CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-129

CROSS DISCIPLINE TEAM LEADER REVIEW

Team Leader Review Addendum
Complete Response to Approvable Letter

Date	February 27, 2009
From	Jill Lindstrom, MD
Subject	Team Leader Review
NDA/BLA #	22-129
Applicant	Sciele Pharma, Inc.
Date of Submission **Complete Response** **Original Application**	 October 17, 2008 June 15, 2007
PDUFA Goal Date	April 17, 2009
Proprietary Name / Established (USAN) names	TRADENAME (benzyl alcohol) Lotion, 5%
Dosage form / Strength	Lotion, 5%
Proposed Indication(s)	Topical treatment of head lice infestation in patients 6 months of age and older.
Recommended Action:	*Approval*

1. Introduction

TRADENAME (benzyl alcohol) Lotion, 5%, is a topical pediculocide for which the applicant seeks approval under Section 505(b)(2) of the Federal Food Drug and Cosmetic Act for the topical treatment of head lice infestation in patients 6 months of age and older. In addition to data which the applicant owns or has right-of-reference, the applicant also submitted literature in support of the application; the applicant is not relying on Agency findings for a listed drug. The initial application, submitted on June 15, 2007, received an Approvable action letter dated July 14, 2008. The applicant submitted a Complete Response on October 17, 2008, and this brief Team Leader Review Addendum will discuss the Complete Response. The reader is referred to my Team Leader Review of July 10, 2008, for discussion of the original application.

2. Background

The following issues were articulated in the Approvable action letter:

1. "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."

2. "In addition, your container/closure proposal, consisting of an orifice reducing plug (b) (4)) and current cap, should be implemented."

3. "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."

Additionally, changes to labeling were requested.

These issues are discussed sequentially below.

4. CMC/Device

Although the applicant provided sufficient CMC information to assure the identity, strength, purity and quality of the drug product in the initial application, inspection of the drug substance manufacturing facility during the first review cycle did not meet cGMP requirements. The applicant resolved the issues, and reinspection was satisfactory.

The applicant initially proposed that their drug product be dispensed in (b) (4) . This container and closure system presented a risk for overdosing and ingestion medication errors, respectively. The applicant subsequently proposed a neutral polypropylene bottle with an orifice-reducing plug. The neutral ((b) (4) bottle is sufficiently translucent to allow ascertainment of the amount of drug product remaining in the bottle, which should reduce the risk of over-application (depending on hair length, a patient may need to apply only half of a bottle). It is anticipated that patients will be better able to ascertain the amount of product remaining in the container when it is packaged in the neutral bottle with the orifice-reducing plug than they were able to do with the (b) (4) without the orifice-reducing plug which was utilized in the clinical trials, as the latter required subjects or their caregivers to observe through the narrow bottleneck the amount of white product remaining within a (b) (4), fully-opaque bottle, whereas with the marketed container the amount of product remaining in the container can be visualized through the container wall. The incorporation of an orifice-reducing plug into the container closure system, similar to that seen on some shampoo bottles, should reduce the risk of ingestion-type medication errors.

The CMC reviewer, Mr. Taru Mehta, recommended *Approval* from the CMC perspective; the reviewer is referred to his reviews for a full discussion of the CMC issues.

5. Clinical Pharmacology/Biopharmaceutics

The applicant identified that saline preserved with benzyl alcohol was used as a flush for the intravenous catheters placed in subjects to facilitate obtainment of serum samples in Study SU-

01-2007, and attributed this as the likely explanation for the aberrant sporadic elevations of benzyl alcohol detected in that study.

Because benzyl alcohol was essentially systemically administered via IV flush with the benzyl alcohol-preserved saline, the applicant conducted a second maximal use systemic exposure study of similar design (Sc-LA-08-01), but used only non-preserved saline (without benzyl alcohol) for catheter flush. In this second study, quantifiable benzyl alcohol concentrations were identified in 4 of 19 subjects, three in the 6 month to 3 years of age cohort at 30 minutes post treatment, and one in the 4 to 11 years of age cohort at 1 hour post treatment. All of the quantifiable samples were below 3 mcg/mL, which is significantly less than the levels identified in infants with gasping syndrome.

The reader is referred to the review by Dr. Abi Adebowale, who now recommends *Approval* from a clinical pharmacology perspective, for a full discussion of the study.

6. Safety

The applicant identified various cosmetic and drug products that contain benzyl alcohol, some of which would be expected to be applied to larger surface areas, to include under occlusion, and for longer durations than TRADENAME Lotion. The applicant also provided expert discussion of the entity "gasping syndrome." The applicant's discussion is addressed in the clinical review by Dr. Gordana Diglisic, who now recommends an *Approval* action.

These topics were addressed independently in my prior review.

7. Other Relevant Regulatory Issues

Benzyl alcohol is monographed for use as an anorectal analgesic, but there are no products with benzyl alcohol as the active ingredient listed in the Orange Book. It does not appear that any other product with benzyl alcohol as the active ingredient has been approved under section 505 of the Act.

8. Labeling

The proprietary name has not been established. The product is referred to as TRADENAME (benzyl alcohol) Lotion, 5%, in this review and in the draft labeling.

The applicant submitted proposed labeling in the format that complies with the Physicians' Labeling Rule. The applicant incorporated the changes requested in the Approvable action letter.

The results from the repeated maximal use systemic exposure study Sc-LA-08-01 were added to the Clinical Pharmacology section of the package insert, replacing the results from the prior study which had been contaminated with benzyl alcohol via IV flush.

Labeling negotiations have not concluded at the time of this review.

9. Recommendations/Risk Benefit Assessment

Recommended regulatory action: *Approval*

Risk Benefit Assessment:
The risk-benefit ratio supports approval of this product for the treatment of head lice infestation in patient six months of age and older.

Recommendation for Postmarketing Risk Management Activities:
Postmarketing risk management beyond professional labeling, prescription status, and routine pharmacovigilance is not needed.

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/s/

Jill Lindstrom
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MEDICAL OFFICER