Office of Clinical Pharmacology Review

NDA or BLA Number	022450/S10, SDN 419, 424, 430, 468, 476, 486
Link to EDR	\\CDSESUB1\evsprod\NDA022450\0091
Submission Date	04/29/2016, 5/16/2016, 5/27/2016/, 10/16/2016, 11/16/2016, 12/19/2016
Submission Type	*[Priority]*
Brand Name	Ofirmev
Generic Name	Acetaminophen Injection
Dosage Form and Strength	Solution for IV Injection
Route of Administration	Intravenous Route
Proposed Indication	Pediatric Indication
Applicant	Mallinckrodt INC
Associated IND	*[INDs associated with EOP2, Pre-NDA, and/or Pediatric Study Plan]*
OCP Review Team	*[Srikanth C. Nallani, Ph.D., Kevin Krudys, Ph.D.]*
OCP Final Signatory	*[Kevin Krudys, Ph.D., Yun Xu, Ph.D.]*

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1. EXECUTIVE SUMMARY

1.1 Recommendations

The submission is acceptable provided that the sponsor agrees to the labeling recommendation made in this clinical pharmacology review.

1.2 Post-Marketing Requirements and Commitments

None.

2. SUMMARY OF CLINICAL PHARMACOLOGY ASSESSMENT

Ofirmev (acetaminophen, or APAP) injection was approved by the FDA on 11/02/2010 for the management of mild to moderate pain, the management of moderate to severe pain with adjunctive opioid analgesics, and for the reduction of fever in both adults and children age 2 years and older. Agency had issued a pediatric written request in 2007 spanning all pediatric age groups (birth to 17 years) and amended the PWR several times at the sponsor's request. Some of the pediatric studies were reviewed in the NDA submitted and approved in 2010 and resulted in pediatric indications down to 2 years of age. In the last amendment of the PWR, Agency had specified a study in pediatric patients below 2 years of age to characterize the efficacy of IV APAP and the APAP plasma concentrations and pain relationship for IV APAP used for short-term use for management of pain following multiple doses in different pediatric age groups (< 2 years of age) requiring IV analgesics. Pediatric Exclusivity was granted for studies conducted on Acetaminophen, effective July 11, 2016.

The sponsor conducted two studies (b) (4).

1. Study CPI-APA-353: A Randomized, Placebo-Controlled, Multicenter Study of the Efficacy, Pharmacokinetics and Pharmacodynamics of Intravenous Acetaminophen for the Treatment of Acute Pain in Pediatric Patients.

2. Study MNK14501041: A Single-Dose, Open-Label Study Comparing the Plasma Acetaminophen Concentrations with Blood Samples Collected at the Same Time with Different Blood Drawing Routes and Collection Methods in Healthy Subjects (See appendix for validation and cross-validation of bioanalytical data).

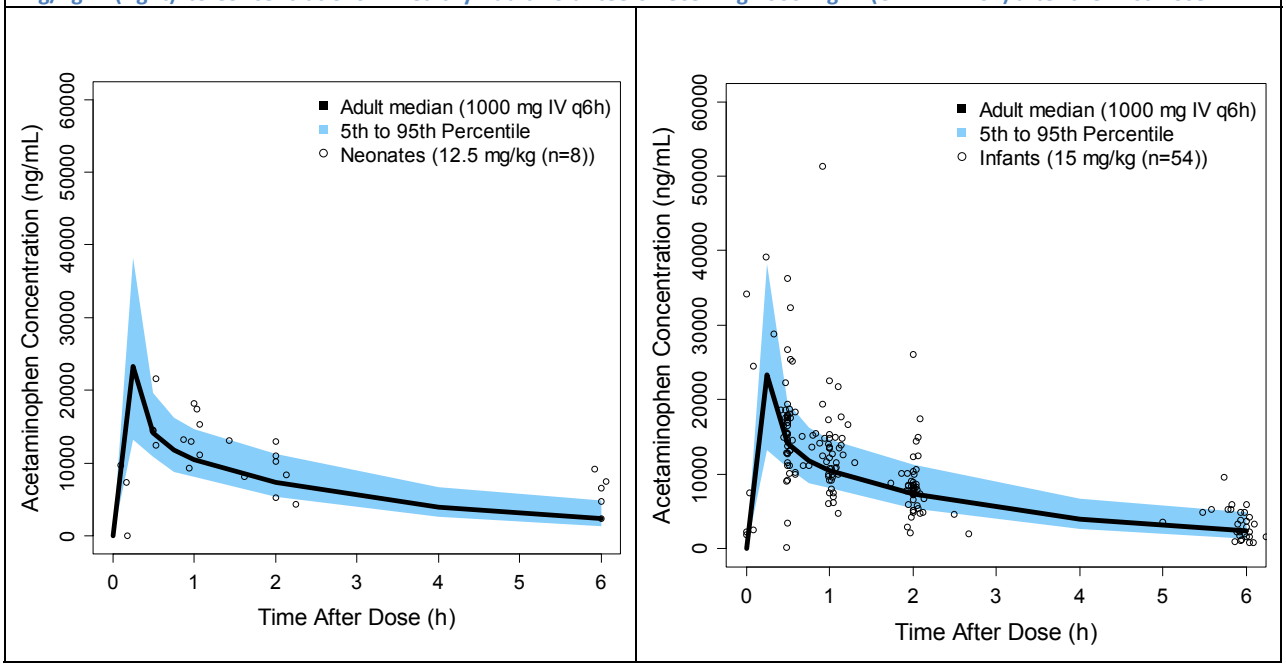
Study CPI-APA-353 was conducted to fulfill the requirements of the PWR and derive PK parameters of IV acetaminophen administered to pediatric patients less than two years of age. Study MNK14501041 was conducted to cross-validate bioanalytical methods used for analysis of acetaminophen in plasma, venous dried blood samples (DBS) and capillary DBS.

2.1 Pharmacology and Clinical Pharmacokinetics

Plasma concentrations of acetaminophen in neonates and infants less than 2 years of age from Study CPI-APA-353 were compared to concentrations in adults and children ≥ 2 years of age from previous

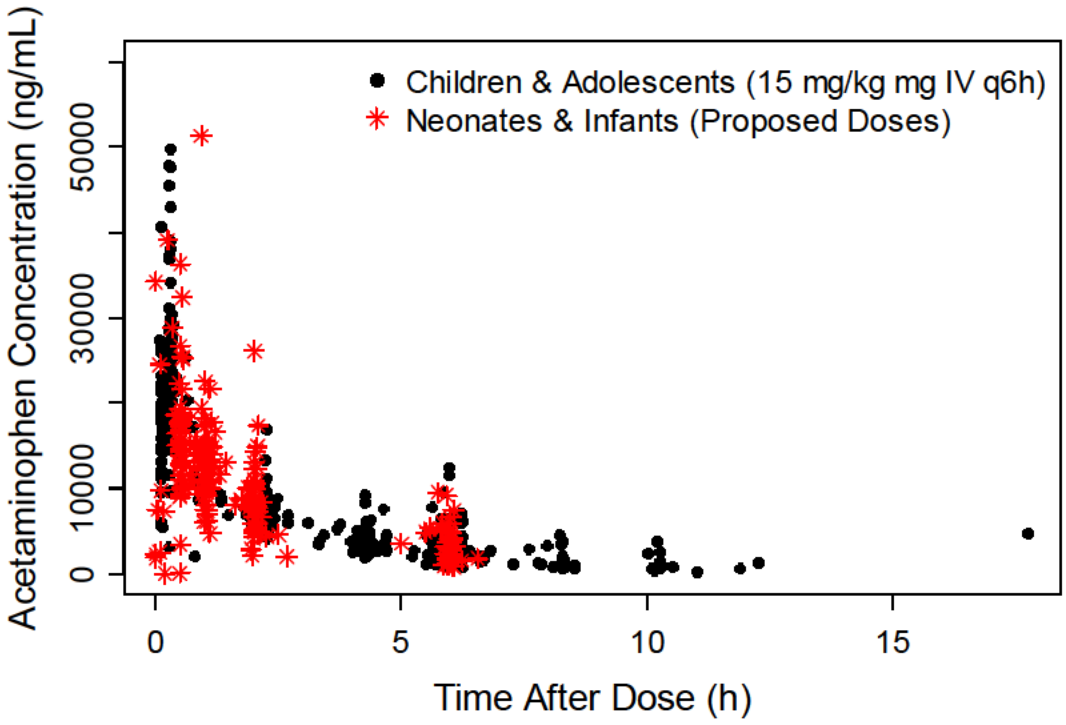
studies. At the Applicant's proposed dose of 12.5 mg/kg every 6 hours in neonates and 15 mg/kg every 6 hours in infants, concentrations of acetaminophen were similar to concentrations observed in healthy adult volunteers at a dose of 1000 mg (Figure 1).

Figure 1: Comparison of Acetaminophen Concentrations in Neonates Receiving 12.5 mg/kg IV (left) and Infants Receiving 15 mg/kg IV (right) to Concentrations in Healthy Adult Volunteers Receiving 1000 mg IV (CPI-APA-101) after the First Dose.



Likewise, acetaminophen concentrations in the same population were compared to concentrations in children ≥ 2 years of age who received the approved dose of 15 mg/kg IV every 6 hours (Figure 2). Based on these graphical comparisons it can be concluded that IV acetaminophen doses of 12.5 mg/kg in neonates and 15 mg/kg in infants are expected to result in similar concentrations to the already approved adult and pediatric doses.

Figure 2: Comparison of Acetaminophen Concentrations in Neonates (12.5 mg/kg IV) and Infants (15 mg/kg IV) in CPI-APA-353 and Children and Adolescents (2 to 17 years of age) Receiving 15 mg/kg IV q6h



2.2 Summary of Labeling Recommendations

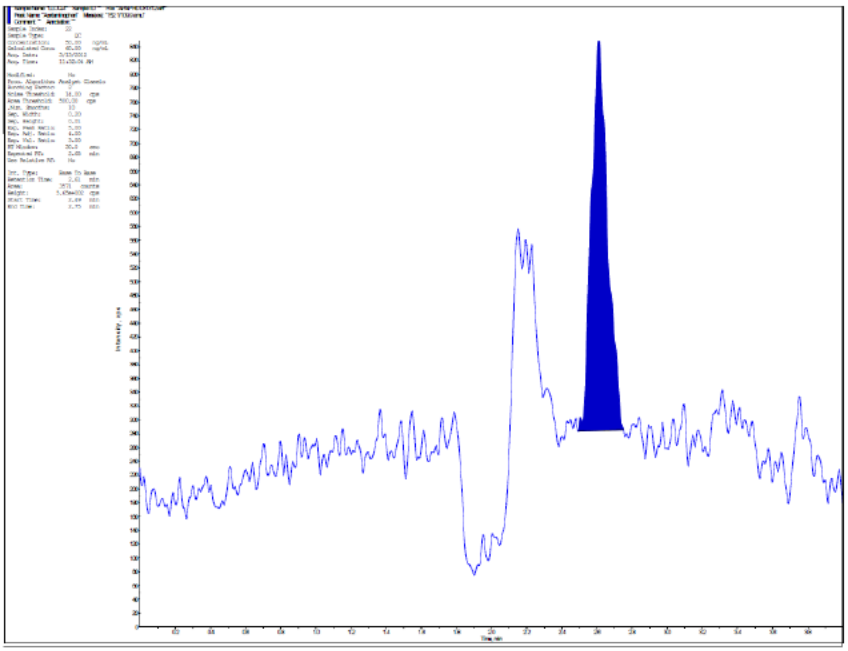
(b) (4)

3. APPENDICES

3.1 Summary of Bioanalytical Method Validation and Performance

Draft Guidance for Industry: Bioanalytical Validation indicates that bioanalytical method used for dried blood spots should be validated. This validation should address, at a minimum, the effects of the following issues: storage and handling temperature, homogeneity of sample spotting, hematocrit, stability, carryover, and reproducibility including ISR.

Figure 7.1: Sample Acetaminophen Chromatogram at LLOQ (50.00 ng/mL)



Source: Bioanalytical report (b) (4) S13-057.

In Pediatric study CPI-APA-353, quantitation of acetaminophen in human dried blood spot (venous and capillary DBS), plasma and urine samples was done using separate validated LC/MS/MS methods.

Assay Methodology Summary	
Method Validation Report	(b) (4) R13-057 [12.2]
Matrix	Human Dried Blood Spot
Anticoagulant	Sodium Heparin
Type of Extraction	Protein-Precipitation
Method of Detection	LC/MS/MS
Sample Aliquot Volume	50.0 µL human whole blood (dried on (b) (4) DBS Sample Collection card containing Ahlstrom 226 paper) with a 5.00-mm sample punch
Quantitation	Peak Area Ratios
Ionization Type	Electrospray, Positive
MS Operation Mode	Selected Reaction Monitoring (SRM)
Platform	API 5000 or API 6500
Calibration Standard Distribution	Calibration standards were placed at the beginning and end of each bioanalytical run.

Assay Methodology Summary		
Quality Control (QC) Distribution	QC samples were distributed throughout each bioanalytical run.	
Injection Sequence	The prepared samples, calibration standards and QCs were injected in a systematic order.	
Assay Carryover	Peaks greater than 20% of the lowest acceptable LLOQ analyte response that were attributable to carryover were detected in control blank samples in Runs 5, 21 and 24 (See Analytical Notes for discussion). It is our policy to evaluate carryover in each acceptable analytical run. If peaks greater than 20% of the lowest acceptable LLOQ are detected in control blank samples, all study samples are reviewed on a sample by sample basis, and any potentially affected samples are repeated per SOP.	
Analyte	Acetaminophen	
Internal Standard	Acetaminophen-d_4 (added to all samples except Blanks)	
Regression and Weighting	Linear $1/x^2$	
LLOQ	50.0 ng/mL	
ULOQ	30,000 ng/mL	
Calibration Standard Concentrations	50.0; 100; 250; 500; 2,500; 5,000; 15,000 and 30,000 ng/mL	
Analytical QC Concentrations	150; 1,000 and 2,000 ng/mL	
Dilution QC Concentration	50,000 ng/mL	
Dilution Factor	DF=10	
Performance of Analytical QCs	Precision (%CV)	Accuracy (%Bias)
	5.5% to 10.1%	-6.5% to 4.0%
Run Performance (see Table 1)	No. of Accepted Runs	No. of Rejected Runs
	9	1*

*See Analytical Notes for discussion

Calibration Standards	
Date(s) of Preparation	22-Nov-2013, 08-Jan-2014, 14-Feb-2014, 04-Apr-2014, 30-Jun-2014 and 16-Jun-2015
Matrix	Human Dried Blood Spot
The calibration curve was prepared in advance as pools of each standard point, 50.0 µL of each standard point was spotted onto (b) (4) DBS Sample Collection card containing Ahlstrom 226 paper ((b) (4) ID# 1417Rev 2). Multiple cards were used as needed on the day of analysis. The calibrator pools were not used beyond their established stability.	

The Calibration Curve Summary and Back-Calculated Standard Concentrations are found in Table 2 and Table 3, respectively.

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Quality Control (QC) Samples	
Date(s) of Preparation	22-Nov-2013, 08-Jan-2014, 14-Feb-2014, 04-Apr-2014, 30-Jun-2014 and 16-Jun-2015
Matrix	Human Dried Blood Spot
Storage Temperature	Room Temperature
Analytical QCs at the low, medium and high levels were assayed in at least duplicate in each analytical run. In addition, for each dilution level, dilution QCs were run in triplicate in any analytical run that contained diluted subject samples.	

The Quality Control and Dilution QC Summaries are found in Table 4 and Table 5, respectively.

Sample Storage Stability	
Maximum Time from Collection to Extraction (Actual)	694 days (including ISRs) 248 days (excluding ISRs)
Demonstrated Storage Stability	175 days at room temperature
Stability Data Reference	(b) (4) R13-057 [12.2]
Samples Collected and Analyzed within Stability Limits	No, see Analytical Notes for discussion

Incurred Sample Reanalysis (ISR)	
Incurred sample reanalysis samples were assayed in singlet in one analytical run.	
Samples Meeting Acceptance Criteria for Acetaminophen	25 out of 33 samples (75.8%)
Incurred Sample Reanalysis was Acceptable for Acetaminophen	Yes

The incurred sample reanalysis results are found in Table 20.

Storage and Handling Temperature (minimum 48 days):

Table 5. Long-Term Stability in Matrix Evaluation Run Summary (Room Temperature)

Run Number	Stability Duration	Preparation Date	Storage Date	Extraction Date	Analysis Date	Analytical Results	Stability Results
(b) (4) S13-057ADD Run 1	104 Days	25-Jul-2013	25-Jul-2013	06-Nov-2013	07-Nov-2013	Accepted	Failed† (QC bias due to matrix)
S13-057ADD Run 2	122 Days	25-Jul-2013	25-Jul-2013	24-Nov-2013	24-Nov-2013	Accepted	Failed† (QC bias due to matrix)
S13-057ADD Run 5	48 Days	22-Nov-2013	22-Nov-2013	09-Jan-2014	09-Jan-2014	Accepted	Passed
S13-057ADD Run 6	88 Days	22-Nov-2013	22-Nov-2013	18-Feb-2014	18-Feb-2014	Accepted	Failed† (Low QC biased high)
S13-057ADD Run 7	89 Days	08-Jan-2014	08-Jan-2014	07-Apr-2014	07-Apr-2014	Rejected†	N/A
S13-057ADD Run 8	89 Days	08-Jan-2014	08-Jan-2014	07-Apr-2014	08-Apr-2014	Accepted	Passed
S13-057ADD Run 9	174 Days	08-Jan-2014	08-Jan-2014	01-Jul-2014	01-Jul-2014	Rejected†	N/A
S13-057ADD Run 10	175 Days	08-Jan-2014	08-Jan-2014	02-Jul-2014	02-Jul-2014	Accepted	Passed

†See Analytical Notes for discussion.

Homogeneity of Sample Spotting:

Table 3. Quality Control Samples (Intra-card DBS Homogeneity) for Acetaminophen

IntraAssay Accuracy and Precision Quality Control Samples

Run Date	Run Number	LLOQ QC 50.0 ng/mL	Low QC 150 ng/mL	Medium QC 1000 ng/mL	High QC 20000 ng/mL
02-Aug-2013	1	47.2	137	917	21800
		***39.6	134	851	20900
		57.8	130	**811	22900
		42.3	**117	**831	21500
		***39.0	153	934	**23500
		45.5	**124	887	20200
Mean		45.2	133	872	21800
SD		6.94	12.3	48.9	1230
%CV		15.4	9.2	5.6	5.6
%Theoretical		90.4	88.7	87.2	109.0
%Bias		-9.6	-11.3	-12.8	9.0
n		6	6	6	6

*** > ±20% deviation from theoretical
** > ±15% deviation from theoretical

Hematocrit:

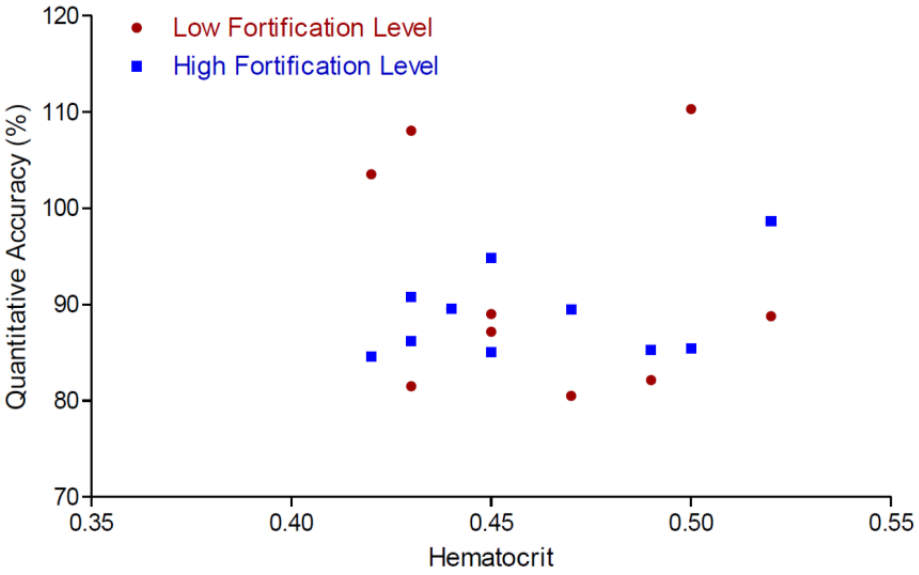
Hematocrit variations were investigated by preparing a whole blood matrix at a low and high hematocrit prior to spotting at three volumes, drying, and subsequent analysis. The low and high hematocrit samples were prepared by allowing whole blood to separate at room temperature for several hours. An aliquot of plasma was removed from the high hematocrit aliquot and added to the low hematocrit aliquot. The two aliquots were then spiked with acetaminophen (1000 ng/mL). Hematocrit levels were determined by spinning an aliquot of blood in a sealed capillary and measuring the percentage of packed cells with a CritSpin digital reader. The highest hematocrit (47%) test sample did not impact the accuracy of the assay at any spot volume investigated (see Table 17.4). The lowest hematocrit (19%) test sample did result in low quantitative values, likely a result of increased spot diffusion resulting in a low volume of blood in the 5 mm punch. However, a hematocrit of less than 20% would be highly unusual as normal hematocrit values are typically between 34 and 50%. The hematocrit range seen within the assessment of assay selectivity ranged from 42 to 52%; hematocrit variations in these samples were not seen to correlate with the performance of the assay as seen in below.

Table 17.4: Acetaminophen Robustness to Hematocrit Levels

Parameter	Hematocrit (38%)								
Variable	19% (-50%)			38%			47% (+23%)		
2nd Variable	30 µL (-40%)	50 µL	70 µL (+40%)	30 µL (-40%)	50 µL	70 µL (+40%)	30 µL (-40%)	50 µL	70 µL (+40%)
Target	1000.00 ng/mL			1000.00 ng/mL			1000.00 ng/mL		
Acceptance Range	850.00 – 1150.00			850.00 – 1150.00			850.00 – 1150.00		
Batch 10	810.09	849.43	816.69	826.90 [1]	966.17	953.66	928.52	969.03	1063.90
	801.82	777.27	795.06	910.40	795.34 [1]	868.59	1014.10	894.79	1087.52
Mean	805.96	813.35	805.88	868.65	880.76	911.13	971.31	931.91	1075.71
Accuracy	80.6% [2]	81.3% [2]	80.6% [2]	86.9%	88.1%	91.1%	97.1%	93.2%	107.6%

1. Value outside of acceptance range; included in summary statistics.
2. Low hematocrit samples are below the acceptance range; experiment fails.

Figure: Lack of correlation between hematocrit and assay accuracy.



Upon further enquiry about use of only mid QC for the hematocrit experiment. The sponsor submitted a justification as follows:

"The validation testing with regard to the impact of hematocrit levels on venous DBS analysis, as reported within "Analysis of Acetaminophen in Human Dried Blood Spots (DBS) via LC-MS/MS Assay Validation", VAL-RPT-1499, was originally performed by (b) (4), and was later transferred to (b) (4) (now part of (b) (4) At the time of the transfer from (b) (4), standard operating procedures (SOPs) governed the transfer. Aligned with the SOPs, the ability of the assay to accurately quantify with the use of varying volumes of extraction solvent was investigated by extracting a mid-QC (1,000 ng/mL), only, and using variable volumes of the solvent (water). This study was not performed with the low (150 ng/mL), nor high (20,000 ng/mL) QC standards. The results of this evaluation showed that hematocrit variations in the samples tested did not correlate with the performance of the assay."

The previously submitted sensitivity analysis with merged dataset, which included studies

CPI-APA-353, and CPI-APA-102, was performed with and without DBS capillary data, and DBS venous data <2,000 ng/mL. The exposure levels in all age groups showed minimal change, and the dose recommendations for the pediatric population study remained the same after removing these data (Sequence 0118).

Therefore, the impact of any potential variability in hematocrit level is not anticipated to result in any significant change with regard to the outcome of the study conclusions, specifically, the critical PK parameters and dose recommendations for the pediatric population studied.

(b) (4) has provided a memo describing the rationale used for the validation testing, as well as the SOPs (CTS-CHROM-SOP-321 Analysis of Acetaminophen in Dried Blood Spots (DBS) via LC-MS/MS, and RD-SOP-002 Bioanalytical Method Validation) in use at the time of the study, which is provided with this response.

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Stability:

Table 14. Spot Drying Stability on Card (1,000 ng/mL)

All results are expressed as instrument response (i.e., analyte area/internal standard area).

Run Date	Run Number	DBS QC 0 Hour (Control)	DBS QC 3 Hour (Protected from Light)	DBS QC 24 Hours (Protected from Light)
06-Aug-2013	2	1.536436	1.241548	1.495579
		1.803626	1.510289	1.472602
		1.641994	1.130196	1.337947
		1.525247	1.561842	1.373715
		1.651491	1.503697	1.359905
		1.623922	1.410440	1.578032
Mean		1.630453	1.393002	1.436297
S.D.		0.101	0.171	0.0942
%CV		6.2	12.3	6.6
%Difference		N/A	-14.6	-11.9
n		6	6	6

Means, standard deviations and %CV were calculated using unrounded data. The %CV and %difference were rounded to one decimal place after completion of the last calculation in the series.

Carryover effect: Sponsor states (Report TSLR13-047)

Analyte carryover was observed in Runs 5 (DBS), 10 (plasma), 21 (DBS) and 24 (DBS) at a level >20% of the lowest acceptable LLOQ standard (Standard 1). A carryover evaluation was conducted on a sample-by-sample basis per SOP and the only study samples shown to have been potentially impacted by carryover were incurred sample reanalysis (ISR) samples. The affected ISR samples were toggled to "not reportable" due to carryover and were not reassayed in subsequent runs (see Non-Calculable ISR samples section below for additional details).

There is no impact on the quality of the data or the integrity of the study.

Reinjection Reproducibility:

Back-Calculated Concentrations of Calibration Standards

All concentrations are expressed as ng/mL.

Run Date	Run Number	50.0	100	250	500	2500	5000	15000	30000
02-Dec-2013	(b) (4) S13-057ADD Run 4	49.1	93.4	278	*399	2530	5030	16000	27800
		49.1	108	260	488	2430	5280	15000	25500
Mean		49.1	101	269	488	2480	5160	15500	26700
S.D.		ISD	ISD	ISD	ISD	ISD	ISD	ISD	ISD
%CV		ISD	ISD	ISD	ISD	ISD	ISD	ISD	ISD
%Bias		-1.8	1.0	7.6	-2.4	-0.8	3.2	3.3	-11.0
n		2	2	2	1	2	2	2	2

* Standard calibrator outside acceptance criteria and excluded from regression
ISD = Insufficient data points for statistical calculations

Table 12. Reinjection Reproducibility for Acetaminophen (202 Hours at 5 °C) [Continued]

Analytical QC Summary

Run Date	Run Number	Low QC 150 ng/mL	Medium QC 1000 ng/mL	High QC 20000 ng/mL
02-Dec-2013	(b) (4) S13-057ADD Run 4	154	**1170	21700
		156	1040	21800
		**184	987	21900
		**174	1020	22600
		165	1030	21900
		162	1020	20500
Mean		166	1040	21700
S.D.		11.4	64.0	683
%CV		6.9	6.2	3.1
%Theoretical		110.7	104.0	108.5
%Bias		10.7	4.0	8.5
n		6	6	6

** > ±15% deviation from theoretical

Incurred Sample Reanalysis (Report TSLR13-047):

During incurred sample reanalysis (ISR), one dried blood spot (DBS) sample (Subject 011008, Custom ID CT000544409, Day 7, 7 Hrs) demonstrated a relative percent difference of >50% when compared to its original result. The raw data and analysis history were reviewed, and there were no documented analytical issues or significant analytical abnormalities in either the original or ISR run to explain the observed difference.

The overall DBS ISR results still met the acceptance criteria with a passing rate of >75% and no impact is expected on the quality of the data or the integrity of the study.

In PK Study MNK14501041 (Also described below), plasma concentrations of acetaminophen from healthy volunteers were determined from blood samples by the following three methods:

1. Whole venous blood (6 mL) was collected by venipuncture in pre-chilled vacuum blood collection tube containing Na heparin as the anticoagulant.
2. Once the whole venous blood was collected, a small amount of the blood was taken from the collection tube and spotted on a dried blood spot card (minimum of 5 spots).
3. Capillary blood was collected by finger pricks and spotted on a dried blood spot card (minimum of 5 spots).

Samples were analyzed from plasma samples (Method 1 and 2 described above) or dried blood spotted on paper (Method 3 described above). All methods used liquid chromatography/tandem mass spectrometry (LC-MS/MS) assays. The methods have been validated over a calibration range of 50 to 30,000 ng/mL for APAP, using 0.05 mL of plasma (venous) samples and 5 mm dried blood discs from 0.05 mL of the venous and capillary dried blood samples, respectively. The methods use a protein-precipitation extraction procedure followed by chromatographic separation and MS/MS detection of the analyte.

A summary of the bioanalytical method for analysis of acetaminophen in plasma was conducted as described in the assay validation report; "Quantitative Determination of Acetaminophen in Human Plasma (Heparin) by LC/MS/MS" (b) (4) study number (b) (4) S13-056.

Table: Bioanalytical method validation summary – Plasma analysis.

Information Requested	Data
Bioanalytical method validation report location	(b) (4) validation report VAL-RPT-810
Analyte	Acetaminophen
Internal standard	Acetaminophen-d_4
Method description	Protein-precipitation extraction
Limit of quantitation	50.0 ng/mL
Average recovery of drug (%)	82.8 (Low), 85.3 (Medium), 80.4 (High)
Average recovery of internal standard (%)	88.2
Standard curve concentrations (ng/mL)	50.0; 100; 250; 500; 2,500; 5,000; 15,000 and 30,000
QC concentrations (ng/mL)	50.0, 150, 400, 1,000, and 20,000
QC Intraday precision range (%)	Insufficient data
QC Intraday accuracy range (%)	-5.7 to 4.0
QC Interday precision range (%)	0.5 to 3.5
QC Interday accuracy range (%)	-4.7 to 4.0
Bench-top stability (hours)	24 hours in water: methanol (50:50 v/v) stored at room temperature
Stock stability (days)	651 days in water: methanol stored at 4 °C
Processed stability (hours)	4 days at 10°C
Freeze-thaw stability (cycles)	3 cycles; stored at -70 °C and thawed at room temperature
Long-term storage stability (days)	13 days at -20°C, 592 days at -70°C
Dilution integrity	80,000 ng/mL (dilution factor = 10)
Selectivity	No interfering peaks noted in blank plasma samples.

Source: (b) (4) Assay Validation Report (b) (4) R13-056.

A summary of the bioanalytical method for analysis of acetaminophen in dried blood was conducted as described in the draft assay validation report; "Quantitative Determination of Acetaminophen in Human Dried Blood Spot (Heparin) by LC/MS/MS" [(b) (4)] study number [(b) (4)]S13-057.

Table: Bioanalytical method validation summary – Acetaminophen in Blood spotted paper.

Information Requested	Data
Bioanalytical method validation report location	[(b) (4)] validation report VAL-RPT-810
Analyte	Acetaminophen
Internal standard	Acetaminophen-d_4
Method description	Protein-precipitation extraction
Limit of quantitation	50.0 ng/mL
Standard curve concentrations (ng/mL)	50.0; 100; 250; 500; 2,500; 5,000; 15,000 and 30,000
QC concentrations (ng/mL)	50.0, 150, 1,000, and 20,000
QC Intraday precision range (%)	Insufficient data
QC Intraday accuracy range (%)	-6.4 to 8.0
QC Interday precision range (%)	2.7 to 10.3
QC Interday accuracy range (%)	-9.4 to 8.7
Extract stability (hours)	73 hours at 5 °C
Long-term storage stability (days)	175 days at room temperature
Dilution integrity	50,000 ng/mL (dilution factor = 10)

Source: [(b) (4)] Draft Assay Validation Report [(b) (4)] R13-057.

3.2 Crossvalidation of bioanalytical data between plasma, venous DBS, and capillary DBS.

Synopsis of PK study MNK14501041:

Study Title: A Single-Dose, Open-Label Study Comparing the Plasma Acetaminophen Concentrations With Blood Samples Collected at the Same Time With Different Blood Drawing Routes and Collection Methods in Healthy Subjects.

This was an open-label, single dose, single center study in healthy subjects. Following a 14 day screening period, subjects checked-in to the study site the evening prior to study drug treatment. Subjects received a single 100 mL infusion of 1,000 mg of IV acetaminophen infused over 15 minutes. Blood samples were collected before, and for up to 12 hours after dosing. At each collection time point, 3 types of blood collection methods were used simultaneously.

Three types of blood samples were collected:

1. Whole venous blood (6 mL) was collected by venipuncture in a pre-chilled vacuum blood collection tube containing sodium heparin as the anticoagulant.
2. Once the whole venous blood is collected into the 6 mL vacuum blood collection tube (from above), a small amount of the blood was taken from the collection tube and spotted on a dried blood spot card (minimum of 5 spots).
3. Capillary blood was collected by finger pricks and spotted on a dried blood spot card (minimum of 5 spots).

Samples were analyzed from plasma samples (Method 1 and 2 described above) or dried blood spotted on paper (Method 3 described above). Both methods used liquid chromatography/ tandem mass spectrometry (LC-MS/MS) assays. The sponsor mentions that only plasma and whole blood concentration of acetaminophen from samples collected in the first 4 hours were considered of interest. This cross-validation study that compares blood sampling routes and collection methods is to support the OFIRMEV pediatric study (Study Protocol CPI-APA-353). In study CPI-APA-353 multiple doses of acetaminophen were administered every 6 hours.

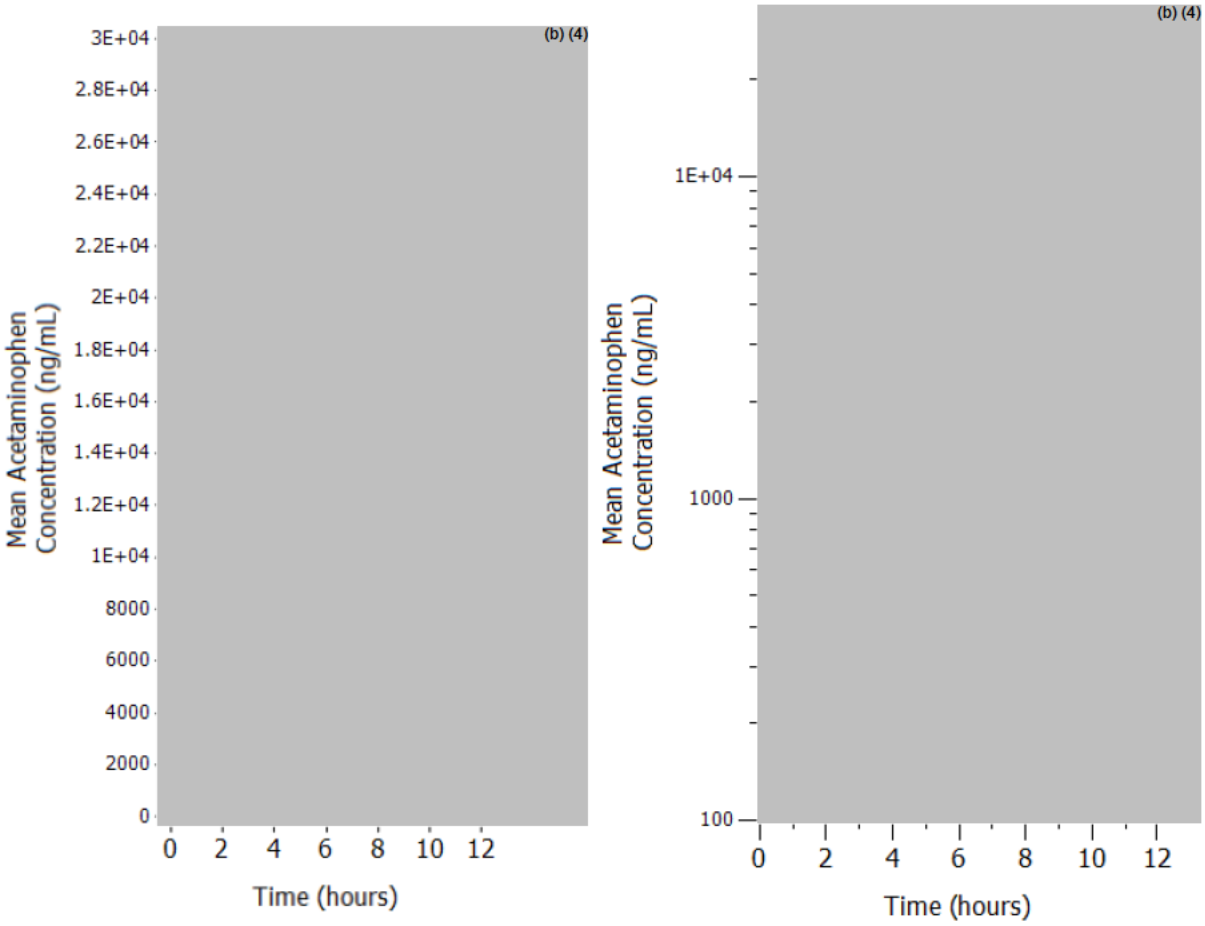
Table: Summary of Plasma or Whole Blood Concentration of IV Acetaminophen (ng/mL) by Blood Drawing Route and Collection Method.

		Sample 1 Venous Plasma (ng/mL)		Sample 2 Venous DBS (ng/mL)		Sample 3 Capillary DBS (ng/mL)	
Time	N	Mean	SD	Mean	SD	Mean	SD
0	14	0	0	0	0	(b) (4)	
0.25	14	23438.5	5857.9	26408.3	5904.9		
0.5	14	17878.6	5370.9	19464.3	5778		
0.75	14	14457.1	4614.8	15617.9	5425.1		
1	14	12505	4022.1	13713.6	4757		
1.5	14	10108.6	3459.6	10458.6	3966.6		
2	14	8357.1	3105.6	8498.6	3488.1		
3	14	5969.3	2268.6	5341.4	2335.2		
4	14	4120	1674.05	3557.1	1535.6		
7	14	1642.7	831.6	1147.5	574.9		
9	14	983.3	569.2	642.5	389.1		
12	14	560.5	383.4	378	280.04		

Source: Recreated from the datafile using n=14 subject data.

It was observed in individuals that the bioanalytical data with venous DBS was similar with plasma acetaminophen up to 2000 ng/mL. After that the PK profile was showing significant difference (see figure below). Hence, venous DBS crossvalidation data was accepted upto 2000 ng/mL concentration of acetaminophen. Note: Even though the average acetaminophen profile shows separation prior to 2000 ng/mL, it majority of individual profiles, out of n=14, the underestimation with venous DBS was noted below 2000 ng/mL. Capillary DBS data consistently underestimated acetaminophen concentration compared to plasma data as shown in the figure below and in each individual profile (not shown). Therefore, the crossvalidation of capillary DBS method with plasma is not established.

Figure: Linear and logarithmic profile of acetaminophen concentration vs. time profile with 2000 ng/mL indicated as a horizontal line.

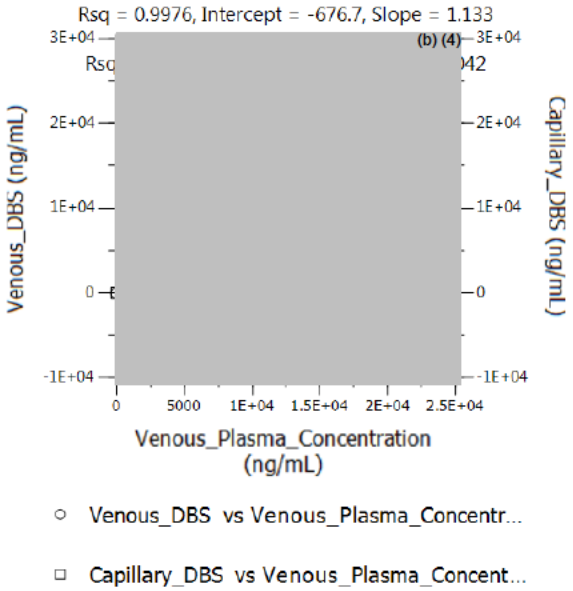


Individual data plots and linear regression comparing venous plasma (Sample method 1) to venous DBS (sample method 2) and capillary DBS (sample method 3) revealed significant correlation as noted with r^2 being close to 1 and slope close to 1 with exceptions noted in the Table below (Also see individual Correlation plots appended to the review).

Table: Linear Regression slope and r^2 for venous DBS and capillary DBS compared to reference venous plasma concentrations.

	Venous Plasma vs. Venous DBS			Venous Plasma vs. Capillary DBS
Subject	**Slope**	**SE**	**r^2**	(b) (4)
1	1.03	0.02	1	
2	1.06	0.02	0.98	
3	1.07	0.03	0.97	
4	0.98	0.05	1	
5	1.14	0.02	0.99	
6	1.25	0.03	0.99	
7	**1.47**	0.14	0.94	
8	1.13	0.04	0.99	
9	1.17	0.04	0.95	
10	1.18	0.03	0.89	
11	1.21	0.03	0.91	
12	1.21	0.05	0.97	
13	1.15	0.02	0.98	
14	1.2	0.04	0.95	

Figure: Correlation of Venous DBS (left Y-axis) and Capillary DBS (right Y-axis) with plasma acetaminophen.



In the current study a single-dose of acetaminophen was administered to all healthy adult subjects. Therefore the sponsor indicates that only relevant acetaminophen concentrations from the current study that can be used to support Study CPI-APA-353 are time points less than 6 hours. In study CPI-APA-353 only samples collected at Hours 0, 0.5, and 2 after the first acetaminophen dose were used (because of the limitation for the pediatric population), the current study included sample collection time points at Hours 0.25, 0.75, 1, 3, 4, 7, 9, and 12.

Table: Summary of Plasma or Whole Blood PK Parameters of IV Acetaminophen (ng/mL) by Blood Drawing Route and Collection Method.

		Sample 1 Venous Plasma		Sample 2 Venous DBS		Sample 3 Capillary DBS (b) (4)
Variable	N	Mean	SD	Mean	SD	
AUCall (ng.h/mL)	14	51355.7	17330.4	49102.5	16684	
AUCINF (ng.h/mL)	14	53612.4	18646.1	50366.4	17399	
AUClast (ng.h/mL)	14	51355.8	17330.5	49102.6	16684	
Cmax (ng/mL)	14	23635.7	5676.3	26092.9	5773	
Kel (per hr)	14	0.272	0.052	0.339	0.069	
Tmax* (hr)	14	0.25	(0.25 - 0.75)	0.25	(0.25 - 0.75)	

*- Tmax is indicated as mean and range. Source: Recreated from the datafile using n=14.

Peak plasma concentrations of acetaminophen were noted at the end of the 15 minute infusion. Bioequivalence analysis revealed that estimates of Cmax for acetaminophen were bioequivalent for venous (Sample 2 method) and capillary blood collected and spotted on blood spot cards (Sample 3 method) when compared with venous blood collected in tubes (Sample 1 method).

Table: Statistical analysis (Bioequivalence) comparing PK parameters of acetaminophen estimated using different bioanalytical methods.

	Reference	**Test: Capillary DBS** (b) (4)	**Test: Venous DBS**			
Parameter	**Venous Plasma/GeoLSM**		**GeoLSM**	**Ratio %Ref**	**90% CI Lower & Upper**	
Cmax	23049		25514	110.70	99.70	122.90
AUCall	48800		46693	95.68	92.52	98.95
AUClast	48800		46693	95.68	92.52	98.95
AUCInf	50786		47806	94.13	90.91	97.47
AUC0-0.25	2742		2884	105.19	89.56	123.54
AUC0-0.5	7675		8272	107.77	96.66	120.16
AUC0-0.75	11614		12599	108.48	100.93	116.58
AUC0-1	14876		16153	108.59	102.59	114.94
AUC0-1.5	20307		21945	108.07	103.18	113.18
AUC0-2	24706		26435	107.00	102.53	111.67
AUC0-3	31488		32938	104.61	100.63	108.74
AUC0-4	36233		37099	102.39	98.66	106.26
AUC0-7	44293		43661	98.57	95.22	102.04
AUC0-9	46704		45304	97.00	93.77	100.35
AUC0-12	48800		46693	95.68	92.52	98.95

Source: Reanalysis including all 14 subject data. Cmax units ng/mL, AUC units ng.h/mL.

While most partial AUC's up to 4 hours were bioequivalent, partial AUCs after 7, 9, and 12 hours and overall AUC failed bioequivalence for capillary blood collected and spotted on blood spot cards (Sample 3 method) when compared with venous blood collected in tubes (Sample 1 method) (See Table below).

Conclusion:

The PK study evaluated the PK profile of acetaminophen using standard venous plasma analysis (method 1), and compared it to methods (crossvalidation) including venous blood spotted on cards (method 2) and capillary sample spotted on cards (method 3).

In addition to validation of the individual methods 1, 2 and 3, which appear to be adequately validated, cross-validation to standard venous plasma concentrations was also attempted in PK study MNK14501041.

The venous DBS sampling method employed in this study produced similar exposure parameters above 2000 ng/mL plasma concentration (Cmax, and partial AUC's) of the PK profile. However, overall exposure (e.g. AUCall, AUCinf) were not predicted well by the capillary DBS method. A consistent underestimation of plasma concentration was noticed with capillary DBS for most samples in the crossvalidation study. (b) (4).

The crossvalidation of the acetaminophen plasma analysis with venous DBS was discussed at the Office of Clinical Pharmacology Senior Leadership Team meeting on 10/25/2016. The peer group agreed with the above recommendations and review plan.

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3.3 Population PK/PD Analyses

The purpose of the PK analysis was to characterize the pharmacokinetics of IV acetaminophen in pediatric patients less than 2 years of age and determine a dose in this population which would achieve plasma concentrations similar to those achieved in older children (≥ 2 years of age) and adults at the approved doses. In the Pediatric Written Request the Applicant was also asked to provide further support for the proposed dose by exploring the relationship between exposure and pharmacodynamic endpoints such as analgesic effects and time to use of rescue medications and safety endpoints such as major adverse events.

3.3.1 Population PK Analysis

During the course of the review there was a considerable amount of exchange between the review team and the Applicant regarding the population PK analysis, most of which was focused on the appropriate set of data to be used for the analysis. In the original submission the Sponsor only included data from the new study (CPI-APA-353). The following review will primarily focus on the results of the modeling using the data requested by FDA and as reported in the response to information request dated November 4, 2016.

3.3.1.1 Applicant's Analysis

Data

Data used for population PK analysis were obtained from studies CPI-APA-353 and CPI-APA-102. The analysis excluded venous DBS samples from CPI-APA-353 with concentrations less than 2,000 ng/mL and all capillary DBS samples. (b) (4)

CPI-APA-102

Study CPI-APA-102 has been described in Dr. Ji's previous review and was used to support the current dosing of Ofirmev in pediatric patients ≥ 2 years of age. Briefly, CPI-APA-102 was a randomized, open-label study in infants, children and adolescents requiring analgesic or antipyretic therapy. Subjects were randomized to one of two dosing regimens within each age strata: 12.5 mg/kg q6h or 15 mg/kg q8h in neonates and 12.5 mg/kg q4h or 15 mg/kg q6h in infants, children, and adolescents. The study enrolled 3 neonates (≤ 28 days), 25 infants (29 days to < 24 months), 25 children (2 to < 12 years), and 22 adolescents (12 to ≤ 16 years). Blood samples for measurement of acetaminophen concentrations were collected following the first and last doses of IV acetaminophen and at several time points in-between.

CPI-APA-353

Study CPI-APA-353 was a randomized, double-blind, placebo-controlled study to evaluate efficacy, safety, PK and PK/PD of IV acetaminophen administered every 6 hours added on to standard of care therapy with an opioid for the treatment of acute pain in pediatric patients less than two years of age. Subjects were randomly assigned to one of two IV acetaminophen dosing groups plus standard of care rescue opioids and two control groups with standard of care only. The study enrolled 215 patients from ≥28 weeks gestational age at birth to < 2 years old categorized by the following age groups:

- Neonates: Birth (≥ 28 weeks gestational age to ≤ 40 weeks gestational age) to < 28 days chorological age
- Younger infants: ≥ 29 days to < 6 months
- Intermediate infants: ≥ 6 months to < 12 months

- Older infants: 12 months to < 24 months

A total of 114 patients treated with IV acetaminophen were available for PK analysis as summarized in Table 1:

Table 1: Distribution of PK Evaluable Patients by Dose Group

Age Group	Dose Group	Number
Neonates	10 mg/kg	11
	12.5 mg/kg	7
Younger Infants	12.5 mg/kg	15
	15 mg/kg	19
Intermediate Infants	12.5 mg/kg	14
	15 mg/kg	17
Older Infants	12.5 mg/kg	13
	15 mg/kg	18

PK assessments were collected in all subjects receiving IV acetaminophen and a subset of subjects receiving placebo. Sample times were pre-dose on Day 1, 0.5 and 2 hours after the first dose and 1 and 6 hours after the start of the second dose. IV acetaminophen doses were delivered over 15 minutes. The total number of subjects (active or placebo group) with reported PK data was 186. Of this total, 27 subjects were excluded because they did not have measurable acetaminophen concentrations after the first dose. One subject (#6105) was also removed because an unexpectedly high dose was reported. The number of remaining subjects in the analysis was 158.

Structural Pharmacokinetic Model

The structure of the PK model was borrowed from the previous analysis (see Dr. Ji's review). Specifically, acetaminophen concentrations were described by a two compartment model with linear elimination, allometric scaling of PK parameters, and an effect of post-menstrual age (PMA) on clearance (CL). The model was parameterized in terms of CL, volume of distribution of the central compartment (Vc) and peripheral compartment (Vp) and inter-compartmental clearance (Q). The effect of size and age were incorporated according to the following maturation model:

(b) (4)

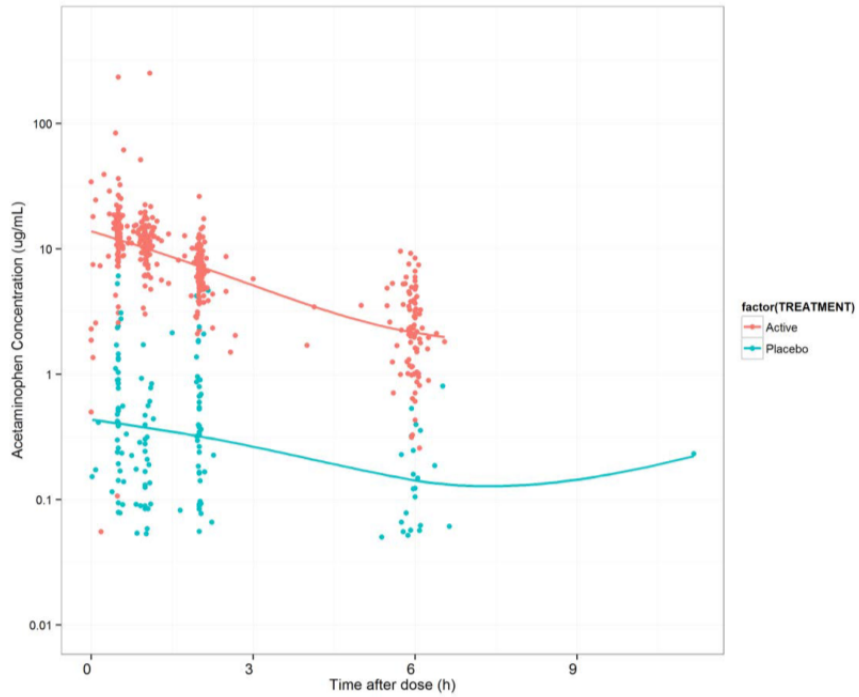
Where CLj is the individual systemic clearance, CLx is the population clearance for a 70 kg patient, θx^{age} is a constant describing age-related changes in systemic clearance, Tx is the maturation half-life of age-related change in clearance in weeks and PMAj is the post-menstrual age in weeks. CL and Vc were assumed to be lognormally distributed. The residual error was modeled assuming a mixed (additive and proportional component). Analysis was performed using NONMEM version VI.

Non-BLQ Acetaminophen Concentrations Pre-Dose

The Applicant reports that a total of 115 non-BLQ concentrations were observed pre-dose due to concomitant administration of other products containing acetaminophen and that up to 44 subjects in

the placebo group had non-BLQ concentrations of acetaminophen. To handle non-BLQ concentrations at pre-dose, the observed concentration was converted to total amount of acetaminophen by multiplying it by the volume of distribution at steady-state (Vss) and subsequently modeled as an IV bolus at the observed sampling time. Vss was derived from population predicted Vc and Vp from the previous analysis. The presence of acetaminophen in placebo-treated patients is illustrated in Figure 3 .

Figure 3: Concentration Time Profile of Acetaminophen in Treatment and Placebo Groups.



Source: MALL-PCS-100, Figure 3, Page 35.

Covariate Analysis

The Applicant explored the following covariates: arm (placebo versus active groups) on CL, age in weeks on CL and matrices (capillary vs blood/plasma) on Vc.

Final Model

The parameter estimates of the final model are displayed in Table 2. Notable aspects of the final model include the following:

- The maturation half-life parameter (Tx) was fixed to the value derived from the previous analysis [redacted] (b) (4). The other maturation parameter (θx^{age}), however, was estimated from the current dataset and its value is approximately 20% lower than the estimate from the previous analysis.
- The model estimates a lower clearance (~50%) of acetaminophen in the placebo arm. The Applicant claims that this finding might be due to "the assumption used to derive the dosing history of acetaminophen-containing products."

Table 2: Population PK Parameter Estimates of Acetaminophen

Parameter	Typical values	BSV
CL (L/h)	(b) (4)	34.2%
Placebo on CL		
Vc (L)		86.0%
CLp (L/h)		-
Vp (L)		-
Residual Error		
Proportional Error	38.5%	

BSV=between subject variability; CL=systemic clearance; CLp=inter-compartmental clearance; PMA=post-menstrual age; PK=pharmacokinetic data; Vc=volume of distribution of the central compartments; Vp=volume of distribution of the peripheral compartment; WT=body weight

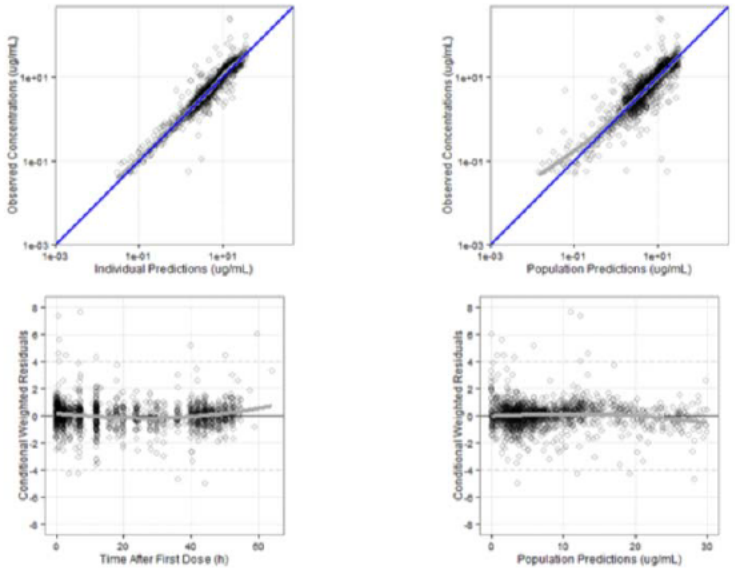
Note: the correlation between BSV of CL, and BSV of Vc was 61.7%

*=fixed at previous values; Shrinkage=17.4% CL and 30.1% Vc

Source: Response to Information Request dated November 4, 2016, Table1.11.3-3, Page 4.

Basic goodness of fit plots are provided in Figure 4 (below).

Figure 4: Goodness of Fit Plots of Final Acetaminophen Model



Source: Response to Information Request dated November 4, 2016, Figure 1.11.3-1, Page 5.

The Applicant reported PK parameters (Table 3) and exposure levels (Table 4) for pediatric patients in CPI-APA-353 based on primary and secondary posthoc parameters derived from the population pharmacokinetic analysis. These parameters were compared to those calculated via noncompartmental analysis with data from a healthy adult population enrolled in Study CPI-APA-101. The Applicant proposes to report the numbers from Table 3 and Table 4 in Section 12 of the label.

Table 3: Descriptive Statistics of PK Parameters of Acetaminophen in Pediatric Patients (CPI-APA-353) and Healthy Adult Volunteers (CPI-APA-101)

Subpopulations N	Mean (SD) Median [Minimum - Maximum]				
	$T_{1/2\beta}$ (h)	CL (L/h/kg)	CL (L/h)	Vss (L/kg)	Vss (L)
Extreme Pre-Term Neonates (N=2)	3.264(0.2599) 3.26 [3.08-3.45]	0.1921(0.02314) 0.192 [0.176-0.208]	0.2377(0.01184) 0.238 [0.229-0.246]	0.8485(0.03485) 0.848 [0.824-0.873]	1.057(0.1364) 1.06 [0.960-1.15]
Pre-Term Neonates (N=2)	3.233(0.7311) 3.23 [2.72-3.75]	0.2201(0.08005) 0.220 [0.163-0.277]	0.4647(0.1254) 0.465 [0.376-0.553]	0.9217(0.1274) 0.922 [0.832-1.01]	1.968(0.07839) 1.97 [1.91-2.02]
Full-Term Neonates (N=14)	3.915(2.603) 3.38 [2.37-14.2]	0.2231(0.04910) 0.217 [0.138-0.311]	0.6991(0.2957) 0.673 [0.229-1.28]	1.253(1.281) 0.916 [0.794-6.36]	4.219(5.567) 2.94 [0.960-26.1]
Younger Infants (N=34)	2.774(1.204) 2.71 [1.56-9.06]	0.3140(0.08617) 0.299 [0.185-0.522]	1.723(0.6719) 1.58 [0.659-3.60]	1.139(0.7517) 0.948 [0.758-5.13]	6.131(4.148) 5.65 [2.51-27.7]
Intermediate Infants (N=31)	2.345(0.5994) 2.29 [1.37-4.11]	0.3568(0.1109) 0.336 [0.152-0.633]	3.009(1.218) 2.46 [1.20-6.00]	0.9941(0.2012) 0.926 [0.833-1.93]	8.339(2.571) 7.50 [5.07-16.2]
Older Infants (N=31)	2.214(0.5574) 2.15 [1.44-4.09]	0.4036(0.09914) 0.368 [0.252-0.664]	4.108(1.140) 3.83 [2.61-7.78]	1.128(0.5686) 0.952 [0.878-3.27]	11.66(7.020) 9.66 [7.78-44.9]
Adults (N=34)	2.391(0.5708) 2.33 [1.72-4.50]	0.2678(0.08236) 0.275 [0.128-0.598]	20.80(5.808) 20.6 [9.24-33.3]	0.8330(0.2238) 0.798 [0.343-1.87]	64.31(12.55) 63.0 [28.0-103]

CL = Systemic clearance; SD = Standard deviation; $T_{½\beta}$ = Terminal elimination half-life; Vss = Total volume of distribution in steady-state

Source: MALL-PCS-101, Table 2, Page 12.

Table 4: Descriptive Statistics of Acetaminophen Exposure Levels Following the First IV Dose in Pediatric Patients (CPI-APA-353) and Healthy Adult Volunteers (CPI-APA-101)

Subpopulations N	Mean (SD) Median [Minimum - Maximum]			
	Low Dose Levels		High Dose Levels	
	C_{max} (µg/mL)	AUC_{τ} (µg×h/mL)	C_{max} (µg/mL)	AUC_{τ} (µg×h/mL)
Extreme Pre-Term Neonates High (10 mg/kg): N=2	NA	NA	20.19(6.259) 21.2 [4.37-30.9]	27.70(8.092) 27.2 [14.1-46.3]
Pre-Term Neonates High (12.5 mg/kg): N=2	NA	NA	22.82(6.629) 22.8 [18.1-27.5]	43.24(11.56) 43.2 [35.1-51.4]
Full-Term Neonates Low (10.0 mg/kg): N=9 High (12.5 mg/kg): N=5	18.13(4.330) 18.3 [10.5-25.2]	36.97(8.325) 34.3 [28.9-54.6]	19.64(11.66) 22.6 [3.52-32.4]	41.77(22.27) 44.6 [10.5-69.4]
Younger Infants Low (12.5 mg/kg): N=15 High (15.0 mg/kg): N=19	23.50(7.144) 21.6 [11.3-38.6]	37.02(10.43) 34.8 [22.2-50.5]	24.69(9.466) 26.7 [3.17-44.2]	41.65(13.82) 41.2 [13.8-73.9]
Intermediate Infants Low (12.5 mg/kg): N=14 High (15.0 mg/kg): N=17	20.76(4.343) 20.8 [8.17-26.2]	30.19(6.329) 30.0 [19.2-41.1]	30.01(9.201) 29.1 [16.1-53.7]	45.52(19.81) 41.6 [23.2-105]
Older Infants Low (12.5 mg/kg): N=13 High (15.0 mg/kg): N=18	20.19(6.259) 21.2 [4.37-30.9]	27.70(8.092) 27.2 [14.1-46.3]	27.07(6.838) 27.9 [5.49-41.4]	38.76(10.87) 38.7 [17.1-68.8]
Adults N=34 at 1000 mg q6h	NA	NA	28.39(21.17) 24.7 [11.8-139]	42.48(10.65) 40.5 [25.5-72.4]

AUC_{τ} = Area under the concentration time curve; C_{max} = Maximum concentration, N= Number of subjects; NA= Not applicable; SD = Standard deviation

Source: MALL-PCS-101, Table 3, Page 15.

Finally, simulations were performed by resampling demographic parameters from CPI-APA-102, (b) (4) and CPI-APA-353 and predicting individual plasma concentrations of acetaminophen on Day 1 and Day 5 for selected dose levels (MALL-PCS-101a). Results were again compared to adult values from CPI-APA-101. The Applicant concluded that "exposure levels in all subgroups of neonates at 12.5 mg/kg were slightly lower than the exposure levels in adults at 1000 mg q6h with difference of AUCτ median between 0% and 7% and C_{max} medians between 7% and 15%. Exposure levels in all subgroups of infants at 15 mg/kg were slightly lower than the exposure levels in adults at 1000 mg q6h with difference of AUCτ median between 2.7% and 27% and C_{max} medians between 7% and 31%."

Reviewer's Comments: The Applicant's approach to population PK analysis is reasonable and generally consistent with the approach used in a previous submission (see Dr. Ji's review). There are, however, several aspects of the current analysis which raise concern:

- (b) (4)
- *Pre-dose concentrations of acetaminophen were observed in a rather large number of placebo patients. Even though these levels were relatively low, their impact on parameter estimates is not fully understood. For example, it is not clear why placebo patients would have a clearance value that is roughly half that of patients receiving active treatment. One would expect the clearance of acetaminophen to be independent of treatment group assignment. The Applicant's suggestion that this may be due to, "the assumption used to derive the dosing history of acetaminophen-containing products" may be correct but it would suggest that the assumption needs to be revised.*
- *The reviewers identified errors in the Applicant's datasets throughout the review cycle. In the November 4 response to information request the Applicant noted that an incorrect interim version of a NONMEM dataset was provided to the Agency (sequence 0094) and that the define.pdf file in sequence 0115 included errors. In the Applicant's submission of the final model/dataset on November 16 (sequence 0118) there was another error in the dataset (pkdatasetlim3.xpt). For study CPI-APA-102, the RATE item in the dataset had incorrect units. Attempts were made by the review team to address all of the known inconsistencies.*

(b) (4)

3.3.1.2 Reviewer's Analysis

Given the concerns regarding the population PK analysis, the reviewer performed a graphical analysis to qualitatively compare the exposures in CPI-APA-353 at the Applicant's proposed doses to exposures in adults and older children at the approved doses.

Data
Data used for the analysis were obtained from studies CPI-APA-353, CPI-APA-102 and CPI-APA-101. Studies CPI-APA-353 and CPI-APA-102 were described above.

CPI-APA-101

This study was an open-label, randomized, crossover PK study comparing oral and IV acetaminophen in healthy volunteers. For the purposed of the comparison, only the 34 adults who received IV acetaminophen q6h for 48 hours were included in the analysis. Blood samples were drawn 0, 0.25, 0.5, 0.75, 1, 2, 4, 6, 12, 18, 24, 30, 36, 42, 42.25, 42.5, 42.75, 43, 44, 46 and 48 hours following the first dose administration. For the purposes of comparison the concentrations after the 1st and 4th dose were both used. Data were summarized as median, 5th and 95th percentiles at the nominal PK collection times.

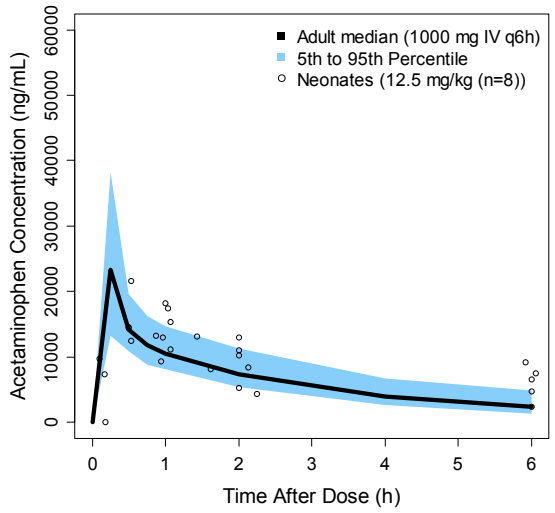
CPI-APA-353
A brief description of the study design was provided earlier in the review. For the purposes of this analysis, only acetaminophen concentrations in patients receiving the Applicant's proposed doses (i.e., 12.5 mg/kg in neonates and 15 mg/kg in infants) are included in the plots. Time is characterized as time after the last dose.

CPI-APA-102
A brief description of the study design was provided earlier in the review. For the purposes of this analysis, only children 2 years of age and older receiving the approved dose (15 mg/kg q6h) were included. Time is characterized as time after last dose. Because of the sparse nature of PK samples, median and percentile were not calculated. For comparison, the data from CPI-APA-102 is simply overlaid with the data from CPI-APA-353.

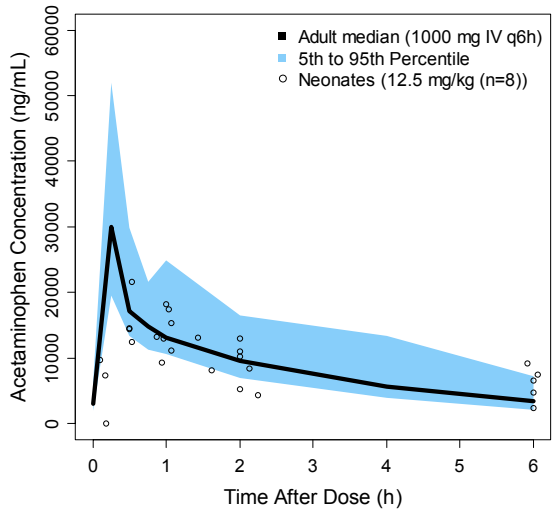
Results

Comparisons between acetaminophen concentrations in neonates and infants at the proposed dose levels (12.5 mg/kg in neonates and 15 mg/kg in infants) and adults at the approved dosing regimen are illustrated in Figure 5 to Figure 8. The comparison of pediatric data at any dose is made to adult data after both the first and fourth doses. Note that the 5th to 95th percentile of the adult data is likely to be a conservative estimate because it is derived from a PK study in homogeneous population of healthy volunteers. It can be concluded that acetaminophen concentrations in neonates and infants following the proposed doses are generally consistent with concentrations observed in adults following the approved dose of 1000 mg q6h.

Figure 5: Comparison of Acetaminophen Concentrations in Neonates Receiving 12.5 mg/kg (CPI-APA-353) and Healthy Adult Volunteers Receiving 1000 mg (CPI-APA-101) after the First Dose (Left) and Fourth Dose (Right).

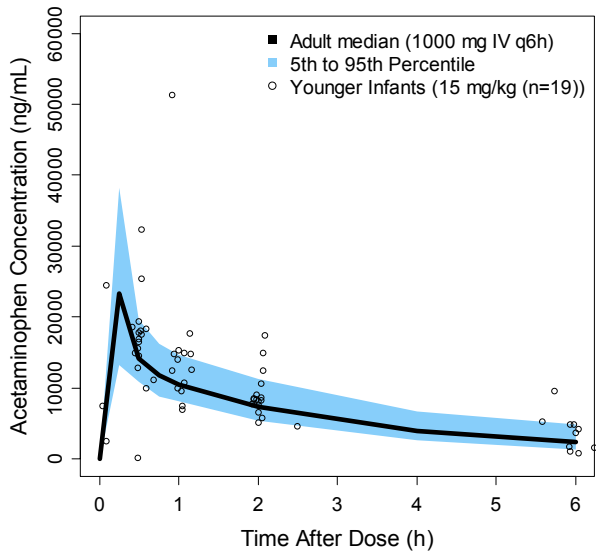


1st Dose

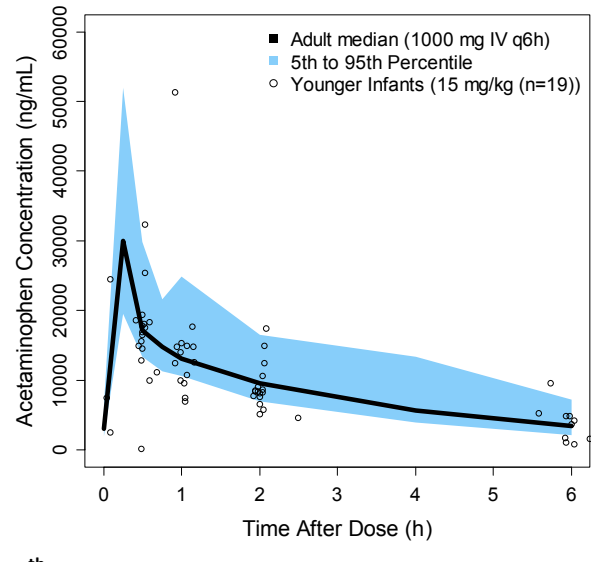


4th Dose

Figure 6: Comparison of Acetaminophen Concentrations in Younger Infants Receiving 15 mg/kg (CPI-APA-353) and Healthy Adult Volunteers Receiving 1000 mg (CPI-APA-101) after the First Dose (Left) and Fourth Dose (Right). *Excludes one outlier with concentration > 80000 ng/mL

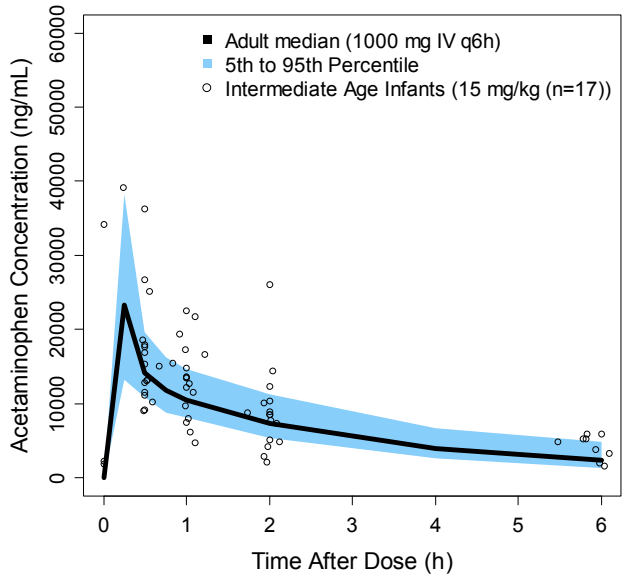


1st Dose

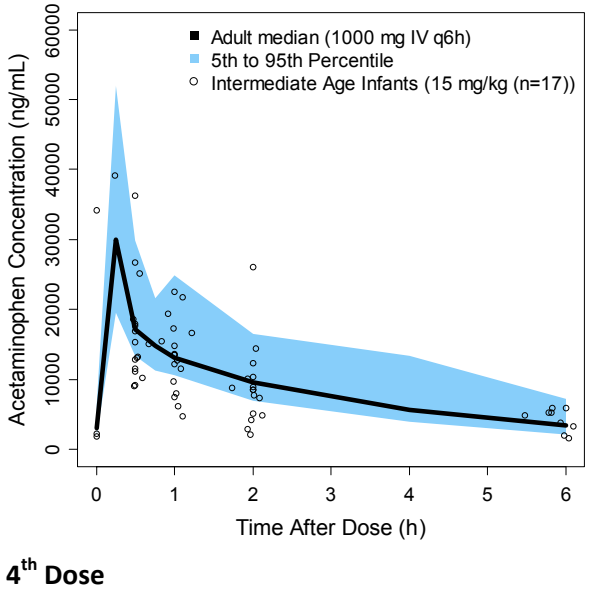


4th Dose

Figure 7: Comparison of Acetaminophen Concentrations in Intermediate Infants Receiving 15 mg/kg (CPI-APA-353) and Healthy Adult Volunteers Receiving 1000 mg (CPI-APA-101) after the First Dose (Left) and Fourth Dose (Right).

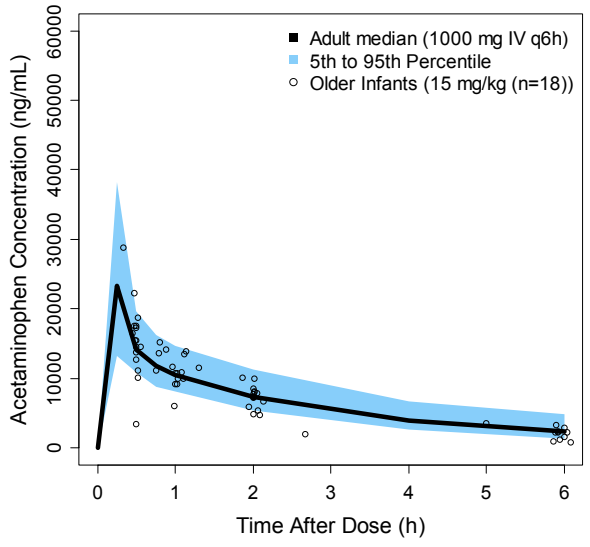


1st Dose

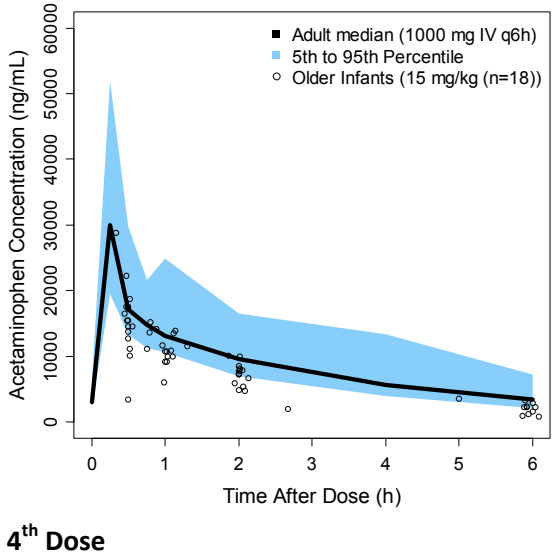


4th Dose

Figure 8: Comparison of Acetaminophen Concentrations in Older Infants Receiving 15 mg/kg (CPI-APA-353) and Healthy Adult Volunteers Receiving 1000 mg (CPI-APA-101) after the First Dose (Left) and Fourth Dose (Right). *Excludes one outlier with concentration > 200000 ng/mL



1st Dose

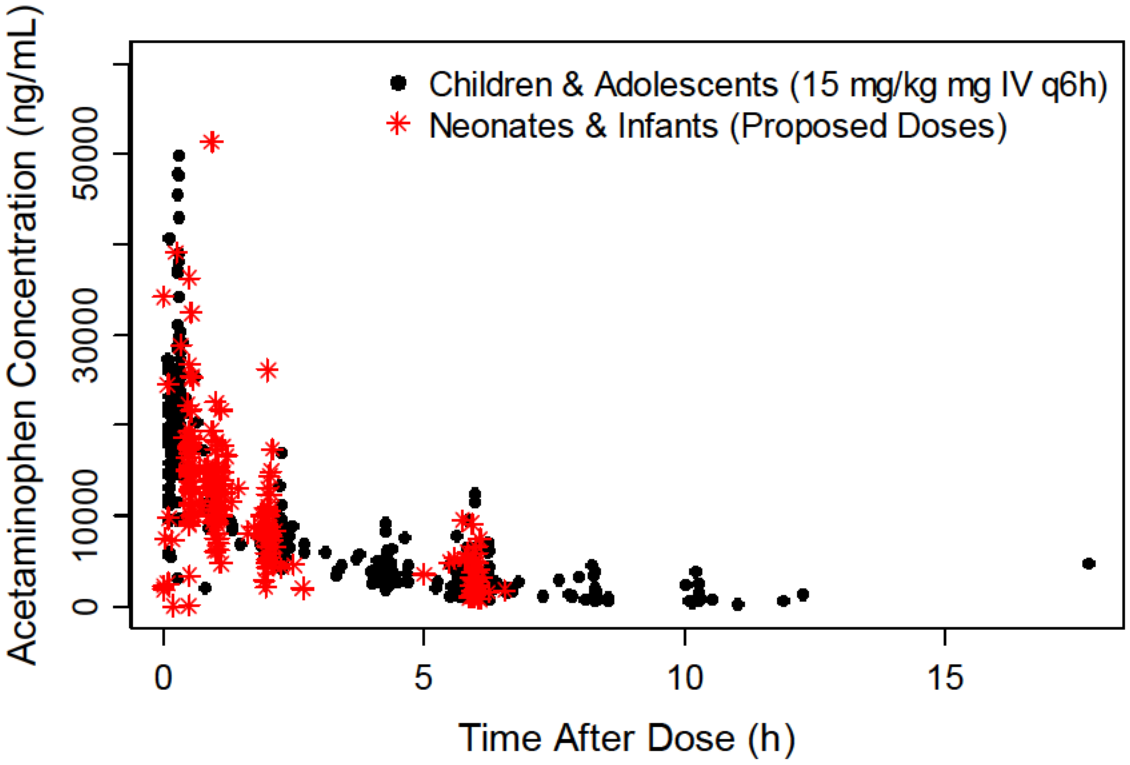


4th Dose

A comparison between acetaminophen concentrations in neonates and infants at the proposed dose levels (12.5 mg/kg in neonates and 15 mg/kg in infants) and children 2 years of age and above at the

approved dose of 15 mg/kg is provided in Figure 9. It is evident from the plot that concentrations in neonates and infants following the proposed doses are generally similar to those in children and adolescents following the approved dose level.

Figure 9: Comparison of Acetaminophen Concentrations in Neonates (12.5 mg/kg) and Infants (15 mg/kg) in CPI-APA-353 and Children and Adolescents (2 to 17 years of age) Receiving 15 mg/kg IV q6h



3.3.2 Population PK/PD Analysis

The Applicant explored the relationship between exposure and efficacy endpoints in terms of pain intensity and amount of rescue in order to fulfill the requirements of the Pediatric Written Request. Because CPI-APA-353 was inadequately designed to evaluate analgesic effects of IV acetaminophen, this analysis was not further reviewed. Also, there were no trends in dose-related adverse events for any individual AEs. Therefore, exposure-response analysis for safety was not further pursued.

15 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/ tS) immediately following this page

CLINICAL PHARMACOLOGY FILING FORM

Application Information			
NDA/BLA Number	022450	**SDN**	419
Applicant	Mallinkckrodt	**Submission Date**	4/29/2016
Generic Name	IV Acetaminophen	**Brand Name**	Ofirmev
Drug Class	Analgesic and Antipyretic		
Indication	(b) (4) fever reduction		
Dosage Regimen	Dose based on bodyweight every 4 to 6 hours		
Dosage Form	IV Injection	**Route of Administration**	Intravenous
OCP Division	DCP2	**OND Division**	DAAAP
OCP Review Team	**Primary Reviewer(s)**	**Secondary Reviewer/ Team Leader**	
Division	Srikanth C. Nallani, Ph.D.	Yun Xu, Ph.D.	
Pharmacometrics	Kevin Krudys, Ph.D.	Kevin Krudys, Ph.D.	
Genomics			
Review Classification	☑ Standard ☐ Priority ☐ Expedited		
Filing Date	6/15/2016	**74-Day Letter Date**	7/15/2016
Review Due Date	Click here to enter a date.	**PDUFA Goal Date**	Click here to enter a date.

Application Fileability

Is the Clinical Pharmacology section of the application fileable?

☑ Yes

☐ No

If no list reason(s)

Are there any potential review issues/ comments to be forwarded to the Applicant in the 74-day letter?

☐ Yes

☑ No

If yes list comment(s)

Is there a need for clinical trial(s) inspection?

☐ Yes

☑ No

If yes explain

Clinical Pharmacology Package

Tabular Listing of All Human Studies	☑ Yes ☐ No	Clinical Pharmacology Summary	☐ Yes ☐ No
Bioanalytical and Analytical Methods	☑ Yes ☐ No	Labeling	☐ Yes ☐ No

Clinical Pharmacology Studies

Study Type		Count	Comment(s)
In Vitro Studies			
☐ Metabolism Characterization			
☐ Transporter Characterization			
☐ Distribution			
☐ Drug-Drug Interaction			
In Vivo Studies			
Biopharmaceutics			
☐ Absolute Bioavailability			
☐ Relative Bioavailability			
☐ Bioequivalence			
☐ Food Effect			
☐ Other			
Human Pharmacokinetics			
Healthy Subjects	☑ Single Dose	1	IV PK study comparing plasma to dried blood spots as bioanalytical method.
	☐ Multiple Dose		
Patients	☐ Single Dose		
	☐ Multiple Dose		
☐ Mass Balance Study			
☐ Other (e.g. dose proportionality)			
Intrinsic Factors			
☐ Race			
☐ Sex			
☐ Geriatrics			
☑ Pediatrics		1	A Randomized, Placebo Controlled, Multicenter Study of the Efficacy, Pharmacokinetics and Pharmacodynamics of Intravenous Acetaminophen for the Treatment of Acute Pain in Pediatric Patients
☐ Hepatic Impairment			
☐ Renal Impairment			
☐ Genetics			
Extrinsic Factors			
☐ Effects on Primary Drug			
☐ Effects of Primary Drug			
Pharmacodynamics			
☐ Healthy Subjects			
☐ Patients			
Pharmacokinetics/Pharmacodynamics			
☐ Healthy Subjects			

☐ Patients		
☐ QT		
Pharmacometrics		
☑ Population Pharmacokinetics	1	
☐ Exposure-Efficacy		
☐ Exposure-Safety		

Total Number of Studies	**In Vitro**		**In Vivo**	2
Total Number of Studies to be Reviewed				2

Criteria for Refusal to File (RTF)		
RTF Parameter	**Assessment**	**Comments**
1. Did the applicant submit bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?	☐Yes ☐No ☑N/A	
2. Did the applicant provide metabolism and drug-drug interaction information? (Note: RTF only if there is complete lack of information)	☐Yes ☐No ☑N/A	
3. Did the applicant submit pharmacokinetic studies to characterize the drug product, or submit a waiver request?	☑Yes ☐No ☐N/A	
4. Did the applicant submit comparative bioavailability data between proposed drug product and reference product for a 505(b)(2) application?	☐Yes ☐No ☑N/A	
5. Did the applicant submit data to allow the evaluation of the validity of the analytical assay for the moieties of interest?	☑Yes ☐No ☐N/A	
6. Did the applicant submit study reports/rationale to support dose/dosing interval and dose adjustment?	☑Yes ☐No ☐N/A	
7. Does the submission contain PK and PD analysis datasets and PK and PD parameter datasets for each primary study that supports items 1 to 6 above (in .xpt format if data are submitted electronically)?	☑Yes ☐No ☐N/A	
8. Did the applicant submit the module 2 summaries (e.g. summary-clin-pharm, summary-biopharm, pharmkin-written-summary)?	☑Yes ☐No ☐N/A	
9. Is the clinical pharmacology and biopharmaceutics section of the submission legible, organized, indexed and paginated in a manner to allow substantive review to begin? If provided as an electronic submission, is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work leading to appropriate sections, reports, and appendices?	☑Yes ☐No ☐N/A	
Complete Application **10.** Did the applicant submit studies including study reports, analysis datasets, source code, input files and key analysis output, or justification for not conducting studies, as agreed to at the pre-NDA or	☑Yes ☐No ☐N/A	

pre-BLA meeting? If the answer is 'No', has the sponsor submitted a justification that was previously agreed to before the NDA submission?		
Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality) Checklist		
Data		
1. Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?	☑Yes ☐No ☐N/A	
2. If applicable, are the pharmacogenomic data sets submitted in the appropriate format?	☐Yes ☐No ☑N/A	
Studies and Analysis		
3. Is the appropriate pharmacokinetic information submitted?	☑Yes ☐No ☐N/A	
4. Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?	☑Yes ☐No ☐N/A	
5. Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?	☑Yes ☐No ☐N/A	
6. Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?	☑Yes ☐No ☐N/A	
7. Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?	☐Yes ☑No ☐N/A	The study employed IV morphine dosing prior to/beginning of the trial, which may have potentially masked IV acetaminophen effects.
General		
8. Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	☑Yes ☐No ☐N/A	
9. Was the translation (of study reports or other study information) from another language needed and provided in this submission?	☐Yes ☐No ☑N/A	
Filing Memo		

Different information requests (IR) were sent to the sponsor to facilitate review of the submission.

IR sent on 5/5/2016:

- Submit population PK/PD report and the datasets along with the codes used in the analyses.
- Submit bioanalytical report and validation report for the study MNK14501041 along with PK dataset.
- Summary documents for Module 2.

On 5/20/2016, the sponsor submitted an annotated response to written request to facilitate review.

IR sent on 6/1/2016:

- Clarify the differences noted in the number of pediatric patients in the neonate age group?
- We did not see how you specifically addressed the relationship of exposure (infusion rate/dose/AUC/Cmax) to safety endpoints. Clarify with information, or direct us to the part of the submission that addresses this requirement.

The sponsor responded with clarification on 6/10/2016. The response was adequate to initiate review of the submission.

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

/s/

KEVIN M KRUDYS
01/13/2017

SRIKANTH C NALLANI
01/13/2017

YUN XU
01/13/2017