

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

22-129

SUMMARY REVIEW

Summary Review for Regulatory Action

Division Director

Date	04 April 2009
From	Susan J. Walker, M.D.
Subject	Division Director Summary Review
NDA	22-129/ 505(b)(2)
Relevant IND	50,076
Applicant Name	Summers Laboratories, Inc.
Date of Submission	15 June 2007 (Original Submission) 14 July 2008 (Approvable action) 17 October 2008 (Current Submission)_
PDUFA Goal Date	17April 2009
Proprietary Name / Established (USAN) Name	Undetermined/ Benzyl Alcohol 5% Lotion
Dosage Forms / Strength	Topical Lotion, 5% (w/w)
Proposed Indication(s)	Treatment of Pediculus humanus capitis
Action/Recommended Action for NME:	<i>Approval</i>

Material Reviewed/Consulted	Names of discipline reviewers
OND Action Package, including:	
Medical Officer Review	Gordana Diglisic, M.D.
Statistical Review	Mat Soukup, Ph.D., Mohamed Al Osh, Ph.D.
Pharmacology Toxicology Review	Barbara Hill, Ph.D.
CMC Review	Tarun Mehta, Ph.D/Moo-Jhong Ree, Ph.D.
Clinical Pharmacology Review	Abimbola Adebowale, Ph.D./Lydia Velazquez, Pharm.D. 01May08
DDMAC	Iris Masucci, PharmD
CDTL Review	Jill Lindstrom, M.D.
OSE/DMETS/DMEP	Loretta Holmes, PharmD.
OSE/DRM	Nancy Carothers; Jodi Duckhorn
Pediatrics and Maternal Health Staff	Hari Sachs, M.D.

OND=Office of New Drugs
 DDMAC=Division of Drug Marketing, Advertising and Communication
 OSE= Office of Surveillance and Epidemiology
 DMETS/DMEP=Division of Medication Errors and Technical Support; Division of Medication Error Prevention
 DSI=Division of Scientific Investigations
 DRM= Division of Risk Management
 CDTL=Cross-Discipline Team Leader

1. Introduction

This application received an Approvable decision on 07/14/08. This memorandum incorporates and extends my comments in the Division Director memorandum for the July08 action. The applicant has now adequately addressed all informational needs.

2. Background

This applicant proposes the topical treatment of head lice (*pediculus humanus capitis*) with a lotion containing benzyl alcohol as the active ingredient. Although benzyl alcohol is present in other products as an excipient, it has not previously been approved as a new drug.

Head lice are wingless insects that are obligate ectoparasites of humans, and humans are their only known host. Head lice spend their entire life cycle on the human scalp, and feed exclusively on human blood. The insects generally cling to the hair shafts where they lay their eggs, and crawl down to the scalp for their blood meal. Head lice and body lice are closely related, but are not identical and infest different anatomic areas on the human host.

Treatment of head lice is a well studied indication and there are multiple approved products, both prescription and over-the-counter. The intended result of treatment of head lice is to eradicate the live lice from the scalp/hair. Living head lice crawl on the scalp for feeding and also cling to the scalp hair, depositing eggs that become “glued” on the hair shaft, generally to the proximal portion of the hair shaft. The female lays approximately 6 eggs every 24 hrs, usually at night, and may lay up to 150 in her lifetime. Eggs incubate in about 8-9 days, and reach adulthood in about 15 days. An effective product must kill the live lice (pediculicide), but must also provide for eradication of any new lice which may hatch from viable eggs (nits). If these eggs are not killed by the treatment product (ovicide) or removed (combing), the cycle of infestation will continue. Products claiming pediculocidal and ovicidal activity may demonstrate efficacy with one application, while products without ovicidal activity may require an additional application(s) to eradicate any lice hatching from viable eggs.

For studies to support an indication of treatment of head lice, the recommended primary efficacy variable is the status of lice infestation (live lice present/absent) and the usual primary efficacy evaluation time point is 14 days after the last treatment. Patients are dichotomized into success/failure based upon this day 14 post-treatment evaluation. The proportion of subjects who are a “success” is compared to the proportion of subjects who are determined to be “failures” at day 14 following the second treatment.

The applicant should provide adequate dose ranging studies (dose, duration, frequency) to establish the appropriate treatment regimen based upon their products performance profile. All patients should be evaluated for local and systemic safety. The primary efficacy evaluation time point is generally 2 weeks after the last treatment. This time point is chosen because it is difficult to determine if all the lice/eggs are dead immediately following the last treatment, and the two weeks will generally allow time for viable eggs to hatch and product visible lice. Even

if no lice are identified at the last treatment visit, remaining eggs may be viable for several days, and evaluation 2 weeks (14 days) after the end-of-treatment will generally reveal live lice if there were viable eggs remaining at the last treatment. Although the problem of “reinfestation” following treatment may also be considered as a reason for the presence of live lice on day 14 following end-of-treatment, the study design described has been used successfully by approved products and continues to be a reasonable approach.

The applicant’s initial submission contained datasets that were challenging to review and which appeared to contain some discrepancies when compared to the study reports. These concerns were communicated to the sponsor and the sponsor resubmitted study reports and some data during the review process. Overall, the determination of safety and efficacy conclusions were consistent.

3. CMC/Device

The product contains 5% (50mg/g) benzyl alcohol as an active ingredient. The identity, strength, and purity of the drug product were evaluated by the following analytical tests conducted during the process, on the released finished product, and on the stability: description, pH, viscosity, specific gravity, benzyl alcohol ID, assay, and related substances. The drug product specifications were deemed satisfactory by the reviewing chemist.

This application provided adequate information on the raw materials controls, manufacturing process, specification and container/closure. It also provided sufficient stability data to assure identity, strength, purity and quality of the drug product during shelf life. An “acceptable” recommendation has now been received from the Office of Compliance for the drug substance manufacturing facility.

I concur with the conclusions reached by the chemistry reviewer regarding the acceptability of the manufacturing of the drug product and drug substance. Manufacturing site inspections were acceptable. There are no outstanding issues.

4. Nonclinical Pharmacology/Toxicology

Lice breathe through 7 paired “spiracles”, one pair on the thorax and 6 pairs on the abdomen. Apparently, these spiracles can be opened/closed in response to wetting and are able to close for up to 12hrs. The purported mechanism of action for this product is a “stunning” of the respiratory spiracles of the louse such that they remain open, leading to blockage and subsequent asphyxiation. The sponsor claims that asphyxiation occurs within minutes in the presence of benzyl alcohol. The mineral oil in the product is purported (b) (4) while the Carbomer 934P provides a (b) (4)

The applicant conducted two in-vitro studies to evaluate the pediculocidal activity of the product. The complete product (b) (4) was compared to the activity of products containing either 5% benzyl alcohol or mineral oil. Virtually complete lice killing was noted for the drug product up to 5 hrs post dose, (b) (4). Scanning electron microscopy demonstrated that when lice were exposed to the drug product their breathing spiracles remain open and allow liquid materials to occlude the breathing apparatus, resulting in death. These studies provide useful insights into the mechanism of action of this product. The applicant is relying upon literature to satisfy some aspects of the nonclinical toxicology information needed to support the safety of benzyl alcohol, primarily repeat dose toxicology and genetic toxicology.

The pharmacology review summarizes the non-clinical findings. Results from 13-week repeat dose oral rat and mouse toxicology studies conducted by the National Toxicology program suggest that high doses of benzyl alcohol could be neurotoxic. However, it was not anticipated that high systemic doses of benzyl alcohol would be achieved after clinical use of the *Tradename* product. No systemic toxicity was noted in 2 week repeat dose dermal toxicology studies conducted with up to 15% lice asphyxiator product in rats and dogs. Very limited systemic exposure was achieved in either study with only 1 hour plasma samples yielding measurable levels of benzyl alcohol. The 5% lice asphyxiator drug product caused minor dermal irritation in both rats and dogs after two weeks of repeat dermal exposure (6 hours/day).

Benzyl alcohol elicited a positive response in some in vitro genetic toxicology assays and a negative response in other in vitro genetic toxicology assays. No evidence of carcinogenic activity was noted for benzyl alcohol in 2 year oral carcinogenicity studies in rats (doses up to 400mg/kg benzyl alcohol) or mice (doses up to 200mg/kg benzyl alcohol) conducted by the NTP. Benzyl alcohol was not teratogenic at high doses that elicited maternal toxicity in systemic rat and rabbit embryofetal development studies.

I concur with the conclusions reached by the pharmacology/toxicology reviewer that there are no outstanding pharm/tox issues that preclude approval.

5. Clinical Pharmacology/Biopharmaceutics

The sponsor requested a waiver of an *in vivo* PK study to determine the systemic exposure under maximal use conditions. This was not granted because, systemic exposure *in vivo*, if feasible, of topical products needs to be determined for purposes of safety assessment. Actual data are needed as the extent of percutaneous absorption depends upon such factors as the formulation and skin conditions. Benzyl alcohol has been associated with “gasping syndrome” in neonates, and the systemic exposure from this product and any implications for “gasping syndrome” in older children has been adequately addressed by the sponsor.

The applicant submitted one study (SU-01-2007) to evaluate the systemic exposure of benzyl alcohol in patients 6 months of age and older with head lice infestation. The study objective was to assess the systemic exposure of benzyl alcohol in *Tradename* lotion following a single

normal 10 minute application or an exaggerated 30 minute application in infested patients 6 months and older (n=45).

The plasma concentrations at 0.5 hr, 1hr, 3hr and 6hrs following 10 minutes exposure in subjects 6 months to 3 yrs (Cohort 1) were all below the quantifiable limit (<1.00 ug/ml) except for a single reading in 7 of the 9 subjects, and these readings were all (b) (4). In the second cohort (4-11 yrs) there were 5 of 9 children with BLQ or readings (b) (4) however, there was 1 subject with 50.8 ug/ml at 1 hr and one subject with 39.9 ug/ml at 1 hrs and 108.3 ug/ml at 3 hrs. Both these subjects had levels BLQ at 6 and 12 hrs. Additionally in this cohort there was one subject with a level of 7.42 at 1 hr and one subject with a level of 13.3 at .5 hrs. In the third cohort (12yrs and older) all levels were BLQ with the exception of one subject with 1.82 ug/ml at .5hrs. The clinical significance of these findings, if any, is unknown.

Information is also provided for 30 minute exposures. For subjects in the 6 months to 3 yrs cohort, the levels were BLQ except for a .5hr level of 2.28 in one subject and levels (b) (4) at .5 and 1 hr in another subject. A third subject had an unexplained level of 324.3 at 6hrs, with BLQ values at preceding time points. This draw was reassayed with similar results, and the applicant offers that this patient had a “difficult draw” that may have affected the result. It is unknown if the area was swabbed with a product containing benzyl alcohol. The second cohort provided results indicating detectable plasma levels in all subjects. Subject 009 demonstrated detectable levels between 0.5 hrs and 6 hrs, with the highest level (131.3) at 6 hrs. Subjects 017 and 023 demonstrated levels at 30 minutes and 1 hr, and subject 039 demonstrated levels at 30 min. All levels in the third cohort were BLQ except for subject 015 with a 0.5hr level at 30.9 and a 1hr level at 2.40, and subject 022 with a 3.18 level at 0.5hrs.

The agency issued a first cycle approvable action because of the potential safety issue regarding the elevated and sporadic systemic exposure to benzyl alcohol observed in Study SU-01-2007. The applicant determined that these levels were likely due to an intermittent use of a bacteriostatic saline (NaCl plus 0.9% benzyl alcohol) catheter flush and were not truly representative plasma concentrations. To support this theory, the applicant conducted a second bioavailability study (LA-08-01) using a catheter flush that was free of benzyl alcohol. The maximum plasma concentration obtained in this second study was about 44 fold lower than the Cmax obtained in the first study (SU-01-2007) for subjects 6months to 11 years. The biopharm and clinical reviewers conclude that this study supports the applicant’s position that it was the flush, rather than the drug product, that was responsible for the sporadic, fluctuating plasma concentrations of benzyl alcohol observed in the first study.

I concur with the conclusions reached by the clinical pharmacology/biopharmaceutics reviewer that there are no outstanding clinical pharmacology issues that preclude approval, and that treatment with the drug product does not expose subjects to elevated systemic levels of benzyl alcohol.

6. Clinical Microbiology

N/A

7. Clinical/Statistical-Efficacy

Two randomized, double blind, vehicle -controlled trials were conducted to support the safety and efficacy of *Tradenname* lotion in the treatment of head lice. Studies SU-01-2005 and SU-02-2005 were multi-center, randomized, double blind, vehicle controlled studies. Study 01 was conducted in 5 centers across the US and enrolled 306 (125 index) subjects. Study 02 was also conducted in 5 centers and enrolled 309 subjects (125 index)

The trials included two cohorts: the primary cohort consisted of the youngest child in a household with at least 3 live lice; the secondary treatment cohort consisted of any other household members who also had an active lice infestation. The trials were identically designed to recruit approximately 120 subjects for the primary treatment cohort who would participate in the trials for approximately 22 days.

Study subjects were instructed to apply *Tradenname* to dry hair ensuring complete coverage, such that all hair and the entire scalp were thoroughly saturated with the product to the point where some dripping would likely occur. The study protocol included usage guidelines (amount of test product per treatment) based upon the hair length, with subjects with longer hair using more product. Subjects were provided a towel and instructed to cover their eyes, forehead and neckline during treatment. The product was left in place for 10 minutes then rinsed, shampoo with regular shampoo, and rinsed again. Treatment was repeated in one week (day 8). On day 9, treatment failures in both cohorts were offered enrollment in an open-label study with the test product or an FDA approved treatment for head lice. On day 15 all subjects were examined again and subjects with live lice were considered treatment failures and provided therapy. Lice free subjects returned 14 days later for final examination, with lice free subjects determined a treatment success and subjects having live lice offered an FDA approved therapy. In both trials the test product demonstrated superiority over vehicle for the primary endpoint defined as the percentage of subjects who were lice free 14 days after the second 10 minute application.

Table 12 summarizes the outcomes, demonstrating that approximately 75% of the *Tradenname* treated subjects were determined to be treatment successes, compared to 5% of vehicle patients in study 01 and 25% of subjects in study 02. It is unclear why the vehicle success rate was higher in study 02. The outcomes are consistent with the lice eradication results in other groups, including the per protocol and the secondary cohort, and are consistent with a sensitivity analyses evaluating the effect of patients with missing data.

Table 12: Lice Eradication Results (Primary Cohort-ITT)

	Study 01		Study 02	
	L.A. 5%	Vehicle	L.A. 5%	Vehicle
N	63	62	64	61
Number Lice Free (%)	48 (76.2)	3 (4.8)	48 (75.0)	16 (26.2)
p-value [†]	-	< .001	-	< .001

[†] Reported p-values are based on CMH stratified by site

Source: Reviewer's analysis and revised Study Report Table 2.

Statistical Review and Evaluation; Mat Soukup, Ph.D.

Both hair type and hair texture showed relatively consistent response between groups. In terms of hair length, the data showed a slight trend towards less efficacy in subjects with longer hair though small sample sizes limit the reliability of this conclusion.

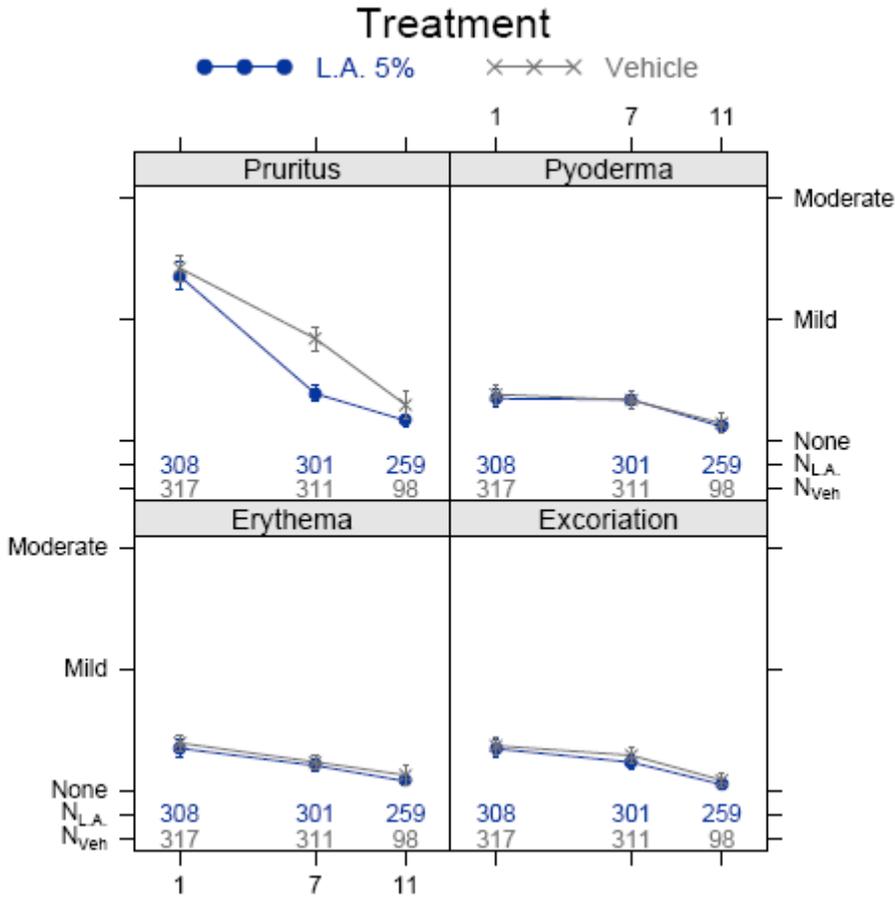
8. Safety

Safety data from eight studies sponsored by the applicant were submitted in the marketing application. The safety of *Tradenname* for treatment of head lice (*Pediculus humanis capitis*) was evaluated in two pivotal clinical studies enrolling 628 subjects (SU-01-2005 and SU-02-2005), an open label study enrolling 128 subjects (SU-03-2005), Phase 2 studies enrolling 167 subjects (SU-02-2003, SU-02-2003A and SU-02-2004), Phase 1 single dose bioavailability study enrolling 45 subjects (SU-01-2007), and a special safety study enrolling 244 healthy subjects (SU-01-2006).

A total of 485 subjects were assigned to be treated with two 10 minute treatments, one week apart. There were no study deaths and no serious adverse events. No subjects discontinued from the pivotal trials due to an adverse event and one subject (01-141) withdrew from the topical safety study due to mild nausea.

No deaths and no serious adverse events were reported in the clinical development of *Tradenname*. There were no laboratory evaluations completed during the course of this study.

Evaluation of local signs and symptoms specifically included assessment of pruritus, erythema, pyoderma, and excoriation. Treatment with *Tradenname* was not demonstrated to worsen or precipitate any of these conditions during the study. Overall, treatment with *Tradenname* appeared to be well tolerated in the clinical studies. The table below from the clinical/biostatistics reviews summarizes the data presented.



The sponsor has fully addressed the outstanding informational need concerning systemic bioavailability of benzyl alcohol.

9. Advisory Committee Meeting

No advisory committee was held for this application.

10. Pediatrics

Pediculosis capitis (head lice infestation) is common in children. The applicant has completed studies and provided sufficient numbers of subjects in the younger pediatric population to establish the efficacy for children 6 months of age and older. Additional information is needed pertaining to the potential systemic absorption of this product and the impact, if any, on safe use in children. The sponsor requested a waiver for pediatric studies in patients less than 6 months, based upon their determination that the studies are impossible or highly impractical because the numbers of patients in this age group (0-8 months) is so small. The applicant

provides information that there are no reports in the literature of head lice occurring in children less than 6 months of age and that experts in the field report never having seen a case of head lice in a child younger than 6 months of age.

As discussed at the PeRC, the applicant should be granted a partial waiver for two selected pediatric populations (neonates 0-1 month and children 1-6 months).

11. Other Relevant Regulatory Issues

Division of Medication Error Prevention has reviewed the proposed tradename and provided consultative advice. I agree that the applicant's proposed tradename(s) are vulnerable to name confusion that could lead to medication errors. The sponsor should continue to provide tradename for agency review and approval.

There are no other unresolved relevant regulatory issues.

12. Labeling

The proprietary name has not been determined. Draft physician's labeling (in conformance with the physician's labeling rule), carton container labeling and patient package insert are under discussion with the sponsor.

13. Decision/Action/Risk Benefit Assessment

I recommend that this product receive an Approval action in this cycle. The risk/benefit assessment supports approval of the product for the treatment of head lice infestation in patients 6 months of age and older.

There are no post marketing risk management activities necessary beyond professional labeling, prescription status, and routine pharmacovigilance. There are no post marketing commitments or requirements.

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/s/

Susan Walker
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DIRECTOR