 2000 mg.

### 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.

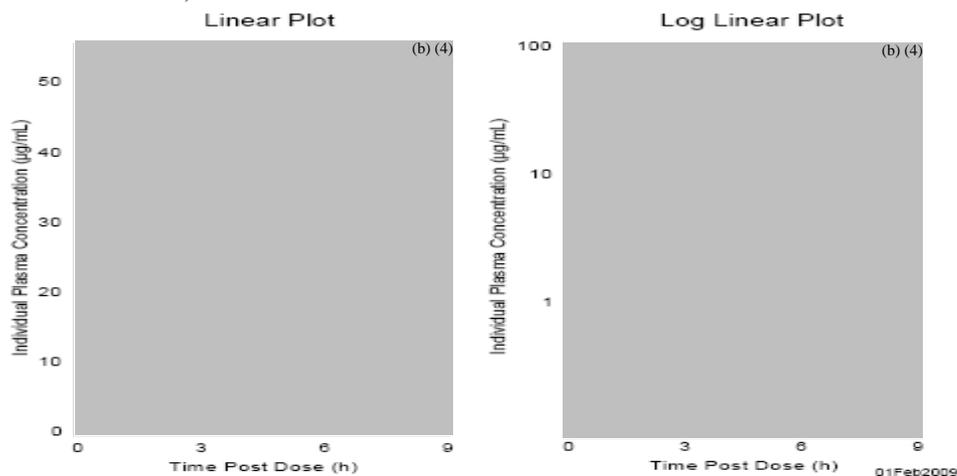
**Pharmacokinetic Results:** Noncompartmental analysis of the PK parameters is presented in the Table below:

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

| Treatment<br>(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:<br><u>12.5 mg/kg</u>  | Dose 1<br><u>12.5 mg/kg</u>                          | Dose 1<br><u>12.5 mg/kg</u>       | Dose 1<br><u>12.5 mg/kg</u>    | Dose 1<br><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<br><u>12.5 mg/kg</u>                       | Last Dose<br><u>12.5 mg/kg</u>    | Last Dose<br><u>12.5 mg/kg</u> | Last Dose<br><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%                       |

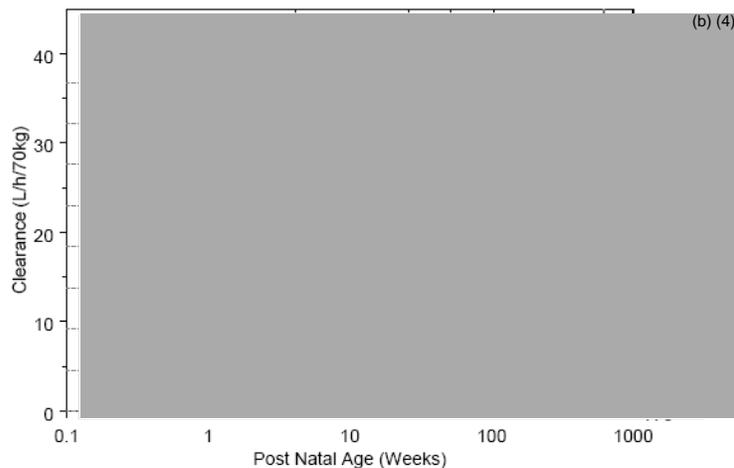
Definitions: See [List of Abbreviations](#)

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-∞</sub> (μg•h/mL) | C <sub>max</sub> (μg/mL) |
| 12.5         | Neonates                   | q6h              | 3.89<br>(2, 0.631)  | 61.2<br>(2, 2.94)            | 25.3<br>(2, 0.103)       |
|              | Infants                    | q4h              | 2.45<br>(13, 0.61)  | 38.7<br>(13, 10.9)           | 25.0<br>(13, 4.72)       |
|              | Children                   |                  | 2.93<br>(9, 1.13)   | 36.6<br>(9, 13.2)            | 26.2<br>(9, 6.89)        |
|              | Adolescents                |                  | 3.67<br>(12, 2.88)  | 40.9<br>(12, 23.1)           | 28.4<br>(12, 9.25)       |
| 15           | Neonates                   | q8h              | 4.19<br>(1, NC)     | 85.1<br>(1, NC)              | 30.3<br>(1, NC)          |
|              | Infants                    | q6h              | 3.18<br>(12, 1.28)  | 80.2<br>(12, 84.8)           | 37.9<br>(12, 34.7)       |
|              | Children                   |                  | 2.98<br>(16, 1.54)  | 49.0<br>(16, 14.2)           | 32.3<br>(16, 7.04)       |
|              | Adolescents                |                  | 2.91<br>(10, 0.685) | 53.1<br>(10, 10.1)           | 34.8<br>(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

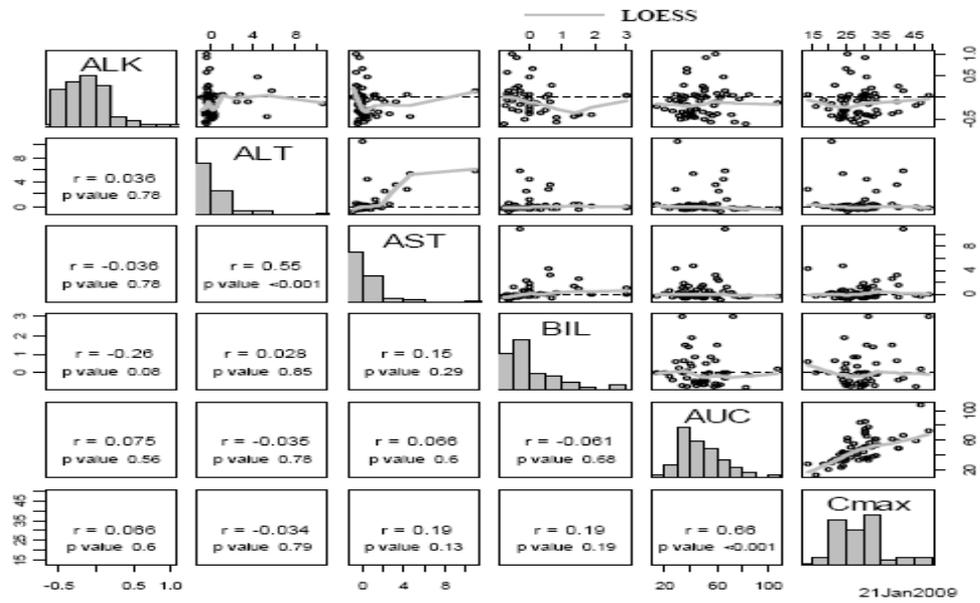
longer than those observed in infants, children, and adolescents (range in mean values of 2.45 to 3.18 h). Mean  $t_{1/2}$  values were comparable across the infant, child, and adolescent age strata. As expected based upon the  $t_{1/2}$  values, mean neonate  $AUC_{0-\tau}$  values (61.2 to 85.1  $\mu\text{g}\cdot\text{h}/\text{mL}$ , 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.

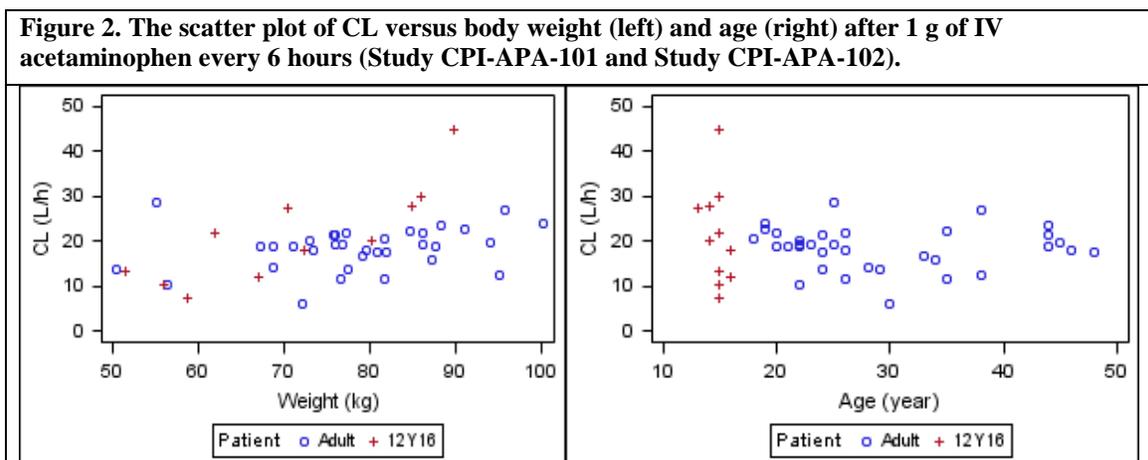
## Key Review Questions

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.



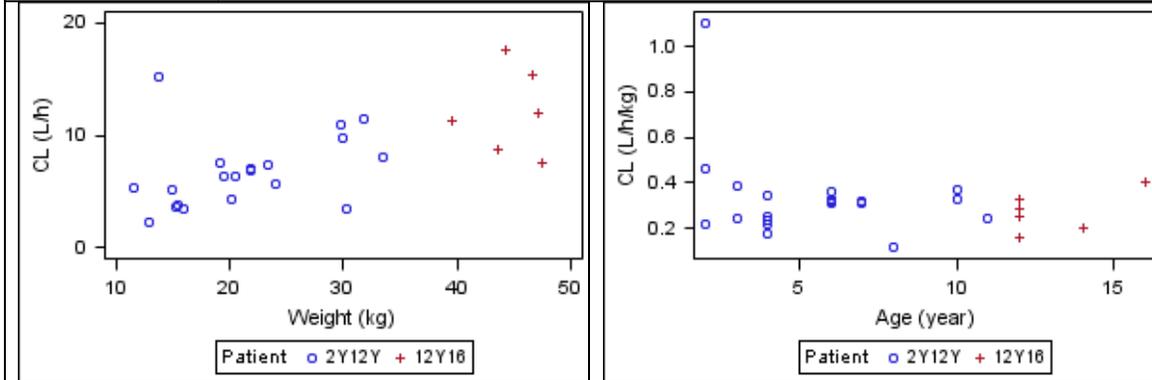
Is the proposed dosing regimen in adolescents and all children appropriate?

*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.

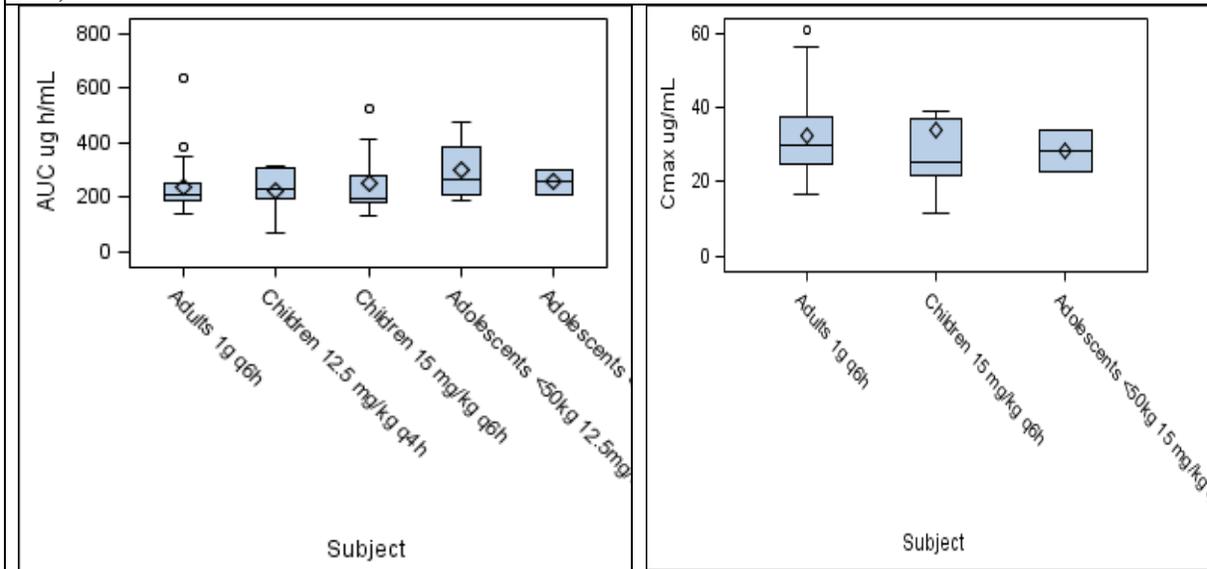
The CL appears to be positively correlated with body weight and body-weight normalized CL appears to be independent of age (Figure 2).

**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.*

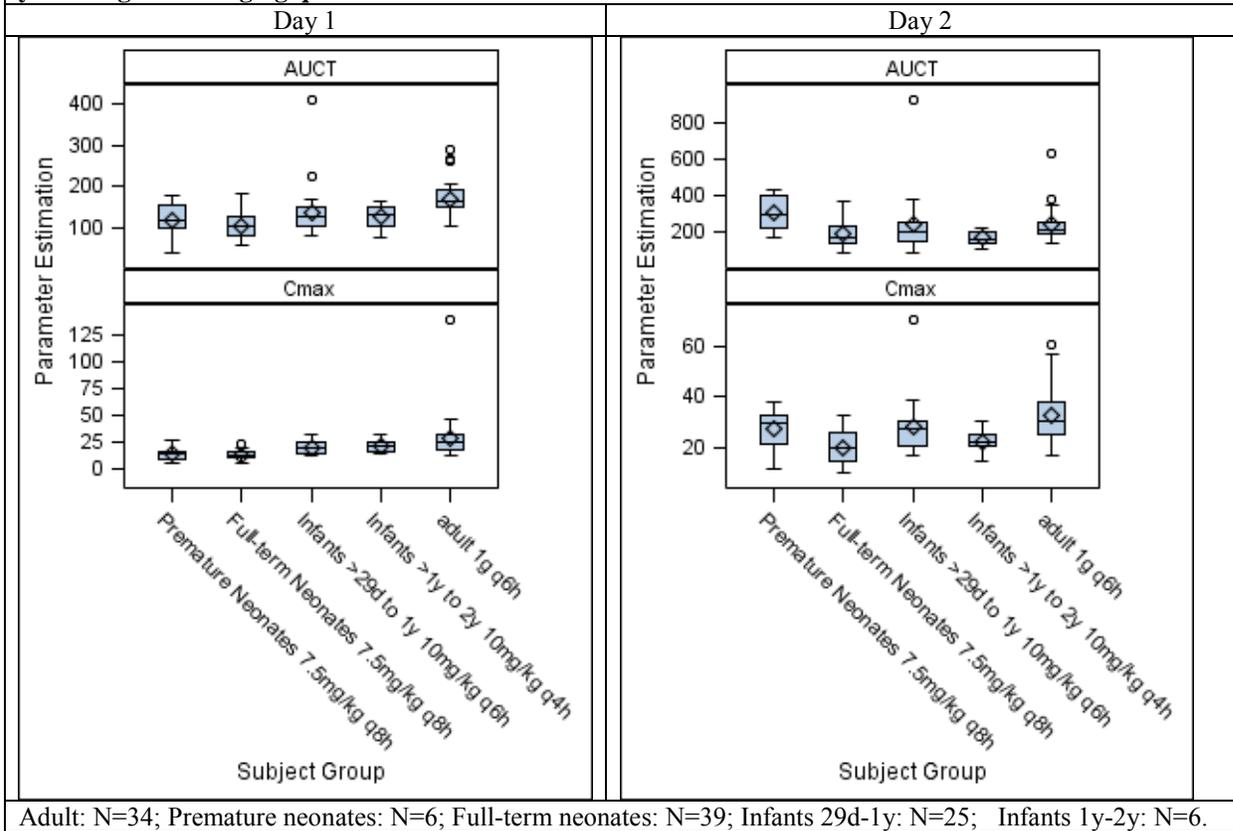
The proposed dosing regimen in neonates and infants are listed below:

- 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.

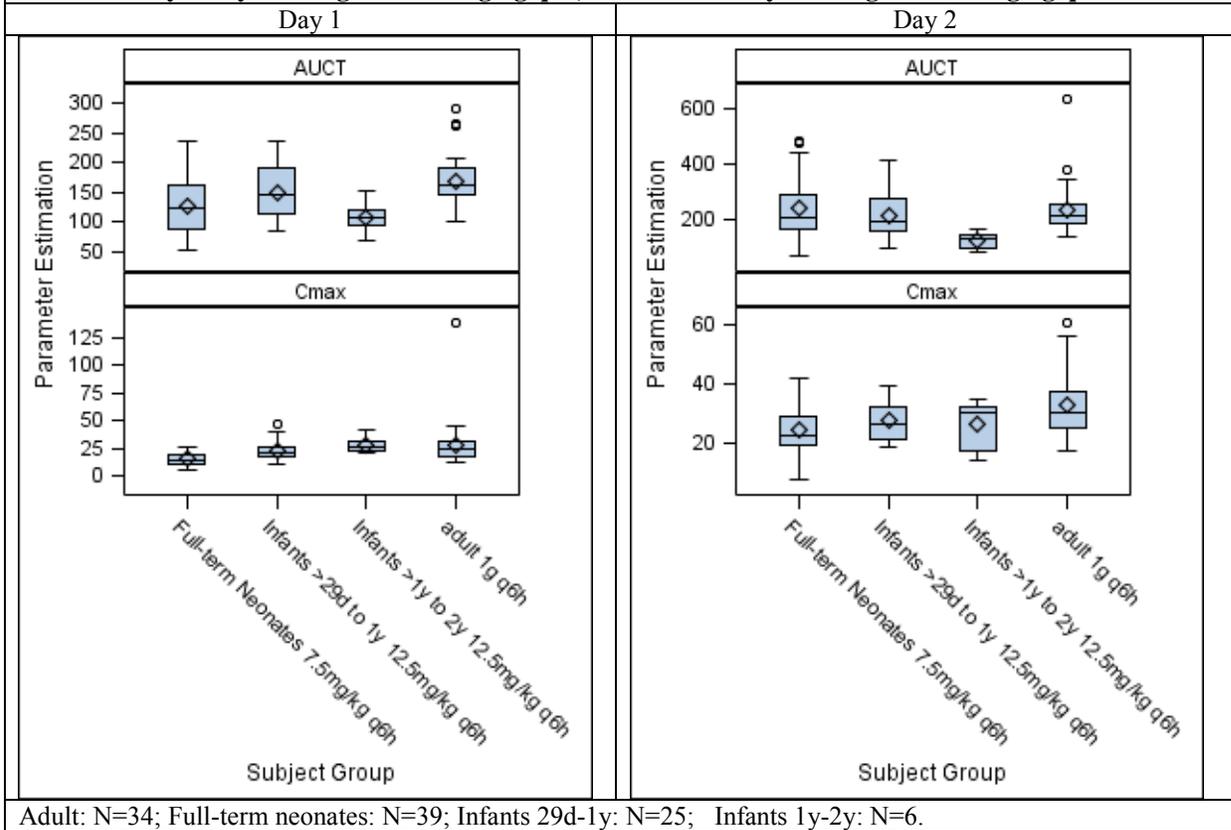
The above proposed dosing regimens were selected from a dose of 7.5, 10, 12.5 and 15 mg/kg given every 4, 6, 8, or 12 hours at variety of combination using trial simulation by sponsor to reach optimal concentration range, which was prespecified based on adult and adolescent concentration data. The optimal 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.**



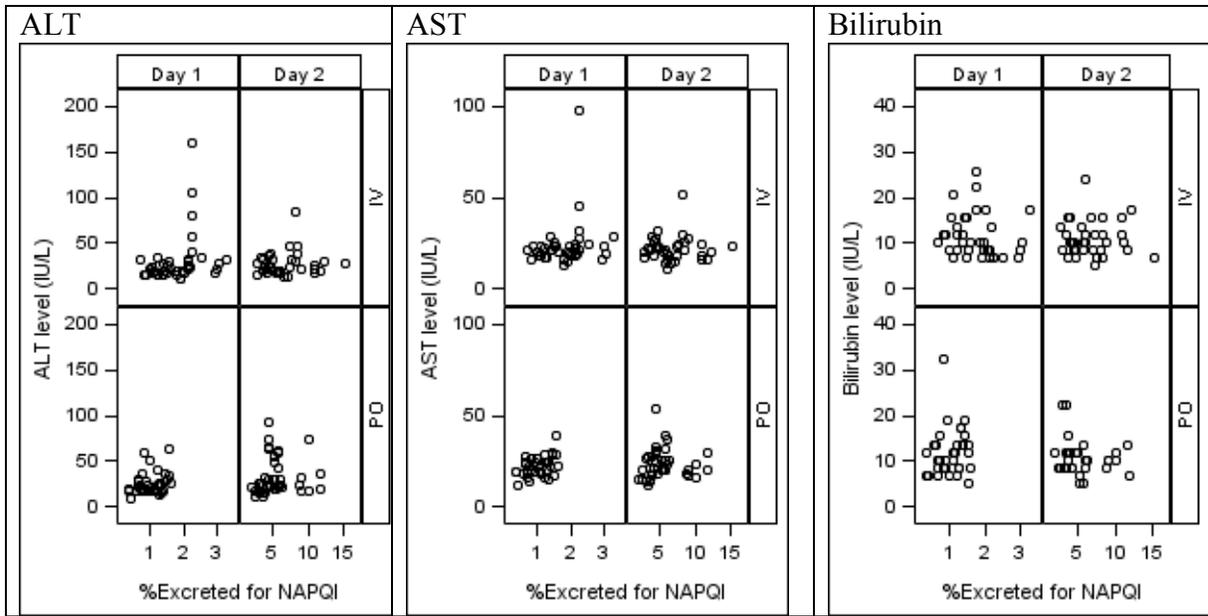
The proposed dosing regimen in pre-term neonates was 7.5 mg/kg q8h only. The model predicted geometric mean AUCTAU after first dose (Day 1) and repeated doses (Day 2) was 106 and 286 ug h/mL, respectively. Therefore, the proposed dosing regimen is appropriate in neonates and infants.

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).*

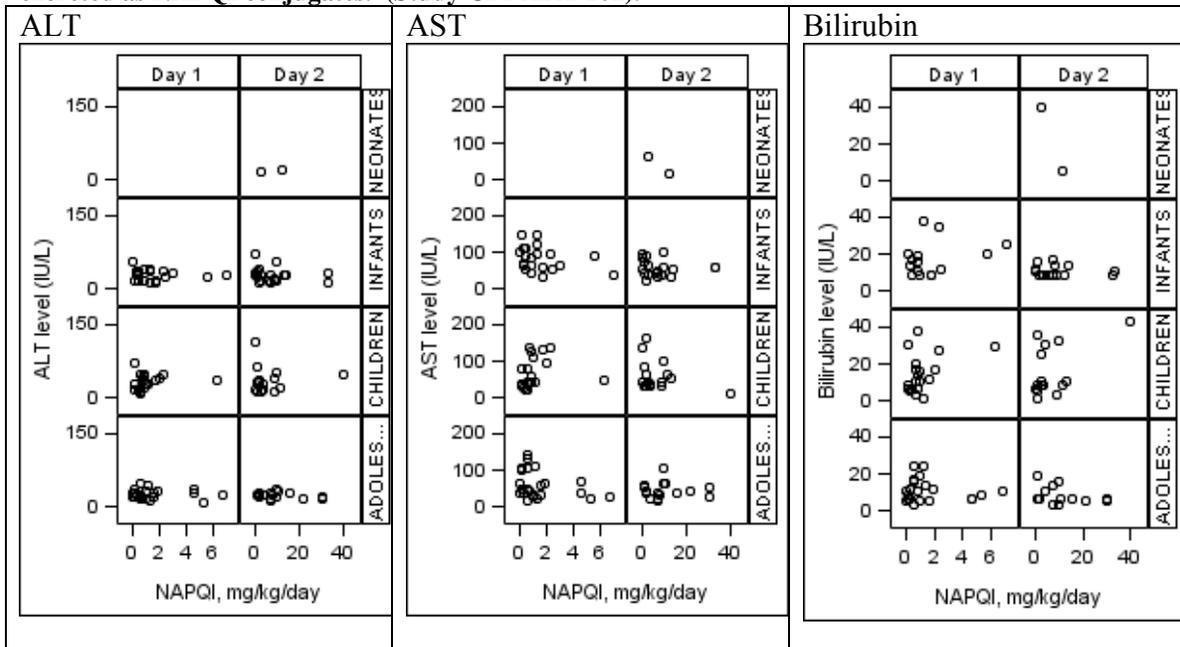
The level of liver function markers (AST, ALT, and Bilirubin) was independent of percent excreted as NAPQI production in adults given as 1 g every 6 hours intravenously.

**Figure 6. Scatter plots of markers of liver function (AST, ALT, and Bilirubin) versus percent excreted as NAPQI conjugates. (Study CPI-APA-101).**



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.



#### **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 15 clinical studies in adults (Table 1) and 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   |
|-----------------------|-----------------------|---------------------------|---|---|
| Phase 1 PK and safety | CPI-APA-101           | n=32, 34 (>50 kg)         | 1 g q4h, 1 g q6h                        | < 50 kg: 15 mg/kg q6h or 12.5 mg/kg q4h<br>> 50 kg: 1000 mg q6h or 650 mg q4h |
|                       | 116-01-03             | n=21 (137-248 lb)         | 1 g IV                                  |   |
|                       | 98051C-CIS            | N=24, 24 (60-83 kg)       | 500 mg, 1 g                             |   |
|                       | CPI-APA-103           | N= 26 (132-229 lb)        | 1 g                                     |   |
| Fever                 | CPI-APF-302 (pivotal) | N=31 healthy (126-232 lb) | 1 g SD                                  |   |
|                       | CPI-APF-303           | n=54 healthy (126-273 lb) | 1 g SD                                  |   |
| Pain                  | RC210 3 002 (pivotal) | N=49 (61-111 kg)          | 1 g                                     |   |
|                       | CPI-APA-301           | N=166 (98-275 lb)         | 1 g                                     |   |
|                       | CPI-APA-304           | N=134 (103-256 lb)        | 1 g q6h, 650 mg q4h                     |   |
|                       | RC210 3 001           | N=51 (40-97 kg)           | 1 g SD                                  |   |
|                       | CN145-004             | N=264 (50-95 kg)          | 1 g SD                                  |   |
|                       | 136-01-03             | N=35 (129-293 lb)         | 1 g SD                                  |   |
|                       | 136-02-03             | N=30 (61-76 kg)           | 1 g repeat dose, 24 h                   |   |
|                       | 136-03-03             | N=23 (108-238 lb)         | 1 g repeat dose, 24 h                   |   |
|                       | CPI-APA-351           | N=183 (43-235 kg)         | 1 g or 650 mg, repeat dose up to 5 days |   |

**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<br>Full-Term Neonates: 12.5 mg/kg q6h, 15 mg/kg q8h (maximum daily dose of 50 mg/kg)<br>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.<br>Premature neonates: 7.5 mg/kg q8h.<br>Minimum dosing interval of 8 hours  |
| 26095 (Palmer et al.) | Phase 1 PK and safety                               | 28-<32 weeks PMA: 10 mg/kg q6h<br>32-<36 weeks PMA: 12.5 mg/kg q6h<br>>=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 3 006 (BMS)     | Phase 3 safety and efficacy No PK                   | R, DB, SD, active-controlled, 2-parallel group<br>15 mg/kg SD APAP (n=95)<br>30 mg/kg SD PPA (n=88) (propacetamol)   | Infants (1 to 2 years old): 12.5 mg/kg q4h or 10 mg/kg q4h<br>Adolescents weighing less than 50 kg and all children: 15 mg/kg q6h or 12.5 mg/kg q4h<br>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)<br>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,<br>29 days to <6 mths: 10-15 mg/kg q6h (n=1)<br>6 to <12 mths: 10-15 mg/kg q6h (n=1)<br>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)<br>12-16 yrs: 6.7-12.5 mg/kg q4h (n=9) and 10-15 mg/kg q6h (n=42) |  |
|--|--|---|--|

### 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).

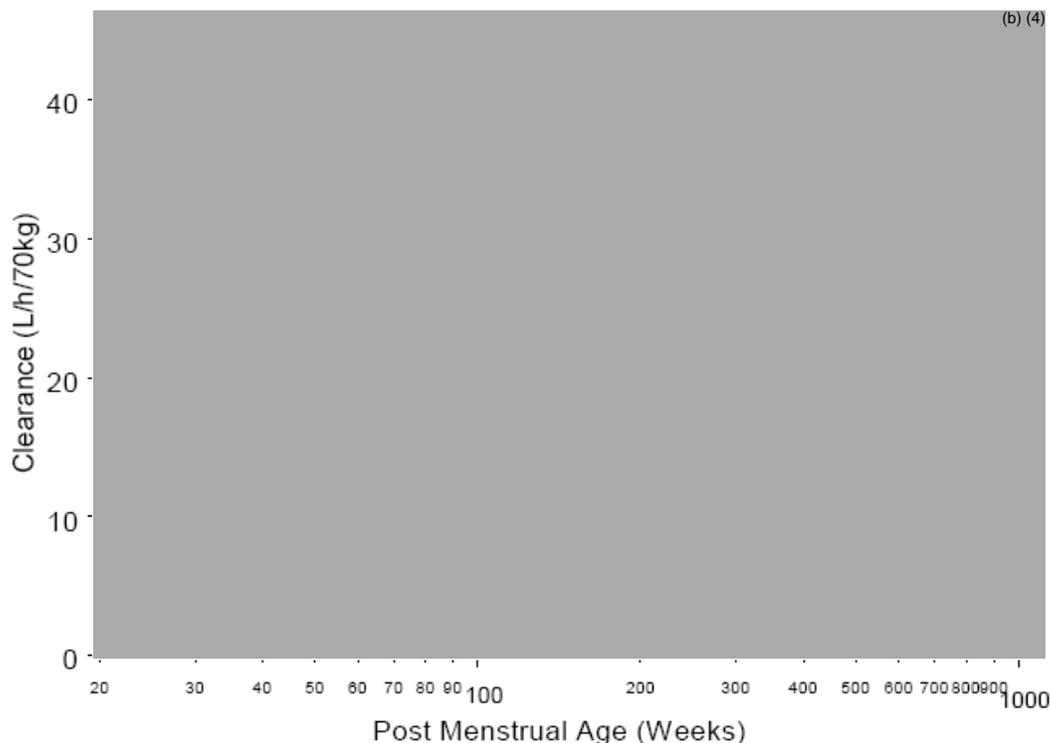
- The median AUC<sub>0-τ</sub> values of acetaminophen in neonates for the 12.5 and 15 mg/kg dose levels were between 1.6- and 1.9-fold higher than those observed in children and adolescents.
- Differences in median C<sub>max</sub> values of acetaminophen across each age strata for a given dose were 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:  $CL(L/h/70\text{ kg})=18.3 \times \left[ 1 - 0.796 \times \exp\left(-\text{PMA} - 40 \times \frac{\ln(2)}{32.6}\right) \right]$

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

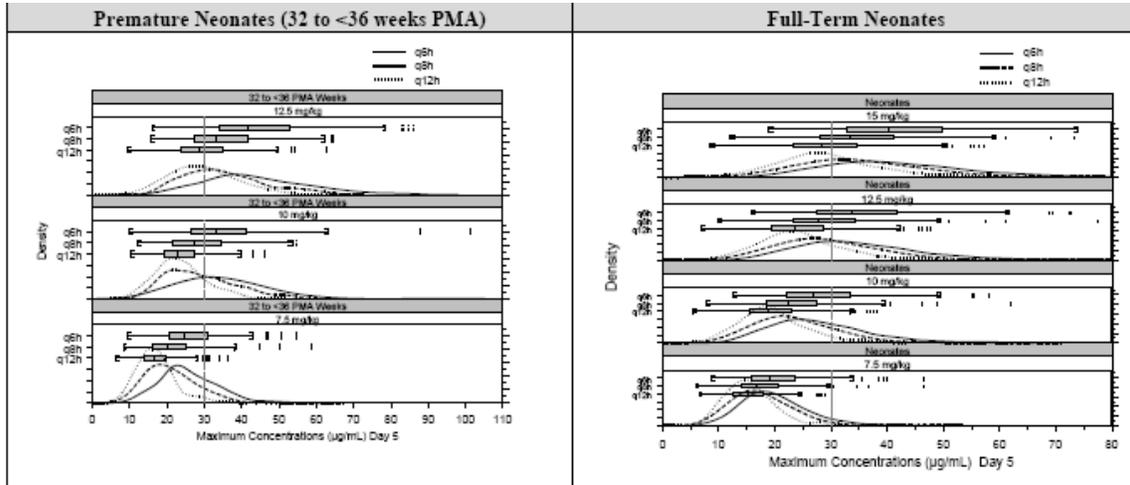
- The volume of distribution of acetaminophen at steady-state ( $V_{ss}$ ) adjusted for body weight was consistent across all subpopulations (i.e., median values: 1.07, 1.10, 1.16 and 1.08 L/kg, respectively for neonates, infants, children and adolescents).
- The mean elimination half-life of acetaminophen 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.

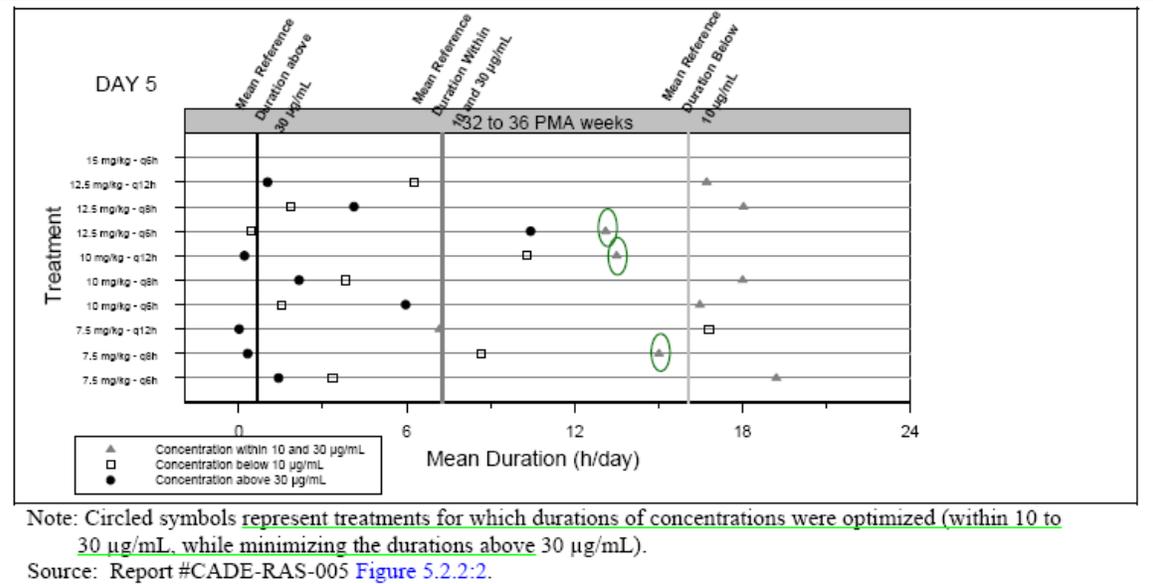
The solid black vertical line at 0.63 h represents the mean duration that adolescent predicted concentrations would exceed 30  $\mu\text{g/mL}$ , based upon an IV acetaminophen regimen of 15 mg/kg q6h. The two vertical gray lines at approximately 7 and 16 hours represents the mean durations at steady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

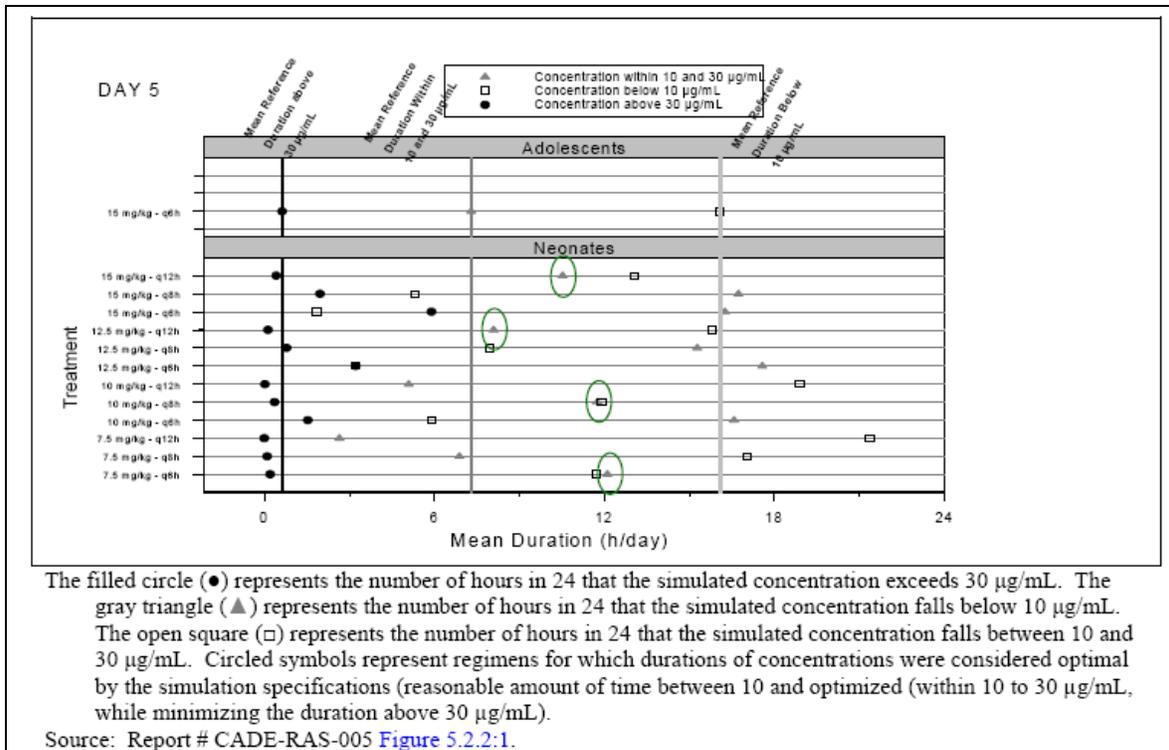
Based upon the prespecified simulation targets, the following should occur for a viable dosing regimen:

- 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)
- CL appeared to be independent of WT and age adults in the range studied in study CPI-APA-101 (WT [50-100 kg] or age [18-48 y]) (Figure 1).
- 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 Cmax) 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).

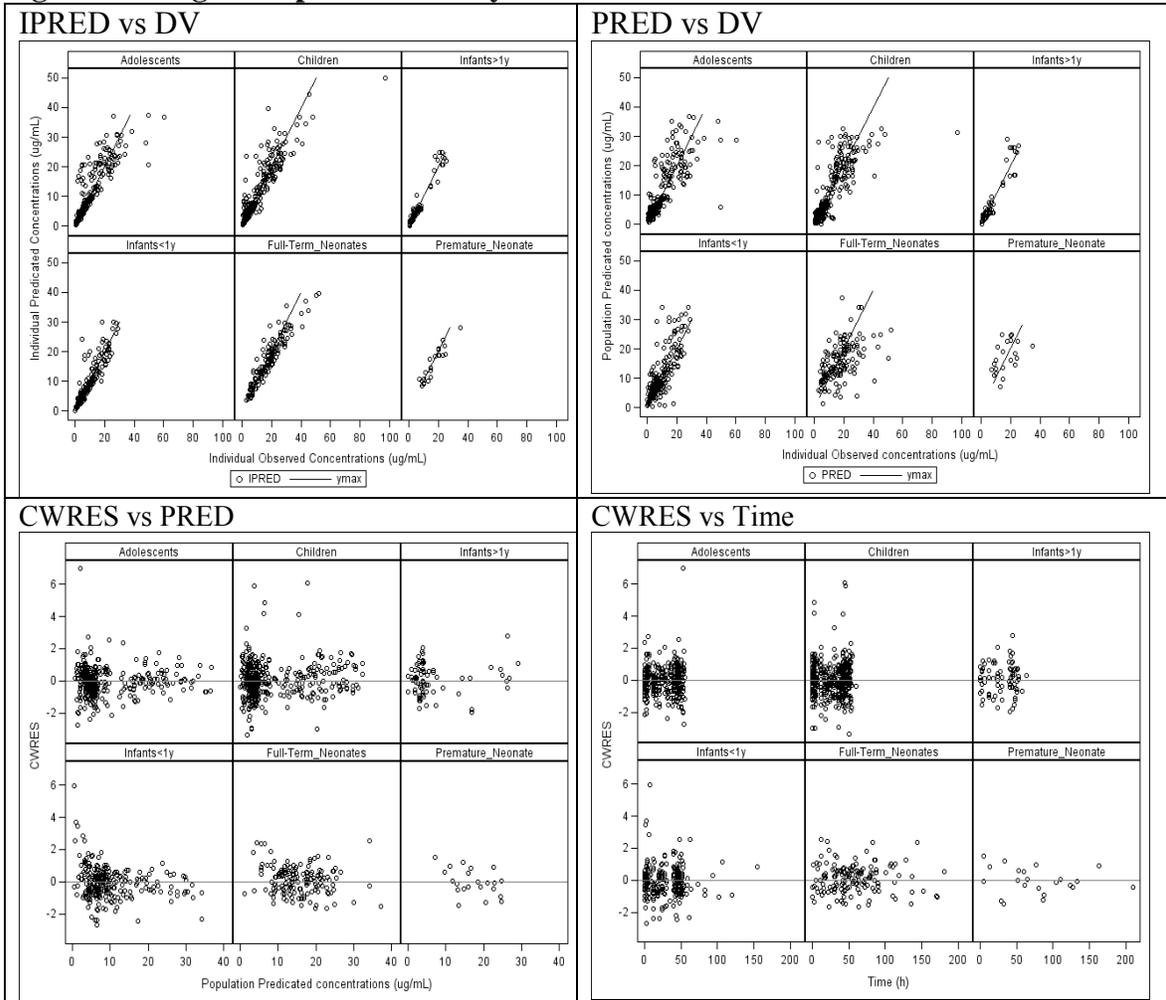
**Table 3: Population Pharmacokinetic Analysis from study CPI-APA-102.**

| Parameters                       | Units | Typical Value (RSE%) | Between Subject Variability (RSE)% |
|----------------------------------|-------|----------------------|------------------------------------|
| Clearance (CL)                   | L/h   | 18.4 (4.9)           | 37.4 (41.7)                        |
| Central Volume (Vc)              | L     | 16 (8.8)             | 61.6 (33.4)                        |
| Intercompartmental Clearance (Q) | L/h   | 97.8 (7.0)           | 19.6 (39.2)                        |
| Peripheral Volume (V2)           | L     | 59.5 (7.1)           | —                                  |
| Slope CL                         | —     | -0.678 (5.7)         | —                                  |
| TCL                              | —     | 41 (51.5)            | —                                  |
| Reta V2                          | —     | 2.03 (17.8)          | —                                  |
| Residual Variability:            |       |                      |                                    |
| Additive                         | —     | 168.2 (44.5)         |                                    |
| Proportional                     | —     | 0.28 (16.8)          |                                    |

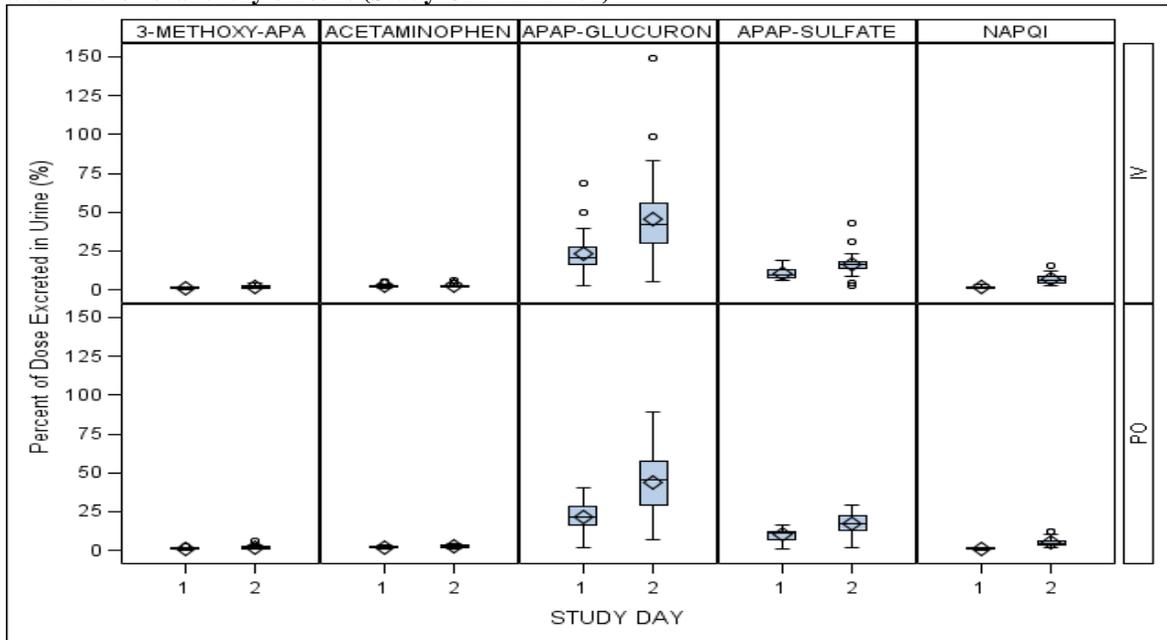
**Table 4: Population Pharmacokinetic Analysis from study CADE-RAS-103.**

| <b>Parameters</b>                | <b>Units</b> | <b>Typical Value<br/>(RSE%)</b> | <b>Between<br/>Subject<br/>Variability<br/>(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)                     |   |

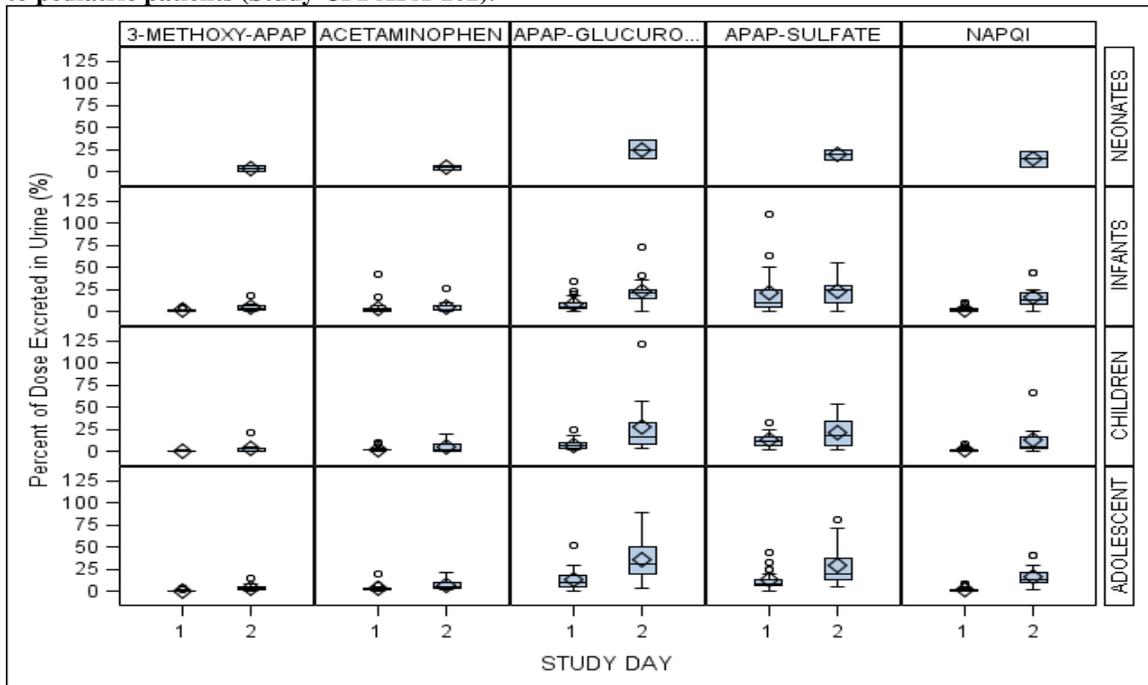
**Figure 8: Diagnostic plot from study CADE-RAS-103.**



**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<br><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<br>PHARMACEUTICA<br>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

### **Addendum to Primary Clinical Pharmacology Review Dated Oct 15, 2009**

|                                 |  |                         |  |
|---------------------------------|--|-------------------------|--|
| <i>NDA</i>                      | 22-450   | <i>Submission Dates</i> | S0025 11/09/2009<br>S0026 11/07/2009<br>S0033 12/14/2009 |
| <i>Brand Name</i>               | Ofirmev (Acetaminophen) Injection  |                         |  |
| <i>Generic Name</i>             | IV acetaminophen   |                         |  |
| <i>Reviewer</i>                 | Ping Ji, Ph.D.   |                         |  |
| <i>Team Leader</i>              | Suresh Doddapaneni, Ph.D.  |                         |  |
| <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. |                         |  |

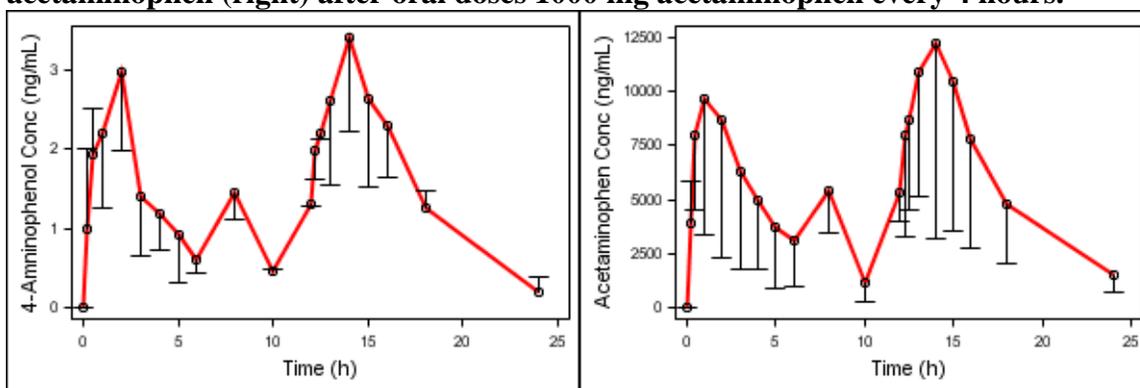
### **Background**

This review is an addendum to the original Clinical Pharmacology Review for NDA 022450 dated Oct 15, 2009. NDA 022450 (S0000) for Acetaminophen Injection, was originally submitted on May 13, 2009 and was proposed for the treatment of acute pain and fever in adults and pediatric patients. In the original review, this reviewer concluded that the submission was 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.

However, from a Pharmacology and Toxicology perspective, there were concerns about the potential levels of 4-aminophenol (4-AP) as an impurity in the IV acetaminophen product. Although 4-AP has been reported to be a metabolite of acetaminophen in several species, confirmatory data in man were not available to justify the safety of the proposed specification. In order to show that 4-AP is a significant human metabolite, sponsor conducted a human PK study where acetaminophen was given orally. The clinical study report (CPI-APA-104) from this study was submitted on Nov 9, 2009. The analysis results on the 4-AP content in Extra Strength Tylenol 500 mg Caplets used in protocol CPI-APA-104 were submitted on Dec 14, 2009. This addendum summarizes these findings from the study CPI-APA-104.

**Pharmacokinetic Findings** Study CPI-APA-104 is a single-center, open-label study. Six subjects received oral acetaminophen 1000 mg (2 x 500 mg caplets) under fasting condition. Twelve subjects assigned to the repeated dose group received three additional 1000 mg doses (2 x 500 mg caplets) of oral acetaminophen at T4, T8, and T12 hours (for a total daily dose of 4000 mg). The drug taken was Tylenol® Extra Strength. After single dose administration of oral acetaminophen 1000 mg, the mean C<sub>max</sub> and AUC<sub>0-12</sub> of 4-aminophenol was approximately 0.027% and 0.025% of that of acetaminophen, respectively. After multiple dose administration of oral acetaminophen 1000 mg, the mean C<sub>max</sub> and AUC of 4-aminophenol after the fourth dose was approximately 0.031% and 0.025% of that of acetaminophen, respectively.

**Figure 1: Mean concentration-time profiles of 4-aminophenol (left) and acetaminophen (right) after oral doses 1000 mg acetaminophen every 4 hours.**



**Table 1: Mean AUC of 4-aminophenol and acetaminophen and their ratio after oral doses of 1000 mg acetaminophen every 4 hours.**

|                                       | N  | 4-Aminophenol | Acetaminophen | Ratio  |
|---------------------------------------|----|---------------|---------------|--------|
| C <sub>max</sub> (first dose) (ng/mL) | 18 | 3.59          | 11740         | 0.027% |
| C <sub>max</sub> (last dose) (ng/mL)  | 12 | 3.64          | 13270         | 0.023% |
| T <sub>max</sub> (first dose) (h)     | 18 | 1.19          | 0.99          | -      |
| T <sub>max</sub> (last dose) (h)      | 12 | 2.21          | 1.88          | -      |
| AUC <sub>0-4</sub> (ng h/mL)          | 18 | 7.6           | 28621         | 0.028% |
| AUC <sub>0-12</sub> (ng h/mL)         | 6  | 11.2          | 49884         | 0.025% |
| AUC <sub>12-16</sub> (ng h/mL)        | 12 | 10.7          | 41022         | 0.025% |

Note: AUC<sub>0-4</sub>: AUC between 0 to 4 hours; AUC<sub>0-12</sub>: AUC between 0 to 12 hours; AUC<sub>12-16</sub>: AUC between 12 to 16 hours.

The 4-Aminophenol content in Extra Strength Tylenol 500 mg Caplets utilized in Cadence clinical study Protocol: CPI-APA-104 were also analyzed. The average of the 4-AP concentrations detected in the three caplet aliquots was below the LOQ of the method (0.197 µg/mL), which is equivalent to less than (b) (4) relative to acetaminophen. One of six analyses had a value greater than the LOQ (0.291 µg/mL), corresponding to (b) (4) of the acetaminophen in the 500 mg Extra Strength

Tylenol Caplet. The results of this study demonstrate that the quantity of 4-AP in the Extra Strength Tylenol 500 mg Caplets is very low.

**Conclusion:** After oral administration of 1 g acetaminophen once every four hours for four times, the ratio of AUC<sub>12-16</sub> of 4-aminophenol and acetaminophen were 0.025%, which is 71% less than that predicted from the maximum specification level (b) (4) in the intravenous formulation if assuming 4-aminophenol and acetaminophen have the same systemic clearance.

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*Reviewer's comments: The C<sub>max</sub> of 4-AP ranged from 0.45 to 11.17 ng/mL after the first dose and from 1.66 to 8.80 ng/mL after the last dose of acetaminophen. The linearity range of 2 to 100 ng/mL did not cover the whole range of the concentration-time profile*

of 4-AP. Therefore, the exposure estimation for 4-aminophenol generated from the analysis can only be considered an approximation.

In sponsor's analysis, AUC was not calculated. As AUC is an important variable for the systemic exposure, reviewer calculated AUC as shown in the Table 1. The ratio of Cmax and AUC of 4-AP and acetaminophen was consistently less than 0.05%, indicating that 4-AP exposure after oral acetaminophen 1000 mg is an insignificant amount. As the quantity of 4-AP in the Extra Strength Tylenol 500 mg Caplets is very low, the carryover of 4-AP from in vitro to in vivo can be neglected. The conversion of acetaminophen to 4-aminophenol can be through either metabolic activity or physical hydrolysis to 4-aminophenol in humans consuming oral acetaminophen in solid form.

Stability studies demonstrated that during storage, some (b) (4) of APAP occurs in solution to produce (b) (4) the impurity, 4-AP, with time. The amount of 4-AP is (b) (4) at room temperature. The limiting factor for shelf life is the proposed amount of 4-AP at the requested expiry (b) (4) given 4 g acetaminophen (4 x 1000 mg). If assuming the systemic clearance of 4-aminophenol and acetaminophen is same, the AUC ratio is (b) (4) at this maximum proposed specification level.

| Application Type/Number | Submission Type/Number | Submitter Name                     | Product Name                              |
|-------------------------|------------------------|------------------------------------|---|
| NDA-22450               | ORIG-1                 | CADENCE<br>PHARMACEUTICA<br>LS INC | ACETAMINOPHEN FOR<br>INJECTION FOR IV USE |

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/s/

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Ping Ji  
01/22/2010

SURESH DODDAPANENI  
01/22/2010