Clinical Pharmacology Review

NDA	22-129	**Submission Date(s)**	October 17th, 2008, December 9th, 2008 and December 11th, 2008
Brand Name		Lice Asphyxiator	
Generic Name		Benzyl Alcohol	
Reviewer		Abimbola Adebowale, Ph.D.	
Division Director (Acting TL)		Dennis Bashaw, Pharm.D.	
OCP Division		DCP-3	
OND division		HFD-540	
Applicant		Sciele Pharma, Inc.	
Submission Type; Code		Resubmission: Complete Response to an Approvable Letter	
Formulation; Strength(s)		Topical Lotion, 5 % (w/w)	
Indication		Treatment of *Pediculus humanus capitas* (head lice) of the scalp hair of infected patients aged 6 months and older	

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1 Executive Summary

This re-submission is the applicant's complete response to the deficiencies cited in the approvable letter dated July 14th, 2008. The original NDA was submitted to the Agency on June 15th, 2007. The clinical pharmacology deficiency cited in the approvable letter was as follows:

> ***The in-vivo pharmacokinetic study SU-01-2007 resulted in a number of plasma concentrations of benzyl alcohol. While the median value of all 32 positive samples was ~2.7ug/mL, the upper quartiles of them were above 48 ug/mL. Because the plasma concentrations of benzyl alcohol observed are sporadic, it is difficult to adequately interpret the observed high concentrations of benzyl***

alcohol. Since these plasma concentrations of benzyl alcohol are used to support the systemic safety of the drug product, it is important that you provide further clarification (e.g. are they true representative concentrations) as to why these plasma concentrations were observed and their potential safety impact, including but not limited to, a discussion vis a vis the reported association of plasma levels of benzyl alcohol and infant gasping syndrome.

1.1 Recommendations

From a clinical pharmacology and biopharmaceutics perspective, the applicant has provided an adequate response to the clinical pharmacology deficiencies cited in the approvable letter and their application is acceptable. Please refer to Section 3 on page 6 for our detailed labeling recommendations.

1.2 Phase IV Commitments

Not Applicable

1.3 Summary of Clinical Pharmacology Findings and Biopharmaceutics Findings

Regulatory History

The Agency issued an approvable (AE) action (letter dated July 14th, 2008) during the first cycle of this NDA submission because of a potential safety issue regarding the elevated and sporadic systemic exposure of benzyl alcohol observed, CMC inspection and labeling. On August 8th, 2008, the Agency had a teleconference with the applicant to discuss the potential systemic safety issue with regards to the elevated and sporadic systemic exposure of benzyl alcohol that was observed in the PK study SU-01-2007. During the teleconference, the applicant stated that the elevated (> 3 mcg/ml, the approximate median value of all the PK samples) and, the sporadic plasma concentrations (ranging from 1.2 to 131.3 mcg/mL) of benzyl alcohol observed in study SU-01-2007 were due to an intermittent use of a bacteriostatic saline (NaCl plus 0.9 % benzyl alcohol) catheter flush that contained benzyl alcohol and, thus not true representative plasma concentrations. The applicant claimed that the NaCl plus benzyl alcohol flush was used to clear the indwelling catheters that facilitated certain blood draws in certain subjects. Unfortunately, the phlebotomists involved with the study did not adequately document the use of the benzyl alcohol containing flush. Therefore, the applicant could not really differentiate those subjects that were truly affected.

In order to support the argument that the flush, rather than the drug product, was responsible for the sporadic and elevated benzyl alcohol plasma concentrations observed in study SU-01-2007, the applicant decided to conduct a second bioavailability study (Sc-LA-08-01) in which the catheter flush used was free of benzyl alcohol. Therefore, to address the clinical pharmacology deficiencies cited in the AE letter, the applicant submitted the following information:

- A copy of the label from the bottles of NaCl plus benzyl alcohol which were used as the catheter flush in the first bioavailability study SU-01-2007

- The study report for the second bioavailability study (Sc-LA-08-01) conducted. The applicant stated that NaCl with benzyl alcohol flush was not used in this study.

- In response to the Agency's request to discuss the relationship between benzyl alcohol plasma concentrations and infant gasping syndrome, the sponsor also included reviews by two consultants

    - The opinion of Dr. Neil Buist who the applicant claims is the lead investigator that identified the occurrence and cause of the "gasping syndrome".
    - A review authored by the (b) (4) of publicly available benzyl alcohol safety data was also included for additional support.

These reports are being reviewed by the clinical reviewer since the discussions provided by the authors are mainly publicly available safety data. This reviewer will only include the component of the reports that relate to clinical pharmacology in this document.

Systemic Exposure:

The systemic exposure of benzyl alcohol after topical application of L.A. 5 % (b) (4) was evaluated in a repeat study (Sc-LA-08-01) in a limited number of subjects (19), aged 6 months to 11 years old. The applicant stated that NaCl with benzyl alcohol flush was not used in this study. Benzyl alcohol, 5% L.A was applied for an exaggerated 30 minute exposure (normal exposure for the proposed indication is 10 minutes) to the hair and scalp of subjects with an active infestation of head lice. The patients were stratified into two age cohorts as follows: 6 months to 3 years (N=6) and 4 to 11 years (N=13). **.** Quantifiable benzyl alcohol concentrations were observed in 4 of the 19 subjects (21 %). Three of these subjects were in the 6 months to 3 years cohort at 0.5 hour post-treatment (ranging from 1.97 mcg/mL to 2.99 mcg/mL) and, one subject was in the 4 to 11 year cohort at 1 hour post-treatment (1.63 mcg/mL). No pharmacokinetic parameters could be obtained because only single benzyl alcohol concentrations were detected in any subject.

The maximum plasma concentration of benzyl alcohol (2.99 mcg/mL) obtained in this second bioavailability study (Sc-LA-08-01) was about 44 fold lower than the Cmax (131.3 mcg/mL) obtained in the first bioavailability study (SU-01-2007) in subjects aged 6 months to 11 years old. In addition, the plasma concentrations of benzyl alcohol were closer in their range of values (ranging from 1.63 to 2.99 mcg/mL) in study Sc-LA-08-01 compared to the sporadic values (1.2 to 131.3 mcg/mL) observed in study SU-01-2007.

Therefore, the data provided in study Sc-LA-08-01 supports the applicant's position that it was the benzyl alcohol in the flush, rather than the drug product that was

responsible for the sporadic, fluctuating plasma concentrations of benzyl alcohol observed in the first bioavailability study SU-01-2007. Based on the aforementioned, the applicant has provided adequate information on the true representative systemic bioavailability of benzyl alcohol from their drug product.

Benzyl alcohol plasma concentrations and the infant gasping syndrome:

The report that was authored by the (b) (4) provided values from published literature reports of the serum benzyl alcohol concentrations that were observed in premature infants reported to have developed the toxic effect characterized as "the gasping syndrome" after multiple injections of heparinized bacteriostatic sodium chloride for flushing the catheters, over several days. The published reports linked the gasping syndrome with the presence of benzyl alcohol (0.9%) as a preservative in solutions used to flush umbilical catheters based on the measurement of levels of benzyl alcohol and/or its metabolites in serum and urine.

Basically**,** the highest plasma concentration (2.99 mcg/mL) of benzyl alcohol that was observed in the second bioavailability study Sc-LA-08-01 was about 44 fold lower than the plasma concentration of benzyl alcohol (~ 109.2 mcg/mL or 1.01 mmol/L) reported (Gershanik et.al, 1982) in infants reported to have developed "the gasping syndrome" (Please refer to the clinical review for further details on the potential safety impact of the systemic absorption of benzyl alcohol).

2 Question-Based Review

Q What is the reason for the elevated and sporadic plasma concentrations of benzyl alcohol that were observed in the bioavailability study SU-01-2007 that was submitted with the initial NDA?

The applicant stated that the elevated (> 3 mcg/ml, the approximate median value of all the PK samples) and, the sporadic plasma concentrations (ranging from 1.2 to 131.3 mcg/mL) of benzyl alcohol observed in study SU-01-2007 were due to an intermittent use of a bacteriostatic saline catheter flush that contained benzyl alcohol (NaCl plus 0.9 % benzyl alcohol). A copy of the label from the bottles of NaCl plus benzyl alcohol which were used as the catheter flush in study SU-01-2007 is attached in the Appendix. Therefore, the plasma concentrations of benzyl alcohol that were obtained in study SU-01-2007 are not true representative plasma concentrations. This is further complicated by the fact that the phlebotomists involved with the study did not adequately document the use of the benzyl alcohol containing flush. Therefore, the applicant could not really differentiate those subjects that were truly affected.

Q. What is the true systemic exposure of benzyl alcohol following topical application of LA 5 % (b) (4)***?***

The applicant conducted a second bioavailability study (Sc-LA-08-01) to determine the true representative plasma concentrations of benzyl alcohol following

exaggerated application of LA 5%. Quantifiable benzyl alcohol concentrations were observed in 4 of the 19 subjects (21 %). Three of these were in the 6 months to 3 years cohort at 0.5 hour post-treatment (ranging from 1.97 mcg/mL to 2.99 mcg/mL) and one in the 4 to 11 year cohort at 1 hour post-treatment (1.63 mcg/mL).

Study (Sc-LA-08-01) was conducted in a limited number of subjects (19), aged 6 months to 11 years old. The applicant stated that a NaCl flush with no benzyl alcohol present was used in this study. Benzyl alcohol, 5% L.A was applied for an exaggerated 30 minute exposure (normal exposure for the proposed indication is 10 minutes) to the hair and scalp of subjects with an active infestation of head lice. The patients were stratified into two age cohorts as follows: 6 months to 3 years (N=6) and 4 to 11 years (N=13). Quantifiable benzyl alcohol concentrations were observed in 4 of the 19 subjects (21 %). Three of these were in the 6 months to 3 years cohort at 0.5 hour post-treatment (ranging from 1.97 mcg/mL to 2.99 mcg/mL) and one in the 4 to 11 year cohort at 1 hour post-treatment (1.63 mcg/mL). The plasma benzyl alcohol concentrations obtained are summarized in the table below:

Patient	Age	Post exposure Timepoint (hour)	µg/mL
008	6 months to 3 years	0.5	1.97
009	6 months to 3 years	0.5	2.99
010	6 months to 3 years	0.5	1.97
007	4 to 11 years	1.0	1.63

Q. How do the plasma concentrations obtained in the second BA study (Sc-LA-08-01) compare to those of the first BA study (SU-01-2007)?

The data provided in study Sc-LA-08-01 supports the applicant's position that it was the benzyl alcohol in the flush used in the first BA study SU-01-2007, rather than the drug product that was responsible for the sporadic, fluctuating plasma concentrations of benzyl alcohol observed in study SU-01-2007.

The systemic exposure (ranging form 1.63 to 2.99 mcg/mL) obtained in the second bioavailability study (Sc-LA-08-01) did not indicate any elevated or sporadic benzyl alcohol plasma concentrations approximating the sporadic plasma concentrations observed in the first bioavailability study (SU-01-2007). The maximum plasma concentration of benzyl alcohol (2.99 mcg/mL) obtained in the second bioavailability study (Sc-LA-08-01) was about 44 fold lower than the Cmax (131.3 mcg/mL) obtained in the first bioavailability study (SU-01-2007) in subjects aged 6 months to 11 years old.

In study SU-01-2007, following a 30-minute exposure period of L.A. 5 %, benzyl alcohol plasma concentrations ranging from 1.2 mcg/mL to 131.3 mcg/mL were observed in 10 of the 18 subjects at 0.5 to 12 hours post-treatment for all three age cohorts evaluated. Two of these subjects were in the 6 months to 3 years cohort at 0.5-1.0 hour post-treatment (ranging from 1.18 mcg/mL to 2.28 mcg/mL), six subjects were in the 4 to 11

years cohort at 0.5 to 13 hours post-treatments (ranging from 1.97 mcg/mL to 131.3 mcg/mL) and, two subjects were in the 12 years and older cohort at 0.5 to 1 hour post-treatment (ranging from 2.40 to 30.9 mcg/mL).

Q. How do the observed plasma concentrations of benzyl alcohol following topical application of LA 5 % (b) (4) compare to those observed in infants reported to have developed the "gasping syndrome"?

The report that was authored by the (b) (4) provided values from published literature reports of the serum benzyl alcohol concentrations that were observed in premature infants reported to have developed the toxic effect characterized as "the gasping syndrome" after multiple injections of heparinized bacteriostatic sodium chloride for flushing the catheters, over several days. The published reports linked the gasping syndrome with the presence of benzyl alcohol (0.9%) as a preservative in solutions used to flush umbilical catheters based on the measurement of levels of benzyl alcohol and/or its metabolites in serum and urine.

Basically**,** the highest plasma concentration (2.99 mcg/mL) of benzyl alcohol that was observed in the second bioavailability study Sc-LA-08-01 was about 44 fold lower than the plasma concentration of benzyl alcohol (~ 109.2 mcg/mL or 1.01 mmol/L) reported (Gershanik et.al, 1982) in infants reported to have developed "the gasping syndrome" (Please refer to the clinical review for further details on the potential safety impact of the systemic absorption of benzyl alcohol). However, the plasma concentrations of benzyl alcohol in premature infants obtained from the published reports should be extrapolated with caution because the authors did not indicate what time the serum samples were collected.

3 Detailed Labeling Recommendations

Please see labeling changes in product package insert in Section 4.1 below. This reviewer's changes are shown as ***deletions*** which are ***"strikethroughs"*** and ***additions which*** are ***"underlined".***

Applicant's Proposed label

12. CLINICAL PHARMACOLOGY

12.3 Pharmacokinetics

(b) (4)

(b) (4)

Reviewer's Revised Label

Please note that deletions are "strikethroughs" and additions are "bolded and underlined".

12. CLINICAL PHARMACOLOGY

12.3 Pharmacokinetics

The absorption of benzyl alcohol from TRADENAME Lotion was evaluated in (b) (4) 19 subjects with head lice infestation. Subjects were divided into two treatment groups **(cohorts)**; 6 months to 3 years and 4 to 11 years. (b) (4) TRADENAME Lotion **was applied for an exaggerated exposure period (3 times the normal exposure period).** (b) (4)

A **single plasma concentration of ~~B~~ b**enzyl alcohol (b) (4) **was** observed in ~~four~~ 4 out of 19 subjects (21%); three **subjects were** in the 6 months to 3 years cohort at 0.5 hour post-treatment (ranging from 1.97 to 2.99 μg/mL) and one **subject** in the 4 to 11 year cohort **(1.63 mcg/mL)** at 1 hour post-treatment, **out of a total of 102 samples analyzed.** (b) (4)

4 Appendices

4.1 Proposed Package Insert

7 pages withheld as b4 draft labeling

4.2. Individual Study Reviews

Documents attached or provided:

A. A copy of the labeling from the bottles of NaCl plus benzyl alcohol which were used as the catheter flush in the first BA study SU-01-2007 was attached to this document.

(b) (4)

B. To support the contention that the flush, rather than the drug product, was responsible for spurious fluctuating blood benzyl alcohol levels in study SU-01-2007, Sciele conducted a second bioavailability study (Sc-LA-08-01) in which any catheter flush used was free of benzyl alcohol. A review of this study is described below:

Study Sc-LA-08-01

Title: Evaluation of the Bioavailability of Lice Asphyxiator (L.A.) 5% in Subjects 6 months and Older with Head Lice Infestation.

Study Investigators: (b) (4)

Study Dates: 27th September, 2008 (1 day study)

Study Objectives: The objective of this study was to evaluate the bioavailability of benzyl alcohol in the final formulation of 5% L.A. in subjects with head lice infestation.

Study Design:

This single center, open label study was designed to evaluate the bioavailability of benzyl alcohol following a single exaggerated 30-minute application of L.A 5%.

Study Population: Study was to enroll up to 20 subjects, Males and females, between 6 months to 11 years of age, with an active infestation (at least 3 live lice) of *Pediculus capitis,* the human head louse and the presence of at least moderate pruritis. At least 3 subjects were to be less than 4 years old.

Dose and Mode of Administration: Clinic staff applied L.A 5% (Lot Number 57830A) topically in sufficient quantity to fully saturate the subjects' hair and scalp for 30 minutes.

Pharmacokinetic Sampling: The volume of blood samples collected to determine the plasma concentrations of benzyl alcohol at the time-points shown in the schedule of events table below for the two age cohorts was as follows:

Table 1:

6 months to 3 years (Cohort 1)	1 ml at pre-dose, and 0.5, 1, 3, and 6 hours after completion of application of 5% L.A 5 % (Total = 5 mLs per patient).
4 to 11 years (Cohort 2)	2 ml at pre-dose and 0.5, 1, 3, 6, and 12 hours after completion of application of L.A 5 % (Total = 12 mLs per patient)

Bioanalytical Methods: HPLC with UV detection at 257 nm (Method Validation Report MC07B-0116).

Pharmacokinetic Measurements: Plasma concentration of benzyl alcohol over time, Area under the curve (AUC), time to maximum concentration (Tmax) and maximum concentration (Cmax)

Safety Measurements: Adverse events

Statistical Methods: Descriptive statistics, namely sample size (n), mean, standard deviation, median, and range were assessed for continuous variables, count and percentage for categorical variables. The summary statistics were presented for the two age cohorts: 6 months to 3 years and 4 to 11 years.

Plasma concentrations of benzyl alcohol were to be reported with summary statistics if absorption of benzyl alcohol was observed for the majority of the subjects. The following pharmacokinetic (PK) parameters were to be determined if there was sufficient blood levels of benzyl alcohol observed: Cmax, Tmax, and AUC (using the trapezoidal rule).

Results:

Demographics: Twenty (20) subjects who met the eligibility criteria were enrolled into this bioavailability study. Of these 20 subjects, six subjects were 6 months to 3 years of age and fourteen were 4 to 11 years of age. One pre-dose PK blood sample could not be collected from one subject (# 01-001) in the 4 to 11 years cohort after multiple attempts; the investigator and the guardian mutually agreed to have the subject drop out from the study prior to treatment. Therefore nineteen (19) subjects (six subjects were 6 months to 3 years of age and thirteen were 4 to 11 years of age) received the treatment and completed the study.

Table 2. Demographics

PARAMETER		_6 Months to 3 Years__ N = 6	_4 Years to 11 Years__ N = 13	___Overall___ N = 19
GENDER	N	6	13	19
	MALE	1(16.7%)	5(38.5%)	6(31.6%)
	FEMALE	5(83.3%)	8(61.5%)	13(68.4%)
ETHNICITY	N	6	13	19
	HISPANIC	6(100%)	13(100%)	19(100%)
	NON-HISPANIC	0(0.0%)	0(0.0%)	0(0.0%)
RACE	N	6	13	19
	CAUCASIAN	6(100%)	13(100%)	19(100%)
	AFRICAN AMERICAN	0(0.0%)	0(0.0%)	0(0.0%)
	NATIVE AMERICAN	0(0.0%)	0(0.0%)	0(0.0%)
	ASIAN/PACIFIC ISLANDER	0(0.0%)	0(0.0%)	0(0.0%)
	OTHER	0(0.0%)	0(0.0%)	0(0.0%)
AGE (year)	N	6	13	19
	MEAN	1.7	6.8	5.2
	SD	1.0	2.1	3.1
	MEDIAN	1.0	7.0	5.0
	RANGE	(1 , 3)	(4 , 10)	(1 , 10)

The body weight ranged from 21 pounds to 132 pounds. The height ranged from 28 inches to 60 inches.

Number of Lice Asphyxiator bottles dispensed:

The number of 8 oz bottles dispensed ranged between 0.5 and 1.5 (i.e. 4-12 oz). The amount of L.A. per treatment was not adjusted for the age of the subject

Bioanalytical Method and Validation:

Sample Preparation: Human plasma samples containing benzyl alcohol, **(b) (4)** as the internal standard (I.S.), and EDTA as the anticoagulant were extracted using solid phase extraction (SPE) well plates. The samples were analyzed by **(b) (4)** high-

performance liquid chromatography using a (b) (4) column maintained at 40°C. Benzyl alcohol was detected by UV at 257 nm.

Table 3: Analytical Method and Validation:

Method	HPLC with UV detection
Compound	Benzyl Alcohol
Internal Standard	(b) (4)
Matrix	Human Plasma
Accuracy (% Bias) *Between-Day*	-5.5 % to 3.7 %
Precision (% CV) *Between-Day*	4.9 % to 6.4 %
Standard curve range	1-100 mcg/mL (r > 0.997)
Sensitivity (LOQ)	1 mcg/mL
Stability	Stable in human plasma for 98 days when stored frozen at -20° C
Conclusion	**Method validation is acceptable**

Plasma Concentrations:

A total of one hundred and two (102) samples were analyzed. The applicant stated that of these 102 samples, 12 samples appeared hemolyzed based on a pinkish appearance (3 samples in the 6 months to 3 year cohort and 9 samples in the 4 to 11 year cohort). The majority of the subjects had plasma concentrations of benzyl alcohol BQL (<1.00 μg/mL). Benzyl alcohol concentrations were observed in four subjects, three in the 6 month to 3 year cohort at 0.5 hour post-treatment (ranging from 1.97 to 2.99 mcg/mL) and one in the 4 to 11 year cohort at 1 hour post-treatment (1.63 mcg/mL).

Table 4

Plasma Concentrations (μg/mL) of Benzyl Alcohol in 6 Months to 3 Year Old Subjects (Cohort 1) Following a 30-Minute Treatment of Lice Asphyxiator 5%

Time	Subject I.D.					
(h)	003	004	008	009	010	018
Pretreatment	BQL	BQL[a]	BQL	BQL	BQL	BQL
0.5	NSR	BQL	1.97	2.99	1.97	BQL
1	BQL	BQL	BQL	BQL	BQL	BQL
3	BQL	BQL[a]	BQL	BQL	BQL	BQL[a]
6	BQL	BQL	BQL	BQL	BQL	BQL

BQL - Below the Quantifiable Limit < 1.00 μg/mL
NSR - No Sample Received
[a] Sample appeared hemolyzed

Table 5

Plasma Concentrations (μg/mL) of Benzyl Alcohol in 4 to 11 Year Old Subjects (Cohort 2) Following a 30-Minute Treatment of Lice Asphyxiator 5%

Time (h)	Subject I.D.												
	002	005	006	007	011	012	013	014	015	016	017	019	020
Pretreatment	BQL	BQL[a]	BQL	BQL	BQL	BQL	BQL[a]	BQL	BQL	BQL	BQL	BQL	BQL
0.5	BQL	NSR	BQL	NSR	BQL	BQL	NSR	BQL	NSR	BQL[a]	BQL	BQL	BQL
1	BQL	BQL	BQL	1.63[a]	BQL[a]	BQL	BQL	BQL	BQL	BQL	BQL	BQL	BQL
3	BQL	BQL	BQL[a]	BQL	BQL[a]	BQL	BQL	BQL	BQL	BQL	BQL	BQL	BQL
6	BQL	BQL	BQL	BQL	BQL	BQL	BQL	BQL	BQL	BQL	BQL	BQL	BQL
12	BQL[a]	BQL	BQL	NSR	BQL	BQL	BQL	BQL	BQL	BQL[a]	BQL	BQL	BQL

BQL - Below the Quantifiable Limit < 1.00 μg/mL
NSR - No Sample Received
[a] Sample appeared hemolyzed

Pharmacokinetic Parameters: No pharmacokinetic analyses were performed due to only four subjects having benzyl alcohol concentration detected at one time point each.

C. Consults

Only the clinical pharmacology component of these reports was reviewed by this reviewer. Please see the clinical review for the details on the safety impact.

In response to the Agency's request to discuss the relationship between benzyl alcohol plasma concentrations and infant gasping syndrome, the sponsor also included a two-page opinion (dated August 29th, 2008) by Dr. Neil Buist of The Oregon Metabolic Disease Foundation in Portland, Oregon. Dr Buist stated that all of the cases of GS were extremely small pre-mature babies who were all receiving multiple IV flushes (over 10-20 flushes) over the each 24 hour period for several days. Dr. Buist discusses the data from study SU-01-2007 and states that the dosage exposures, blood levels provided and the ages of the intended patient population for the 5 % benzyl alcohol Lice Asphyxiator drug product are orders of magnitude removed from that which caused gasping syndrome.

In addition, a review authored by the (b) (4) of publicly available information on the safety and human exposure of benzyl alcohol was also included for additional support. This report provided values from published literature reports of the serum benzyl alcohol concentrations that were observed in premature infants reported to have developed the toxic effect characterized as "the gasping syndrome". The published reports linked the gasping syndrome with the presence of benzyl alcohol as a preservative in solutions used to flush umbilical catheters based on the measurement of levels of benzyl alcohol and/or its metabolites in serum and urine. It was reported by Gershanik et. al. (1982) that the mean serum benzyl alcohol concentration measured in six of the ten premature infants who developed Gasping Syndrome was 1.01 ± 0.13 mmol/L (~109.2 ± 14.1 mcg/mL). The affected premature infants were of low birth weight (< 2,500 grams) in weight, with gestational ages ranging from 26-34 weeks

Basically**,** the highest plasma concentration (2.99 mcg/mL) of benzyl alcohol that was observed in the second bioavailability study Sc-LA-08-01 was about 44 fold lower than the plasma concentration of benzyl alcohol (~ 109.2 mcg/mL or 1.01 mmol/L) reported (Gershanik et.al, 1982) in infants reported to have developed "the gasping syndrome" (Please refer to the clinical review for further details on the potential safety impact of the systemic absorption of benzyl alcohol).

Reviewer's Comments: The plasma concentrations of benzyl alcohol in premature infants obtained from the published reports should be extrapolated with caution because the authors did not indicate what time the serum samples were collected.

The reports also indicated that premature infants may be uniquely susceptible to GS because of an inability to adequately metabolize and excrete benzoic acid, the immediate metabolite of benzyl alcohol. This is suggested to be due to a diminished ability of the premature infants to form hippuric acid via glycine conjugation of benzoic acid.

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