Medical Officer's Review of NDA 22-129:
COMPLETE RESPONSE TO APPROVABLE LETTER

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Complete Response to Approvable Letter
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Established name: TRADENAME (benzyl alcohol), 5% Lotion
Trade name: Undetermined
Therapeutic Class: Pediculicide
Applicant:
Sciele® Pharma, Inc.
5 Concourse Parkway
Suite 1800, Atlanta, GA 30328
Priority Designation: S

Formulation: Lotion
Dosing regimen: Two 10-minute applications one week apart
Indication: For patients infected with *Pediculus humanis capitis* (head lice and their ova) of the scalp hair
Intended Population: Six months of age and older

Reviewer Name: Gordana Diglisic, M.D.
Team Leader: Jill Lindstrom, M.D.
RPM: Nichelle Rashid
Review start date: 12/12/08
Review completion date: 02/06/09

EXECUTIVE SUMMARY

This application was submitted as a "complete response" by the applicant to an approvable action letter issued by the division dated July 14, 2008.

The original application was submitted on Jun 15, 2007. The applicant submitted a new drug application for a lotion formulation of benzyl alcohol 5% (TRADENAME, 5% Lotion) proposed for the topical treatment of head lice (*Pediculosis capitis)* infestation in

subjects 6 months of age and older. This product is the first drug product to have benzyl alcohol as an active ingredient (NME).

Two well-controlled Phase 3 trials were conducted with the objective of establishing the superiority of two 10 minute application of TRADENAME, 5% Lotion one week apart to vehicle. In both Phase 3 trials, TRADENAME, 5% Lotion demonstrated superiority over vehicle. Safety data included eight studies conducted in the clinical development program. The incidence of adverse events was low for both the active and vehicle arms; none were considered serious.
(The reader is referred to the Clinical Review of the original NDA in DFS dated 6/27/08)

However, the original NDA received "Approvable" action for the following deficiencies:

1. Insufficient information regarding the systemic bioavailability of benzyl alcohol from their drug product and potential safety impact resulting from systemic absorption of benzyl alcohol (including but not limited to infant gasping syndrome):

   > *"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 quartile 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."*
   > (See Approvable Letter, 07/14/08)

2. Inspection of the drug substance manufacturing facility did not meet cGMP requirements.

(The reader is referred to Appendix 1 for the entire contents of the Approvable Letter)

To address the first deficiency, the applicant conducted the second bioavailability study (Sc-LA-08-01). The objective of this study was to evaluate the bioavailability of benzyl alcohol following a single, exaggerate 30- minute application of TRADENAME, 5% Lotion in subjects with head lice infestation. 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 to 2.99 mcg/mL), and one in the 4 to 11 year cohort at 1 hour post -treatment (1.63 mcg/mL).
None of subjects experienced adverse events.

Additionally, the applicant provided discussion regarding the relationship between benzyl alcohol and infant gasping syndrome (authored by Neil Buist,M.D.), and a review (authored by the (b) (4) of publicly-available benzyl alcohol safety data.

Based on above data, the applicant has provided sufficient and adequate information regarding the systemic bioavailability of benzyl alcohol from their drug product and potential safety impact resulting from systemic absorption of benzyl alcohol in pediatric and adult population.

Regarding the second deficiency, an "Acceptable" site recommendation from the Office of Compliance has been made.
(The reader is referred to the CMC Review, T. Mehta, M.Sc dated 02/11/09)

Current Submission:

On October 17, 2008, the applicant submitted a **"Complete Response to Approvable Letter"** containing the following:

1. **Response to request for clarification of the plasma benzyl alcohol concentrations observed during the study SU-01-2007, and the potential safety impact, resulting from systemic absorption of benzyl alcohol in children.** To address this issue, the sponsor submitted:

    a. Copy of the label from the bottles of NaCl/benzyl alcohol which were used as catheter flush in the first bioavailability study (SU-01-2007)
    b. Study Report from the second bioavailability study (Sc-LA-08-01)
    c. Discussion regarding the relationship between benzyl alcohol and infant gasping syndrome by Neil Buist, M.D.
    d. Review authored by the (b) (4) of publicly available benzyl alcohol safety data

2. **Update on a final response to the PAI inspection deficiencies**

3. **Draft labeling carton/container and PI**

4. **Safety update**

Discussion:

1. **Response to request for clarification of the plasma benzyl alcohol concentrations observed during the study SU-01-2007, and the potential safety impact, resulting from systemic absorption of benzyl alcohol in children:**

    a. Bioavailability Study SC-LA-09-01:

In response to request for clarification of the plasma benzyl alcohol concentrations observed during the study SU-01-2007, the sponsor stated that the elevated (> 3 mcg/mL) and sporadic plasma concentration of benzyl alcohol in Study SU-01-2007 were due to an intermittent use of a bacteriostatic saline (NaCl with 0.9% benzyl alcohol as a preservative) catheter flush, and thus were not "true", representative plasma concentrations (reflective of cutaneous exposure). The NaCl plus benzyl alcohol flush was used to clear the indwelling catheters that facilitated certain blood draws in some subjects. The applicant provided a copy of labeling from the bottles of NaCl plus benzyl alcohol which were used as the catheter flush. However, the phlebotomist did not adequately document the use of the benzyl alcohol containing flush in the study protocol. For that reason, the applicant conducted a second bioavailability study (Sc-LA-08-01) in which any catheter flush used was free of benzyl alcohol.

The objective of this single center, open-label study was to evaluate the bioavailability of benzyl alcohol following a single, exaggerated 30- minute application of TRADENAME, 5% Lotion in subjects (6 month to 11 years old) with active (at least 3 live lice) head lice infestation. All subjects (N=19) were observed to have at least moderate pruritus and excoriation of the scalp.
Clinic stuff applied a sufficient amount of the clinical material to thoroughly saturate the subject's hair and scalp for 30 minutes. Blood samples were collected for analysis of plasma benzyl alcohol concentration before application of TRADENAME, 5% Lotion (time 0) and at specified times after completing treatment application.

A total of 102 unique samples were analyzed. 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 to 2.99 mcg/mL), and one in the 4 to 11 year cohort at 1 hour post -treatment (1.63 mcg/mL).
No pharmacokinetic analyses were performed since only single benzyl alcohol concentrations were detected in any subject.

Table 1: Plasma Concentration (µg/mL) of Benzyl Alcohol – 6 Month to 3 Years Old Subjects (Cohort 1)

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

[a] Sample appeared hemolyzed
BQL - Below the Quantifiable Limit < 1.00 ug/mL
NSR - No sample received

Table 2: Plasma Concentration (µg/mL) of Benzyl Alcohol – 4 Years to 11 Years Old Subjects (Cohort 2)

Time (h)	Subject I.D.												
	002	005	006	007	011	012	013	014	015	016	017	019	020
Pre-treatment	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

[a] Sample appeared hemolyzed
BQL - Below the Quantifiable Limit < 1.00 ug/mL
NSR - No sample received

None of subjects experienced adverse events.

The maximum plasma concentration of benzyl alcohol (2.99 mcg/mL) obtained in this second bioavailability study was about 44 hold lower than the C_{max} (131.3 mcg/mL) obtained in the first bioavailability study in subjects 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. (See Clinical Pharmacology Review, 01/26/09).

The highest plasma concentration of benzyl alcohol (2.99 mcg/mL) that was observed in the second bioavailability study was ~ 37 fold lower than serum mean concentration of benzyl alcohol obtained from 6 infants with gasping syndrome (109.2 mcg/mL or 1.01 mmol/L)[1]

Reference
1. The New England Journal of Medicine; 1982 Nov 25; Vol 307; Issue 22; p1384-8; The gasping Syndrome and Benzyl Alcohol Poisoning; Garshanik, J.; Boecler, B.; Ensley, H.; McCloskey, S.; George, W.

Based on above data, the applicant has provided sufficient and adequate information regarding the systemic bioavailability of benzyl alcohol from their drug product.

b. Discussion regarding the relationship between benzyl alcohol and infant gasping syndrome by Neil Buist, M.D., Professor Emeritus, Oregon Health & Science University; (dated August 29, 2008). Dr. Nail Buist was the lead investigator that identified the occurrence and cause of "gasping syndrome".

The applicant submitted the document authored by N. Buist, M.D. in which Dr. Buist discusses the data from study SU-01-2007, and states that *"the dosage exposures, and proven blood levels provided and the ages of the subjects are orders of magnitude less than that caused the gasping syndrome in preemies."*

c. Review authored by the (b) (4) of publicly available benzyl alcohol safety data

The (b) (4) conducted searches of publicly accessible database to indentify information on the safety and human exposure to benzyl alcohol. The searches included published literature, internet, and U.S. and foreign government database.

Based on these searches, data were identified demonstrating that:

- Gasping syndrome is a relevant concern only for small premature infants, population distinct from the proposed patient population for TRADENAME, 5% Lotion
  - The infants who developed infant gasping syndrome were low-birth-weight premature neonates with limited ability to metabolized and excrete benzyl alcohol and its metabolite
  - Benzoic acid was accumulated because of immature livers of the preterm infants (unable to conjugate the benzoic acid with glycine and excrete the product, hippuric acid, in the urine)[1, 2]
  - Preterm infants also have low glomerular filtration rate (GFR). Adult levels of GFR are typically achieved by 2.5 to 5 months of age. Thus, inability to filter and excrete benzoic acid may also have contributed to the build up of serum benzoic acid and the resulting acidosis. [3]
  - Even the youngest proposed users of 5% L.A.(6months) have greatly superior metabolic and excretory capabilities compared to preterm neonates
  - A review of the literature indentifies no cases of gasping syndrome in full term infants.

- Numerous topical cosmetic and drug products containing benzyl alcohol are present on the market that could potentially yield higher exposure to benzyl alcohol than would be expected if the TRADENAME, 5% Lotion is used according to labeling instructions
  - Benzyl alcohol is used in large number of topical cosmetic products either as preservative, fragrance, solvent, or viscosity-decreasing agent (Table 3) (Cosmetic Safety Database 2008a)

Table 3: Cosmetic Products Containing Alcohol

Product Category	Number Containing Benzyl Alcohol
Hair Color and Bleaching	274
Sunscreen with SPF 15 and Above	195
Facial Moisturizer/Treatment	193
Moisturizer	168
Conditioner 154	154
Anti-aging	111
Shampoo	83
Facial Cleanser	69
Fragrance for Women	66
Anti-itch/Rash Cream	42
Others	294

- It is considered by the Cosmetic Ingredient Review Expert Panel to be safe at concentration of up to 5% in cosmetic formulations and up to 10% in hair dyes (CIREP 2001)
- Although actual concentrations used in products are not available, use at concentration of 1-3% has been recommended for preservative use (Beauty Products Made Easy 2008)
- Of 1,649 products currently on the market that contain benzyl alcohol, 39 are marketed for infants according to the Cosmetic Safety Database (Table 4)

Appears This Way On Original

Table 4: Topical Baby Products Containing Benzyl Alcohol

Product Types	Products
Moisturizer	Aveeno Daily Baby Moisturizing Lotion Aveeno Baby Daily Baby Lotion Aveeno Baby Lotion Daily Moisture Aloe Vesta 2-n-1 Skin Conditioner Cream Moisturel Therapeutic Lotion, Dry Sensitive Skin Formula Therapeutic Lotion Dry Sensitive Skin Formula Aveeno Baby Calming Comfort Baby Lotion Aveeno Baby Lotion Calming Comfort Johnson & Johnson Johnson's Baby Lotion, Bedtime Arbonne Baby Care (ABC) Body Lotion Johnson & Johnson Johnson's Baby Lotion Aloe Vera & Vitamin E Johnson & Johnson Johnson's Baby Bedtime Lotion Johnson & Johnson Johnson's Baby Lotion, Original Rite Aid Gentle Baby Lotion Johnson & Johnson Johnson's Bedtime Lotion Johnson & Johnson Johnson's Baby Lotion
Shampoo	Jason Natural Cosmetics Earth's Best Shampoo & Body Wash by JASON
Sunscreen	AVON SUN Baby Sunscreen Lotion, SPF 40 (2005 formulation) Avalon Baby Natural Mineral Sunscreen, SPF 18 Avalon organics Baby Natural Mineral Sunscreen SPF 18 Rite Aid Baby Sunscreen, SPF 45 (2005 formulation) Coppertone Water BABIES Lotion Sunscreen, SPF 50 CVS Baby Sunscreen Lotion, SPF 50 Coppertone Water BABIES Lotion Sunscreen, SPF 50 Walgreens Baby Sunscreen, SPF 50 Coppertone Water BABIES Quickcover Lotion Spray Sunscreen, SPF 50 Preferred Plus Products Sunblock Baby Lotion, SPF 45 Preferred Plus Products Sunblock Baby Lotion, SPF 30 Walgreens Baby Sunscreen Lotion Spray, SPF 50 Walgreens Baby Sunblock
Anti-Itch/Rash Cream	A+D Ointment Zinc Oxide
Baby Wipes	Pampers Wipes Natural Aloe Unscented Pampers Baby Wipes Unscented Luvs Natural Touch Tub with Lightly Scented Wipes Pampers Kandoo Flushable Wipes, Magic Melon Pampers Lavender Calming Baby Wipes Pampers Kandoo Flushable Wipes Tub Magic Melon

- While it is likely that above baby products contain lower concentrations of benzyl alcohol than TRADENAME, 5% Lotion, their application may result in greater benzyl alcohol absorption because of the difference in the way that the product are used(e.g. TRADENAME, 5% Lotion. product is applied to scalp and hair, left for 10 minutes and than rinsed off; while the baby products listed above may be applied over most of the skin surface area, applied repeatedly over the course of the day, may not be rinsed off between application, and are frequently covered by diapers or clothing resulting in an occluded application site*).

  *Occlusion of the application site increase benzyl alcohol absorption (32% over 24 hour from an unoccluded site versus 80% from an occluded site; Bronaugh et all 1990)

- Benzyl alcohol is also used as an excipient in a variety of topical over-the-counter and prescription drugs (Physician Desk Reference 2008; Table 5)

Table 5: Prescription and Non-Prescription Drugs Listed With Benzyl Alcohol

Product Name
Aldara™ Cream 5%
Anbesol® Cold Sore Therapy Ointment
Anbesol® Junior Gel
Maximum Strength Anbesol® Gel and Liquid
Bactroban Cream® 2%
Desenex® Athletes Foot Cream
Head and Shoulders® Intensive Solutions Dandruff Shampoo
IvyBlock®
LamisilAT® Creams
Lotrimin® Cream
Lotrisone® Lotion
Mentax® Cream
Naftin® Cream

- Although the percentages of benzyl alcohol present in the creams, lotion, and ointments are less than is present in TRADENAME, 5% Lotion the directions for use of these products allow for longer time exposures (the products are not rinsed off) and potential occlusion of the application site.

2. Update on a final response to the PAI inspection deficiencies

- The cGMP issues have been be resolved
  - As a corrective action, the drug substance containers were changed from a (b) (4)
  - Drug substance manufacturer, (b) (4), passed a re-inspection by the (b) (4) during the week of November 3, 2008.

3. Draft labeling carton/container and PI

- Draft labeling has been submitted:
  - The Division's comments have been incorporated into the present versions of the package insert, carton label, immediate container label and patient direction leaflet.
- The sponsor states that, other than bioavailability study, no additional information relating to safety or effectiveness has become available and that the label has been updated to reflect the data collected in the second clinical bioavailability study.

4. Safety update:

- The applicant stated that there is no new safety information to report

SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

CMC

From the Chemistry review:

Container Closure System [Tradename (benzyl alcohol) 5% Lotion] Satisfactory

- The proposed container/closure system for the drug product is an 8 oz (b) (4) Information provided for the proposed container/closure is deemed adequate.
- Based on the adequate 24 months stability data, the expiration-dating period of 30 months is granted.

Drug Substance

- (b) (4) manufactures the benzyl alcohol. The chemistry, manufacturing, and controls information on the drug substance is provided in DMF (b) (4), which is deemed adequate to support this application.

Container Closure System [Benzyl Alcohol NF] Satisfactory

- (b) (4) However, during the site inspection Office of Compliance found them unsatisfactory. Therefore, DMF holder replaced the storage container to (b) (4) (amendment 0030 December 30, 2008).

Post approval Stability Protocol and Stability Commitment

- The applicant commits to place the first three production batches of the drug substance manufactured by (b) (4) and stored in (b) (4) on stability at 25^0C/60% RH condition with following timetable: 3, 6, 9, 12, 18 and 24 months. Thereafter, applicant will include at least one lot of drug substance per year for long-term stability (cover letter amendment 0030).
- Applicant commits to conduct the stability studies on the first three commercial lots of the drug product after approval of this application. Once the initial stability protocol met the requirements, one batch per calendar year will be placed on the stability at long-term storage condition. The applicant has agreed to perform full-scale ICH stability studies on first three commercial batches to support the switch to the natural bottles.

Labeling and Package Insert:

Sponsor revised the labeling and carton labels (see Appendix 1- Approvable Letter, 07/14/08)

- Insert labeling deemed adequate for CMC prospect
- Immediate container label is deemed adequate.
- Carton and immediate container labels are deemed adequate.

Recommendation and Conclusion on Approvability:
This NDA has provided sufficient CMC information to assure the identity, strength, purity, and quality of the drug product. The labels have adequate information as required. An "Acceptable" site recommendation from the Office of Compliance has been made. Therefore, from the CMC perspective, this NDA is now recommended for approval."
(See CMC Review dated 02/11/09, Tarun Mehta, M.Sc., Office of New Drug Quality Assessment; Division of Pre-Marketing Assessment II; Branch III)

Animal Pharmacology/Toxicology

There was no pharmacology/toxicology issues in the Approvable Letter dated July 14, 2008.

From the pharmacology/toxicology review:
"This NDA 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). No specific listed drug products are referred to in these literature references. In addition, the sponsor conducted 14-day dermal toxicity studies with the lice asphyxiator drug product in rats and dogs and oral embryofetal development studies with benzyl alcohol in rats and rabbits. Based on the nonclinical data submitted to NDA 22-129 for benzyl alcohol and the lice asphyxiator drug product, Pharmacology/Toxicology recommended approval of NDA 22-129 provided that the recommended changes in the label described in the review were incorporated into the drug product label. The reader is referred to the Pharmacology/Toxicology review of the original NDA entered into DFS on February 19, 2008 for additional details, if needed."

"**Conclusion:** This NDA can be approved from a Pharmacology/Toxicology perspective"
(See Pharmacology/Toxicology Memorandum dated 01/30/09, B. Hill, PhD, Pharmacology/Toxicology Supervisor)

Clinical Pharmacology

From the clinical pharmacology review:
"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)."

"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."

Other Relevant Materials:

TRADENAME:

The applicant initially submitted two tradenames, (b) (4) .The Division of Drug Marketing, Advertising, and Communications (DDMAC) objected to the use of those names from a promotional perspective. Thus, the Applicant submitted the names (b) (4) and (b) (4) for review. However, those names were withdrawn by the Applicant on March 28, 2008. Subsequently, the Applicant submitted the names (b) (4) and (b) (4). The Division of Medication Error Prevention and Analysis (DMEPA) objected to the name (b) (4) due to look-alike similarities with (b) (4) , and to the name (b) (4) due to orthographic similarities to (b) (4) and orthographic and phonetic similarities to (b) (4) .
Subsequently, the name (b) (4) was submitted. DMEPA did not object to the use of the proprietary name (b) (4) . However, DDDP objected to the name (b) (4) due to sound-alike similarity with (b) (4) (OTC product) which could cause confusion that subsequently leads to medication errors (oral ingestion) in the clinical setting.

Conclusion:

- The applicant has provided sufficient clinical data to establish safety and efficacy of their drug product for topical treatment of head lice infestation in patients 6 months of age and older.
- Because of the potential for systemic exposure, it would be prudent to contraindicate the use of 5% L.A. in children less than 6 months of age.
- The cGMP issues has been be resolved
- Draft labeling has been submitted

Therefore, this submission adequately addressed all deficiencies outlined in the action letter (dated 07/14/08).

Recommendation on Postmarketing Actions:

Risk Management activities

- There are no recommendations for a specific postmarketing risk management plan. Routine risk minimization measures such as professional labeling, prescription status, and spontaneous adverse event reporting, comprise an adequate risk management plan for this drug at this time.

Required Phase 4 Commitments

- There are no Phase 4 Commitments

Recommendation for Regulatory Action

It is recommended that from a clinical perspective, NDA 22-129, for TRADENAME (benzyl alcohol) Lotion 5%, for the topical treatment of head lice (*Pediculosis capitis*) infestation in patient 6 months of age and older, be approved.

APPENDIX 1

Approvable Letter – July 14, 2008

NDA 22-129

Sciele Pharma, Inc.
ATTENTION: Debra Hayes, RAC
Five Concourse Parkway
Suite 1800
Atlanta, GA 30328

Dear Ms. Hayes:

Please refer to your new drug application (NDA) dated June 15, 2007, received June 15, 2007, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for TRADENAME (benzyl alcohol) Lotion 5%.

We acknowledge receipt of your submissions dated July 19, August 31, September 17, September 21, September 28, October 12, and December 28, 2007; January 25, February 5, March 4, March 19, April 14, May 23, and June 5, 2008.

We also acknowledge receipt of your submission dated July 10, 2008. This submission was not reviewed for this action. You may incorporate this submission by specific reference as part of your response to the deficiencies cited in this letter.

We completed our review of this application, as amended, and it is approvable. Before the application may be approved, however, it will be necessary for you to address the following:

> 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 quartile 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.

Also, it will be necessary for you to submit draft labeling. The draft texts for the package insert and the patient package insert should be revised according to the enclosed labeling.

The draft texts for the immediate container and carton labels should be revised as follows.

1. Delete the proposed tradename, (b) (4)

2. Change the dosage form statement from (b) (4)" to "Lotion."

3. Delete the (b) (4) designation after the dosage form statement.

4. Relocate the wording (b) (4) from the side panel of the carton label to the principal display panel and increase the size of the wording to make it more prominent on the label. Consider rewording this statement to (b) (4) in order to make the warning more specific.

5. Add "Warning: Keep out of reach of children" on both the immediate container and carton labels to help prevent accidental oral ingestion of the product. Also, consider adding the warning, "Harmful if swallowed" to both the immediate container and carton labels.

6. The instructions for use in the Dosage and Administration, as presented on the side panel of the carton label, are incomplete. Revise the statement, (b) (4) to "See package insert, including the patient information section, for complete information."

7. Delete Product Description, including the indication statement. Reword the section as follow: Contents Description: TRADENAME is supplied as a white topical lotion containing benzyl alcohol, 5%. Inactive ingredients in this formulation are water, mineral oil, sorbitan monooleate, polysorbate 80, carbomer 934P and trolamine.

8. Decrease the size of the distributor's name logo.

9. Increase the size of the statement of strength "8 oz. (227 g)," slightly, in order to increase its visibility on the label.

10. Add Lot #, Expiration Date, and barcode on the immediate container label.

In addition, your container/closure proposal, consisting of an orifice reducing plug (b) (4) and current cap, should be implemented.
If additional information relating to the safety or effectiveness of this drug becomes available, revision of the labeling may be required.
During a recent inspection of the manufacturing facility for this application, our field investigator conveyed deficiencies to the facility's representative. Satisfactory resolution to these deficiencies is required before this application may be approved.

SAFETY UPDATE

When you respond to the above deficiencies, include a safety update as described at 21 CFR 314.50(d)(5)(vi)(b). The safety update should include data from all non-clinical and clinical studies of the drug under consideration regardless of indication, dosage form, or dose level.

1. Describe in detail any significant changes or findings in the safety profile.

2. When assembling the sections describing discontinuations due to adverse events, serious adverse events, and common adverse events, incorporate new safety data as follows:
    - Present new safety data from the studies for the proposed indication using the same format as the original NDA submission.
    - Present tabulations of the new safety data combined with the original NDA data.
    - Include tables that compare frequencies of adverse events in the original NDA with the retabulated frequencies described in the bullet above.
    - For indications other than the proposed indication, provide separate tables for the frequencies of adverse events occurring in clinical trials.

3. Present a retabulation of the reasons for premature study discontinuation by incorporating the dropouts from the newly completed studies. Describe any new trends or patterns identified.

4. Provide case report forms and narrative summaries for each patient who died during a clinical study or who did not complete a study because of an adverse event. In addition, provide narrative summaries for serious adverse events.

5. Describe any information that suggests a substantial change in the incidence of common, but less serious, adverse events between the new data and the original NDA data.

6. Provide a summary of worldwide experience on the safety of this drug. Include an updated estimate of use for drug marketed in other countries.

Provide English translations of current approved foreign labeling not previously submitted.

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling.
To do so, submit, in triplicate, a cover letter requesting advisory comments, the proposed materials in draft or mock-up form with annotated references, and the package insert to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications

5901-B Ammendale Road
Beltsville, MD 20705-1266

Within 10 days after the date of this letter, you are required to amend this application, notify us of your intent to file amendment, or follow one of your other options under 21 CFR 314.110. If you do not follow one of these options, we will consider your lack of response a request to withdraw the application under 21 CFR 314.65. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

The drug product may not be legally marketed until you have been notified in writing that this application is approved.

If you have any questions, call Maria Walsh, Project Management Officer, at (301) 796-1017.

Sincerely,
{See appended electronic signature page}
Daniel Shames, M.D.
Deputy Director
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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

/s/

Gordana Diglisic
2/17/2009 02:02:20 PM
MEDICAL OFFICER

Jill Lindstrom
2/19/2009 05:08:06 PM
MEDICAL OFFICER