CLINICAL REVIEW

Application Type	NDA
Application Number(s)	022450
Priority or Standard	Priority
Submit Date(s)	13 May 2009
Received Date(s)	15 May 2009
PDUFA Goal Date	13 November 2009
Division / Office	Anesthesia, Analgesia & Rheumatology Products
Reviewer Name(s)	Jacqueline A. Spaulding, M.D.
Review Completion Date	06 October 09
Established Name	Acetaminophen injection for intravenous use
(Proposed) Trade Name	(b) (4)
Therapeutic Class	Non-opioid analgesic
Applicant	Cadence
Formulation(s)	Intravenous
Dosing Regimen	**Adults and adolescents weighing 50 kg and over:** 650 to 1000 mg every 4-6 hours **Adults and adolescents weighing under 50 kg and all children::** 12.5 to 15 mg/kg every 4-6 hours **Infants 1 to 2 years old:** 50 to 60 mg/kg per 24 hours in divided doses **Infants 29 days to 1 year old:** 40 to 50 mg/kg per 24 hours in divided doses **Full term neonates:** 22.5 to 30 mg/kg per 24 hours in divided doses **Premature neonates (postmenstrual age 32-36 weeks):** 22.5 mg/kg per 24 hours in divided doses

Indication(s)	Acute pain and fever
Intended Population(s)	Adult and Pediatric

Template Version: March 6, 2009

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

In the context of the finding of efficacy, based on my review of the safety data submitted in this application, I recommend the approval of intravenous acetaminophen for the indications of the treatment of acute pain and fever in adult and pediatric patients.

1.2 Risk Benefit Assessment

The assessment of efficacy was conducted by Christina Fang, M.D. with a secondary review by Ellen Fields, M.D., MPH. Dr. Fang found that IV acetaminophen was efficacious for the indications of fever and pain in adults (b) (4) Pediatric efficacy was extrapolated from the adequate and well-controlled studies of IV acetaminophen in adults and the use of oral acetaminophen in pediatric patients.

No new or unexpected safety signals were detected upon my review of the safety database. As with oral acetaminophen, the use of IV acetaminophen requires caution when administered to patients with pre-existing hepatic disease, hepatic dysfunction or when other hepatic risk factors are present including: alcoholism, malnutrition, or hypovolemia.

Across the (b) (4) clinical studies, safety data was derived from a variety of medical and surgical conditions in adult and pediatric populations in the hospital setting. . In addition, the Applicant has fulfilled the Division's requirement that the safety database include a minimum of (b) (4) 300 pediatric exposures; and a minimum o (b) (4) 50 pediatric patients treated with IV acetaminophen for five days.

The risk benefit assessment of IV acetaminophen is adequate for the treatment of acute pain and fever in adults and pediatric patients.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

None.

1.4 Recommendations for Postmarket Requirements and Commitments

None.

2 Introduction and Regulatory Background

2.1 Product Information

Please see Dr. Fang's review for this information.

2.2 Tables of Currently Available Treatments for Proposed Indications

Please see Dr. Fang's review for this information.

2.3 Availability of Proposed Active Ingredient in the United States

Please see Dr. Fang's review for this information.

2.4 Important Safety Issues With Consideration to Related Drugs

The key safety issue related to the use of acetaminophen containing products is drug-induced hepatotoxicity. Acetaminophen hepatotoxicity is believed to be most closely related to dose and, in overdose, the mechanism of hepatic injury is well studied and understood. However, acetaminophen hepatotoxicity has been observed at doses that are at or below recommended dose of 4 grams per day. In these latter cases factors such as alcohol, starvation, use of drugs that induce CYP2E1 and genetics are believed to enhance the hepatotoxic effect of acetaminophen.

Acetaminophen is one of the most commonly used medications. The moiety is available as a single agent as an over-the-counter product or in combination with other medications like opioids and antihistamines as either prescription of over-the-counter products. Acetaminophen is classified as safe and effective when used within the recommended daily dose of 4 g in adults. More importantly, the acetaminophen monograph instructs that the use of acetaminophen in doses higher than the recommended dose, or in patients with hepatic impairment, hepatic disease, alcoholism, malnutrition, and renal disease may result in hepatic injury including hepatotoxicity and death

2.5 Summary of Presubmission Regulatory Activity Related to Submission

Please see Dr. Fang's review for this information.

2.6 Other Relevant Background Information

Please see Dr. Fang's review for this information.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

Please see Dr. Fang's review for this information.

3.2 Compliance with Good Clinical Practices

Please see Dr. Fang's review for this information.

3.3 Financial Disclosures

Please see Dr. Fang's review for this information.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

Please see Dr. Fang's review for this information.

4.2 Clinical Microbiology

Please see Dr. Fang's review for this information.

4.3 Preclinical Pharmacology/Toxicology

Please see Dr. Fang's review for this information.

4.4 Clinical Pharmacology

Please see Dr. Ji's review for this information

5 Sources of Clinical Data

Please see Dr. Fang's review for this information.

6 Review of Efficacy

Please see Dr. Fang's review for this information.

7 Review of Safety

Safety Summary

The emphasis in the safety review of this application was to assess whether the safety profile of IV acetaminophen differed from that of established oral acetaminophen. In general, there were no unexpected on unusual findings in either the adult or pediatric clinical programs. As per the End-of-Phase 2 meeting requirements set forth by the Division, the Applicant has exposed adequate numbers of patients to IV acetaminophen (b) (4) A total of 355 pediatric patients have received IV acetaminophen in clinical trials including 59.7% (n=212) who received 5 or more doses and 43.1 % (n=153) who received more than 10 doses.

(b) (4)

In the pediatric population, there were no placebo-controlled trials. There were no deaths. The incidence of serious adverse events was 8.5% in pediatric clinical trials with the children's (2-12 years old) age stratum experiencing the highest proportion (10.5%) of SAEs as compared to neonates, infants and adolescents. There was no evidence these SAEs were associated with IV acetaminophen but were consistent with the underlying disease processes. In pediatric patients, the overall incidence of adverse events leading to discontinuation was low (n=5/355, 1.4%), however all 5 of these discontinuations were secondary to liver function test elevations. These five cases had confounding factors (concomitant hepatotoxic medications, posterior spinal fusion surgery) that may have contributed to hepatic enzyme elevations. The most common

adverse events in pediatric patients treated with IV acetaminophen (incidence ≥ 5%) were nausea, vomiting, constipation, pruritus, agitation and atelectasis. No new safety information related to hepatic laboratory analyses and hepatic related adverse events were identified.

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7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

Due to the short duration of IV acetaminophen exposure (≤ 5 days), an assessment for carcinogenic effects was not performed in support for this NDA.

7.6.2 Human Reproduction and Pregnancy Data

Pregnancy Category B has been assigned to IV acetaminophen. Clinical experience with intravenous administration of acetaminophen is limited. However, epidemiological data from the use of oral therapeutic doses of acetaminophen indicate no undesirable effects on pregnant women or on the health of the fetus.

There have been no adequate and well-controlled studies with IV acetaminophen in labor and delivery.

7.6.3 Pediatrics and Assessment of Effects on Growth

This section of the review will be dedicated to the review of safety data from the pediatric safety database. The format of the safety review will be identical to that of the adults

7.6.3.1 Studies/Clinical Trials Used to Evaluate Safety

Safety data from a total of 5 studies conducted in pediatric patients are included in the submission. An overview of these trials is presented in Table 20.

There are no placebo-controlled data in the pediatric population. Two of the five pediatric studies were Phase 3, randomized, double-blind, active-control, single-dose efficacy and safety studies (CN145-001 and RC 210 3 006). One study was an open-label, repeated-dose efficacy and safety study for up to 7 days for the treatment of either pain or fever (CPI-APA-352). The remaining two studies were phase 1, open-label, repeated dose, PK evaluations.

Table 21: Overview of Pediatric Clinical Studies of IV Acetaminophen

Protocol	Phase	Population	Indication	Study design	Single (S) Repeated (R) dose Duration	Dose and No.		
						IV APAP	Control	Total
CPI-APA-102	1	Inpatient	Pain Fever	O/L, PK, safety	R/48h	N=75	N/A	75
EHRC #26095	1	Inpatient	Pain or Fever	O/L, PK, safety	R/72h	N=50	N/A	50
CN145-001	3	Inpatient	Fever	Randomized, DB,AC, efficacy, safety	S/6h	N=35	PPA n=32	67
RC 210 3 006	3	Inpatient	Pain	Randomized, DB, AC, inguinal herniorrhaphy efficacy, safety	S/6h	N=74	N/A	75
CPI-APA-352	3	Inpatient	Pain or Fever	O/L, efficacy, safety	R/168 h	N=100	N/A	100

Source: Applicant's submission (ISS-Pediatric, pg. 16)

A brief description of each trial follows:

1. Study CPI-APA-102: was a Phase 1, prospective, multicenter, open-label, repeat-dose PK study that examined the PK and safety of IV acetaminophen in pediatric populations of various age groups (full-term neonates, infants, children and adolescents) using a weight-based dosing regimen of IV acetaminophen over a 48 hour period
2. Study EHRC # 26095: was a Phase 1, prospective, investigator-initiated, single center (Royal Children's Hospital in Melbourne, Australia), open-label, repeat-dose PK study that examined the PK of IV acetaminophen in premature and full-term neonates weighing at least 1 kilogram (kg), and infants up to 6 months of age using a gestational age-and weight-based dose regimen of IV acetaminophen given Q6h over a 72-hour period.
3. Study CN 145-001: was a phase 3, prospective, multi-center, parallel groups, active-controlled, single-dose study comparing 15 mg IV acetaminophen to 30

mg IV propacetamol in infants and children (ages 1 month to 12 years) with fever (38.5 degrees Celsius to 41 degrees Celsius) of infectious origin.

4. Study RC 210 3 006: was a phase 3, prospective, multi-center, parallel group, active-controlled, single-dose study comparing 15 mg IV acetaminophen to 30 mg IV propacetamol in infants and children (ages 1 to 12 years) status post hernia repair
5. Study CPI-APA-352: was a phase 3, prospective, multi-center, open-label, repeat-dose, 5 day study examining safety and efficacy of IV acetaminophen in pediatric inpatients (full-term neonates to adolescents) with pain and fever.

7.6.3.2 Categorization of Adverse Events

All adverse events from these studies were coded using version 10.0 of the Medical Dictionary for Regulatory Activities (MEDRA) (Q1, 2008: English language version) The appropriateness of the applicant's coding was assessed by comparing the preferred term to the verbatim terms recorded by investigators within a sampling of case report forms . The coding was found to be accurate.

7.6.3.3 Pooling of Data across Studies/Clinical Trials to Estimate and Compare Incidence

The data for pediatric patients who received IV acetaminophen from all 5 studies conducted were pooled according to age category as seen in Table 21 below.

Table 22: Distribution by Study and Age Category for Analysis of Pediatric Safety Data

Protocol Identifier	Number Exposed to IV acetaminophen			
	Neonates[1]	Infants[2]	Children[3]	Adolescents[4]
CN145-001	0	15	20	0
RC210 3 006	0	9	86	0
CPI-APA-102	3	25	25	22
CPI-APA-352	1	8	40	51
EHRC #26095 (Palmer)	**43**	**7**	**0**	**0**
Total Dosed with IV acetaminophen	47	64	171	73

[1] Neonates: ≤ 28 days old
[2] Infants: 29 days to < 2 years old
[3] Children: 2 years to < 12 years old
[4] Adolescents: 12 years to < 18 years old

Source: Applicant's Submission (ISS- Pediatrics, pg. 21)

The summary tabulations as seen in Table 2 for the pediatric clinical trials include the following categories based on age of patient at time of IV acetaminophen exposure;

1. Neonates (≤ 28 days old)

- Premature neonates (< 37 weeks post- menstrual age at birth)
- Full –term neonates (≥ 37 weeks post –menstrual age at birth)

2. Infants (29 days to < 2 years old)
3. Children (2 years to < 12 years old)
4. Adolescents (12 years to < 18 years old)

The safety dataset for Pediatrics was reviewed in toto.

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

Table 22 that follows shows the exposure of IV acetaminophen in the pediatric population by age stratum

Table 23: Exposure to IV Acetaminophen (Pediatric Safety Population)

Parameter	Neonates (N = 47)	Infants (N = 64)	Children (N = 171)	Adolescents (N = 73)
No. doses, N (%)				
1	0	24 (37.5)	106 (62.0)	0
2-4	2 (4.3)	3 (4.7)	5 (2.9)	3 (4.1)
5-6	4 (8.5)	1 (1.6)	2 (1.2)	2 (2.7)
7-10	9 (19.1)	12 (18.8)	20 (11.7)	9 (12.3)
> 10	32 (68.1)	24 (37.5)	38 (22.2)	59 (80.8)
No. of doses				
Mean (SD)	12.5 (4.80)	7.8 (6.69)	6.0 (7.91)	16.0 (6.76)
Median	13.0	8.0	1.0	15.0
Min, Max	3, 24	1, 24	1, 30	4, 34
Duration (days)				
Mean (SD)	3.64 (1.534)	1.77 (1.594)	1.38 (1.754)	3.67 (1.595)
Median	3.43	2.01	0.26	4.02
Min, Max	0.7, 7.7	0.3, 6.4	0.3, 6.8	0.8, 7.1
Total dose (mg)				
Mean (SD)	532.0 (247.61)	886.7 (528.29)	2018.7 (3086.65)	10895.4 (4915.73)
Median	510.00	1000.00	600.00	10500.0
Min, Max	90.0, 1260.0	114.0, 2760.0	140.0, 20000.0	2100.0, 21000.0
Ave. Daily Dose (mg)[1]				
Mean (SD)	150.9 (49.30)	401.1 (185.91)	1453.8 (802.24)	3069.2 (750.72)
Median	148.26	399.60	1190.48	3233.53
Min, Max	36.0, 262.3	100.0, 835.8	477.8, 3976.1	1365.8, 4306.7

Definitions: Ave. = average; min = minimum; max = maximum; No. = number; SD = standard deviation
[1] For patients who received repeated doses.

Source: Applicant's submission (ISS-Pediatrics, pg. 30)

Overall, 60% (212/355) of pediatric patients received ≥ 5 doses of IV acetaminophen including: 96% (45/47) of neonates, 58% (37/64) of infants, 35% (60/171) of children and 96 % (70/73) of adolescents. Adolescents and neonates both have the highest percentages of patients (96%) who received 5 or more doses of IV acetaminophen.

Table 23 summarizes the demographic and descriptive characteristics including sex, age, race, ethnicity, and weight across age category for all 355 pediatric patients who received IV acetaminophen.

Table 24: Demographics (Pediatric Safety Population)

Parameter	**Neonates (N=47)**	**Infants (N=64)**	**Children (N=171)**	**Adolescents (N=73)**
Gender				
Male	30 (63.8 %)	37 (57.8%)	103 (60.2%)	30 (41.1%)
Female	17 (36.2%)	27 (42.2%)	68 (39.8%)	43 (58.9%)
Age				
N	47	64	171	73
Mean (SD)	8.2 (7.87)	9.6 (7.02)	5.7 (2.82)	14.3 (1.35)
Median	5.0	7.0	5.0	15.0
Min-Max	1-27	1-23	2-11	12-16
Race				
American Indian	0	0	0	0
Asian	0	3 (4.7%)	3 (1.8%)	2 (2.75)
Black	0	6 (9.4%)	11 (6.4%)	4 (5.5%)
Hispanic	0	0	0	0
Native Hawaiian	0	1 (1.6%)	2 (1.2%)	0
Caucasian	3 (6.4%)	36 (56.3%)	65 (38%)	65 (89%)
Unknown	43 (91.5%)	16 (25%)	86 (50.3%)	0
Other	1 (2.1%)	2 (3.1%)	4 (2.3%)	2 (2.7%)
Ethnicity				
Hispanic/Latino	0	8 (12.5%)	11 (6.4%)	8 (11%)
Non-Hispanic/Latino	4 (8.5%)	25 (39.1%)	53 (31%)	65 (89%)
Unknown	43 (91.5%)	31(48.4%)	107 (62.6%)	0

Parameter	Neonates (N=47)	Infants (N=64)	Children (N=171)	Adolescents (N=73)
Body weight (kg)				
<50	47 (100%)	64 (100%)	165 (96.5%)	25 (34.2%)
>=50	0	0	6 (3.5%)	48 (65.8%)
Mean (SD)	2.98 (0.69)	7.51 (2.8)	22.58 (10.8)	56.07 (14.4)
Median	3.00	7.65	19.80	54.70
Min-Max	1.2-4.5	1.8-12.4	10.0-76.6	31.5-105.5

Definitions: SD = standard deviation; KG = kilograms
Neonates (<28 days), infants (>28 days - < 24 months), children (2 years - < 12 years) , adolescents (12 years - < 18 years)
Age of neonates presented as days, infants as months, and children/adolescents as years
Source: Applicant Submission (ISS-Pediatrics Appendix table 2.1.2, pp. 196-197)

Overall, there were more males than females (56% and 44 % respectively) in the pediatric safety base and there were more males than females across age categories except for the adolescent population. Across racial lines, Caucasians represented 48% of the pediatric safety database. Mean ages were 8.2 for neonates, 9.6 months for infants, 5.7 years for children and 14.3 years for adolescents. All infants and neonates were less than 50 kg in body weight as were the majority (97%) of children. A higher percentage (65.8%) of adolescents weighed more than 50 kg in body weight.

7.6.3.5 Routine Clinical Testing

Four out of the five pediatric trials (CN145-001, RC 210 3 006, CPI-APA-102, and CPI-APA-352) used standard clinical testing to evaluate the safety of IV acetaminophen including monitoring for adverse events, physical examinations, clinical laboratory tests (hematology, chemistry and liver function tests), and vital signs prior to and following drug treatment. In addition, in trials CPI-APA-102 and trial CPI-APA-352 a urinalysis was also performed at screening and end of study/early termination.

In trial RC 210 3 006 no clinical lab tests were performed. In the investigator-initiated trial (EHRC #26095) safety testing included monitoring for adverse events, clinical labs (liver function tests only at baseline and once daily during dosing). Also, in the investigator trial, physical exams were not performed and vital signs were not collected. The applicant's rationale for exclusion of these safety monitors was that due to the nature of the neonatal patient population, blood sampling and vital sign assessments were limited.

The primary safety concern for intravenous acetaminophen is drug induced liver injury. Per the requirements set forth by the Division at the EOP2 meeting, the applicant was required to have 300 pediatric exposures to IV acetaminophen of which 50 having been exposed for at least 5 days. In Study RC 210 3 006, a single-dose, active-controlled study involving post-operative hernia repair patients, all 95 patients enrolled did not

have lab data collected. The clinical lab (specifically LFTs) information utilized from a single-dose trial would have been limited. Despite the lack of clinical lab data from the single-dose study (RC 210 3 006), and, in light of (b) (4) the pediatric population for which laboratory data are available, I do not believe that the fact that laboratory data was not available for all 300 pediatric patients affected our ability to assess risks in the pediatric population.

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

Please see section 7.3.5 for discussion of this topic.

7.6.3.7 Deaths

There were no deaths that occurred in the pediatric population during the study periods.

7.6.3.8 Nonfatal Serious Adverse Events

In the pediatric population 8.5% (30/355) of patients experienced a serious TEAE, including 2.1% of neonates, 6.3 % of infants, 10.5 % of children and 9.6% of adolescents. There were no placebo groups in the five clinical studies.

Case narratives for 15/30 pediatric patients with serious TEAEs were reviewed and are discussed in detail following. My selection of cases involved safety issues that I believe are relevant to pediatric patients receiving IV acetaminophen including: hepatic events, renal events, and the most common serious adverse events by organ system.

Patient 00303, a 3-year-old male in Study CPI-APA-352, received a total of 20 doses of IV acetaminophen at 15 mg/kg (wt = 15 kg) = 225 mg q6h for pain between 21 July 2008 and 26 July 2008 following a laparoscopic appendectomy on (b) (6). His medical history was significant only for a several day history of bilious emesis, abdominal pain and fever. His admission diagnosis was appendicitis and peritonitis that was confirmed by CT scan.

Table 25: Patient 00303: Liver Function Test Values

LFT:	Screening	Day:							
		1	2	3	4	5	7	10	28
IV APAP dosed:		*X*	*X*	*X*	*X*	*X*			
ALT (U/L)	21	19	17	21	24	210*	144	105	14
AST (U/L)	35	29	35	34	48	257*	108	47	33
ALP (U/L)	76	80	101	106	123	189	194	196	NR
GGT (U/L)	18	20	27	29	51	174	150	131	NR
TBL (mg/dL)	ND	0.2	0.2	0.2	0.2	0.2	0.2	0.2	NR

* ALT or AST value >3 x ULN (> 165 or > 132, respectively)
Definitions: ALT = Alanine Aminotransferase (ULN = 55 U/L); ALP = Alkaline Phosphatase (ULN = 147 U/L); AST = Aspartate Aminotransferase (ULN = 45 U/L); GGT = Gamma Glutamyltransferase (ULN =56 U/L); IV APAP=IV acetaminophen; LFT = Liver function test; ND = Not done; NR=Not reported; TBL = Total bilirubin (ULN = 1.5 mg/dL)

Source: Applicant's submission (ISS- Pediatrics, pg. 48)

As seen in Table 24, this patient's LFT values were normal at screening and until day 5 of IV acetaminophen treatment. Approximately 6 hours after receiving his last dose of IV acetaminophen the patient was reported to have bilious emesis and abdominal distension. At that time, ALT and AST values were 210 U/L (3x ULN) and 257 U/L (5.6x ULN) respectively with a normal TBL of 0.2 mg/dL. He was made NPO, reportedly for symptoms consistent with a small bowel obstruction and begun on treatment for this diagnosis. On days 7 and 10, post IV acetaminophen treatment LFT values have improved and returning to normal. At a follow-up visit on Day 28 (23 days post IV acetaminophen treatment) ALT (14 U/L) and AST (33 U/L) values had returned to normal. This patient 's isolated ALT/AST elevations occurred 6 hours after the last dose of IV acetaminophen .

This SAE of hepatic enzyme elevations is not likely to be related to IV acetaminophen.

Patient 00310, a 15-year-old female enrolled in Study CPI-APA-352 received a total of 13 doses of IV acetaminophen at 15mg/kg (wt = 63.6 kg) = 954 mg q6h for lower extremity pain from Guillain-Barre syndrome (GBS) between 21 October 2008 and 24 October 2008. Her medical history was insignificant until over 2.5 weeks prior to IV acetaminophen treatment when she developed symptoms of fever, cough, headache and malaise which subsequently progressed into pain in bilateral lower extremities followed by weakness, areflexia and tingling in her extremities. After presentation to an emergency department she was subsequently diagnosed with GBS and received a 5 day course of IV immunoglobulin (IVIG). Her IVIG treatment ended 3 days prior to begninning IV acetaminophen treatment. Concomitant medications included enoxaparin, famotidine, gabapentin, labetalol, odansetron, methadone, macrogol, biscodyl, hydralazine, and ketamine.

Table 26: Patient 00310 Liver Function Test Values

LFT	Screening	Day: 1	2	3	3, #2	4	7	10	27
IV APAP dosed:		*X*	*X*	*X*	*X*				
ALT (U/L)	42	47	43	134	162	218*	504*	157	56
AST (U/L)	57	55	52	137	171*	193*	295*	59	60
ALP (U/L)	104	95	82	105	104	90	102	81	NR
GGT (U/L)	31	28	30	52	58	60	70	40	NR
TBL (mg/dL)	0.9	0.8	0.4	0.5	0.6	0.4	0.4	0.2	NR

*ALT or AST value > 3 × ULN (> 165 or > 135, respectively)
Definitions: ALT = Alanine Aminotransferase (ULN = 55 U/L); ALP = Alkaline Phosphatase (ULN = 147 U/L); AST = Aspartate Aminotransferase (ULN = 45 U/L); GGT = Gamma Glutamyltransferase (ULN =50 U/L); IV APAP=IV acetaminophen; LFT=Liver function test; NR=Not reported; TBL = Total bilirubin (ULN = 1.5 mg/dL) (Patient 00310)
Source: Applicant's submission (ISS – Pediatrics, pg. 49))

As displayed in Table 25, the patient's LFTs up to Day 3 of IV acetaminophen treatment were normal except for slightly elevated AST levels of 57 U/L, 55 U/L, and 52 U/L respectively, however on day 3 of IV acetaminophen ALT and AST were 134 U/L (2.4x ULN) and 137 3x ULN) respectively and the decision was made to discontinue IV acetaminophen. Later on the same day, her labs showed an ALT of 162 U/L and AST of 171 U/L with normal ALP, GGT and TBL values. Her ALT and AST values continued to rise 1 day after and 3 days after early termination of IV acetaminophen as displayed in Table 8 on days 4 and 7 respectively. On her follow up visit on Day 10, her ALT and AST values were returning to normal. During a subsequent hospitalization and treatment for GBS symptoms, her liver enzymes were normal as seen on Day 27 with an ALT of 56 U/L and AST of 60 U/L. I cannot completely rule out possible involvement of IV acetaminophen in this patient's LFT elevation.

This SAE of hepatic enzymes elevation is possibly related to IV acetaminophen.

Patient 00704, a 15-year-old male enrolled in Study CPI-APA-352 received a total of 10 doses of IV acetaminophen at 10 mg/kg (wt= 65.6 kg) = 650 mg q4h for pain between 18 August 2008 and 20 August 2008 following T4 - L1 posterior spinal fusion surgery on the same day, (b) (6) . The patient's medical history was significant for scoliosis. Concomitant medications included vancomycin, cefazolin, diazepam, morphine, and midazolam.

Table 27: Patient 00704 Liver Function Test Values

LFT	Screening 18 Aug Day -1 08:20	Day: -1 18 Aug 14:00 Prior T0	1 19 Aug 07:11 Post T0	2 20 Aug 07:18 ET	2 20 Aug 16:28 Post	3 21 Aug	4 22 Aug
IV APAP dosed:			*X*	*X*			
ALT (U/L)	11	16	25	84	77	65	55
AST (U/L)	40	31	143	240*	222*	169	137
ALP (U/L)	144	94	84	93	93	NR	NR
GGT (U/L)	24	20	24	62	58	NR	NR
TBL (mg/dL)	0.4	0.2	1.0	0.7	0.3	NR	NR

* ALT or AST value > 3 × ULN (> 165 or > 135, respectively)
Definitions: ALT = Alanine Aminotransferase (ULN = 55 U/L); ALP = Alkaline Phosphatase (ULN = 147 U/L); AST = Aspartate Aminotransferase (ULN = 45 U/L); ET = Early termination; GGT = Gamma Glutamyltransferase (ULN =50 U/L); IV APAP=IV acetaminophen; NR = Not reported; TBL = Total bilirubin (ULN = 1.5 mg/dL)
Source: Applicant's submission (ISS – Pediatrics, pg. 52))

Table 26 shows screening and daily LFTs for this patient were normal until day 2 of IV acetaminophen treatment when ALT and AST were both elevated at 84 U/L and 240 U/L (5x ULN) respectively. The patient was discontinued from the trial the same day (20 Aug 08) but started on oral acetaminophen at 10 mg/kg Q4h the following day (21 Aug 08) with LFT values decreasing and returning to normal by follow-up on 22 August 2008. Although muscle injury has been associated with transaminase elevations (particularly AST) and given the nature of this patient's surgery this is the most likely, however I cannot completely rule out IV acetaminophen. In addition, his LFT values remained elevated while being given oral acetaminophen.

This patient's SAE of hepatic enzyme (AST) elevation is possibly related to IV acetaminophen.

Patient 00608, an 8-year-old male in Study CPI-APA-352 received a total of 4 doses of IV acetaminophen at 10 mg/kg (wt= 27.1 kg) = 270 mg q6h for pain between 23 May 2008 to 24 May 2008 following video-assisted thoracic surgery for spinal release and posterior spinal fusion (b) (6). Post-operative complications included tachycardia, hypotension and fever to 39.1˚ C which were treated with fluid resuscitation and prophylactic cefazolin respectively. He also experienced an episode of airway obstruction which was treated with neck support and racemic epinephrine. His medical history included neuromuscular scoliosis, hydrocephalus, seizure disorder, static encephalopathy, macrocephaly, asthma, gastroesophageal reflux disease and developmental delay. His prior surgical history included ventriculoperitoneal shunt and

gastrostomy tube placement. His concomitant medications included cefazolin, docusate, levetiracetam, phenobarbital, diazepam, clonazepam, salbutamol, ibuprofen, epinephrine for inhalation and budesonide.

Table 28: Patient 00608 Liver Function Test Values

LFT	Screening	Day: 1	2	3	4	7
IV APAP dosed:		*X*	*X*			
ALT (U/L)	32	198	229*	115	80	23
AST (U/L)	67	291*	207	72	58	28
ALP (U/L)	95	100	100	103	118	103
GGT (U/L)	20	66	63	57	73	48
TBL (mg/dL)	0.4	0.5	0.3	0.2	0.1	0.2

* ALT or AST value > 3 × ULN (> 165 or > 135, respectively)
Definitions: ALT = Alanine Aminotransferase (ULN = 55 U/L); ALP = Alkaline Phosphatase (ULN = 147 U/L); AST = Aspartate Aminotransferase (ULN = 45 U/L); GGT = Gamma Glutamyltransferase (ULN =50 U/L); IV APAP=IV acetaminophen; TBL = Total bilirubin (ULN = 1.5 mg/dL)
Source: Applicant's submission (ISS – Pediatrics, pg. 51)

Table 27 shows LFT screening labs were normal. Between day 1 and day 2 of IV acetaminophen treatment the patient experienced peak elevations in ALT and AST values of 229 U/L (4x ULN) and 207 U/L (4.5x ULN) respectively with a normal TBL. The patient was discontinued from trial medication on Day 2 and ALT and AST showed a marked decrease the following day (ALT of 115 U/L and AST of 72 U/L) with subsequent normalizing of LFT over the next several days. Possible etiologies of this patient's hepatic enzyme elevation include: hypovolemia, hypoxia, concomitant potential hepatotoxic medications (phenobarbital, levetiracetam) and IV acetaminophen. This patient's SAE of hepatic enzyme elevation is possibly related to IV acetaminophen.

Patient 01402, a 13-year-old male enrolled in Study CPI-APA-352 received a total of 16 doses of IV acetaminophen at 15 mg/kg (wt = 61.8 kg) = 927 mg q6h for pain between 30 October 2008 and 04 November 2008 following surgical debridement and irrigation of spinal surgical incision due to infection on (b) (6). His medical history was significant for idiopathic scoliosis, and postoperative spine infection. His prior surgical history included scoliosis surgery. Concomitant medications included morphine, vancomycin, nafcillin, rifampin, and ondansetron. Following surgical debridement of spinal abscess, the patient's surgical cultures were positive for methicillin-resistant Staphylococcus aureus for which he was started on vancomycin, nafcillin and rifampin. Per the patient narrative in the applicant submission, by day 3 of IV acetaminophen treatment the patient's serum creatinine had increased from 0.5 mg/dL at screening to

2.5 mg/dL at which time the vancomycin antibiotic was discontinued. The following day this creatinine was reported to have decreased to 1.8 mg/dL and cefazolin antibiotic was added to the treatment plan. On follow-up visit, the creatinine was down to 1.0 mg/dL. Vancomycin well known for its nephrotoxicity, as well as rifampin and nafcillin being associated with cases of interstial nephritis are the most likely etiologies of this patient's acute renal failure.

This SAE of acute renal failure is not likely related to IV acetaminophen

Patient 00515, a 14-year-old female enrolled in Study CPI-APA-352 received a total of 25 doses of IV acetaminophen at 10 mg/kg (wt = 82.0 kg) = 820 mg q4h for pain initially between 22 October 2008 and 25 October 2008 following craniotomy for resection of a pineal tumor on (b) (6). On the 3rd day of IV acetaminophen a protocol deviation for having exceeding the 4000 mg daily maximum was noted and thereafter, from 26 Oct 2008 to 27 Oct 2008 the patient received 4 doses of IV acetaminophen. Other than the protocol deviation, her hospital course was remained unremarkable and she completed the trial without event and discharged home. Approximately, 10 days after her last dose of IV acetaminophen the patient was readmitted to the hospital due to worsening headaches and which time CT scan reportedly showed a pseudomenigocele.

This patient's SAE of headache is not related to IV acetaminophen treatment.

Patient 00201, a 16-year-old male enrolled in Study CPI-APA-352 received a total of 8 doses of IV acetaminophen at 15 mg/kg (wt = 51 kg) = 750 mg q6h for pain between 18 June 2008 and 20 June 2008 following total colectomy and ileal pouch ileostomy on (b) (6) Her medical history was significant for familial adenopolyposis and early colon adenocarcinoma. There was no prior surgical history reported. Concomitant medications included ketorolac, ondansetron, and hydromorphone. She was reported to have an uneventful postoperative course, completed the course of trial medications and discharged to home without event. Approximately 3 days after her last dose of IV acetaminophen the patient was re-admitted to the hospital for complaints of abdominal pain, vomiting and inability to pass stools at which time history, physical and x-rays revealed a localized ileus. She was subsequently discharged the next day after treatment with hydration.

This patient's SAE of abdominal pain is not related to IV acetaminophen treatment.

Patient 00510, a 4-year-old male enrolled in Study CPI-APA-352 received a total of 20 doses of IV acetaminophen at 10 mg/kg (wt = 16.3 kg) = 160 mg q6h for pain between 03 June 2008 and 08 June 2008 following a reanastomosis surgery, colsostomy

takedown and appendectomy on (b) (6). His medical history included Crohn's disease, Meckel's diverticulum, colonic perforation, asthma, allergic rhinitis, eczema, and multiple food allergies. His prior surgical history included a previous diverting colostomy. Concomitant medications included clonidine, ropivacaine, morphine, , hydrocortisone, inhaled albuterol, salbutamol, diphenhydramine, lorazepam, multivitamins, calcium, prednisone, hydromorphone and topical ointments for eczema. The patient was reported to have a uneventful post-operative course, completed the course of IV acetaminophen and was subsequently discharged home (b) (6). The following day (3 days after his last dose of IV acetaminophen), the patient presented to the emergency department with complaints of abdominal pain with distention and was subsequently re-admitted to the hospital with a tentative diagnosis of small bowel obstruction. He was treated with IV hydration and bowel rest, advanced to a regular diet over the next 3 days and discharged home.

This patient's SAE of bowel obstruction is not related to IV acetaminophen treatment.

Patient 01001, an 8-year-old male enrolled in Study CPI-APA-352 received a total of 20 doses of IV acetaminophen at 15 mg/kg (wt = 35.1 kg) = 530 mg q6h for pain between 11 June 2008 and 16 June 2008 following bladder augmentation on (b) (6). His medical history included hydrocephalus, neurogenic bowel and bladder, bilateral club feet, myelomeningocele, reactive airway disease, history of urinary tract infections, cauda equine syndrome and hypermetropia. His prior surgical history included VP shunt placement, repair of myelomeningocele, tonsillectomy and eye surgery Concomitant mediations included ciprofloxacin, fluticasone, melatonin, metronidazole, montelukast, vancomycin, ondanestron, , potassium chloride, Fleets enema, bisacodyl, inhaled albuterol, inhaled fluticasone-salmeterol, furesomide, morphine and chlorpheniramine/phenylephrine. Two days after completion IV acetaminophen treatment, the patient was reported to complain of severe abdominal pain and found to have an abdominal abscess for which he underwent surgical drainage and nasogastric tube placement and started on antibiotic treatment consisting of clindamycin, fluconazole, and meropenem. The remainder of his hospital course was benign and was discharged home without event.

This patient's SAE of an abdominal abscess is not related to IV acetaminophen treatment.

Patient 00618, a 3-year-old male in Study CPI-APA-352 received a total of 16 doses of IV acetaminophen at 10 mg/kg (wt = 13.4 kg) = 134 mg q6h for pain between 12 December 2008 and 16 December 2008 following open heart surgery on (b) (6) His medical history was significant for double-outlet right ventricle, dextro-rotation of the great arteries, ventricular septal defect, coarctation of the aorta, tricuspid valve regurgitation, left diaphragm paresis and cyanosis at birth. His surgical history included

Damus-Kaye-Stansel procedure, aortic arch reconstruction, balloon angioplasty of the aorta, bidirectional Glenn procedure, Blalock-Taussig shunt and Rastelli procedure. His concomitant medications included ranitidine, metoclopramide, vancomycin, furosemide, silver sulfadiazine, pancuronium, naloxone,acetaminophen, sodium bicarbonate, sulfamethoxazole, cefazolin, spironolactone, midazolam, glycerin, diphenhydramine, epinephrine, morphine, lorazepam, dopamine, milrinone, vasopressin and heparin. Post-operative complications included chylous fluid drainage from chest tube that begain 3 days after the last dose of IV acetaminophen and multiple failed extubations over the course of several days. Subsequent echocardiogram and chest ultrasound procedures demonstrated a possible left diaphragmatic paresis which required placation. The following day the patient was able to be extubated, he required biphasic positive intermittent pressure support (BiPap) for one day, however the remainder of his hospital course was uneventful and he was discharged home in stable condition on room air.

This patient's SAEs including chylothorax and left diaphragm paresis are not related to IV acetaminophen.

Patient 00314, a 15-year-old female enrolled in Study CPI-APA-352 received a total of 4 doses of IV acetaminophen at 10 mg/kg (wt = 70 kg) = 700 mg q6h for pain between 17 December 2008 and 18 December 2008 following a laparascopic appendectomy on (b) (6) for a ruptured appendicitis. Her medical and surgical history was significant for her admitting ruptured appendicitis and subsequent appendectomy. Concomitant medications included morphine, famotidine, ondanestron and ertapenem Her post-operative and hospital course was reported as uneventful, and she was discharged home without event. Approximately, 9 days after her last dose of IV acetaminophen the patient was re-admitted to the hospital secondary to fever of 102 °F and abdominal pain and subsequent abdominal CT scan showed multiple abdominal abscesses. She received broad spectrum antibiotics, oral acetaminophen and IV hydration and was discharged home on antibiotic therapy.

This patient's SAE of fever secondary to multiple abdominal abscesses is not related to IV acetaminophen.

Patient 00305, a 11-year-old female enrolled in Study CPI-APA-352 received a total of 20 doses of IV acetaminophen at 15 mg/kg (wt = 50 kg) = 750mg q6h for pain between 23 July 2008 and 25 July 2008 and then 500 mg (10 mg/kg) Q6h from 25 July 2008 to 28 July 2008 following colectomy with ilneoanal pouch anastomosis on (b) (6). I note that, on review of the CRF, this patient received 700 mg of IV acetaminophen. Her medical history included familial adenomatous polyposis and seasonal allergic rhinitis. There is was no reported prior surgical history. Concomitant medications included morphine, ropivacaine, metronidazole and ampicillin/sulbactam. Her post-operative and hospital course was reported as uneventful and she was discharge home. Approximately 10 days after her last dose of IV acetaminophen, the patient was re-

admitted to the hospital secondary to presenting with erythema, induration and purulent drainage from the surgical site. She was treated with antibiotic therapy for a presumed wound infection without complications and subsequently discharged home.

This patient's SAE of wound infection is not related to IV acetaminophen.

Patient 00609, a 4-year-old female enrolled in Study CPI-APA-352 received a total of 27 doses of IV acetaminophen at 10 mg/kg (wt = 16.2 mg) = 162 mg q6h for pain between 04 June 2008 and 09 June 2008 following repeat laryngotracheal reconstruction to treat stridor and airway obstruction. Her medical history was significant for prematurity,subglottic stenosis from a prolonged intubation, inspiratory stridor, grade IV intraventricular hemorrhage, aspiration pneumonia, RSV infection, tracheal infections, developmental delay, bronchopulmonary dysplasia, cerebral palsy,and seizure disorder. She was also s/p PDA ligation, supraglottoplasty, laryngotrachealreconstruction, and tracheostomy. Her concomitant medications included azithromycin, cefepime, levofloxacin, docusate, Lacriube/Refresh eye ointment, fentanyl, ibuprofen, bacitracin ointment, chloral hydrate, diphenhydramine, glycerin suppository, hydralazine, racemic epinephrine, salbutamol, budesonide, ipratropium, lorazepam, ketamine, dexmedetomidine, vecuronium, propofol, midazolam, rocuronium, pentobarbital, pantoprazol, and montelukast. The patient failed multiple attempts at extubation after her surgery and 5 days after her last dose of IV acetaminophen she was taken back to the operating room for tracheostomy and permanent tracheostomy tube placement. The remainder of hospital course was uneventful.

This patient's SAE of respiratory failure is not related to IV acetaminophen.

Patient 00617, a 5-week-old infant enrolled in Study CPI-APA-352 received a total of 15 doses of IV acetaminophen at 10 mg/kg (wt= 3.1 kg) = 310 mg q8h for pain between !4 November 2008 and 19 November 2008 following a primary transanal endorectal pull-through procedure on (b) (6). His medical history was significant for Hirschsprung's disease. No prior surgical history was reported. Concomitant medictions included: morphine and ranitidine. His postoperative course was uneventful and he was subsequently discharged home. Approximately 23 days after the last dose of IV acetaminophen, the patient was re-admitted to the hospital after presenting to surgery clinic with a one day history of abdominal distension, irritability, loss of appetite and occasional emesis with a greenish tint. He was afebrile with a negative physical exam. His treatment included IV hydration and parental nutrition, daily Hagar dilations per rectum, ciprofloxacin, metronidazole, multivitamins, and rantidine. Two days after admission he resumed passing stools and was subsequently discharged home.

This patient's SAE of exacerbation of Hirshsprung's disease is not related to IV acetaminophen.

Patient 00615, a 4-month-old male enrolled in Study CPI-APA-352 received a total of 20 doses of IV acetaminophen at 10 mg/kg (wt = 6.0 kg) = 60 mg q6h for pain between 07 November 2008 and 12 November 2008 following a hemi-Fontan procedure (HFP) and triscuspid valve repair on (b) (6). His medical history included left hypoplastic heart syndrome, congestive heart failure, chylous effusion, systemic to pulmonary artery shunt, pneumothorax and positive C. difficiletoxin in stools. Prior surgical history included a Norwood repair procedure. Concomitant medications included pancuronium, dexamethasone, furosemide, spironolactone, sodium bicarbonate, chlorothiazide, levalbuterol, cefazolin, metronidazole,acetaminophen, lorazepam, ipratropium, vecuronium, milrinone, morphine, dopamine, vasopressin, ranitidine, dexmedetomidine, midazolam, and heparin. On day four of IV acetaminophen, the patient was reported to be unable to tolerate extubation and had to be reintubated. An ultrasound showed an immobile diaphragm at which time the patient returned to the operating room for bilateral diaphragm placation. The patient remained intubated over the next 3 weeks with a labile respiratory course but was extubated with high flow oxygen. Approximately 5.5 weeks after his last dose of IV acetaminophen, due to persistent respiratory insufficiency the patient underwent a tracheostomy to promote continued ventilatatory support.

This patient's SAE of respiratory failure secondary to left hypoplastic heart syndrome is not related to IV acetaminophen.

7.6.3.9 Dropouts and/or Discontinuations

A review of the safety database shows 5 out of the 355 pediatric patients were reported to have been discontinued from IV acetaminophen treatment due to an adverse event, including 2 children and 3 adolescents. All 5 patients were discontinued due to elevations in hepatic enzymes, including 3 patients were serious TEAES that have been previously discussed in Section 7.6.3.7 (Non-fatal Serous Adverse Events) and 2 patients with non serious TEAES of which their narratives are included below.

Patient 1001-005, a 15-year-old male enrolled in Study CPI-APA-102 received a total of 4 doses of IV acetaminophen at 15 mg/kg (wt = 55. 9 kg) = 835 mg q6h between 17 July 2007 and 18 July 2008 for pain following C4 to T12 posterior-spinal fusion surgery on (b) (6). Intra-operative complications reported were hypotension that was treated by IV fluids and phenylephrine. His medical history included severe congenital scoliosis, Ehler-Danlos syndrome, astigmatism, and acne. No other surgical history was reported in the CRF. Concomitant medications included cefazolin, fentanyl, furosemide, magnesium sulfate, rantidine, lorazepam, midazolam, morphine, potassium, calcium gluconate and phenylephrine.

Table 29: Patient 1001-005 Liver Function Test Values

Date	Visit	Liver Function Test				
		ALT (U/L)	ALP (U/L)	AST (U/L)	TBL (mg/dL)	GGT (U/L)
17Jul07	Screen[1]	12	84	27	0.8	22
18Jul07	24-hour	45	64	112	1.4	23
19Jul07	ET	54	75	113	1.3	37

Definitions: ALT = Alanine Aminotransferase (ULN = 55 U/L); ALP = Alkaline Phosphatase (ULN = 147 U/L); AST = Aspartate Aminotransferase (ULN = 45 U/L); GGT = Gamma Glutamyltransferase (ULN =50 U/L); LFT=Liver function test; TBL = Total bilirubin (ULN = 1.5 mg/dL)

[1] Postoperative baseline LFT values were not obtained

Source: Applicant's submission (ISS-Pediatrics, pg.46)

Liver function values for this patient are displayed in Table 28. Baseline LFT values were normal. At 24 hours, the AST value is elevated at 112 U/L (2.5 x ULN) and on the beginning of Day 2 of trial drug the patient was discontinued from the trial and switched to oral acetaminophen (650 mg Q6h as needed for fever) . The AST value remained elevated at 113 U/L (2.5x ULN) on that same day. No other LFT values were reported on this patient. Other possible etiologies [surgical muscle trauma, concomitant medication (ranitidine), and intra-operative complication (hypotension)] of this patient's AST elevation have to be considered, I cannot completely rule out IV acetaminophen as a possible etiology as well.

The adverse event of LFT elevation leading to this patient's discontinuation is possibly related to IV acetaminophen.

Patient 00412, a 10-year-old female enrolled in Study CPI-APA-412 received a total of 12 doses of IV acetaminophen at 12.5 mg/kg (wt = 35.5 kg) = 420 mg q6h for pain between 18 November 2008 and 21 November 2009 following posterior spinal fusion surgery on (b) (6). Her medical history was significant for neuromuscular scoliosis, spastic cerebral palsy, seizure disorder, mental retardation and allergic rhinitis. There was no reported prior surgical history. Concomitant medications included diazepam, ketamine, morphine, cefazolin, bisacodyl, rantidine, risperidone, and albuterol inhalation.

Table 30: Patient 00412 Liver Function Tests

LFT:	Screening	Day: 1	2	3 ~8 a.m.	3 ~4 p.m.	4	6	7
IV APAP dosed:		*X*	*X*	*X*				
ALT (U/L)	21	46	55	76	84	75	56	64
AST (U/L)	21	108	144	165*	169*	115	42	35
ALP (U/L)	80	91	98	115	116	104	86	118
GGT (U/L)	12	20	18	27	33	36	31	40
TBL (mg/dL)	1.2	0.3	0.4	0.4	ND	0.5	0.2	0.2

* ALT or AST value > 3 × ULN (> 165 or > 135, respectively)
Definitions: ALT = Alanine Aminotransferase (ULN = 55 U/L); ALP = Alkaline Phosphatase (ULN = 147 U/L); AST = Aspartate Aminotransferase (ULN = 45 U/L); GGT = Gamma Glutamyltransferase (ULN =50 U/L); IV APAP=IV acetaminophen; ND = not done; TBL = Total bilirubin (ULN = 1.5 mg/dL)
Source: Applicant's submission (ISS- Pediatrics, pg. 50)

As seen in Table 29, all LFTs were normal at screening. Her AST level was elevated on Days 1 and 2, however when her AST peaked at 169 U/L (3.8x ULN) with a ALT of 84 (1.5x ULN) of day 3 of IV acetaminophen, the patient was discontinued from treatment. Her follow up labs show AST and ALT levels returning to normal range. Although, the pattern of AST > ALT elevation is more likely indicative of surgical muscle trauma I cannot completely rule out IV acetaminophen as a etiology as well.

The adverse event of hepatic enzyme elevation leading to this patient's discontinuation is possibly related to IV acetaminophen.

Patient 00608, Patient 00310 and Patient 00740 were all participants in IV acetaminophen treatment that were discontinued secondary to reported serious adverse events. Please refer to the section on non-fatal serious events for their case narratives.

7.6.3.10 Significant Adverse Events

Please see section 7.6.3.11

7.6.3.11 Submission Specific Primary Safety Concerns

Hepatic Events

Similar to the adult population, the MedDRA SMQ of hepatic disorders was used to assess the incidence, severity, and baseline characteristics of pediatric patients who

experienced a hepatic event. The overall incidence of hepatic events was 3.9 % (14/355) with a higher incidence in adolescents (8.2%) compared to children (4.1%), infants (1.6%) and neonates (0%). There was no meaningful difference in the incidence of hepatic events between males (n=200, 4.0%) and females (n=155, 3.9%). There were no deaths related to a hepatic TEAE. The incidence of serious hepatic TEAE was 1.1 % (4/355). The incidence of hepatic TEAE resulting in discontinuations was 1.4 % (5/355).

Four patients had hepatic events that were assessed as serious. Three patients had their study drug discontinued. Three of the four patients were enrolled post-surgical procedures (appendectomy, posterior spinal fusion) and the remaining patient was enrolled post IVIG treatment for Guillain-Barre syndrome (GBS). Three of the four patients had elevations in both ALT and AST> 3x ULN with normal TBL. The remaining patient had an isolated elevation in AST > 3x ULN. All four cases of serious hepatic TEAEs were deemed possibly related to IV acetaminophen treatment.

Five patients experienced hepatic TEAEs that resulted in discontinuations from their trials. Four of the five patients enrolled had posterior spinal fusion surgeries and the remaining patient was enrolled post IVIG treatment for GBS. The AST>ALT pattern of elevation in the patients involving posterior spinal fusion suggests that muscle trauma was a plausible etiology in addition to concomitant hepatotoxic medications. In the GBS patient, both ALT and AST were elevated > 3x ULN however these values remained elevated up to 7 days post drug early termination. In all 5 cases, the hepatic events leading to discontinuation were deemed possibly related to IV acetaminophen treatment.

Although there were no cases that met Hy's Law criteria, there were pediatric patients who had marked LFT levels (AST/ALT > 3x ULN) with normal TBL. These cases primarily involved patients with congenital heart disease who had elevated LFTs at baseline.

7.6.3.12 Common Adverse Events

Treatment emergent adverse events reported in ≥ 1% of the 355 pediatric patients who received IV acetaminophen are displayed in Table 30 by MedDRA preferred term in descending order of frequency. I verified the counts submitted by the applicant using jmp software and found identical total adverse events except for nausea (n=57), vomiting (n=42) and headache (n=10) common TEAEs where the applicant chose to count patients experiencing the same adverse event > 1 as one event. These differences do not substantially affect my perception of the adverse event profile and I accept the Applicant's table.

Table 31: Most Common ≥1 % of All Patients TEAEs Pediatric Safety Population

MedDRA Preferred Term	Neonates (N=47) n (%)	Infants (N=64) n (%)	Children (N=171) n (%)	Adolescents (N=73) n (%)	Total (N=355) n (%)
Nausea	0	2 (3.1)	19 (11.1)	33 (45.2)	54 (15.2)
Vomiting	0	1 (1.6)	18 (10.5)	18 (24.7)	37 (10.4)
Constipation	0	3 (4.7)	12 (7.0)	14 (19.2)	29 (8.2)
Pruritus	0	3 (4.7)	13 (7.6)	12 (16.4)	28 (7.9)
Agitation	0	9 (14.1)	8 (4.7)	3 (4.1)	20 (5.6)
Atelectasis	2 (4.3)	6 (9.4)	7 (4.1)	4 (5.5)	19 (5.4)
Pyrexia	0	0	9 (5.3)	6 (8.2)	15 (4.2)
Hypokalaemia	0	8 (12.5)	5 (2.9)	1 (1.4)	14 (3.9)
Hypomagnesaemia	1 (2.1)	4 (6.3)	4 (2.3)	5 (6.8)	14 (3.9)
Pleural effusion	1 (2.1)	5 (7.8)	3 (1.8)	4 (5.5)	13 (3.7)
Anaemia	0	4 (6.3)	3 (1.8)	4 (5.5)	11 (3.1)
Injection site pain	0	1 (1.6)	11 (6.4)	0	12 (3.4)
Headache	0	0	1 (0.6)	8 (11.0)	9 (2.5)
Hypotension	0	1 (1.6)	5 (2.9)	3 (4.1)	9 (2.5)
Pulmonary oedema	1 (2.1)	4 (6.3)	3 (1.8)	1 (1.4)	9 (2.5)
Wheezing	0	7 (10.9)	1 (0.6)	0	8 (2.3)
Diarrhoea	0	0	5 (2.9)	3 (4.1)	8 (2.3)
Muscle spasms	0	0	1 (0.6)	6 (8.2)	7 (2.0)
Stridor	0	4 (6.3)	3 (1.8)	0	7 (2.0)
Hypoalbuminaemia	0	1 (1.6)	4 (2.3)	1 (1.4)	6 (1.7)
Hypophosphataemia	0	1 (1.6)	2 (1.2)	2 (2.7)	5 (1.4)
Oliguria	0	3 (4.7)	1 (0.6)	1 (1.4)	5 (1.4)
Abdominal pain	0	0	2 (1.2)	2 (2.7)	4 (1.1)
Hepatic enzyme increased	0	0	2 (1.2)	2 (2.7)	4 (1.1)
Hypertension	0	2 (3.1)	2 (1.2)	0	4 (1.1)
Hypervolaemia	0	0	2 (1.2)	2 (2.7)	4 (1.1)
Hypoxia	0	0	1 (0.6)	3 (4.1)	4 (1.1)
Insomnia	0	1 (1.6)	2 (1.2)	1 (1.4)	4 (1.1)
Oedema peripheral	0	0	3 (1.8)	1 (1.4)	4 (1.1)
Pain in extremity	0	0	2 (1.2)	2 (2.7)	4 (1.1)
Periorbital oedema	0	0	3 (1.8)	1 (1.4)	4 (1.1)
Rash	0	1 (1.6)	3 (1.8)	0	4 (1.1)
Tachycardia	0	0	3 (1.8)	1 (1.4)	4 (1.1)
Wound infection	0	0	4 (2.3)	0	4 (1.1)

Definitions: TEAE = Treatment-Emergent Adverse Event; MedDRA = Medical Dictionary for Regulatory Activities

Source: Applicant's submission (ISS – Pediatrics, pg. 33)

The most commonly reported TEAEs involved the gastrointestinal system: nausea (15.2%), vomiting (10.4 %) and constipation (8.2%). Other common TEAEs reported included pruritus (7.9%), agitation (5.6%) and atelectasis (5.4%) with the remainder of TEAEs being reported in < 5% of all pediatric patients.

In the adolescent category the most common TEAEs reported were nausea (45.2%), vomiting (24.7%), constipation (19.2%), pruritus (16.4%) and injection site pain (11.0%). In the children category the most common TEAEs reported were nausea (11.1%), vomiting (10.5%), pruritus (7.6%), constipation (7.0%) and injection site pain (6.4%). In the infant's category the most common TEAEs reported were agitation (14.1%), hypokalemia (12.5%), wheezing (10.9%), atelectasis (9.4%) and pleural effusion (7.8%). In the neonate category, very small percentages of this population were reported to have experienced common TEAEs including atelectasis (4.3%), hypomagnesaemia (2.1%), pleural effusion (2.1%) and pulmonary edema (2.1%).

7.6.3.13 Laboratory Findings

In the pediatric clinical development program, the laboratory evaluation of safety was conducted using standard hematology and chemistry (including liver function tests) investigations. At times the analysis of laboratory safety data was confounded by

- Lack of comparator group
- Physiological differences among the age categories
- In trial RC 210 3 006 that enrolled 95 patients (86-children, 9-infants) no clinical laboratory data was collected
- In trial EHRC #26095 that enrolled 50 patients (43 –neonates, 7-infants) only liver function tests were reported

Hematology Analysis
Analysis focused on measures of central tendency

A summary of mean hematology values at baseline and mean changes from baseline to last value on study is displayed in Table 31 by age statum.

Table 32: **Mean (SD) Hematology Values at Baseline and Change from Baseline to Last Value on Study (Pediatric Safety Population)**

Parameter	Neonates (N = 47)		Infants (N = 64)		Children (N = 171)		Adolescents (N = 73)	
Timepoint	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)
Hemoglobin (g/dL)								
Baseline	4	14.75 (0.580)	44	12.05 (2.474)	70	11.78 (1.987)	67	11.74 (2.249)
Δ to last value	4	0.55 (1.418)	44	0.13 (1.802)	70	-0.23 (1.844)	67	-0.61 (2.422)
Hematocrit (%)								
Baseline	4	41.8 (2.01)	44	35.4 (7.13)	70	34.5 (5.89)	67	33.9 (6.28)
Δ to last value	4	2.1 (4.34)	44	0.4 (5.47)	70	-0.5 (5.41)	67	-1.3 (6.89)
Leukocytes (10^9/L)								
Baseline	4	10.70 (3.868)	44	11.56 (7.173)	70	11.27 (6.150)	67	8.46 (4.368)
Δ to last value	4	-1.38 (4.094)	44	-0.36 (7.124)	70	-0.83 (6.864)	67	0.71 (4.046)
Platelets (10^9/L)								
Baseline	4	234.3 (105.48)	43	326.6 (148.93)	69	274.7 (117.99)	66	257.7 (83.96)
Δ to last value	4	31.0 (199.81)	43	-13.9 (178.69)	69	107.3 (225.23)	66	195.4 (255.19)

Source: Applicant's submission (ISS – Pediatrics, pg. 92))

Mean hemoglobin, hematocrit and leukocytes counts at baseline varied across age categories. The changes in values from baseline to last visit for all hematology parameters across age categories were not clinically meaningful.

Analysis focused on outliers or shifts from normal to abnormal

Hematology shifts from baseline to worst value on study are presented in Table 32.

Table 33: Hematology Shifts from Baseline to Last Value on Study (Pediatric Safety Population)

Parameter	Shift	Neonates (N = 47) n/N (%)[1]	Infants (N = 64) n/N (%)[1]	Children (N = 171) n/N (%)[1]	Adolescents (N = 73) n/N (%)[1]
Hemoglobin	Shift to High[2]	0/4	5/43 (11.6)	3/70 (4.3)	0/67
	Shift to Low[3]	0/4	3/43 (7.0)	12/70 (17.1)	17/67 (25.4)
Leukocytes	Shift to High[2]	1/4 (25.0)	8/43 (18.6)	14/70 (20.0)	9/67 (13.4)
	Shift to Low[3]	0/4	1/43 (2.3)	2/70 (2.9)	1/67 (1.5)
Platelets	Shift to High[2]	1/4 (25.0)	4/42 (9.5)	21/69 (30.4)	27/66 (40.9)
	Shift to Low[3]	1/4 (25.0)	2/42 (4.8)	7/69 (10.1)	1/66 (1.5)

[1] n=number of patients with shift, N = total number of patients included in analysis.
[2] Shift from normal or low value at baseline to a last value on study that was above the upper limit of the normal range (high).
[3] Shift from normal or high value at baseline to a last value on study value that was below the lower limit of the

Source: Applicant's submission (ISS- Pediatrics, pg. 92))

As previously stated, in the context of no placebo comparator group assessing clinical meaningful hematology the assessment of shifts is difficult. Shifts to low hemoglobin were highest in the adolescent category as well shift to high platelets were highest in this sub-population as well.

Marked outliers and dropouts for hematology abnormalities

There were no marked outliers and dropouts for hematology abnormalities within the pediatric population.

Chemistry analysis

Analysis focused on measures of central tendency

A summary of mean clinical chemistry values at baseline and mean changes from baseline to last visit is provided in Table 33.

Table 34: Mean (SD) Chemistry Values at Baseline and Change from Baseline to Last Value on Study (Pediatric Safety Population)

Parameter	Neonates (N = 47)		Infants (N = 64)		Children (N = 171)		Adolescents (N = 73)	
Timepoint	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)
Sodium (mmol/L)								
Baseline	4	142.8 (3.30)	44	138.9 (5.12)	70	138.4 (3.86)	70	138.7 (2.44)
Δ to last value	4	-5.3 (4.99)	44	-1.1 (5.16)	70	-0.6 (4.70)	70	0.1 (3.82)
Potassium (mmol/L)								
Baseline	4	3.55 (0.640)	43	4.32 (0.812)	69	3.94 (0.503)	70	4.09 (0.437)
Δ to last value	4	0.25 (0.332)	43	-0.27 (1.021)	69	0.18 (0.634)	70	0.08 (0.624)
Chloride (mmol/L)								
Baseline	4	105.8 (7.41)	31	103.1 (4.60)	54	105.3 (4.67)	70	105.5 (3.45)
Δ to last value	4	-8.3 (5.91)	31	-3.4 (6.81)	54	-3.6 (5.68)	70	-4.0 (4.22)
Glucose (mg/dL)								
Baseline	4	96.3 (22.31)	32	109.4 (32.94)	66	119.0 (41.49)	67	102.2 (28.89)
Δ to last value	4	0.5 (30.43)	32	-8.3 (44.85)	66	-10.3 (91.84)	67	-12.2 (29.46)
Albumin (g/dL)								
Baseline	44	2.53 (0.650)	27	3.85 (0.973)	18	3.74 (0.618)	19	3.44 (0.627)
Δ to last value	44	0.06 (0.661)	27	-0.53 (0.556)	18	-0.34 (0.579)	19	-0.32 (0.567)
BUN (mg/dL)								
Baseline	4	19.0 (7.79)	28	11.8 (6.16)	53	11.1 (4.82)	69	11.5 (4.75)
Δ to last value	4	-4.0 (9.69)	28	0.8 (7.94)	53	1.8 (7.48)	69	-0.2 (5.03)
Creatinine (mg/dL)								
Baseline	3	0.50 (0.000)	42	0.52 (1.029)	70	0.46 (0.170)	70	0.60 (0.175)
Δ to last value	3	-0.13 (0.058)	42	-0.21 (1.030)	70	0.07 (0.779)	70	0.01 (0.112)

Definitions: SD = standard deviation; mmol = millimoles, mg = milligrams, g = grams; dL = deciliter; L = liter, Δ = change

Source: Applicant's submission (ISS- Pediatric, pg. 94))

Mean chemistry parameters and the mean change from baseline to last value were comparable across each age stratum except for the neonate age stratum. The differences noted in neonates can be attributed to physiologic factors in newborns.

Analysis focused on outliers or shifts from normal to abnormal

Chemistry shifts from baseline to the last value on study across each age stratum are presented in Table 34 that follows.

Table 35: Clinical Chemistry shifts from Baseline to Last Value on Study (Pediatric Safety Population)

Parameter	Shift	Neonates (N = 47) n/N (%)[1]	Infants (N = 64) n/N (%)[1]	Children (N = 171) n/N (%)[1]	Adolescents (N = 73) n/N (%)[1]
Albumin	Shift to High[2]	0/44	1/27 (3.7)	1/18 (5.6)	0/19
	Shift to Low[3]	6/44 (13.6)	5/27 (18.5)	5/18 (27.8)	5/19 (26.3)
Sodium	Shift to High[2]	0/4	0/44	0/70	0/70
	Shift to Low[3]	0/4	6/44 (13.6)	7/70 (10.0)	6/70 (8.6)
Potassium	Shift to High[2]	0/4	2/43 (4.7)	2/69 (2.9)	2/70 (2.9)
	Shift to Low[3]	0/4	8/43 (18.6)	5/69 (7.2)	4/70 (5.7)
Glucose	Shift to High[2]	0/4	5/32 (15.6)	5/66 (7.6)	3/67 (4.5)
	Shift to Low[3]	0/4	2/32 (6.3)	4/66 (6.1)	0/67
Creatinine	Shift to High[2]	0/3	0/42	2/70 (2.9)	0/70
	Shift to Low[3]	0/3	1/42 (2.4)	4/70 (5.7)	4/70 (5.7)

[1] n=number of patients with shift, N = total number of patients included in analysis.
[2] Shift from normal or low value at baseline to a last value on study that was above the upper limit of the normal range (high).
[3] Shift from normal or high value at baseline to a last value on study value that was below the lower limit of the normal range (low).

Source: Applicant's submission (ISS – Pediatrics, pg. 95)

The most frequent shift seen was in the albumin parameter (shift to low) with 26.3% of adolescents, 27.8 % of children, 18.5 % of infants and 13.6% of neonates included in the analysis experiencing this shift. Neonates did not experience any shifts in chemistry parameters except for what was previously noted. Two children experienced creatinine shifts to high levels. One of these cases will be briefly discussed in the next section on marked outlier.

Marked outliers and dropouts for chemistry abnormalities

There were no cases of marked outliers that were discontinued for chemistry abnormalities however there was one case of acute renal failure with a maximum creatinine of 2.5 mg/dL that has been previously discussed in the section on non-fatal serious adverse events. Per the applicant, this patient's creatinine elevation was thought to be secondary to nephrotoxic aminoglylycoside therapy (vancomycin) so, the patient was continued on IV acetaminophen treatment. Aminoglycosides can be nephrotoxic especially in combination with another aminoglyoside or other nephrotoxic

drugs such as rifampin and naficillin which were this patient's other concomitant medications.

Hepatic enzyme analysis

Analysis focused on measures of central tendency

A summary of mean liver function test values at baseline to last value on trial are displayed in Table 35

Table 36: Mean (SD) Liver Function Test Values at Baseline and Change from Baseline to Last Value on Study (Pediatric Safety Population)

Parameter Timepoint	Neonates (N=47)		Infants (N=64)		Children (N=171)		Adolescents (N=73)	
	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)
AST (U/L)								
Baseline	4	253.5 (373.99)	43	67.7 (53.01)	80	51.4 (68.45)	73	31.2 (20.48)
Δ to last value	4	-215.3 (360.14)	43	-21.3 (58.05)	80	70.3 (673.82)	73	5.4 (34.76)
ALT (mmol/L)								
Baseline	44	46.0 (84.76)	50	33.0 (20.29)	80	31.0 (28.63)	73	23.8 (10.14)
Δ to last value	44	-10.4 (76.45)	50	6.9 (44.40)	80	16.7 (147.86)	73	7.3 (23.57)
GGT (U/L)								
Baseline	43	96.2 (102.64)	22	35.0 (37.49)	44	22.0 (36.31)	49	18.1 (15.26)
Δ to last value	43	23.4 (94.05)	22	21.0 (69.52)	44	8.3 (33.00)	49	35.2 (48.73)
TBL (mg/dL)								
Baseline	47	5.19 (3.227)	37	1.19 (1.387)	63	0.76 (0.728)	62	0.63 (0.450)
Δ to last value	47	-1.47 (4.177)	37	-0.20 (0.884)	63	-0.22 (0.504)	62	-0.17 (0.482)
ALP (g/dL)								
Baseline	44	120.2 (57.73)	43	250.4 (192.28)	74	183.1 (82.19)	73	110.5 (55.72)
Δ to last value	44	19.4 (47.87)	43	-38.2 (113.09)	74	-15.9 (79.19)	73	9.4 (51.32)

Definitions: Δ=change; ALP=alkaline phosphatase; ALT=alanine transaminase; AST=aspartate transaminase;

Source: Applicant's submission (ISS – Pediatric, pg. 97)

LFT parameters (AST, ALT, GGT, TBL and ALP) in the neonate category were overall higher and are likely reflective of issues related to premature and gestational neonates such as hyperbilirubinemia. A larger increase in ALT and AST from baseline to last value was seen in the children's category and per the applicant is due to a marked outlier that will be discussed later. Overall, it is difficult to assess a trend in mean LFT parameters due to no comparative placebo-population for each age category and physiologic differences across pediatric age categories.

Analysis focused on outliers or shifts from normal to abnormal

A summary of Pediatric patient data for maximum elevations of > 3x ULN in ALT, AST, TBL, ALP and GGT are summarized in Table 36 below.

Table 37: Post-baseline Liver Function Test Results Relative to the Normal Range (Safety Population)

Laboratory Test Abnormality	Neonates (N = 47) n (%)	Infants (N = 64) n (%)	Children (N = 171) n (%)	Adolescents (N = 73) n (%)
AST or ALT (maximum AT), n	47	52	81	73
≤ 3xULN	45 (95.7)	47 (90.4)	72 (88.9)	67 (91.8)
> 3 - ≤ 5xULN	1 (2.1)	4 (7.7)	5 (6.2)	4 (5.5)
> 5 - ≤ 10xULN	1 (2.1)	1 (1.9)	3 (3.7)	2 (2.7)
> 10xULN	0	0	1 (1.2)[1]	0
AST, n	4	45	81	73
≤ 3xULN	3 (75.0)	41 (91.1)	72 (88.9)	67 (91.8)
> 3 - ≤ 5xULN	0	3 (6.7)	5 (6.2)	4 (5.5)
> 5 - ≤ 10xULN	1 (25.0)	1 (2.2)	3 (3.7)	2 (2.7)
> 10xULN	0	0	1 (1.2)[1]	0
ALT, n	47	52	80	73
≤ 3xULN	45 (95.7)	50 (96.2)	77 (96.3)	72 (98.6)
> 3 - ≤ 5xULN	2 (4.3)	1 (1.9)	2 (2.5)	0
> 5 - ≤ 10xULN	0	1 (1.9)	0	1 (1.4)
> 10xULN	0	0	1 (1.3)[1]	0
TBL, n	47	46	73	69
≤ 3xULN	18 (38.3)	43 (93.5)	73 (100.0)	69 (100.0)
> 3 - ≤ 5xULN	10 (21.3)	1 (2.2)	0	0
> 5 - ≤ 10xULN	14 (29.8)	1 (2.2)	0	0
> 10xULN	5 (10.6)	1 (2.2)	0	0
ALP, n	47	48	76	73
≤ 3xULN	47 (100.0)	46 (95.8)	75 (98.7)	73 (100.0)
> 3 - ≤ 5xULN	0	1 (2.1)	1 (1.3)	0
> 5 - ≤ 10xULN	0	1 (2.1)	0	0
> 10xULN	0	0	0	0

Definitions: ALP = alkaline phosphatase; ALT = alanine transaminase; AST = aspartate transaminase; AT = alanine or aspartate transaminase; TBL = total bilirubin; ULN = upper limit of normal

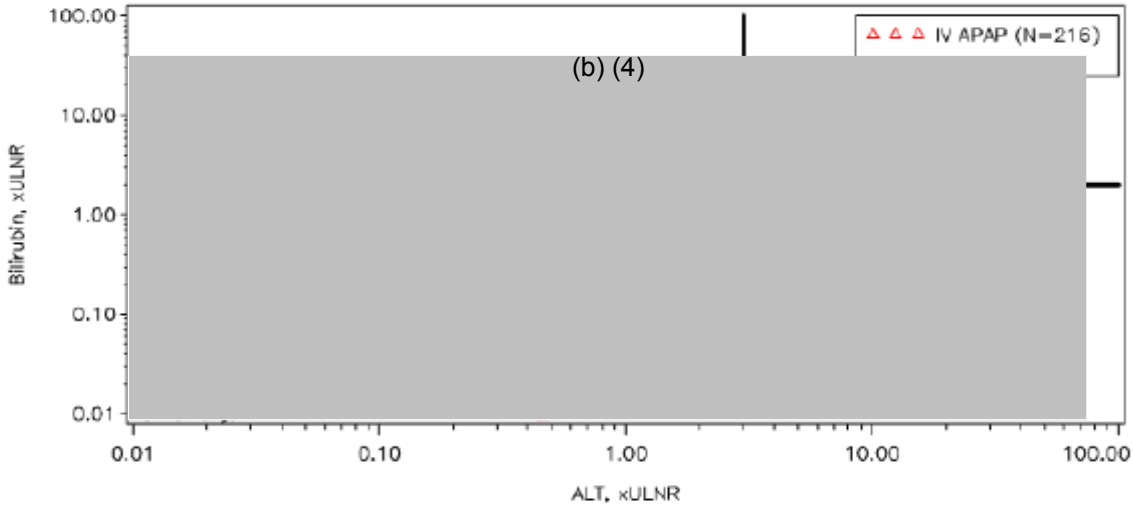
[1] Patient 00322 in Study CPI-APA-102; with L-transposition of the great arteries, dextrocardia, double outlet right ventricle, ventricular septal defect, subpulmonic and pulmonic stenosis, cyanosis, and elevated liver enzymes who was granted a waiver for study entry. The increased AST and ALT were associated with multi-organ failure and the patient's underlying condition.

Source: Applicant's submission (ISS – Pediatric, pg. 99)

There was one patient in the children age category that experienced >10x ULN in ALT and ALT, this outlier will be discussed in the next sub-section. Elevations > 3 - ≤ 5x ULN and >5 - ≤ 10x ULN were comparable between infants, children and adolescents. Elevations in TBL > 3X ULN were seen more frequently in neonates as compared to other age groups.

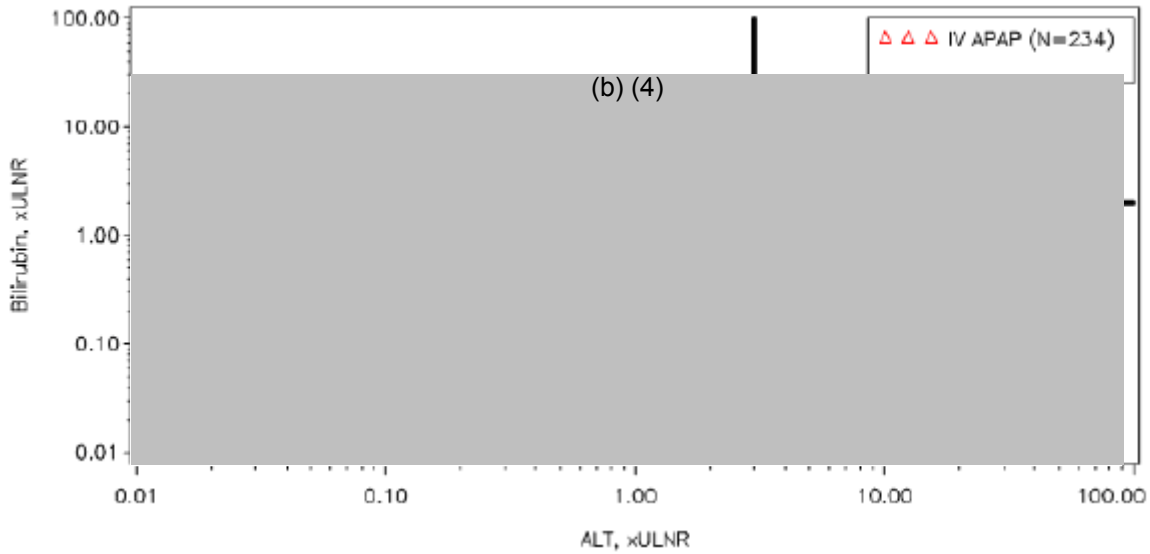
Figures 3 and 4 are scatterplots of baseline and worst baseline ALT versus TBL value in the pediatric safety population.

Figure 4: Scatterplot of Baseline ALT versus TBL: Pediatric Safety Population



Source: Applicant's submission (ISS- Pediatric, pg. 103))

Figure 5: Scatterplot of Worst Baseline ALT versus TBL: Pediatric Safety Population



Source: Applicant's submission (ISS – Pediatric, pg. 103))

The case located in the Hy's Law quadrant is present in both baseline and worst baseline ALT and TBL plots. The cases represented in the left upper quadrant

(elevated TBL and normal/near ULN ALT quadrant) were, according to the applicant, submission patients from the trial that enrolled mainly premature neonates and the remainder of cases were neonates or infants that undergone surgical repairs of congenital heart disease and had received blood transfusions. The cases in this quadrant were proportionately similar baseline and worst baseline. Finally, there were approximately 7 patients with ALT values > 3x ULN for worse value post baseline (right lower quadrant) **.** Three of these seven cases involved patients with complicated congenital heart disease (i.e. Tetralogy of Fallot, Coarctation of Aorta, Transposition of Great Arteries), with one of the three having elevated ALT levels at baseline and the remaining two patients suffering post-operatively complications of either hypotension or blood loss requiring transfusion. One of the seven patients was admitted with a diagnosis of gastroenteritis with dehydration and had elevated ALT levels at baseline. One patient received IV acetaminophen post-operatively from posterior spinal fusion surgery and suffered post-operative complications including hypoxia, hypovolemia and was on concomitant hepatotoxic medications (phenobarbital and levetiracetam). One patient experienced ALT elevations after his last dose of IV acetaminophen, and coinciding with his symptoms of bilious emesis and abdominal pain for which he was later diagnosed with a small bowel obstruction. The seventh patient in the quadrant displaying ALT values >3x ULN received IV acetaminophen while hospitalized for treatment for Guillain-Barre Syndrome and experienced LFT elevations from day 3 of study drug treatment until 4 days post early termination from study. In all of seven patients having ALT values >3x ULN for worst post baseline, there were confounding factors that may have contributed to this finding.

Marked outliers and dropouts for liver function test abnormalities

There was one Pediatric patient (1 child) who had marked LFT elevations and was subsequently discontinued from IV acetaminophen treatment. This outlier case is seen on Figures 1 and 2 DISH displays in the Hy's Law quadrant. Her case narrative is discussed below.

Patient 00322, a 10 year-old female enrolled in Study CPI-APA-102 received a total of 3 doses of IV acetaminophen at 10 mg/kg (wt=67 kg) = 660 mg Q4h for pain on 28 June 2008 following a Fontan procedure. Her medical history was significant for L-transposition of the great arteries, dextrocardia, double outlet right ventricle, ventricular septal defect, subpulmonic and pulmonic stenosis, cyanosis, and elevated liver enzymes. Her surgical history was significant for a Blalock-Taussig shunt, bidirectional Glenn shunt with Blalock-Taussig shunt takedown, and repair of the right coronary artery secondary to pacing wire injury. Concomitant medications included aspirin, morphine, cefazolin, heparin, milrinone, protamine, dopamine, epinephrine, and amiodarone

Table 38: Patient 00322 LFT Values

Patient 00322 (12.5 mg/kg q4h)	ALT (U/L)	AST (U/L)	AP (U/L)	TBL (mg/dL)
Screening	225	549	100	3.3
24 hour	ND	ND	ND	ND
48 hour/ET	1533	6565	116	2.3

Definition: ALT = alanine aminotransferase; AP = alkaline phosphatase; AST = aspartate aminotransferase; EOS = end of study; TBL = total bilirubin; ND = not done

Source: Applicant's submission (ISS – Pediatric, pg. 108)

The patient was granted an exemption to enter the study with elevated liver enzymes (see Table 37), but with plans for treatment discontinuation if the enzymes failed to decrease as expected on reassessment later that day. No decreases in liver enzymes were observed and the patient was discontinued from the trial after the third dose. Postoperatively she experienced low cardiac output syndrome with marked diastolic dysfunction, respiratory failure, acute renal failure, acute liver failure (maximum ALT and AST of 1533 and 6565 U/L respectively with TBL of 3.3 mg/dL), disseminated intravascular coagulation, heparin-induced thrombocytopenia, extremity ischemic necrosis, delirium and withdrawal syndrome. Resuscitative efforts included numerous vasoactive infusions, continuous renal replacement therapy, and multiple transfusions. She suffered massive multiorgan failure with presumed sepsis that did not respond to treatments including several broad spectrum antibiotics. She died in the post-stduy period greater than 30 days after her last dose of IV acetaminophen

This outlier case does not represent an Hy's Law case because this patient's AST and ALT > 3x ULN with TBL > 2x ULN existed before the start of IV acetaminophen treatment and were likely due to her underlying complex heart disease.

7.6.3.14 Vital signs

Vital signs were collected in all the pediatric clinical trials. Standard vital sign assessments included systolic blood pressure (SBP), diastolic blood pressure (DBP), heart rate (HR), respiratory rate (RR) and temperature (T).

Interpreting vital sign changes was confounded by the following:

- No placebo control group
- Large differences in the number of patients included in each age category analysis population
- Vital sign data was not included for patients who did not have completed trial information (i.e. early termination, discontinuation due to early hospital discharge)

Analysis focused on outliers or shifts from normal to abnormal

Vital signs shifts from baseline to the last value on study are displayed in Table 38.

Table 39: Vital Sign Shifts from Baseline to Last Study on Trial (Pediatric Safety Population)

VS	Shift	Neonates (N = 47) n/N[1] (%)	Infants (N = 64) n/N[1] (%)	Children (N = 171) n/N[1] (%)	Adolescents (N = 73) n/N[1] (%)
SBP	Shift to High[2]	0/4	7/56 (12.5)	10/170 (5.9)	1/73 (1.4)
	Shift to Low[3]	0/4	0/56	2/170 (1.2)	4/73 (5.5)
DBP	Shift to High[2]	0/4	2/56 (3.6)	3/170 (1.8)	0/73
	Shift to Low[3]	0/4	4/56 (7.1)	7/170 (4.1)	1/73 (1.4)
HR	Shift to High[2]	1/4 (25.0)	6/56 (10.7)	4/168 (2.4)	9/73 (12.3)
	Shift to Low[3]	0/4	0/56	6/168 (3.6)	1/73 (1.4)
RR	Shift to High[2]	0/3	5/19 (26.3)	5/55 (9.1)	5/57 (8.8)
	Shift to Low[3]	0/3	3/19 (15.8)	6/55 (10.9)	0/57

Definitions: VS = vital sign; SBP = systolic blood pressure; DBP = diastolic blood pressure; HR = heart rate; RR = respiratory rate.

1 n=number of patients with shift, N = total number of patients included in analysis.

2 Shift from normal or low value at baseline to high value (relative to normal range) at last evaluation.

3 Shift from normal or high value at baseline to low value (relative to normal range) at last evaluation.

Source: Applicant's submission (ISS – Pediatric, pg. 111)

Overall, infants included in the analysis had a higher frequency of vital sign shifts to high and low values in comparison to neonates, children, and adolescents. Neonates included in the analysis had only 1 case of an abnormal vital sign shift (HR from normal to high). Shifts to low SBP were seen in 6 out of the 303 pediatric patients analyzed. Shifts to low DBP were seen in 12 out of the 303 pediatric patients analyzed

Table 39 below shows vital sign abnormalities reported as TEAES overall and across pediatric age stratum

Table 40: TEAEs associated with Vital Sign Abnormalities (Pediatric Safety Population)

MedDRA Preferred Term	Neonates (N = 47) n (%)	Infants (N = 64) n (%)	Children (N = 171) n (%)	Adolescents (N = 73) n (%)	Total (N = 355) n (%)
Blood Pressure Events					
Hypotension	0	1 (1.6)	5 (2.9)	3 (4.1)	9 (2.5)
Hypertension	0	2 (3.1)	2 (1.2)	0	4 (1.1)
Blood pressure increased	0	0	1 (0.6)	0	1 (0.3)
Heart Rate Events					
Tachycardia	0	0	3 (1.8)	1 (1.4)	4 (1.1)
Body Temperature Events					
Pyrexia	0	0	9 (5.3)	6 (8.2)	15 (4.2)

Definitions: MedDRA = Medical Dictionary for Regulatory Activities.

Source: Applicant submission (ISS – Pediatric, pg. 112)

The most common vital sign abnormality reported as a TEAE was pyrexia at 4.2 % in all pediatric patients. In the neonate age category no TEAEs associated with vital sign abnormalities were reported. Adolescents had a higher number of TEAEs (13.6 %)

associated with vital sign abnormalities as compared to children (11.6%), infants (4.7%) and neonates (0%) respectively.

7.6.3.15 Electrocardiograms

Electrocardiograms were not performed for any of the pediatric clinical trials.

7.6.3.16 Special Safety Studies/Clinical Trials

No additional special safety studies or clinical trials were performed during the pediatric clinical development program.

7.6.3.17 Drug-Demographic Interactions

The applicant tabulated TEAEs reported in ≥ 3 infants, children, or adolescents who received IV acetaminophen and presented this data by gender and race category. Overall, there were no clinically meaningful differences in the incidence rates of common TEAEs between genders across age categories(neonates vs. infants vs. children vs. adolescents).. Similarly, as with gender there were no clinically meaningful differences in the occurrences of common TEAEs between races (caucasian vs. non-caucasian). I will note that how the applicant chose to analyze drug-demographics with the pediatric data base by stratifying by age, then by gender or race made it difficult to discuss these interactions.

7.6.3.18 Drug-Disease Interactions

This section is not applicable to this sNDA.

7.6.3.19 Drug-Drug Interactions

Please see section 7.5.5

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

Please see Section 7.3.5

7.7 Additional Submissions / Safety Issues

The applicant submitted the 120 day safety update on 11 September 2009. The safety review incorporates all submitted data. A total of three additional submissions regarding safety were made in response to queries from the Division and these submissions are displayed in Table 40.

Table 41: Additional Requested Clinical Submissions to NDA 22-450

Submission Date	Information Submitted
29 June 2009	Datasets containing all adverse event data for all patients, repeated-dose trials
28 July 2009	Additional clinical information for one patient 001-32
11 August 2009	Additional clinical information for patients

8 Post market Experience

Since 2001, an IV formulation of acetaminophen identical to the proposed commercial formulation for marketing in the US has been approved for use, initially in France and subsequently in approximately 80 countries. This product has been marketed by Bristol-Myers Squibb as Perfalgan in most countries; however, other trade names have also been used. Perfalgan is marketed for the same indications of acute pain and fever, both alone and in conjunction with parental opioids and non-steroidal anti-inflammatory drugs, and in both the adult and pediatric populations.

To date, the applicant has provided periodic safety update reports (PSURs) on an annual basis since June 2001. Per the applicant, approximately (b) (4) patients have been treated with IV acetaminophen to date.

The summary of safety in foreign post-marketing experience has been prepared by the applicant using nine clinical categories identified in the periodic safety update reports from June 2001 to January 2009. These 9 categories are organized as follows:

- Adverse events with death as an outcome
- Hepatic adverse events
- Allergic/Hypersensitivity/Dermatologic adverse events
- Overdose
- Medication errors
- Cardiovascular adverse events

- Renal adverse events
- Respiratory adverse events
- Hematologic adverse events

In the review of the categories: adverse events with death as outcome, hepatic adverse events, anaphylaxis, angioedema, and serious cutaneous reactions), the applicant has indentified certain individuals as independent experts.

Adverse events with death as an outcome in IV acetaminophen post-marketing experience

Per the applicant's submission, a total of (b) (4) reports with one or more AEs resulted in death from the estimated (b) (4) patients exposed during the review period (June 2001 – January 2009) including (b) (4) and 5 pediatric patients (3- neonates, 1-infant, 1-child) . The applicant has chosen to summarize deaths with a reasonable causal association with IV acetaminophen as deemed by an independent expert analysis performed by (b) (4)
I performed a review of the line listings of all adverse events with death as an outcome as well as an evaluation of the causal relationship table as assessed by this independent "expert" (b) (4) and found that a higher proportion of death events occurred in the hepatic category (i.e. fulminant hepatitis, hepatic failure, acute hepatic failure, and hepatotoxicity) as compared to cardiovascular, allergic, hematologic, respiratory, overdose and other event categories (See Table 41 below). Several of these patients had medical histories significant for alcoholism, and /or prior liver disease.

Table 42: Summary of Events with Death as Outcomes, by Causal Relationship as Assessed by an Independent Expert ((b) (4)

Event category	Reasonable causal association with IV acetaminophen	Causal relationship with IV acetaminophen not definitely	Total
Hepatic	(b) (4)		
Cardiovascular			
Allergic			
Hematologic			
Respiratory			
Overdose			
Other			

Source: Applicant's submission (Post-Marketing safety data analysis)

Hepatic adverse events in IV acetaminophen post-marketing experience

Per the applicant's submission, there were (b) (4) reports of medically significant hepatic adverse events from the estimated (b) (4) exposed during the review period (June, 2001 to January 2009) including (b) (4) and 23 pediatric patients (4- neonates, 3–infants, 8–children, 7- adolescents), and (b) (4) reports where the age of the patient was not given.

Similarly as in the analysis of deaths, the applicant consulted, (b) (4)

to review the reports of liver injury associated with IV acetaminophen and to assess the relative safety of the drug. Dr. (b) (4) review shows 12 out of the (b) (4) reports where the available data met the quantitative criteria of "Hy's Law." Of these 12 reports there were 2 liver transplants, 3 deaths, and the remaining 7 cases recovered. Also Dr. (b) (4) reports in his review that 10 cases raised a strong index for drug-induced liver injury (DILI); three of which were assessed as probably due to IV acetaminophen, seven assessed as possibly due to IV acetaminophen (b) (4)

I reviewed a substantial number of the (b) (4) case narratives for this category as well. The narratives and PSURs within this category showed that a large proportion of hepatic adverse events involved patients with conditions including: hepatocellular dysfunction, alcoholism, malnutrition, dehydration or severe renal insufficiency. These patients may have been at increased risk for developing acetaminophen induced hepatotoxicity. The postmarketing summary provided by the Applicant is consistent with the known safety profile of oral acetaminophen.

Allergic, Hypersensitivity and Dermatologic adverse events In IV acetaminophen post-marketing experience

Per the applicant's submission, there were (b) (4) reports of medically significant allergic/dermatologic adverse events from the estimated (b) (4) patients exposed during the review period (June 2001 to January 2009) including (b) (4), 26 pediatric patients (2-infants, 14-children, 10-adolescents) and (b) (4) reports that did not include the age of the patient.

These events were grouped and reported by the applicant in the following categories:

- Anaphylactic shock (n (b) (4))
- Anaphylactoid reactions (n (b) (4))
- Angioedema (n (b) (4))
- Urticaria (n=(b) (4))
- Stevens-Johnson syndrome (n=(b)
- Toxic epidermal necrolysis (n (b) (4))
- Erythema multiforme (n (b) (4))
- Acute generalized exanthematous pustulosis (n=(b) (4))
- Minor immediate hypersensitivity cutaneous and other allergic reactions such as erythema, rashes, localized edema or swelling, and pruritus

The applicant idenitfied (b) (4) as an independent expert to review the cases of allergic/hypersensitivity and dermatologic adverse events and provide his own assessment of diagnosis and causality in each of these (b) (4) cases. Overall, Dr. (b) (4) diagnosis and causality assessment was similar to that of the applicant across categories. For example, in Dr (b) (4) review (b) (4) cases were considered to be anaphylaxis or anaphylactoid reactions as compared to the applicant's review showing (b) (4) cases of anaphylaxis or anaphylactoid reactions out of approximately (b) (4) patients exposed.

The post-marketing reports associated with this category of adverse events were limited due to several factors including limited medical history reported; diagnoses without supportive documentation, and presence of concomitant medications.

Overdose events in IV acetaminophen post-marketing experience

Per the applicant's submission, there were (b) (4) reports of overdose events from the estimated (b) (4) patients exposed during the review period (June 2001 to January 2009) including (b) (4), 23 pediatric patients (8-neonates, 9-infants, 7-children) and (b) (4) reports where the age of the patient was not given. The following categories were used to summarize the data from post-marketing experience:

(b) (4)

3. Pediatric patients receiving more than applicant recommended maximum dose: the applicant reports 17 cases including infants and children and 7 cases of neonates who met this criteria. Of these 17 reports, five cases were reported to have adverse sequelae (two reports of vomiting, and three reports of LFT elevations)

4. Pediatric patients receiving > 140 mg/kg total daily dose: the applicant reports five pediatric cases including 1 neonate and 4 infants) who received doses > 140 mg/k total daily dose. Of these five reports, three were reported to have increased LFTs with no sequalae and one patient received N-acetylcysteine empirically. Two of these five patients died however the applicant purports that relationship of IV acetaminophen in these cases in uncertain.

Overall, there were more reports of overdoses in the pediatric population as compared to the adult population. Most cases that had adverse sequelae involved LFT elevations.

Medication errors in IV acetaminophen post-marketing experience

Per the applicant submission, there have been (b) (4) medication error reports from the estimated (b) (4) patients exposed during the review period (June 2001 to January 2009) including (b) (4), 7 pediatric cases (1-neonate, 1-infant, 3-children, 2-adolescents) and (b) (4) reports where the ages of the patients were not given. Of these (b) (4) reports, four included fatal events. I reviewed PSUR for these deaths and found that one event involving an air embolism after administration of IV acetaminophen was possibly related and possibly related to this patient's death. The following categories were used to summarize medications errors with and without adverse sequelae:

1. Drug maladministration (n=(b) (4): the administration errors involved subcutaneous infusion, intramuscular infusion, epidural infusion, enteral infusion, and intra-arterial infusions
2. Medication error (n=(b) (4): the medication errors involved infusion times either < or > recommended times, expired drug given, air in infusion set, accidental exposure, medication bottle breakage and patients with medical conditions representing possible contraindication to IV acetaminophen.

Cardiovascular adverse events in IV acetaminophen post-marketing experience

Per the applicant submission, there have been (b) (4) cardiovascular adverse events reported from the estimated (b) (4) patients exposed during the review period (June 2001 to January 2009) including (b) (4) adults, nine pediatric patients (4-neonates, 1-infant, 1-child, 3-adolescents) and (b) (4) reports where the age of the patient was not given. Of these (b) (4) reports, the events were classified as follows:

- Hypotension (n = (b) (4))
- Cardiac arrest (n = (b))
- Cardiovascular or circulatory collapse (n = (b))
- Shock (n = (b))
- Ventricular tachycardia (n = (b) (4))
- Ventricular fibrillation (n = (b))
- Torsade de Pointes (n = (b))

Hypotension was the most frequently reported event in this category with a total of 55 case reports. In my review of some of the cardiovascular case narratives involving hypotension, cardiovascular or circulatory collapse, and shock there were other etiologies (i.e. trauma, post operative hypovolemia/hemorrhage, and anesthesia) possibly related to these adverse events. In the cases of arrhythmia, medication errors involving incorrect infusion times were noted. The case report of Torsade de Pointes involved a patient with a pre-existing cardiac condition undergoing cardiac procedures.

Renal adverse events in IV acetaminophen post-marketing experience

Per the applicant submission, there have been (b) (4) renal adverse events reported as primary or in conjunction with hepatic adverse events from the estimated (b) (4) patients exposed during the review period (June 2001 to January 2009) including (b) (4) adults, two pediatric patients (1-neonate, 1-child) and (b) reports where the age of the patient was not given. Three of these (b) (4) reports included fatal events of which 2/3 included renal failure as a part of multi-organ failure (including hepatic failure). The renal adverse events were classified in the following categories:

- Renal failure (n (b) (4))
- Acute renal failure (n = (b) (4))
- Renal tubular necrosis (n = (b))
- Urinary retention (n = (b))
- Interstitial nephritis (n = (b))
- Decreased creatinine clearance (n (b) (4))

The applicant purports that in the majority of cases of renal failure, there was documentation that supported other possible etiologies that were more likely to cause nephrotoxicity including the use of IV contrast and antibiotics such as aminoglycosides and vancomycin.

Respiratory adverse events in IV acetaminophen post-marketing experience

Per the applicant submission, there have been (b) (4) respiratory adverse events reported from the estimated (b) (4) patients exposed during the review period (June 2001 to January 2009) including (b) (4), 9 pediatric patients (3-neonates, 1- infant, 3-children, 2-adolescents) and 11 reports where the age of the patient was not given. Of these (b) (4) reports, these medical significant events were classified as:

- Respiratory depression (n = (b)
- Respiratory distress (n = (b) (4)
- Respiratory failure (n = (b) (4)
- Bronchospasm (n = (b)
- Respiratory arrest (n = (b)
- Respiratory disorder (n = (b)
- Respiratory acidosis (n = (b)

I will note that of these (b) (4) reports, eight included fatal events, one of which the applicant states that the event (anaphylaxis with dyspnea) was possibly related to IV acetaminophen. Otherwise, the majority of respiratory adverse events occurred in the respiratory distress and respiratory depression category

Hematologic adverse events in IV acetaminophen post-marketing experience

Per the applicant submission there have been (b) (4) hematologic adverse events reported from the estimated (b) (4) patients exposed during the review period (June 2001 to January 2009) including (b) (4) in adults, 8 in pediatric patients (1-neonate, 1-infant, 4-children, 2-adolescents). Of these (b) (4) reports, the events were classified as follows:

- Thrombocytopenia (n = (b) (4)
- Agranulocytosis or neutropenia (n = (b) (4)
- Hemolytic anemia (n = (b)
- Coagulopathy (n = (b) (4)
- Pancytopenia (n = (b) (4)

Thrombocytopenia appears to be the most commonly reported hematologic adverse event in the post-marketing analysis.

In summary, review of safety data from foreign post-marketing use of IV acetaminophen appears to show a similar pattern of adverse events compared to oral acetaminophen. Like oral acetaminophen, the applicant's post-marketing analysis of IV acetaminophen shows the drug has the potential to increase hepatic adverse outcomes when used in "high risk" conditions (alcoholic disease, and prior and current liver dysfunction) at therapeutic doses and when given in excess of the recommended dose (accidental overdose). Overall, IV acetaminophen accidental overdoses were more prevalent in the pediatric population as compared to adults. In the majority of the pediatric accidental overdose cases the most common adverse sequelae involved LFT elevations. In the severe overdose cases an IV acetaminophen induced hepatotoxic picture was observed requiring anecdotal (n-acetyl-cysteine) treatment in some cases. The applicant has addressed the potential for these specific adverse events in the warning and precautions section of the proposed IV acetaminophen label.

9 Appendices

9.1 Literature Review/References

To support its claims regarding the safety of IV acetaminophen, the applicant relied upon the safety experience of oral acetaminophen.

9.2 Labeling Recommendations

The proposed label for IV acetaminophen has been reviewed and recommendations include the following:

- The Highlights' section should be limited in length to one-half page
- Do not include the pregnancy category in the Hightights'section

9.3 Advisory Committee Meeting

In June 2009, an expert panel was convened at the Center for Drug Evaluation and Research Joint Meeting of the Drug Safety and Risk Management Advisory Committee, the Agency's Nonprescription Drugs Advisory Committee and the Anesthetic and Life Support Drugs Advisory Committee to discuss safety issues of acetaminophen and greater regulation of this commonly used drug. This particular drug was not discussed.

Key recommendations from the panel included:

- Decrease the maximum total daily dose of acetaminophen in non-prescription single ingredient and combination products to less than 4 grams/day

- Decrease the maximum non-prescription single adult dose of acetaminophen to 650 mg
- Require a boxed warning for prescription acetaminophen combination products
- Unbundle prescription acetaminophen narcotic combination products
- Provide label dosing directions for pediatric patients < 2 years of age
- Limit the non-prescription acetaminophen liquid suspension to a single concentration.

The overall theme that came out of the acetaminophen advisory committee meeting is that preventing and decreasing the misuse and overdose of acetaminophen is critical.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22450	ORIG-1	CADENCE PHARMACEUTICALS INC	ACETAMINOPHEN FOR INJECTION FOR IV USE

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

/s/

JACQUELINE A SPAULDING
10/13/2009

ROBERT B SHIBUYA
10/13/2009
I concur with Dr. Spaulding's review and conclusions.