CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-129

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

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	

Table of Contents

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)

(b) (4) A **single plasma concentration of ~~B~~ b**enzyl alcohol **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 (h)	Subject I.D. 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.

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

/s/

Abi Adebowale
1/26/2009 04:09:00 PM
BIOPHARMACEUTICS

Dennis Bashaw
1/26/2009 04:30:42 PM
BIOPHARMACEUTICS

Clinical Pharmacology Review

NDA	22-129	**Submission Date(s)**	June 15th, 2007,December 28th, 2007 and April 14th, 2008
Brand Name		Lice Asphyxiator	
Generic Name		Benzyl Alcohol	
Reviewer		Abimbola Adebowale, Ph.D.	
Team Leader		Lydia Velazquez, Pharm.D.	
OCP Division		DCP-3	
OND division		HFD-540	
Applicant		Summers Laboratories, Inc.	
Relevant IND(s)		50,076	
Submission Type; Code		505 (b) (2) NDA Application	
Formulation; Strength(s)		Topical Lotion, 5 % (w/w)	
Indication		Treatment of *Pediculus humanus capitas* (head lice) of the scalp hair	

Table of Contents

1 Executive Summary

Summers laboratories has developed Lice Asphyxiator (benzyl alcohol) 5 % lotion as a treatment for lice infestation. The proposed labeling is two 10-minute applications one week apart. Lice Asphyxiator (L.A.) 5% (b) (4) is a topical, non-pesticide pediculicide

that is believed to act by blocking the respiratory spiracles of human head lice causing asphyxiation of the lice.

L.A. 5% lotion is the first prescription drug product to have benzyl alcohol as the active ingredient. Benzyl alcohol has been used as a bacteriostatic preservative and excipient in different prescription products ranging from parenteral solutions to topical drug products, oral and otic medications. This submission is a 505 (b) (2) application because the sponsor is relying on literature references to satisfy some aspects of nonclinical toxicology information needed to support the safety of benzyl alcohol (primarily systemic repeat dose toxicology and genetic toxicology). However, the sponsor did conduct a full clinical program to support the efficacy and safety of L.A. 5% lotion.

1.1 Recommendations

The clinical pharmacology and biopharmaceutics information included in this submission is acceptable. We recommend that the labeling changes included in the product package insert (see section 4.1) be conveyed to the applicant.

1.2 Phase IV Commitments

Not Applicable

1.3 Summary of Clinical Pharmacology Findings and Biopharmaceutics Findings

Overview of the Clinical pharmacology Drug Development Program

The applicant submitted one study (SU-01-2007) to support the clinical pharmacology and biopharmaceutics of L.A.5 % lotion. This study evaluated the systemic exposure of benzyl alcohol in patients aged 6 months and older with head lice infestation, and this was the only study reviewed.

Regulatory History:

Regulatory guidance for planning the pharmacokinetic study was provided by the FDA at the Pre-NDA meeting held on March 12th, 2007 following the denial of the applicant's request for a waiver of the PK study. During this meeting, the sponsor was told to submit a protocol for the PK study in the target population 2 months after receiving the meeting minutes and the PK study should be initiated no later than 4 months after receipt of the meeting minutes. The applicant submitted the PK protocol to the agency on May 21st, 2007. Revised protocols based on feedback from the Agency were then submitted to the Agency on July 27th, 2007 and August 24th, 2007. On November 21st, 2007, the agency sent a fax to the applicant stating that Protocol No. SU-01-2007 as submitted on August 24th, 2007 was acceptable from the clinical pharmacology standpoint.

However, the NDA was submitted on June 15th, 2007 with no PK study included. Although this was acceptable based on the communications between the Agency and the applicant on March 12th, 2007, the applicant was advised to provide specific timelines on

when the PK study report will be submitted. The applicant responded on August 1st, 2007 with the following timeline: ***initiation date was set for September 7th, 2007, date of completion was to be September 30th, 2007 and the final report was to be submitted on October 31st, 2007***. However, the applicant was unable to submit the final report until December 28th, 2007 (i.e. 2 months later than previously specified) since the study was not completed until October 21st, 2007. Although, this delay did not result in a major amendment from the Agency but it is not considered the most efficient approach to handle NDA submissions for the reviewers.

Systemic Exposure:

In study SU-01-2007, the systemic exposure of benzyl alcohol was observed to range from a low level (~ 1 to 131 mcg/mL) to below the limit of quantitation (BLQ < 1 mcg/mL) after topical application of L.A.5% for up to 30 minutes to the hair and scalp of patients with an active infestation with head lice. The objective of this study was to assess the systemic exposure of benzyl alcohol in L.A. 5% (b) (4) following a single normal 10-minute application or an exaggerated 30-minute application in patients aged 6 months and older (n=45 patients) with a symptomatic (at least moderate pruritus) and active infestation (at least 3 live lice) of head lice. The patients were stratified into three age cohorts as follows: 6 months to 3 years, 4 to 11 years, or 12 years and older. For the 10-minute treatment group, 9 subjects were stratified to each of the three age cohorts (N=27) and for the 30-minute treatment group 6 subjects were stratified to each age cohort (N=18).

Benzyl alcohol plasma concentrations ranging from 1.0 mcg/mL to 108.3 mcg/mL were observed in 15 of the 27 subjects at 0.5 to 3 hours post-treatment for all three age cohorts in the 10 minute treatment group. For the 30-minute treatment group, 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.

Plasma concentrations of benzyl alcohol observed following the 10-minute and 30-minute application were generally comparable for the 6 months to 3 year old and 4 to 11 year old patients. Therefore, it does not appear that the longer (3-fold) contact time resulted in a proportional increase in systemic exposure in this patient population. In contrast, the plasma concentrations observed in the 12 years and older cohort was higher (up to ~16 fold) following the 30-minute application compared to the 10-minute application. The number of subjects (N=3) with quantifiable plasma concentrations of benzyl alcohol in the 12 years and older cohort is so small that it is difficult to really draw any definite conclusions from this data.

No pharmacokinetic parameters were obtained due to the low levels of exposure and the paucity of the data observed in the study.

Relationship between Systemic Exposure and the Length of the Hair:
Although the head lice infestation (i.e. the presence of active lice) of the patients was consistent with that of the patients included in the phase 3 clinical trials, it was noted that

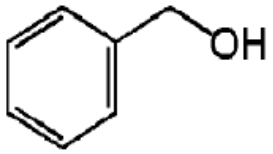
none of the patients included in the PK study had long hair. This indicates that the systemic exposure of benzyl alcohol in patients with long hair was not evaluated in this PK study. However, since the highest plasma concentrations were observed in patients in the 4 to 11 year old cohort with short hair after a 10-minute normal application and an exaggerated 30-minute application, it does not appear that the level of systemic exposure is dependent on the length of the hair. In addition, in the clinical trials there was only one patient (Caucasian, 5 year old, female, patient with medium length of hair) who was identified as having a possibly drug related systemic effect (see clinical review by Dr. Gordana Diglisic for further details).

2 Question-Based Review

2.1 General Attributes of the drug

Q What are the highlights of the chemistry and physical-chemical properties of the drug substance

Benzyl alcohol is a clear, colorless liquid with a mild pleasant aromatic odor. It has a molecular mass of 108.14 g/mol. The molecular formula is C_7H_8O. The chemical structure of benzyl alcohol is as follows:



Q What are the proposed therapeutic indication(s) and mechanism(s) of action?

The target indication for L.A. 5% (b) (4) is for the treatment of *Pediculus humanus capitas* (head lice and their ova) of the scalp hair of infected patients aged 6 months and older. The sponsor's proposed mechanism of action for their drug product is that the benzyl alcohol inhibits lice from closing their respiratory spiracles (breathing holes) causing the lice to asphyxiate.

Q What are the proposed dosage(s) and route(s) of administration?

L.A. 5% (b) (4) is to be used for 10 minutes once per week for two weeks. It is to be applied directly to dry hair, making certain that the entire hair and scalp area are completely covered. After the 10 minutes application, benzyl alcohol 5% (b) (4) should be thoroughly rinsed from the hair with water.

2.2 General Clinical Pharmacology

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

Table 1: Tabular listing of all clinical studies

Study Number	Study Objective	Study Design and Type of Control	Test Product(s)	Dosage Regimen /Number of Subjects
Pivotal Studies				
SU-01-2007	Evaluate the bioavailability of L.A	Single center, randomized, open label evaluation of the absorption of benzyl alcohol in patients infested with *Pediculus Capitis*	5% L.A.	A single application of L.A. 5 % randomly assigned to either a 10-minute or 30-minute application N= 45 (Age range = 6 months to 144 months [~ < 1 year old to 12 years old])
SU-01-2005	Evaluate the efficacy and safety of home-use of two 10-minute treatments of 5% L.A. (applied one week apart)	Multicenter, double blind, randomized, placebo controlled study in patients infested with *Pediculus Capitis*	5% L.A. Vehicle control	Two 10-minute applications one week apart N=125 (Age range = 13 months to 636 months [~1 year old to53 years old])
SU-02-2005	Evaluate the efficacy and safety of home-use of two 10-minute treatments of 5% L.A. (applied one week apart)	Multicenter, double blind, randomized, placebo controlled study in patients infested with *Pediculus Capitis*	5% L.A. Vehicle control	Two 10-minute applications one week apart N = 125 (Age range = 12 months to 584 months [~1 year old to 49 years old])
Supporting Studies				
SU-03-2005	Evaluate the efficacy and safety of home-use of two 10-minute treatments of 5% L.A. (applied one week apart)	Multicenter, Open label study in patients infested with *Pediculus Capitis*	5% L.A.	Two 10-minute applications one week apart N = 128 (Age range = 6 months to 581 months old [~ < 1 year old to 48 years old])

SU-02-2003	Evaluate the safety and efficacy of two concentrations of L.A. in comparison with vehicle placebo and an active control	Single center, randomized, evaluator blinded, open label study in patients infested with *Pediculus Capitis*	5% L.A. 10% L.A. Vehicle, RID shampoo	A 10-minute application at Visit 1. L.A. and vehicle were applied one week later if live lice were found. RID was applied twice as per the package insert regardless of the status of the lice at Day 8. N = 81 (age range = 2 to 70 years old)
SU-02-2003A	Evaluate the safety and efficacy of 5% L.A at two durations of application time (10-minute and 30-minute) regimens for the treatment of head lice	Single center, randomized, evaluator blinded, open label study in patients infested with *Pediculus Capitis*	5% L.A.	Two 10- or 30- minute applications one week apart N = 44 (Age range = 2 to 70 years old)
SU-02-2004	Determine the minimum effective dose of L.A for the treatment of head lice	Single center, Randomized, evaluator blinded, open label study in patients infested with *Pediculus Capitis*	2.5% L.A. 5% L.A.	Two 10- minute applications one week apart N = 42 (age range = 2 to 70 years old)
Dermal Safety Study				
SU-01-2006	Combined skin irritation and sensitization for local safety	Single center, double blind, placebo controlled, within-subject randomized study in healthy subjects	5 % L.A., vehicle, 0.9 % sodium chloride, 0.4 % sodium lauryl sulfate	Induction: Group 1: 21 daily patch applications. Group 2: 9 patch applications 3 times per week Challenge: Groups 1 and 2: 1 challenge patch per application (N=244 healthy adult subjects)

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

The primary efficacy measurement in the pivotal clinical studies was treatment success (%) at Day 22, 14 days after the second application. Treatment success was defined as the absence of live lice based on the ability of L.A 5% to kill the lice by asphyxiation. Basically, the absence of live lice was evaluated under sunlight or good lighting by the evaluator with a 5X lighted magnifier. The evaluators used a wide tooth comb to part and separate the subject's hair to enable them to examine close to the scalp. The absence of live lice was confirmed with a 10X loupe (i.e. a small magnifying glass usually set in an eye piece).

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

Yes, refer to section 2.6 for further details.

Q What are the characteristics of the exposure-response relationships (dose-response, concentration-response) for efficacy and safety?

Exposure-Response for Efficacy:
The optimal treatment regimen of L.A. 5%; concentration, duration of application, i.e., the amount of time the L.A. 5% was applied to the hair and scalp, and the number of treatments; was determined in three Phase II studies (SU-02-2003, SU-02-2003A, and SU-02-2004). The applicant stated that these studies demonstrated that two treatments one week apart were found to be necessary and, thoroughly saturating the hair with the product during treatment was important. In addition a 10-minute application was found to be as effective as a 30-minute application, and 5 % benzyl alcohol in the formulation was as effective as (b) (4) and more effective than the (b) (4) concentration. Therefore, based on this data, L.A. 5% applied as two 10 minute applications, separated by one week, was chosen for evaluation in the pivotal studies.

Exposure-Response for Safety:

The applicant did not conduct an exposure-response analysis for safety because there was none observed in the Phase II studies (SU-02-2003, SU-02-2003A, and SU-02-2004) that evaluated the dose-response for efficacy.

Q What are the pharmacokinetic properties of Lice Asphyxiator?

Absorption: The systemic exposure of benzyl alcohol was observed (study SU-01-2007) to range from a low level (~ 1 to 131 mcg/mL) to below the limit of quantitation (BLQ < 1 mcg/mL) after topical application of L.A.5% to the hair and scalp of patients with an active infestation with head lice infestation for up to 30 minutes. The objective of this study was to assess the systemic exposure of benzyl alcohol in L.A.5% (b) (4) following a single normal 10-minute application or an exaggerated 30-minute application in patients aged 6 months and older (n=45 patients) with a symptomatic (at least moderate pruritus) and active infestation (at least 3 live lice) of head lice. The patients were stratified into three age cohorts as follows: 6 months to 3 years, 4 to 11 years, or 12 years and older. A summary of the plasma concentrations observed are shown in the tables below:

Table 2: Plasma concentrations of benzyl alcohol following a 10-minute or 30-minute application of L.A 5% (b) (4) to patients aged 6 months to 3 years old (Cohort 1)

Time (hr)	10-minute application (N=9)	30-minutes application (N=6)

	Plasma Concentration (mcg/mL)	Number of subjects with quantifiable plasma concentrations	Plasma Concentration (mcg/mL)	Number of subjects with quantifiable plasma concentrations
0.5	1.03-2.67	6	1.86-2.28	2
1	1.08	1	1.18	1
3	BQL	0	BQL	0
6	BQL	0	324.3*	1

BLQ= Below the limit of quantitation < 1.00 mcg/mL
*This subject had a difficult draw at 6-hour post-treatment which could have led to contamination

Table 3: Plasma concentrations of benzyl alcohol following a 10-minute or 30-minute application of L.A 5% (b) (4) to patients aged 4 to 11 years old (Cohort 2)

Time (hr)	**10-minute application (N=9)**		**30-minutes application (N=6)**	
	Plasma Concentration (mcg/mL)	Number of subjects with quantifiable plasma concentrations	Plasma Concentration (mcg/mL)	Number of subjects with quantifiable plasma concentrations
0.5	1.00-13.30	5	1.97-77.7	6
1	7.42-50.80	3	2.18-81.30	3
3	35.20-108.30	2	BQL	0
6	BQL	0	81.50	1
12	BQL	0	131.30	1

BLQ= Below the limit of quantitation < 1.00 mcg/mL

Table 4: Plasma concentrations of benzyl alcohol following a 10-minute or 30-minute application of L.A 5% (b) (4) to patients aged 12 years and older (Cohort 3)

Time (hr)*	**10-minute application (N=9)**		**30-minutes application (N=6)**	
	Plasma Concentration (mcg/mL)	Number of subjects with quantifiable plasma concentrations	Plasma Concentration (mcg/mL)	Number of subjects with quantifiable plasma concentrations
0.5	1.82	1	3.18 – 30.9	2

1	BQL	0	2.40	1

BLQ= Below the limit of quantitation < 1.00 mcg/mL
*All plasma samples were BQL for the 3 hr to 24 hr sampling times following both the 10-minute and 30-minute application.

Reviewer's Comments:

Following the 10-minute-normal application of L.A.5%, plasma concentrations of benzyl alcohol ranging from 1.00 to 108.3 mcg/mL were observed in 15 of the 27 patients between 0.5 hrs and 3 hrs post-treatment across all 3 cohorts. The highest concentration observed was 108.3 mcg/mL at 3 hours post-treatment in an 11 year old male Caucasian patient with short hair (used 4 oz of L.A. 5% (b) (4)).

Following the 30-minute exaggerated application of L.A.5%, plasma concentrations of benzyl alcohol ranging from 1.18 to 131.3 mcg/mL was observed in 10 of the 18 patients between 0.5 hrs and 12 hrs post-treatment across all 3 cohorts. The highest concentration observed was 131.3 mcg/mL at 12 hours post-treatment in a 7 year old female Caucasian patient with short hair (used 8 oz of L.A. 5% (b) (4)). Although one patient (subject 002, 10 month old, male Caucasian patient with short hair (used 4 oz of L.A. % (b) (4))) had a plasma concentration value of 324.3 mcg/mL at 6 hours post-treatment, this value is being interpreted with caution due to poor sampling techniques during the collection of this blood sample.

Plasma concentrations of benzyl alcohol observed following the 10-minute and 30-minute application were generally comparable for the 6 months to 3 year old and 4 to 11 year old patients. Therefore, it does not appear that the longer (3-fold) contact time resulted in a proportional increase in systemic exposure in this patient population. In contrast, the plasma concentrations observed in the 12 years and older cohort was higher (up to ~16 fold) following the 30-minute application compared to the 10-minute application. The number of subjects (N=3) with quantifiable plasma concentrations of benzyl alcohol in the 12 years and older cohort is so small that it is difficult to really draw any definite conclusions from this data.

No pharmacokinetic parameters were obtained due to the low levels of exposure and the paucity of the data observed in the study.

Although the head lice infestation of the patients was consistent with that of the patients included in the phase 3 clinical trials, it was noted that none of the patients included in the PK study had long hair. This indicates that the systemic exposure of benzyl alcohol in patients with long hair was not evaluated in this PK study. However, since the highest plasma concentrations were observed in patients in the 4 to 11 year old cohort with short hair after a 10-minute normal application and an exaggerated 30-minute application, it does not appear that the level of systemic exposure is dependent on the length of the hair. In addition, in the clinical trials there was only one patient (Caucasian, 5 year old, female, patient with medium length of hair) who was identified as having a possibly drug related systemic effect (see clinical review by Dr. Gordana Diglisic for further details).

Distribution: No Pharmacokinetic studies evaluating the distribution of benzyl alcohol was conducted.

Metabolism: No pharmacokinetic studies evaluating the metabolism of benzyl alcohol was conducted. However, it is reported in the literature that benzyl alcohol is oxidized by alcohol dehydrogenase in the liver to benzoic acid. Benzoic acid is then conjugated with glycine to form hippuric acid.[1]

Excretion: No pharmacokinetic studies evaluating the excretion of benzyl alcohol was conducted. However, it is reported in the literature that following administration of an oral dose of 1.5 g to humans, 75 % to 85 % was eliminated in the urine as hippuric acid within 6 hours after administration[1]. Benzyl alcohol plasma half-life was reported as 1.5 hours in dogs receiving intravenous doses[2]. No information on the half-life in man was available.

2.3 Intrinsic Factors

Q. What intrinsic factors influence exposure (PK usually) and/or response and what is the impact of any differences in exposure on efficacy or safety responses?

The effect of age on the systemic exposure of L.A. 5% (b) (4) was assessed. The results of the bioavailability study SU-01-2007 indicated that the age of the patient did not seem to have an effect on the systemic exposure observed. The highest plasma concentrations were observed in patients in the 4 to 11 year old cohort with short hair. The 12 years and older cohort had the lowest number of subjects (n=4) with quantifiable plasma concentrations of benzyl alcohol. There were 21 subjects in the 4 to 11 years old cohort and 12 patients in the 6 months to 3 years old cohort with quantifiable plasma concentrations of benzyl alcohol. Therefore, taking into account the small sample sizes a correlation between the age of the patients and the systemic exposure was not observed. In addition, since the amount of L.A 5 % (b) (4) per treatment was not based on the age of the patient, a correlation would not be expected.

2.4 Extrinsic Factors

Q What extrinsic factors influence exposure and/or response?

No studies were conducted to evaluate the effect of extrinsic factors (e.g. drug-drug interactions) on the exposure or response of L.A.5% (b) (4).

2.5 General Biopharmaceutics

[1] Clayton GD & Clayton FE: Patty's Industrial Hygiene and Toxicology, Volume 2D, Toxicology, 4th ed, John Wiley & Sons, New York, NY, 1994, pp 2590-2591;2704-2707.
[2] Kimura ET, Darby TD, & Krause RA: Parenteral toxicity studies with benzyl alcohol. Toxicol Appl Pharmacol 1971; 18:60-68.

Drug Product Composition: The quantitative composition of the drug product is provided in the table below:

Table 5

Name of ingredients	% (w/w)	Unit Quantity (g)	Function	Compendial grade
Drug Substance				
Benzyl Alcohol	5.00	(b) (4)	Active substance	NF
Excipients				
Purified Water	(b) (4)	(b) (4)	(b) (4)	USP
Mineral Oil (b) (4)	(b) (4)	(b) (4)	(b) (4)	NF
Sorbitan Monooleate	(b) (4)	(b) (4)	(b) (4)	NF
Polysorbate 80	(b) (4)	(b) (4)	(b) (4)	NF
Carboxypolymethylene (Carbomer 934P)	(b) (4)	(b) (4)	(b) (4)	NF
Trolamine	(b) (4)	(b) (4)	(b) (4)	NF
Total weight	100.00	(b) (4)		

Reviewer's Comment: The formulation used in the BA study and the Phase 3 clinical studies was the same as the to-be-marketed formulation. The drug product used in the bioavailability study was a commercial batch (Batch size of (b) (4) *) that was manufactured on May 22nd, 2007.*

2.6 Analytical Section

Q What bioanalytical methods were used to assess plasma concentrations of benzyl alcohol?

The bioanalytical method used was reversed-phase high-performance liquid chromatography (HPLC) with ultraviolet detection (UV) at 257 nm.

Q Were the bioanalytical methods adequately validated?

Table 6: Analytical Method and Validation:

Method	HPLC with UV detection @ 257 nm
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**

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".***

4 Appendices

4.1 Proposed Package Insert (Original)

7 pages withheld as b4 draft labeling

4.2. Individual Study Reviews

Study SU-01-2007

Please note that the applicant initiated this BA study on September 7th, 2007 (~3 months after submitting the NDA on June 15th, 2007) and the final study report was submitted on December 28th, 2007 (~2 months after the date stated by the sponsor (i.e. October 31st, 2007) after the filing of the NDA. Although, the FDA agreed to the applicant submitting the study report after the submission of the NDA (Fax sent to applicant on April 3rd, 2007), the applicant did not stick to their stated timelines for submission.

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

Study Investigators: (b) (4)

Study Dates: Start date: 10th Oct, 2007 and, End date: 21st Oct, 2007

Study Objectives: The objective of this open label 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, randomized, open label study was designed to evaluate the bioavailability of benzyl alcohol following a single normal 10-minute or an exaggerated 30 minute application of 5% L.A.

Diagnosis, Main Inclusion Criteria and Study Population: Males and females, 6 months of age or older, with a symptomatic (at least moderate pruritus) and active infestation (at least 3 live lice) of *Pediculus capitis,* the human head louse. At least 42

subjects were to be enrolled into the study. For the 10- minute treatment group, a minimum of eight subjects were to be stratified into each of the three age cohorts: 6 months to 3 years, 4 to 11 years, or 12 years and older, and for the 30-minute treatment group, a minimum of 6 subjects were to be stratified to each age cohort. One study visit was scheduled for this study.

Dose and Mode of Administration: 5% L.A (Lot Number 50142) was applied topically in sufficient quantity to fully saturate the hair and scalp for a single 10-minute or 30-minute application.

Reviewer's Comments: The drug product used in this study was the to-be-marketed formulation manufactured on May 22nd, 2007 consisting of a batch size of **(b) (4)** .

Table 1: Study Schedule of Events:

Activity	Screening	Treatment / Time 0	0.5 hours	1 hour	2 hours	3 hours	6 hours	9 hours	12 hours	24 hours
Informed Consent	X									
Confirm Diagnosis	X									
Demographics	X									
Medical History	X									
Current Medications	X									
Inclusion/Exclusion	X									
Treatment Application		X								
Blood Samples										
6 months to 3 years		X	X	X		X	X			
4 to 11 years		X	X	X		X	X		X	
12 years and older		X	X	X	X	X	X	X	X	X
Adverse Events		X	X	X	X	X	X	X	X	X

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 above for the three age cohorts was as follows:

Table 2:

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 (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 5% L.A (Total = 12 mLs per patient)
12 years and older (Cohort 3)	5 ml at pre-dose and 0.5, 1, 2, 3, 6, 9, 12 and 24 hours after completion of application of 5% L.A (Total = 45 mLs per patient).

Bioanalytical Methods: HPLC with UV detection at 257 nm.

Pharmacokinetic Measurements: Area under the curve (AUC), time to maximum concentration (Tmax) and maximum concentration (Cmax)

Safety Measurements: Adverse events

Statistical Methods: Three subject populations were used for statistical analysis:

- Intent to treat (ITT) population consisted of all subjects who received medication.
- Per protocol (PP) population consisted of all subjects treated with 5% L.A. and had at least one blood sample collected after treatment.
- Safety population consisted of all subjects treated with 5% L.A. For this study, the safety population was identical to the ITT population.

Descriptive statistics, namely sample size (n), mean, standard deviation, median, and range were assessed for continuous variables, count and percentage for categorical variables. All results were presented by the 10-minute and 30-minute 5% L.A. treatment groups. There were no imputations for missing data.

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). The summary statistics were also to be presented for the subgroup analysis by age: 6 months to 3 years, 4 to 11 years, and 12 years or older.

Reviewer's Comments: The study design was consistent with the previous clinical pharmacology communications that were held with the sponsor at the pre-NDA meeting held on March 12th, 2007 and the revisions to the protocol provided to the applicant on July 17th, 2007, August 21st, 2007 and November 21st, 2007.

Results:

Demographics: Forty five (45) subjects were enrolled in the study. 27 subjects were assigned to the 10-minute treatment group and 18 were assigned to the 30-minute treatment group. For the 10-minute treatment group, 9 subjects were stratified to each of the three age cohorts: 6 months to 3 years, 4 to 11 years, or 12 years and older. For the 30-minute treatment group, 6 subjects were stratified to each age cohort. All subjects completed the study except for one (01-033, a 3 year old female) in the 10-minute treatment group who was voluntarily withdrawn from the study

Table 3: Demographics:

PARAMETER		10-Minute N = 27	30-Minute N = 18
GENDER	N	27	18
	MALE	2(7.4%)	1(5.6%)
	FEMALE	25(92.6%)	17(94.4%)
ETHNICITY	N	27	18
	HISPANIC	27(100%)	18(100%)
	NON-HISPANIC	0(0.0%)	0(0.0%)
RACE	N	27	18
	CAUCASIAN	27(100%)	18(100%)
	AFRICAN AMERICAN	0(0.0%)	0(0.0%)
	NATIVE AMERICAN	0(0.0%)	0(0.0%)
	ASIAN/PACIFIC ISLANDER	0(0.0%)	0(0.0%)
	OTHER	0(0.0%)	0(0.0%)
AGE (year)	N	27	18
	MEAN	10.3	10.7
	SD	9.3	10.7
	MEDIAN	8.0	8.5
	RANGE	(1 , 33)	(0 , 40)

Number of Lice Asphyxiator bottles dispensed:

The treatment was administered according to the labeled instructions for use with a sufficient amount of 5 % L.A. applied to thoroughly saturate the subject's hair and scalp. The number of 8 oz bottles dispensed ranged between 0.5 and 2 (i.e. 4-16 oz). Therefore there were 31 patients with short length of hair (i.e. they used 0.5 to 1 bottle (= 4-8 oz) and14 patients with medium length of hair (i.e. they used 1.5 to 2 bottles (= 12-16 oz.) The amount of L.A. per treatment was not adjusted for the age of the subject

Reviewer's Comments: The amount of L.A. 5 % used per treatment was consistent with the usage guidelines for the clinical trials. Although the head lice infestation of the patients was consistent with that of the patients included in the phase 3 clinical trials, it was noted that none of the patients included in the PK study had long hair. This indicates that the systemic exposure of benzyl alcohol in patients with long hair was not evaluated in this PK study.

However, since the highest plasma concentrations were observed in patients in the 4 to 11 year old cohort with short hair after a 10-minute normal application and an exaggerated 30-minute application, it does not appear that the level of systemic exposure is dependent on the length of the hair. Please note that the highest amount used in the PK study (16 oz = 454g) was within the range of the overall average amount used in the Phase 3 trials (385g-493g). In addition, in the clinical trials there was only one patient (Caucasian, female, 5 year old patient with medium length of hair) who was identified as having a possibly drug related systemic adverse event (please see clinical review by Dr. Gordana Diglisic for further details). The amount used by this patient was within the range of the amount used in the PK study (i.e. this patient used 313g for the first dose and 392 g for the second dose).

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 4: 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**

A total of three hundred (300) samples were received from (b) (4) between October 16, 2007 and October 25, 2007. The samples were stored in a freezer set to maintain -20°C prior to analysis. All samples were analyzed within the established sample stability duration.

Plasma Concentrations:

A total of three hundred (300) samples were analyzed. The vast majority of the subjects' samples had plasma concentrations of benzyl alcohol BQL (<1.00 μg/mL). Benzyl alcohol concentrations were sporadically observed at 0.5 to 12 hours post-treatment in various subjects for all three age cohorts in both the 10- and 30-minute treatment groups. One protocol deviation occurred in one subject (01-016) in the "4 to 11 year" age cohort who had an additional 2-hour post-treatment pharmacokinetic sample taken on 13th October, 2007. The subject completed the study with no other issues.

Table 5: Plasma Concentrations (μg/mL) of Benzyl Alcohol following a 10-Minute Treatment of L.A. 5% - 6 Months to 3 Year Old Subjects (Cohort 1)

Time (hr)	Subject I.D.								
	025	026	029	030	031	032	033	034	035
Pre-dose	BQL	BQL	BQL	BQL	BQL	BQL	BQL	BQL	BQL
0.5	1.03	BQL	BQL	1.53	1.07	2.67	BQL	1.08	1.17
1	BQL	BQL	BQL	BQL	BQL	BQL	1.08	BQL	BQL
3	BQL	BQL	BQL	BQL	BQL	BQL	BQL	BQL	BQL
6	BQL	BQL	BQL	BQL	BQL	BQL	NSR	BQL	BQL

BQL - Below the Quantifiable Limit < 1.00 μg/mL

NSR - No Sample Received because patient voluntarily withdrew

Reviewer's Comments: Plasma concentrations ranging between 1.03 and 2.67 µg/mL (close to the BQL) were observed in 7 out of 9 patients between 0.5 h and 1.0 h in this cohort of 6 months to 3 year old patients following a 10-minute application of 5 % L.A.

Table 4: Plasma Concentrations (µg/mL) of Benzyl Alcohol following a 30-Minute Treatment of LA 5% - 6 Months to 3 Year Old Subjects (Cohort 1)

Time (hr)	Subject I.D.					
	001	002*	006	007	027	028
Pre-dose	BQL	BQL	BQL	BQL	BQL	BQL
0.5	2.28	BQL	BQL	BQL	BQL	1.86
1	BQL	BQL	BQL	BQL	BQL	1.18
3	BQL	BQL	BQL	BQL	BQL	BQL
6	BQL	324.3	BQL	BQL	BQL	BQL

BQL - Below the Quantifiable Limit < 1.00 µg/mL
*Subject 002 had a difficult draw at 6-hour post-treatment which could have led to contamination

Reviewer's Comments: Plasma concentrations ranging between 1.18 and 324.3 µg/mL were observed in 3 out of 6 patients between 0.5 h and 6.0 h post drug application in this cohort of 6 months to 3 year old patients following a 30-minute application of 5 % L.A. The applicant did state that Subject 002 was observed to have anomalous results at the 6 hour sampling time-point. The sample in question was reanalyzed in duplicate. The reanalysis did not reveal any significant differences in the results (re-assay values were 321.2 µg/mL and 328.2 µg/mL, respectively). The results for this subject could not be explained as it occurred more than one hour after the product was shampooed from the hair. One possible explanation offered by the applicant was that this patient had a difficult draw at 6-hour post treatment which could have led to contamination. This reviewer agrees that the 6 hour plasma concentration for Subject 002 is unusual.

Table 4: Plasma Concentrations (µg/mL) of Benzyl Alcohol following a 10-Minute Treatment of LA 5% - 4 to 11 Year Old Subjects (Cohort 2)

Time (hr)	Subject I.D.								
	012	013	014	018	019	021	040	043	044
Pre-dose	BQL	BQL	BQL	BQL	BQL	BQL	BQL	BQL	BQL
0.5	1.22	BQL	1.30	1.30	1.00	13.3	BQL	BQL	BQL
1	7.42	BQL	BQL	BQL	BQL	BQL	50.8	39.9	BQL
3	BQL	BQL	BQL	BQL	BQL	BQL	35.2	108.3	BQL
6	BQL	BQL	BQL	BQL	BQL	BQL	BQL	BQL	BQL
12	BQL	BQL	BQL	BQL	BQL	BQL	BQL	BQL	BQL

Reviewer's Comments: Plasma concentrations ranging between 1.00 and 108.3 µg/mL were observed in 7 out of 9 patients between 0.5 h and 3.0 h post drug application in this cohort of 4 to 11 year old patients following a 10-minute application of 5 % L.A. Comparison of this data to the 6 months to 3 year old patients suggests that systemic exposure is higher in this older age group of 4 to 11 year old patients. The applicant noted that two subjects, 040 and 043, had BQL levels of benzyl alcohol at 0.5 hours and

elevated levels at 1 and 3 hours. This is probably due to the interindividual variability between the subjects.

Table 5: Plasma Concentrations (µg/mL) of Benzyl Alcohol following a 30-Minute Treatment of LA 5% - 4 to 11 Year Old Subjects (Cohort 2)

Time (hr)	Subject I.D.					
	009*	010	016**	017	023	039
Pre-dose	BQL	BQL	BQL	BQL	BQL	BQL
0.5	77.7	14.1	5.18	2.61	1.97	26.3
1	63.8	2.18	81.3	BQL	BQL	BQL
3	NR	BQL	BQL	BQL	BQL	BQL
6	81.5	BQL	BQL	BQL	BQL	BQL
12	131.3	BQL	BQL	BQL	BQL	BQL

BQL - Below the Quantifiable Limit < 1.00 µg/mL
NR - Not Reportable
* Subject 009 had the same butterfly IV through the trial, which could have led to contamination.
** An unscheduled 2-hour post-treatment draw with BQL of Benzyl Alcohol

Reviewer's Comments: Plasma concentrations ranging between 1.97 and 131.3 µg/mL were observed in all 6 patients between 0.5 h and 12 h post drug application in this cohort of 4 to 11 year old patients following a 30-minute application of 5 % L.A. Comparison of this data to the 6 months to 3 year old patients suggests that systemic exposure is higher in this older age group of 4 to 11 year old patients. However, the plasma concentration values obtained in the 4 to 11 year old patients following a 10-minute and 30-minute application are comparable.

The applicant did state that Subject 009 was observed to have anomalous results at all the sampling time-points. The sample in question was reanalyzed in duplicate. The reanalysis did not reveal any significant differences in the results (re-assay values were not that different from the original values). One possible explanation offered by the applicant was that this patient had the same butterfly IV throughout the trial which could have led to contamination. This reviewer agrees that the plasma concentration values for Subject 009 were unusual but still comparable to the values obtained for the other subjects.

Table 6. Plasma Concentrations (µg/mL) of Benzyl Alcohol following a 10-Minute Treatment of LA 5% - 12 Years and Older Subjects (Cohort 3)

Time (hr)	Subject I.D.								
	003	004	005	036	037	038	041	042	045
Pre-dose	BQL	BQL	BQL	BQL	BQL	BQL	BQL	BQL	BQL
0.5	1.82	BQL	BQL	BQL	BQL	BQL	BQL	BQL	BQL
1	BQL	BQL	BQL	BQL	BQL	BQL	BQL	BQL	BQL
2	BQL	BQL	BQL	BQL	BQL	BQL	BQL	BQL	BQL
3	BQL	BQL	BQL	BQL	BQL	BQL	BQL	BQL	BQL
6	BQL	BQL	BQL	BQL	BQL	BQL	BQL	BQL	BQL
9	BQL	BQL	BQL	BQL	BQL	BQL	BQL	BQL	BQL
12	BQL	BQL	BQL	BQL	BQL	BQL	BQL	BQL	BQL
24	BQL	BQL	BQL	BQL	BQL	BQL	BQL	BQL	BQL

BQL - Below the Quantifiable Limit < 1.00 µg/mL

Reviewer's Comments: Only 1 out of 9 patients had a quantifiable plasma concentration value of 1.82 µg/mL at 0.5 h post drug application in this cohort of 12 years and older patients following a 10-minute application of 5 % L.A.

Table 7. Plasma Concentrations (µg/mL) of Benzyl Alcohol following a 30-Minute Treatment of LA 5% - 12 Years and Older Subjects (Cohort 3)

Time (hr)	Subject I.D.					
	008	011	015	020	022	024
Pre-dose	BQL	BQL	BQL	BQL	BQL	BQL
0.5	BQL	BQL	30.9	BQL	3.18	BQL
1	BQL	BQL	2.40	BQL	BQL	BQL
2	BQL	BQL	BQL	BQL	BQL	BQL
3	BQL	BQL	BQL	BQL	BQL	BQL
6	BQL	BQL	BQL	BQL	BQL	BQL
9	BQL	BQL	BQL	BQL	BQL	BQL
12	BQL	BQL	BQL	BQL	BQL	BQL
24	BQL	BQL	BQL	BQL	BQL	BQL

BQL - Below the Quantifiable Limit < 1.00 µg/mL

Reviewer's Comments: Only 2 out of 9 patients had quantifiable plasma concentration values ranging from 2.40 to 30.9 µg/mL between 0.5 h and 1.00 h post drug application in this cohort of 12 years and older patients following a 30-minute application of 5 % L.A.

Pharmacokinetic Parameters: No pharmacokinetic analyses were performed due to the paucity of and low benzyl alcohol concentration levels detected.

Reviewer's Summary:

Following the 10-minute-normal application of L.A.5%, plasma concentrations of benzyl alcohol ranging from 1.00 to 108.3 mcg/mL were observed in 15 of the 27 patients between 0.5h and 3 hrs post-treatment across all 3 cohorts. The highest concentration observed was 108.3 mcg/mL at 3 hours post-treatment in an 11 year old male Caucasian patient with short hair (used 4 oz of L.A. 5% lotion).

Following the 30-minute exaggerated application of L.A.5%, plasma concentrations of benzyl alcohol ranging from 1.18 to 131.3 mcg/mL was observed in 10 of the 18 patients between 0.5 h and 12 hrs post-treatment across all 3 cohorts. The highest concentration observed was 131.3 mcg/mL at 12 hours post-treatment in a 7 year old female Caucasian patient with short hair (used 4 oz of L.A. 5% (b) (4). Although one patient (subject 002, 10 month old, male Caucasian patient with short hair (used 4 oz of L.A. % (b) (4)) had a plasma concentration value of 324.3 mcg/mL at 6 hours post-treatment, this value is being interpreted with caution due to poor sampling techniques during the collection of this blood sample.

Plasma concentrations of benzyl alcohol observed following the 10-minute and 30-minute application were generally comparable for the 6 months to 3 year old and 4 to 11 year old patients. Therefore, it does not appear that the longer (3-fold) contact time resulted in a proportional increase in systemic exposure in this patient population. In contrast, the plasma concentrations observed in the 12 years and older cohort was higher (up to ~16 fold) following the 30-minute application compared to the 10-minute application. The number of subjects (N=3) with quantifiable plasma concentrations of benzyl alcohol in the 12 years and older cohort is so small that it is difficult to really draw any definite conclusions from this data.

No pharmacokinetic parameters were obtained due to the low levels of exposure and the paucity of the data observed in the study.

Although the head lice infestation of the patients was consistent with that of the patients included in the phase 3 clinical trials, it was noted that none of the patients included in the bioavailability study had long hair. This indicates that the systemic exposure of benzyl alcohol in patients with long hair was not evaluated in this PK study. However, since the highest plasma concentrations were observed in patients in the 4 to 11 year old cohort with short hair after a 10-minute normal application and an exaggerated 30-minute application, it does not appear that the level of systemic exposure is dependent on the length of the hair. In addition, in the clinical trials there was only one patient (Caucasian, female, 5 year old patient with medium length of hair) who was identified as having a possibly drug related systemic adverse event (please see clinical review by Dr. Gordana Diglisic for further details).

Applicants' Conclusions: Benzyl alcohol plasma concentrations were determined using a validated HPLC methodology in samples after 10 minutes or 30 minutes application of LA 5% in subjects with head lice infestation. A total of three hundred (300) unique samples were analyzed. The majority of the subjects' samples had plasma concentrations of benzyl alcohol below the quantifiable limit (BQL) of<1.00 µg/mL. Benzyl alcohol concentrations were sporadically observed at 0.5 to 3 hours post-treatment in various subjects for all three age cohorts in both the 10- and 30-minute treatment groups. No pharmacokinetic analyses were performed due to the paucity of and low benzyl alcohol concentration levels detected.

Reviewer's Comments: Generally, this reviewer agrees with the applicant's conclusions. However, the data does show that the plasma concentrations were observed at 0.5 to 12 hours post treatment and not just 0.5 to 3 hrs that was concluded by the applicant. In addition, the patients in the 4 to 11 year old cohort had the highest systemic exposure compared to the other two cohorts. However, the clinical significance of this finding is unknown.

4.3 Consult Reviews (including Pharmacometric Reviews): Not Applicable

4.4 Cover Sheet and OCP Filing/Review Form

Office of Clinical Pharmacology and Biopharmaceutics

New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA Number	22-129	**Brand Name**	Lice Asphyxiator
OCPB Division (I, II, III)	DCP 3	**Generic Name**	Benzyl Alcohol (5 %) (b) (4)
Medical Division	HFD-540	**Drug Class**	Pediculicde
OCPB Reviewer	Abi Adebowale	**Indication(s)**	To treat head lice (infestation of *Pediculus humanis capitis* and their ova) of the scalp and hair
OCPB Team Leader	Lydia Velazquez	**Dosage Form**	(b) (4)
		Dosing Regimen	Apply directly to the scalp and hair. Allow it to remain in the hair for at least 10 minutes. After 10 minutes thoroughly rinse from the hair with water. Treatment must be repeated in one week to completely eliminate any lice that hatched after the first treatment.
Date of Submission **Filing Date**	15th June, 2007 14th August, 2007	**Route of Administration**	Topical
Estimated Due Date of OCPB Review	29th April, 2008	**Sponsor**	Summers Labs, Inc.
PDUFA Due Date	15th, April, 2008 (Original) 15th, July, 2008 (extended date	**Priority Classification**	Standard
Division Due Date	1st, March, 2008	**IND Number**	50,076

Clinical Pharmacology and Biopharmaceutics Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Study Numbers If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	X			
Tabular Listing of All Human Studies	X			
HPK Summary	X			
Labeling	X			
Reference Bioanalytical and Analytical Methods	X			
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				

Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:				
multiple dose:				
Patients-				
single dose:	X	1		SU-01-2007
multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
PD:				
Phase 2:				
Phase 3:				
PK/PD:				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability:				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies:				
Dissolution:				
(IVIVC):				
Bio-wavier request based on BCS				
BCS class				
III. Other CPB Studies				
Genotype/phenotype studies:				
Other (in vitro percutaneous absorption study)				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies		**1**	**1**	
Filability and QBR comments				

	"X" if yes X	Comments
Application filable?	**Yes**	Based on the applicant's commitment to submit the final report for the in vivo bioavailability study SU-01-2007 by October 31st, 2007 and the decision to review this submission as a standard 10 month cycle, the application is fileable.
Comments sent to firm?	**Yes**	Comments were faxed to the firm on July 30th, 2007 with regards to the time-line for the submission of their ongoing bioavailability study. The applicant sent the following response back to the Agency on 08/01/2007: ***The date of initiation of the ongoing bioavailability study (Study number SU-01-2007) is set for September 7, 2007. The expected date of completion is September 30 and final report submitted October 31, 2007. However, the submission was not received until December 28th, 2007 (2 months late)***
QBR questions (key issues to be considered)	What is the systemic absorption of benzyl alcohol in the target population under maximal use conditions?	
Other comments or information not included above	**NA**	
Primary reviewer Signature and Date	**Abi Adebowale (07/30/07)**	
Secondary reviewer Signature and Date	**Lydia Velazquez**	

CC: NDA 22-009, HFD-850 (P.Lee), HFD-540 (M.Bauerlein), DCP 3 (L.Velazquez, H. Ahn, D. Bashaw)

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

/s/

Abi Adebowale
5/1/2008 10:16:01 AM
BIOPHARMACEUTICS

Lydia Velazquez
5/1/2008 12:12:33 PM
BIOPHARMACEUTICS

Office of Clinical Pharmacology and Biopharmaceutics

New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA Number	22-129	**Brand Name**	(b) (4)
OCPB Division (I, II, III)	DCP 3	**Generic Name**	Benzyl Alcohol (5 %) (b) (4)
Medical Division	HFD-540	**Drug Class**	Pediculicde
OCPB Reviewer	Abi Adebowale	**Indication(s)**	To treat head lice (infestation of *Pediculus humanis capitis* and their ova) of the scalp and hair
OCPB Team Leader	Sue Chih-Lee	**Dosage Form**	(b) (4)
		Dosing Regimen	Apply directly to the scalp and hair. Allow it to remain in the hair for at least 10 minutes. After 10 minutes thoroughly rinse from the hair with water. Treatment must be repeated in one week to completely eliminate any lice that hatched after the first treatment.
Date of Submission **Filing Date**	15th June, 2007 14th August, 2007	**Route of Administration**	Topical
Estimated Due Date of OCPB Review	15th February, 2008	**Sponsor**	Summers Labs, Inc.
PDUFA Due Date	15th, April, 2008	**Priority Classification**	Standard
Division Due Date	1st, March, 2008	**IND Number**	50,076

Clinical Pharmacology and Biopharmaceutics Information

Lice Asphyxiator (L.A.) contains 5% benzyl alcohol as the active ingredient and works by mechanically blocking the respiratory spiracles of the head lice, therefore causing a quick-acting suffocation that will not result in the development of resistance.

The applicant did not provide any clinical pharmacology or biopharmaceutics data in this NDA. However the applicant did state the following:

> "To determine systemic exposure for the topical treatment an in vivo pharmacokinetic (PK) clinical study, SU-01-2007, *Evaluation of the Bioavailability of Lice Asphyxiator 5% in Subjects with Head Lice Infestation*, has been initiated. The study is on going and will evaluate whether benzyl alcohol is absorbed to an appreciable extent during a normal 10-minute application as well as exaggerated 30-minute application duration in subjects with symptomatic lice infestation. Regulatory guidance for planning this study was provided at the Pre-NDA meeting on March 12, 2007. The study was to be initiated 4 months after receipt of the meeting minutes. The final study report will be submitted during the review period of the NDA".

Reviewer's Comments: Please note that the sponsor did submit a protocol on 05/21/07, however, the Agency did not send them comments until 07/17/07 (3 days before the expected date of 4 months after receipt of the meeting minutes of 03/19/2007). Since the applicant did not provide any information with regards to the date the study was initiated, the expected date of completion and the expected date of submission of the final study report, a fax was sent to the applicant on July 30th, 2007 requesting that they submit this information. A determination of fileability cannot be made without a definite commitment from the applicant on the expected date of submission of the final report.

	"X" if included at filing	**Number of studies submitted**	**Number of studies reviewed**	**Study Numbers If any**
STUDY TYPE				

Table of Contents present and sufficient to locate reports, tables, data, etc.	X			
Tabular Listing of All Human Studies	X			
HPK Summary	X			
Labeling	X			
Reference Bioanalytical and Analytical Methods				
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:				
multiple dose:				
Patients-				
single dose:				
multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
PD:				
Phase 2:				
Phase 3:				
PK/PD:				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability:				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies:				
Dissolution:				
(IVIVC):				
Bio-wavier request based on BCS				
BCS class				
III. Other CPB Studies				
Genotype/phenotype studies:				
Other (in vitro percutaneous absorption study)				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies				

Filability and QBR comments		
	"X" if yes **X**	**Comments**
Application filable?	**Yes**	Based on the applicant's commitment to submit the final report by October 31st, 2007 and the decision to review this submission as a standard 10 month cycle, the application is fileable.
Comments sent to firm?	**Yes**	Comments were faxed to the firm on July 30th, 2007 with regards to the time-line for the submission of their ongoing bioavailability study. The applicant sent the following response back to the Agency on 08/01/2007: ***The date of initiation of the ongoing bioavailability study (Study number SU-01-2007) is set for September 7, 2007. The expected date of completion is September 30 and final report submitted October 31, 2007.***
QBR questions (key issues to be considered)	What is the systemic absorption of benzyl alcohol in the target population under maximal use conditions?	
Other comments or information not included above		
Primary reviewer Signature and Date	**Abi Adebowale (07/30/07)**	
Secondary reviewer Signature and Date	**Sue-Chih Lee**	

CC: NDA 22-009, HFD-850 (P.Lee), HFD-540 (M.Bauerlein), DCP 3 (S. Lee, H. Ahn, D. Bashaw)

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

/s/

Abi Adebowale
8/15/2007 05:50:26 PM
BIOPHARMACEUTICS

Sue Chih Lee
8/15/2007 08:10:35 PM
BIOPHARMACEUTICS
The study protocol dated 5/21/07 to determine the maximal systemic exposure was not received by DCP3 until 7/3/07.