CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

022408Orig1s000

MEDICAL REVIEW(S)

Medical Officer's Review of NDA 22-408:
Complete Response to Complete Response Letter from FDA

Application Type: NDA 505(b)(1)
Supporting Document #: 18
Submission Type/Number: Original-1

Letter Date: July 23, 2010
Stamp Date: July 26, 2010
PDUFA Goal Date: January 26, 2010

Established name: Spinosad
Proposed Trade Name: Natroba™ Suspension, 0.9%
Therapeutic Class: Anti-lice product
Applicant: ParaPRO
Priority Designation: Standard

Formulation: Suspension
Dosing Regimen: One 10 minute application: if live lice seen, an additional application 7 days after first application
Indication: Topical treatment of head lice infestations
Intended Population: Four years of age and older

Reviewer Name: Patricia C. Brown, M.D.
Team Leader: Gordana Diglisic, M.D.
RPM: Dawn Williams
Review Start Date: September 8, 2010
Review Completion Date: December 9, 2010

EXECUTIVE SUMMARY

The submission dated July 23, 2010 contains the applicant's complete response to a complete response letter issued by the Division on November 18, 2009.

The original application was submitted January 21, 2009. The applicant, ParaPro Pharmaceuticals, submitted a 505(b)(1) application for Tradename (spinosad) Suspension, 0.9%. The proposed indication is topical treatment of head lice infestations in patients (b) (4) The active ingredient, spinosad, is a new molecular entity which is not marketed as a drug in the United States.

Tradename (spinosad) Suspension, 0.9% was demonstrated to be statistically superior to an active comparator NIX (permethrin 1%) in each of two well-controlled pivotal, Phase 3 trials. In these trials the spinosad product was applied for 10 minutes. A second application was made one week later if live lice were seen. NIX was used as labeled. Safety was evaluated in the two pivotal trials. Supportive safety data is also available from nine other Phase 1 and Phase 2 trials. In the pivotal Phase 3 trials, the three most common adverse events (application site erythema, ocular hyperemia, application site irritation) were local and the rate for these was less than that for the active comparator, NIX. In the clinical development program, no deaths occurred, and three serious adverse events, not considered related to study drug, occurred among those exposed to spinosad formulations. (Please see Clinical Review of the original NDA, dated October 30, 2009.)

After review of the original NDA by the various disciplines, the action taken was a Complete Response on November 18, 2009. The reasons for this action included the following:

1. FDA agrees that spinosad, containing spinosyns A and D in a ratio of approximately 5:1, is a single active ingredient. However, we have recently approved a product containing benzyl alcohol (present at 5%) as an active ingredient for the treatment of head lice. This would indicate that your product contains two active ingredients: spinosad and benzyl alcohol (b) (4).

    A. Provide information to support approval of your product according to the regulations for fixed-combination prescription drugs at 21 CFR 300.50.

    B. Provide pharmacokinetic data for benzyl alcohol in lice-infested subjects.

    C. Submit complete CMC information on the drug substance, benzyl alcohol.

    D. Submit complete nonclinical information to support the safety of benzyl alcohol per the ICH M3 (R2) guidance titled “Guidance on Non-Clinical Safety Studies for the Conduct of Human Clinical Trials for Pharmaceuticals”.

2. Although your maximal usage pharmacokinetic trials detected no systemic exposure of spinosad from the use of TRADENAME (spinosad) Suspension, 0.9%, only 8 healthy subjects under the age of 4 years were evaluated. The youngest subjects with head lice are at greatest risk for systemic exposure due to their greater surface-to-volume ratio and the effects of the infestation itself on the scalp.

(b) (4)

3. Sufficient information has not been submitted to assure the identity, strength, purity and quality of the spinosad drug substance and the drug product.

To address the first deficiency, items # 1 A through D, in the FDA complete response letter, the applicant relies on existing clinical, pharmacokinetic, CMC, and nonclinical information to support the safety and efficacy of Tradename (spinosad) 0.9% Suspension as a single active ingredient medication. The applicant states that their intent was that benzyl alcohol would not be an active ingredient. The applicant also makes a reasonable argument for benzyl alcohol as a legitimate component of the formulation.

To address the second deficiency regarding pk data, (b) (4) The data obtained by the applicant was in healthy subjects under age 4. Since normal skin is a poor surrogate for diseased skin, "…The Division of Clinical Pharmacology has maintained that for topically applied products, bioavailability testing must be performed in subjects with the disease of interest…" (Clinical Pharmacology Review of NDA (22-408) Resubmission)

To address the third deficiency, the applicant has provided sufficient information to assure the identity, strength, purity, and quality of the drug product. From the CMC perspective, this NDA is recommended for approval.

Regulatory Background:

A Complete Response Letter was issued November 18, 2009. With a letter dated December 29, 2009 the applicant requested a Type A meeting to discuss their response to the Complete Response Letter. The applicant submitted a briefing document dated January 22, 2010 for a Type A meeting. At the March 25, 2010 a Type A, post-action meeting the Agency indicated that further clarity was requested regarding the following principal issues (presented as excerpts of the meeting minutes that were sent to the applicant on 4/9/10):

1. Whether the presence of benzyl alcohol in the ParaPRO product is a formulation necessity, that is, must the product be formulated in benzyl alcohol? Are there data suggesting that the product cannot be formulated in a benzyl alcohol-free vehicle? Your intent that (b) (4) cannot be the sole basis for determining that the benzyl alcohol is an inactive ingredient.

2. The scientific data upon which your assertion that benzyl alcohol be considered an inactive ingredient is based. We would like your perspective on the vehicle response rates and the inconsistency in these rates in the following studies:
    - a 22% and 89% treatment success rate for the vehicle in phase 2 study SPN-201-05 at days 7 and 14, respectively;
    - a 49% and 26% treatment success rate for the vehicle in phase 2 study SPN-202-06 at days 7 and 14, respectively.

    Meeting Discussion:

    The applicant noted that study SPN-202-05 had a different design than study SPN-202-06, including the number of treatments and combing which led to

differences in efficacy results for benzyl alcohol. The Agency requested that the applicant utilize study SPN-202-05 findings to obtain an estimate of the treatment effect for benzyl alcohol if it were to be used for 2 treatments as it was in the Phase 3 trials. Such an estimate may provide information to evaluate the contribution of spinosad over that of benzyl alcohol (vehicle).

3. Your methodology used to determine the benzyl alcohol exposure to the head louse and to the patient

The applicant responded with a submission dated April 13, 2010 containing responses to the FDA questions. The applicant's response discussion included:

- Document summarizing the position that benzyl alcohol is a pharmaceutical necessity and is required in the spinosad formulation
- Statistical analysis conducted to estimate the effect of benzyl alcohol in the ParaPRO formulation

Current Submission:

On July 23, 2010 the applicant submitted a "complete response to FDA's Complete Response Letter dated November 18, 2009," containing the following:

1. Response to FDA statement 1 in the complete response letter:

The applicant's response discussion includes:

- Statistical analysis (Appendix 2) conducted to estimate the effect of benzyl alcohol in the ParaPRO formulation
- Document (Appendix 3) summarizing the position that benzyl alcohol is a pharmaceutical necessity and is required in the spinosad formulation

For items # 1 A through D, in the FDA complete response letter, the applicant proposes to rely on existing clinical, pharmacokinetic, CMC, and nonclinical information to support the safety and efficacy of the ParaPRO product as a single active ingredient medication

2. Response to FDA statement 2 in the complete response letter:

3. Response to FDA statement 3 in the complete response letter:

4. A. Updated labeling, carton packaging, and bottle label

   B. A new proposed proprietary name request

5. Safety update

Discussion:

1. Response to FDA statement 1 (below) in the complete response letter:

> **FDA agrees that spinosad, containing spinosyns A and D in a ratio of approximately 5:1, is a single active ingredient. However, we have recently approved a product containing benzyl alcohol (present at 5%) as an active ingredient for the treatment of head lice. This would indicate that your product contains two active ingredients: spinosad and benzyl alcohol** (b) (4)

The applicant's response discussion includes:

- Statistical analysis conducted to estimate the effect of benzyl alcohol in the ParaPRO formulation
- Document summarizing the position that benzyl alcohol is a pharmaceutical necessity and is required in the spinosad formulation

At the Post-Action meeting of March 25, 2010, the Agency requested that the applicant utilize study SPN-202-05 findings to obtain an estimate of the treatment effect for benzyl alcohol if it were to be used for 2 treatments as it was in the Phase 3 trials. The applicant has responded to this by providing a statistical report in Appendix 3 of the current submission. This report is evaluated in statistical review (of supporting document 15) dated May 19, 2010. A summary of the statistical comments is provided in the current document in "Statistics" under "Significant Findings from Other Review Disciplines."

The applicant responds to the suggestion that their spinosad drug product has two active ingredients by arguing that although Ulesfia Lotion was approved with 5% benzyl alcohol as the active ingredient, the (b) (4) benzyl alcohol in Tradename (spinosad) 0.9% Suspension is not an active ingredient principally because the intent of the formulation (b) (4) for the intended active ingredient spinosad.

The applicant submits the following three items (in bold) to support the assertion that benzyl alcohol is a necessary inactive ingredient.

A. The intent of having benzyl alcohol in the Spinosad product formulation is (b) (4) **as the alcohol of choice with minimal interference to hair and scalp quality.**

The applicant states that they purchased the formulation and related technology from Johnson and Johnson. The applicant asserts that typical hair treatment formulations are aqueous based products. For the Tradename (spinosad) 0.9% Suspension drug product, (b) (4) spinosad, the active ingredient. The applicant states that benzyl alcohol is preferred (b) (4) because it is a USP/NF ingredient (b) (4)

A search of the FDA website Inactive Ingredient Search for Approved Drug Products (http://www.accessdata.fda.gov/scripts/cder/iig/index.cfm performed by this reviewer on

9/23/2010) reveals 87 approved drug products containing benzyl alcohol at concentrations up to 10.96%, in a product for intramuscular injection, and up to 50%, for a topical gel product.

The applicant states that they never intended benzyl alcohol in the product to be an active ingredient.

Per 21CFR210.3(b)7, *Active ingredient* means any component that is intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease, or to affect the structure or any function of the body of man or other animals.

Clinical Comment for Statement A:
The applicant's intent is a legitimate factor to consider in evaluation whether benzyl alcohol is an active ingredient in the drug product, Tradename (spinosad) 0.9% Suspension.

B. Benzyl alcohol is a formulation necessity (b) (4)

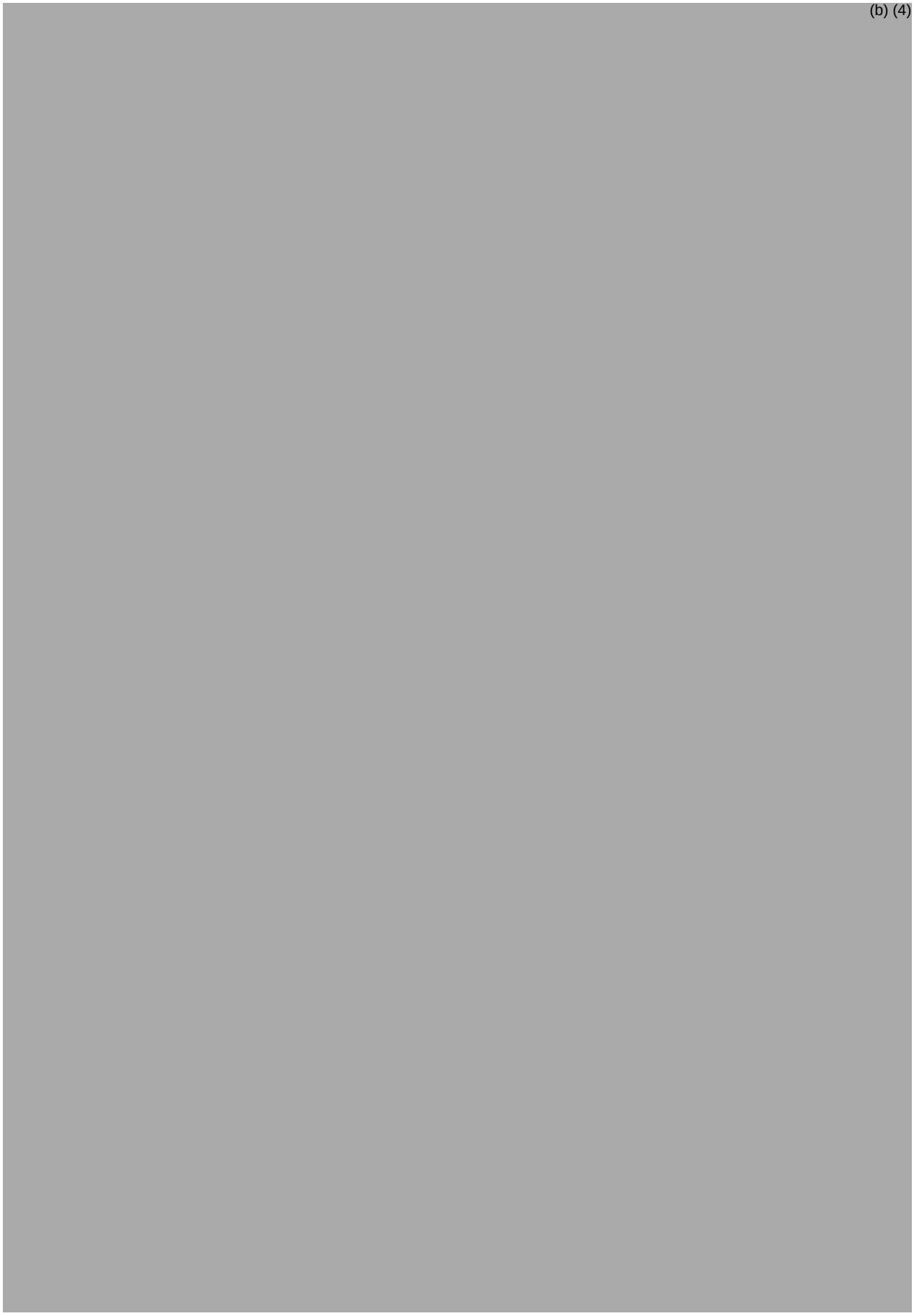
The response to this is based on information provided in Appendix 3 of the current submission and consists of a document summarizing the position that benzyl alcohol is a pharmaceutical necessity and is required in the spinosad formulation.

The applicant asserts that typical hair treatment formulations are aqueous based products. For the Tradename (spinosad) 0.9% Suspension product (b) (4) were needed to (b) (4) spinosad, the active ingredient.

The formulation evaluated in the spinosad NDA consists primarily of (b) (4) isopropyl alcohol, (b) (4) benzyl alcohol, (b) (4) hexylene glycol, (b) (4) propylene glycol and (b) (4) water. Spinosad solubility in water is very limited. (b) (4)

(b) (4)

(b) (4)



(b) (4)

pH Effects:
The applicant states that net, the pH can be adjusted in the range of 5.0-7.5 for the spinosad formulations. (b) (4) Therefore, pH is not likely to have a significant influence to cause an increase in spinosyn D solubility in the pH range used for the spinosad formulation.

Clinical Comments for Statement B:
A reasonable argument appears to be made for benzyl alcohol as a legitimate component of the formulation.

C. The volume exposure to benzyl alcohol in the Ulesfia treatment versus the Spinosad product treatment is substantially different.

The applicant states that in the complete response letter it was noted that the spinosad product contained (b) (4) benzyl alcohol versus Ulesfia Lotion at 5% with a potential impression that there is higher exposure to benzyl alcohol from the spinosad product than from Ulesfia Lotion.

The applicant calculated the benzyl alcohol exposure to the patient, for Tradename (spinosad) 0.9% Suspension and Ulesfia Lotion based on the directions for use.

(b) (4)

Table 3: Calculation of Benzyl Alcohol Exposure to Patient

	Spinosad product	**Ulesfia**
Specific Gravity (g/mL)	(b) (4)	
Weight of bottle contents (g)		
Benzyl Alcohol (BA) content (%)		
BA content (g/bottle)		
Bottles per application		
Required applications		
Total bottles used		
Total BA exposure per application		
Total BA per Treatment		

Based on applicant's table in submission dated April 13, 2010

The applicant argues based on the above calculations that the exposure to benzyl alcohol in Tradename (spinosad) 0.9% Suspension will be less than that for benzyl alcohol in Ulesfia, for all Ulesfia treatment regimens except for the one with the shortest hair (0-2 inches).

However, the argument presupposes that there will only be one treatment with Tradename (spinosad) 0.9% Suspension. Tradename (spinosad) 0.9% Suspension will be labeled for one treatment and a second treatment one week (7 days) later if live lice are seen. Then by the above calculations exposure to benzyl alcohol in the spinosad product will be higher than that than in Ulesfia Lotion for treatment regimens for hair lengths 0-2 inches and 2-4 inches.

Additionally it may be argued that patient exposure to benzyl alcohol in the formulation is more a function of the degree to which the scalp is made wet by the product. Once there is a layer of product at the scalp surface, excess volume of product will only increase exposure of non-vital hair shafts (and lice.) In this type of situation, differing concentrations 5% versus (b) (4) might be expected to play a larger role in patient exposure.

Clinical Comment for Statement C:
The applicant does not make a convincing argument that the volume of exposure to benzyl alcohol in the Ulesfia treatment is substantially different (more) than that in Tradename (spinosad) 0.9% Suspension.

2. Response to FDA statement 2 (below) in the complete response letter:

> **Although your maximal usage pharmacokinetic trials detected no systemic exposure of spinosad from the use of TRADENAME (spinosad) Suspension, 0.9%, only 8 healthy subjects under the age of 4 years were evaluated. The youngest subjects with head lice are at greatest risk for systemic exposure due to their greater surface-to-volume ratio and the effects of the infestation itself on the scalp.**

(b) (4)

The applicant argues that compared with Ulesfia Lotion, providing PK data on subjects 6 subjects from 6 to 36 months, with Tradename (spinosad) 0.9% Suspension PK data has been provided on 8 subjects ages 6 to 24 months. Ulesfia Lotionreceived a use claim for subjects 6 months and older and ParaPRO has been asked to provide more PK data, representing to ParaPRO a non-level playing field.

The important distinction is that the subjects studied for Ulesfia Lotion had active head lice infestation with at least 3 live lice and all subjects were observed to have at least moderate pruritus and excoriation of the scalp. The PK study performed by ParaPRO involved 8 healthy subjects without lice infestation.

At the pre-IND meeting May 12, 2003, the Agency stated that:

> Pediatric PK studies should be done in patients with head lice infestation as the presence of scalp irritation could result in increased systemic absorption. This would mirror the use of the final marketed product and would be a better measure of true systemic exposure upon use since it will maximize dermal/scalp absorption.

Although patients with lice can be asymptomatic, pruritus is common[1]. Pruritus may take 2 to 6 weeks to develop after first exposure. This reflects an immunologic response thought to be to components of louse saliva or anticoagulant. Common findings include excoriations, erythema, pyoderma, and scaliness of the scalp and posterior neck.[2] These findings represent alterations of the skin barrier, which can affect topical drug absorption. Thus it is important to have PK data in subjects having lice infestation. Please also see Clinical Pharmacology Review of NDA 22-408 Resubmission.

Clinical Comment:

(b) (4)

3. Response to FDA statement 3 (below) in the complete response letter:

> **Sufficient information has not been submitted to assure the identity, strength, purity and quality of the spinosad drug substance and the drug product.**

Details of CMC information needed as found in complete response letter of November 18, 2009

Drug Substance:

A. In addition to a cross reference to DMF 17795, submit a regulatory specification for acceptance of spinosad to the NDA.

Drug Product:

B. Include ID tests in the excipient specifications for ceteareth-20 and stearalkonium chloride.

[1] Ko CJ and Elston DM. Pediculosis. Continuing Medical Education. J Am. Acad. Dermatology 2004;50:1-12.
[2] Meinking TL et al. Chapter 83. Infestations in Dermatology e-edition, 2nd Edition: Bolognia JL and Jorizzo JL, Elsevier, Inc. © 2009.

C. Submit an updated drug product specification which reflects the revised definition for “active ingredient”. The specification should also reflect the revised definitions for "Related Substances", "Impurities", and the Acceptance limit, based on clarifications you provided in the teleconference held on August 28, 2009.

D. Based on the retention time table for the HPLC method used, placebo (b) (4) and spinosyn D (b) (4) very closely. Provide data to demonstrate that the assay value for spinosyn D is not compromised by the placebo peak.

E. Provide more detailed information regarding (b) (4) the drug product when stored under accelerated stability conditions.

F. (b) (4) was observed in the drug product samples provided in May 2009. Provide the following information to address the effects (b) (4) on drug product quality:

1) Data indicating when the (b) (4) starts during storage and whether the storage conditions have any effect (b) (4);

2) Data to demonstrate that content uniformity for the (b) (4) drug product is re-established after shaking; and

3) A description for the physical form of the drug product (e.g., lotion-like, solution-like, etc.) in the Appearance specification for the drug product. This description is needed, in addition to color as proposed, in the Acceptance criteria for the Appearance test.

In the current submission, the applicant has provided information in response to each of the requests detailed above. This information has been reviewed by the chemistry reviewer, Zhengfang Ge, Ph.D., Chemistry Review dated September 28, 2010. According to her review:

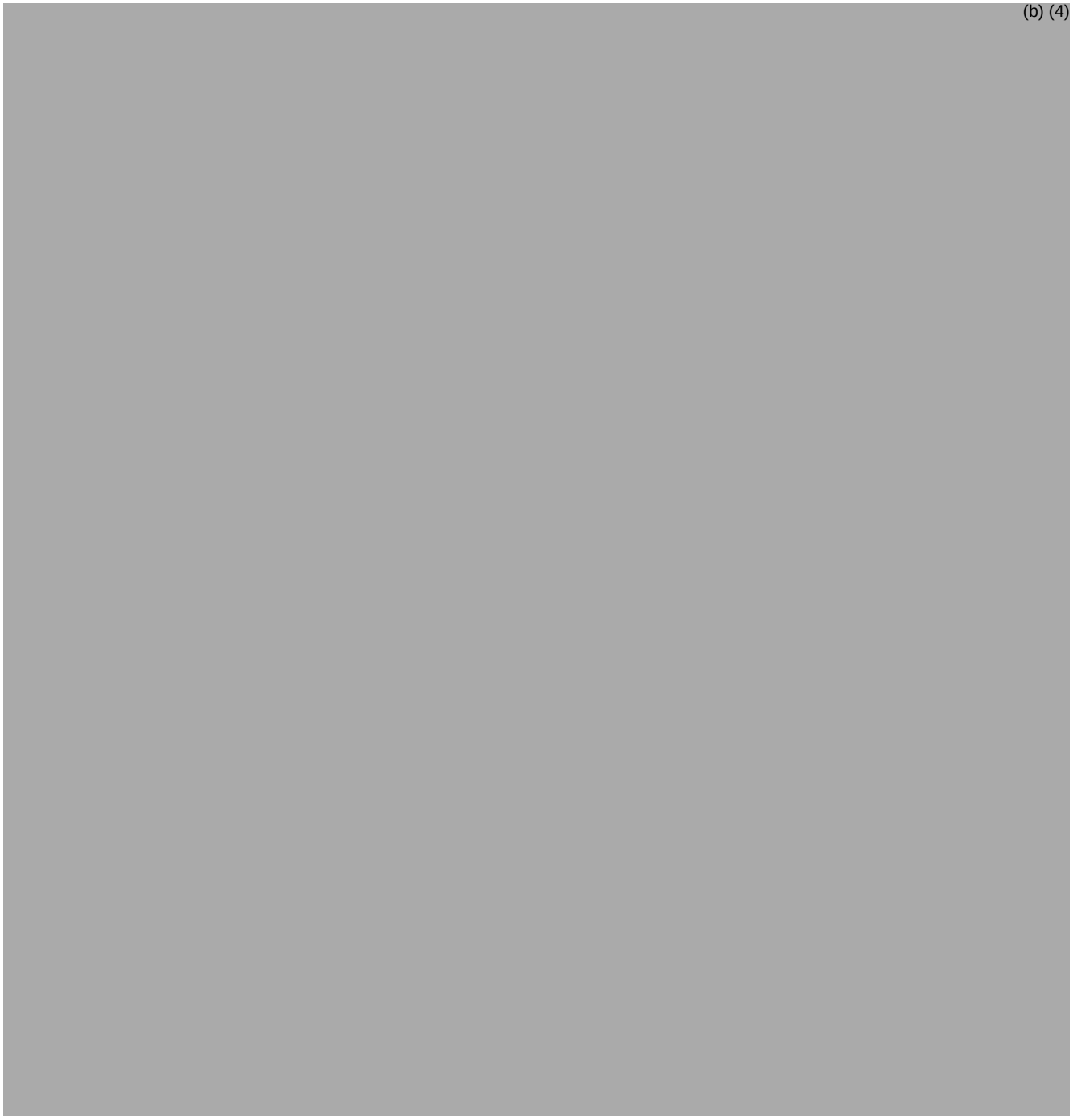
> The sponsor has provided sufficient information on raw material controls, manufacturing processes and process controls, and adequate specifications for assuring consistent product quality of the drug substance and drug product. The NDA also has provided sufficient stability information on the drug product to assure the strength, purity, and quality of the drug product during the 36-month of expiration dating period.
>
> All labels and labeling have adequate information as required.
>
> All facilities have “Acceptable” site recommendations from the Office of Compliance.

Clinical Comment:
The applicant has provided sufficient information to assure the identity, strength, purity, and quality of the spinosad drug substance and the drug product.

4. A. Updated labeling, carton packaging, and bottle label

The applicant submitted updated labeling, carton packaging, and bottle label for Agency comment. DMEPA review of carton and bottle label was pending at time of closure of this review.

(b) (4)



Physician's Insert Labeling: at the time of closure of this review (12/8/2010) physician's insert labeling was under negotiation.

4. B. A new proposed proprietary name request

The complete response letter of November 18, 2009 included the following:

On July 23, 2010 as part of the current submission, the applicant resubmitted a request for proprietary name review by the FDA. The applicant requests that the FDA evaluate the name "Natroba" as the primary proprietary name for use for the spinosad drug product.

The Division of Dermatology and Dental Products (DDDP) requested a review of the proprietary name from the Division of Medication Error Prevention and Analysis (DMEPA). Please see Proprietary Name Review for Natroba (Spinosad) Suspension, 0.9%, dated October 22, 2010.

A promotional assessment of the proposed name, Natroba, was performed by DDMAC and the name was determined to be acceptable. The Division of Dermatology and Dental Products and the Division of Medication Error Prevention and Analysis concurred.

A safety assessment was performed by DMEPA and it was determined that the proposed name, Natroba, is vulnerable to name confusion with the proposed proprietary name for a pending application. This name confusion could lead to medication errors. Comments sent to the applicant (October 22, 2010) included the following:

> …Natroba and the pending proprietary name are orthographically similar and share overlapping product characteristics. Therefore, at this time, the acceptability of the proposed proprietary name, Natroba, is dependent upon which application is approved first. If the Agency approves the Natroba NDA first, we will recommend the other applicant seek an alternate name. If the other application is approved prior to your application, then you will be requested to submit another name.

5. Safety update

The applicant states that there is no new safety information to report.

Significant Findings from Other Review Disciplines

CMC

From the Chemistry Review, dated September 28, 2010:

> **Drug Substance:**
>
> The proposed drug substance, spinosad, is a new molecular entity, and a fermentation product produced by the actinomycete, *Saccharopolyspora spinosa*. Spinosad contains two components, spinosyn A and D. The applicant cross referenced to DMF 17795 held by Dow AgroSciences LLC (Michigan, USA) for CMC information of spinosad. The DMF was reviewed and found adequate to support the NDA. In this amendment, the applicant provided an updated regulatory specification for the drug substance which is acceptable.
>
> **Drug Product:**
>
> The proposed drug product, Natroba (spinosad) suspension 0.9% w/w, is a light orange colored, slightly opaque, viscose liquid. (b) (4) The product is packaged in a 4 ounce,

white, HDPE bottle with a white, child resistant, snap top cap closure and spout. The drug product contains (b) (4) benzyl alcohol. In the Agency's CR letter to the applicant, the clinical division requested the applicant to provide information to support approval of the proposed product with a single active ingredient, spinosad, and to demonstrate why benzyl alcohol is not an active ingredient. Based on the information submitted in 23-July-2010 amendment, the clinical division made the decision that benzyl alcohol is an excipient. Therefore, the CMC information for benzyl alcohol as reviewed in CMC Review #1 is adequate. In this amendment, the applicant updated specification for the drug product according to the Agency's request in the CR letter and during the teleconference held on 20-Sep-2010. The applicant also adequately addressed (b) (4) issues raised during the previous review circle. Based on the information provided in this amendment, the proposed 36 months expiation period is acceptable.

The applicant provided revised labeling according to the CMC comments and the revision is acceptable.

(CMC) Recommendation and Conclusion on Approvability

This NDA has ***now*** provided sufficient/adequate information to assure the identity, strength, purity, and quality of the drug product. An "Acceptable" site recommendation from the Office of Compliance has been made. The labels and labeling (Description and How Supplied sections) have adequate information as required.

Therefore, from the CMC perspective, this NDA is recommended for ***approval.*** (See CMC Review dated September, 28, 2010, Zhengfang Ge, Ph.D., Branch IV, Division of Drug Qulaity Assessmnet II, Office of New Drug Quality Assessment

Animal Pharmacology/Toxicology

Please see pharmacology/toxicology Memorandum by Jianyong Wang, Ph.D., dated September 30, 2010.

From the Pharmacology/toxicology Memorandum:

Discussion and conclusions (excerpted)**:**

The Agency has determined that benzyl alcohol, (b) (4) in the Natroba product, is not a second active ingredient. No new nonclinical information is required at this time. The NDA for Natroba Suspension (0.9% spinosad) is approvable from a pharmacological/toxicological perspective, provided that the recommended changes in the label discussed in the next section are incorporated into the Natroba Suspension label. No nonclinical postmarketing studies are recommended for this drug product.

It is noted that the Maternal Health Team proposed further changes to the suggested wording for Section 8.1 of the Natroba label. An additional sentence was added and became the second sentence in the first paragraph of Section 8.1: "Studies in humans did not assess for the absorption of benzyl alcohol contained in Natroba Suspension." This proposed change obtained concurrence from clinical during the final labeling meeting and it is also acceptable from a pharmacology/toxicology perspective.

Clinical Pharmacology

From the Complete Response Letter of November 18, 2010:

> **Although your maximal usage pharmacokinetic trials detected no systemic exposure of spinosad from the use of TRADENAME (spinosad) Suspension, 0.9%, only 8 healthy subjects under the age of 4 years were evaluated. The youngest subjects with head lice are at greatest risk for systemic exposure due to their greater surface-to-volume ratio and the effects of the infestation itself on the scalp.**
>
> (b) (4)

See Clinical Pharmacology Review of NDA Resubmission by CAPT E. Dennis Bashaw, Pharm.D, OCP, DCP III, dated October 6, 2010. From the Clinical Pharmacology Review:

> The sponsor cites a "precedent" from the approval of the Ulesfia (NDA 22-129) application where the product received a pediatric indication for subjects 6 mos and older with a seemingly lesser amount of information…
>
> The sponsor goes on to state (b) (4) that they are concerned with "a level playing field" for their product.
>
> FDA Discussion
> The FDA supports and strongly encourages a "level playing field" for sponsors. However, in doing so we must be cognizant that the primary difficulty in their comparision to the Ulesfia data is that in the Ulesifa NDA (as indicated in both the approved label and in the NDA reviews available on Drugs@FDA) the study was done in patients with lice infestation. We draw attention to the first paragraph of FDA's comment #2 where it is made quite clear that we are concerned not only with the small numbers but the lack of information in subjects with lice infestation. The comment goes on to discuss our concerns in this area "*The youngest subjects with head lice are at greatest risk for systemic exposure due to their greater surface-to-volume ratio and the effects of the infestation itself on the scalp"*

In comparison, the six subjects below the age of 2 cited in the Ulesfia dataset did have concomitant lice infestation. Thus, in fact, instead of "a level playing field" the sponsor is "mixing apples and oranges" or equating data in healthy subjects with those with lice infestation which does not represent "a level playing field" towards Ulesfia. The sponsor did conduct a trial in children with lice infestation, but the cut-off in that study was 4yrs of age...

Conclusion

CR Letter Item 2

(b) (4) The issue cited in the CR letter was related to the lack of in vivo pk data in subjects with active lice infestation below the age of 4yrs. The data cited by the sponsor vis a vis the Ulesfia approval overlooks the fact that the Ulesfia data was collected in subjects with an active infestation. This point is clearly indicated in the current Ulesfia package insert. The Division of Clinical Pharmacology has maintained that for topically applied products, bioavailability testing must be accomplished in subjects with the disease of interest as normal skin is a poor surrogate for diseased skin and is not accepted as such by the Division and Office of Clinical Pharmacology.

Statistics

According to the statistical reviewer, the applicant's statistical analysis (Appendix 2 of Complete Response submission) is the same as that presented in the statistical report (submitted April 19, 2010). That report was reviewed by the statistical reviewer, May 19, 2010 and the reader is referred to the review for comments. Please see NDA Statistical Report Reviews dated August 25, 2010 and May 18, 2010, Carin Kim, Ph.D., DBIII.

Background:

Ulesfia (NDA 22-129) was approved for the treatment of head lice while NDA 22-408 was under review. From the statistical review:

> Ulesfia's active ingredient is benzyl alcohol at a concentration of 5%. The sponsor's product (spinosad (b) (4)) contained benzyl alcohol at a higher concentration (b) (4) Because neither of the Phase 3 studies contained a benzyl alcohol treatment arm, the data from the Phase 3 studies cannot be used to discern the contribution of spinosad.

A Type A post-action meeting was held on March 25, 2010. During the meeting discussion, the Agency requested that the applicant utilize study SPN-202-05 findings to obtain an estimate of the treatment effect for benzyl alcohol if it were to be used for 2 treatments as it was in the Phase 3 trials. It was hoped that this estimate would provide information to evaluate the contribution of spinosad over that of benzyl alcohol.

The applicant responded with a submission dated April 13, 2010 containing responses to the FDA questions. The applicant's response included a statistical analysis using the

results of Study SPN 202-06 (not study SPN 202-05) results to predict the treatment effect of benzyl alcohol if it were to be used for two treatments as it was used in the Phase 3 trials. From the statistician's review (Conclusion and Discussion):

> As for Study 201-05, this reviewer agrees with the Sponsor's conclusion (although the reviewer's arguments are different in reaching this conclusion) that Study 201-05 cannot be used to obtain an estimate of the treatment effect for benzyl alcohol if it were to be used for two treatments as it was in the Phase 3 trials.

In the statistical analysis, data from the Phase 3 studies for the ParaPRO product without nit combing were used to develop an optimized tree-diagram to predict idealized treatment results. According to the applicant, the tree-diagram was then used, along with observational data from one of the Phase 2 study, SPN-202-06, to predict idealized efficacy rates for the benzyl alcohol-vehicle. Regarding the benzyl alcohol treatment effect if it were to be used for two treatments without combing, from the statistician's review (Conclusion and Discussion):

> This reviewer's position is that such information can not be extrapolated from Study 202-06 either, as the study only involved one treatment at Day 0, therefore, the sponsor's tree diagram to predict the success rate of benzyl alcohol cannot be justified….Clearly, the sponsor did not have a benzyl alcohol arm of two treatments without combing as a part of their clinical program, therefore, the sponsor's studies cannot be used to predict the efficacy for the benzyl alcohol if it were to be used for two treatments without combing.

Clinical Comment:
The applicant's statistical analysis does not support the applicant's statement, form submission of April 13, 2010, that the "…efficacy of the ParaPRO product is substantially greater than the benzyl alcohol-vehicle (2.7 times greater)."

Other Relevant Materials:

Pediatrics:
For a new drug application, the Pediatric Research Equity Act of 2007 (PREA) requires that applicant assess the safety and effectiveness of the drug product for the claimed indication in all relevant pediatric subpopulations using age appropriate formulations. Studies must include data to support dosing and administration. For NDA 22-408, this would include relevant pharmacokinetic data for subjects having lice infestation from age 6 months up to 4 years. Additional pharmacokinetic study data will be needed.

Pediatric Plan:
The applicant submitted:

- Request for Waiver of Pediatric Studies on September 14, 2010

Under 21 CFR 314.55(c)(3)(i) the applicant requests a waiver of pediatric research in infants 0 to 6 months of age.
The reasons given were that
a) Studies are highly impractical or impossible
b) The product fails to represent a meaningful therapeutic benefit over existing therapies for pediatric patients and is unlikely to be used in a substantial number of patients in these age groups.

- A commitment to provide pharmacokinetic data for pediatric subjects

The applicant agrees to commit to conducting a post-approval pharmacokinetic study in lice infested subjects in the 6 month to 4 year age range.

- Dates for submission for the PMR pharmacokinetic study

Protocol Submission: March (b)(4) 2011
Study Initiation: September (b)(4) 2011
Study Completion: December (b)(4), 2011
Final Study report Submission: March (b)(4) 2012

The application was presented to PeRC (Pediatric Review Committee) on September 22, 2010. The Pediatric Review Committee had the following comments.

A) The Waiver for Pediatric Studies ages 0 up to 6 months is appropriate. The Committee agreed with the reasons as provided above, but also recommended including the reason: The product would be unsafe in the pediatric age group for which a waiver is being requested. This reason would apply to the benzyl alcohol component of the Tradename (spinosad) 0.9% Suspension drug product. Language regarding safety for benzyl alcohol is being included in section 8.4 of Tradename (spinosad) 0.9% Suspension product labeling. Please see discussion of labeling in this review below under Pediatric and Maternal Health Staff.

B) A Deferral ages 6 months to 4 years is appropriate.
Because the company did not submit this information with adequate detail as part of an explicit Pediatric Plan, PeRC requested that the applicant submit a Pediatric Plan that would provide a pediatric assessment for patients ages 0 up to 4 years (including the 0 to 6 months and 6 months to 4 years of age groups).

C) The Pediatric Assessment provided by the applicant for ages 4 and older is satisfactory.

D) Regarding the deferred study (PREA PMR), pharmacokinetic data should be requested in pediatric patients with head lice 6 months to less than 4 months of age. The deferred study should be enriched with pediatric patients in the younger age and weight groups.

As developed by the clinical review team in consultation with clinical pharmacology, a suggested outline for the PREA PMR follows:

The study would be an open label study PK study of Tradename (spinosad) 0.9% Suspension under maximum use conditions in patients with an active head lice infestation, aged 6 months to 4 years, with a minimum of 24 evaluable patients. The 24 children should be divided by age into two groups: Group 1 - 12 patients between 6 months and < 2 years; Group 2 - 12 between 2 years and 4 years. Within each of the groups there should be a generally equal distribution of males and females. Patients should otherwise be healthy, except for the active lice infestation. The primary pharmacokinetic analysis of spinosad and of benzyl alcohol is to include a determination of the following parameters: single dose AUC, C_{max}, and T_{max}. Safety assessment should include; a) systemic safety (vital signs, lab evaluation), b) local safety (scalp/ocular evaluation; query for pruritus), and c) adverse events. Given the age range studied a mutually agreeable reduced pk sampling program is acceptable.

Follow Up with Applicant Regarding Pediatric Plan;
The applicant was notified that the information they had submitted regarding the pediatric deferral was insufficient. More detail was need about their proposed study that provide a pediatric assessment for patients ages 0 up to 4 years (including the 0 to 6 months and 6 months to 4 years of age groups).

On October 1, 2010 the applicant provided a draft Pediatric Plan that included:
A) a request for a waiver from age 0 up to 6 months
B) a request for a deferral for ages 6 months up to 4 years - This was accompanied by the following:

Specifically, our intent is:
a. To assess subjects from 6 months to 4 years of age.
b. To have 2 groups of 12 subjects; the first group being 6 months to 1 year of age, and the second group being 1 year to 4 years of age.
c. To divide equally the subjects between male and female.
d. To enroll only healthy subjects except for active lice infestation.
e. To do a Pharmacokinetic analysis on both Spinosad and BA, single dose AUC, Cmax, Tmax. Safety assessment will include systemic safety, vital signs, lab evaluations, local safety such as scalp and ocular irritations, pruritus, and any other adverse events.

C) Timelines for protocol submission, study intitiation and completion, and submission of final study report.

The revised Pediatric Plan was provided to PeRC. On 10/12/10 PeRC provided an addendum to their review which stated that they now agreed with the Division to grant a deferral because the product is ready for approval in adults. The PeRC also had the following comments:

- PeRC members noted that enrollment should be clarified: pediatric patients with active lice infestation who are otherwise healthy.

- The PeRC is unsure what studies the Division will require under a PREA PMR and unless there are other safety data that can be applied to this product, a sample size of 24 (divided into 2 groups) appears inadequate.

A response was provided to these comments that noted:

- The sponsor indicated that they intended to enroll only healthy subjects except for active lice infestation

- Other safety data are available for patients 6 months to 3 years from the Phase 3 trials. In this age group safety data are available on 67 patients. When data from the PREA PMR are added, then safety data will be available on 91 patients. This will be a greater number than was asked for by the division for a similar application, Ulesfia (80 patients).

On 10/14/10 the following response was received:

> Your responses are noted and will be forwarded to PeRC members. The comments provided were done so as advisory to the Division. The PeRC review this product concluded with the review of the sponsor's submitted pediatric plan. The Division is free to take action on the product when ready.

Conclusion Regarding PMR:
It is this reviewer's opinion that the PMR as proposed above will be adequate to fulfill clinical information needs for safety.

Pediatric and Maternal Health Staff:
Regarding the Pediatric Use, Pregnancy, and Nursing Mothers subsections of labeling, consultation was obtained with the Pediatric and Maternal Health Staff, including the PMHS-Pediatric Team and the PMHS-Maternal Health Team. Please see Pediatric and Maternal Health Staff Review dated October 6, 2010.

The Pediatric and Maternal Health Staff (PHMS) made the following recommendations:

1. Notify the Sponsor that they are required to submit an updated Pediatric Plan that includes the deferral request and proposed pediatric studies of Natroba Suspension in pediatric patients 6 months to less than 4 years of age prior to product approval. The plan must include timelines with specific dates.

2. Request pharmacokinetic data on both spinosad and benzyl alcohol in the deferred study in pediatric patients with head lice 6 months to less than 4 years of age.

3. Notify the Sponsor that any deferred pediatric study will be considered a required pediatric postmarketing study and when submitted for review to the Agency must be clearly designated as "Required Pediatric Assessment".

PHMS recommendations #1 and #2 have been incorporated as described above, under pediatrics. Additionally, the sponsor will be notified that any deferred pediatric study will be considered a required pediatric postmarketing study and when submitted for review to the Agency must be clearly designated as "Required Pediatric Assessment".

PHMS recommendation regarding pregnancy and nursing mothers are incorporated into proposed labeling as follows:

> **8 USE IN SPECIFIC POPULATIONS**
>
> 8.1 Pregnancy
>
> Pregnancy Category B.
>
> There are no adequate and well-controlled studies with NATROBA Topical Suspension in pregnant women. Studies in humans did not assess for the absorption of benzyl alcohol contained in NATROBA Topical Suspension. Reproduction studies conducted in rats and rabbits were negative for teratogenic effects. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed…
>
> 8.3 Nursing Mothers
>
> Spinosad, the active ingredient in NATROBA Topical Suspension is not systemically absorbed; and therefore, will not be present in human milk. However, NATROBA Topical Suspension contains benzyl alcohol, which may be systemically absorbed through the skin, and the amount of benzyl alcohol excreted in human milk with use of NATROBA Topical Suspension is unknown. Caution should be exercised when NATROBA Topical Suspension is administered to a lactating woman. A lactating woman may choose to pump and discard breast milk for 8 hours after use to avoid infant ingestion of benzyl alcohol.

PHMS recommendations regarding pediatric labeling are as follows:

> 8.4 Pediatric Use
>
> The safety and effectiveness of NATROBA Topical Suspension have been established in pediatric patients 4 years of age and older with active head lice infestation *[see Clinical Studies (14)]*.
>
> Safety in pediatric patients below the age of 4 years has not been established. NATROBA Topical Suspension is not recommended in pediatric patients below the age of 6 months because of the potential for increased systemic absorption due to a high ratio of skin surface area to body mass and the potential for an immature skin barrier.
>
> NATROBA Topical Suspension contains benzyl alcohol which has been associated with serious adverse reactions and death, particularly in pediatric patients. The "gasping syndrome" (characterized by central nervous system depression, metabolic acidosis, gasping respirations, and high levels of benzyl alcohol and its metabolites found in the blood and urine) has been associated with benzyl alcohol dosages >99 mg/kg/day in neonates and low-birthweight infants. Additional symptoms may include gradual neurological deterioration, seizures, intracranial hemorrhage, hematologic abnormalities, skin breakdown, hepatic and renal failure, hypotension, bradycardia, and cardiovascular collapse.

> The minimum amount of benzyl alcohol at which toxicity may occur is not known. Premature and low-birthweight infants, as well as patients receiving high dosages, may be more likely to develop toxicity *[see Warnings and Precautions (5.1)]*.

The pediatric labeling recommended by PHMS includes the statement: "NATROBA Topical Suspension contains benzyl alcohol which has been associated with serious adverse reactions and death, particularly in pediatric patients." In the opinion of this reviewer this statement may be inappropriate for situation of use as labeled for Tradename (spinosad) 0.9% Suspension. Benzyl alcohol used as preservative in saline flush solutions has been associated with 16 neonatal deaths. The deaths occurred in pre-term neonates weighing 2500 grams who had central intravascular catheters flushed periodically each day with bacteriostatic saline containing 9 mg/ml benzyl alcohol. Estimates of daily intake of benzyl alcohol ranged from 99 to 405 mg/kg/day.[3] It should be noted that the intended population for the current application is children ages 4 and older. Proposed labeling also provides for short topical application (10 minutes) to a limited part of the body (hair and scalp) and for one and sometimes two treatments one week apart. It is highly unlikely, for the intended population and with topical and not parenteral application, that blood levels of benzyl alcohol would be achieved that are high enough to cause serious adverse reactions or death.

Recommended labeling that would be appropriate to the expected level of risk with use of Tradename (spinosad) 0.9% Suspension includes the following modifications (deletions = strikeout; additions = underline):

> (b) (4)
>
> (b) (4) Neonates could be at risk for gasping syndrome if treated with NATROBA Topical Suspension because it contains benzyl alcohol. Intravenous administration of products containing benzyl alcohol has been associated with neonatal gasping syndrome. The "gasping syndrome" (characterized by central nervous system depression, metabolic acidosis, gasping respirations, and high levels of benzyl alcohol and its metabolites found in the blood and urine) has been associated with benzyl alcohol dosages >99 mg/kg/day in neonates and low-birthweight infants. Additional symptoms may include gradual neurological deterioration, seizures, intracranial hemorrhage, hematologic abnormalities, skin breakdown, hepatic and renal failure, hypotension, bradycardia, and cardiovascular collapse.

The modifications recommended above would make this section of labeling for Tradename (spinosad) 0.9% Suspension more consistent with the labeling for Ulesfia, a product currently approved for treatment of head lice and containing 5 % benzyl alcohol.

[3] Neonatal Deaths Associated with Use of Benzyl Alcohol – United States: CDC; MMWR 1982; 31:290-291.

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/s/

PATRICIA C BROWN
12/09/2010

GORDANA DIGLISIC
12/09/2010

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: November 18, 2009
TO: NDA 022408 TRADENAME (spinosad) Suspension, 0.9%
ParaPRO Pharmaceuticals, LLC

FROM: Julie Beitz, MD
Director, Office of Drug Evaluation III

SUBJECT: Complete Response Action

TRADENAME (spinosad) Suspension, 0.9%, is a topical drug product consisting of spinosad, a new molecular entity, and benzyl alcohol. Spinosad is a naturally-derived fermentation product produced by the actinomycete, *Saccharopolyspora spinosa*, and is believed to cause neural excitation in insects. (b) (4) TRADENAME (spinosad) Suspension, 0.9%, has been evaluated as a treatment for head lice infestation in subjects (b) (4). On April 9, 2009, FDA approved NDA 022129, TRADENAME (benzyl alcohol) Lotion, 5%, for the topical treatment of head lice; the product is currently marketed under the tradename ULEFSIA. As a consequence of this action, TRADENAME (spinosad) Suspension, 0.9%, contains two active ingredients: spinosad and benzyl alcohol.

This memorandum documents my concurrence with the Division of Dermatology and Dental Product's (DDDP's) recommendation for a complete response action for TRADENAME (spinosad) Suspension, 0.9%. Before this application may be approved, the applicant should 1) satisfactorily address the deficiencies involving chemistry, manufacturing, and controls (CMC), 2) provide information to support approval of the product according to the regulations for fixed-combination prescription drugs at 21 CFR 300.50, and 3) provide the requisite CMC, nonclinical safety, and human pharmacokinetic information for benzyl alcohol. (b) (4) (b) (4) (b) (4) As of this writing, discussions regarding product labeling and postmarketing requirements and commitments have not been resolved. Lastly, FDA has determined that the proposed proprietary name, (b) (4), is not acceptable.

REGULATORY HISTORY

Selected aspects of the proposed phase 3 trials were discussed with the applicant in the context of a special protocol assessment request dated May 18, 2007. DDDP documented the agreements reached in a letter dated July 31, 2007. NDA 022408 was originally submitted on January 21, 2009, received on January 22, 2009, and granted a standard review. The application was not discussed before an FDA Advisory Committee because no systemic exposure to spinosad was detectable and no concerning safety

signals were identified in clinical trials evaluating the use of TRADENAME (spinosad) Suspension, 0.9%, for the treatment of head lice.

EFFICACY

The efficacy of TRADENAME (spinosad) Suspension, 0.9%, was demonstrated in two multi-center, prospective, randomized, double-blind trials. Subjects were randomized 1:4:4 to receive either TRADENAME (spinosad) Suspension, 0.9%, without combing, TRADENAME (spinosad) Suspension, 0.9%, with combing, or active treatment with NIX (permethrin 1%). All subjects in a household received the same treatment. Subjects applied enough of the product to cover the scalp and hair for 10 minutes on day 1, and repeated the application on day 7 if live lice were still present. Efficacy was assessed 14 days after the last treatment (i.e., on day 14 for subjects who received one treatment, or on day 21 for subjects who received two treatments). Treatment success was defined as the absence of live lice. In both studies, > 80% of subjects treated with TRADENAME (spinosad) Suspension, 0.9%, experienced treatment success, whereas only 43% or 45% of NIX-treated subjects achieved success. Nit combing did not contribute further to the treatment success shown with use of TRADENAME (spinosad) Suspension, 0.9%, alone.

CLINICAL PHARMACOLOGY

Three maximal usage pharmacokinetic trials to assess systemic exposure resulting from use of TRADENAME (spinosad) Suspension, 0.9%, were conducted. The trials were conducted using a formulation that contained a 2-fold higher spinosad concentration (i.e., spinosad 1.8%) compared to the to-be-marketed formulation. No systemic spinosad exposure was detected; benzyl alcohol was not assayed. Given FDA's determination that benzyl alcohol is an active ingredient, the applicant should obtain pharmacokinetic data for benzyl alcohol in lice-infested subjects.

In the trials performed to date, only 8 healthy subjects under the age of 4 years were evaluated. The youngest subjects with head lice are at greatest risk for systemic exposure due to their greater surface-to-volume ratio and the effects of the infestation itself on the scalp. (b) (4) the applicant should obtain pharmacokinetic data for spinosad, as well as for benzyl alcohol, in lice-infested pediatric subjects aged 6 – 24 months.

NONCLINICAL

Spinosad was non-irritating to the skin of rabbits and was not a skin sensitizer in guinea pigs. In a one-year chronic neurotoxicity study in rats, spinosad did not result in neurotoxicity at any dose level. Spinosad was not carcinogenic in mice or rats. In *in vitro* and *in vivo* genotoxicity testing, spinosad was not mutagenic or clastogenic. Reproductive toxicity studies in rats and rabbits did not identify spinosad as a teratogen, and support a pregnancy category designation of Category B.

No preclinical information was provided to support the safety of benzyl alcohol per ICH M3 (R2) guidance. The applicant should provide these data in their complete response.

SAFETY

In the applicant's clinical development program, 1036 subjects aged 6 months to 84 years were exposed to various concentrations of TRADENAME (spinosad) Suspension (ranging from 0.5% to 2.0%). In the phase 3 trials, 552 subjects received the to-be-marketed formulation, TRADENAME (spinosad) Suspension, 0.9%. There were no serious adverse events reported and no discontinuations due to adverse events. The most common adverse reactions observed with TRADENAME (spinosad) Suspension application were local erythema and irritation, and ocular hyperemia. If approved, the WARNINGS AND PRECAUTIONS section of the product label will advise to avoid contact with eyes.

PRODUCT ISSUES

Spinosad. Spinosad is a naturally-derived fermentation product containing two components, spinosyns A and D, which are present in a fixed ratio of approximately 5:1. On May 17, 2007, FDA informed the applicant that spinosad would be considered a single active ingredient.

The applicant cross-referenced all CMC information related to spinosad to DMF 17795 held by Dow AgroSciences LLC. This information was reviewed and found acceptable; however, the applicant should also provide a regulatory specification for acceptance of spinosad in the NDA submission.

Benzyl alcohol. Given FDA's determination that benzyl alcohol is a second active ingredient in TRADENAME (spinosad) Suspension, 0.9%, the applicant should submit complete CMC information on benzyl alcohol.

Drug product. Several deficiencies involving the drug product were identified that will have to be addressed before the NDA may be approved: 1) drug product samples provided at the time of NDA submission developed (b) (4); the applicant should provide information to ensure tha (b) (4) does not adversely affect product quality, 2) more information is needed regarding the cause of drug product (b) (4) under accelerated stability conditions, 3) ID tests in the excipient specifications for ceteareth-20 and stearalkonium chloride are needed, 4) an updated drug product specification should be submitted that reflects revised definitions for "active ingredient," "Related Substances," "Impurities," and the Acceptance limit, and 5) additional data are needed regarding the HPLC peaks for spinosyn D and placebo.

In addition, agreement has not been reached on the nomenclature for the dosage form. The applicant's proposal (b) (4) is not a recognized dosage form. FDA informed the applicant that (b) (4) was unacceptable on April 6, 2009, and

requested that the dosage form for this product be changed to “suspension” on September 3, 2009. The applicant’s response to this request is pending at this time.

Inspection of the drug product manufacturing site identified CGMP deficiencies that were described in a 483 on July 30, 2009. The deficiencies were satisfactorily addressed and the Office of Compliance determined that the site was acceptable on November 2, 2009.

TRADENAME REVIEW

(b) (4)

(b) (4). If the applicant intends to have a proprietary name for this product, a new request for a proposed proprietary name review should be submitted.

_____

Julie Beitz, MD
Director, Office of Drug Evaluation III
CDER, FDA

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22408	ORIG-1	PARAPRO PHARMACEUTICALS LLC	SPINOSAD

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/s/

JULIE G BEITZ
11/18/2009

Cross-Discipline Team Leader Review Addendum

Date	November 5, 2009
From	Jill Lindstrom, MD
Subject	Cross-Discipline Team Leader Review Addendum
NDA #	22-408
Applicant	ParaPRO
Date of Submission	21 January 2009
PDUFA Goal Date	21 November 2009
Proprietary Name	TRADENAME ([redacted] (b) (4)
Established (USAN) names	spinosad
Dosage forms / Strength	suspension/0.9%
Proposed Indication	topical treatment of head lice infestation in patients [redacted] (b) (4)
Recommended:	*Complete Response*

This addendum will correct an error in my initial review and clarify and update the status of the Office of Compliance recommendation with regard to the inspection of the drug product manufacturing site (see Section 3, CMC, last bullet, p5, of my review dated October 30, 2009 and archived November 2, 2009).

Correction to my original review:

Section 3, CMC, of my initial review erroneously states that the inspection of the drug product manufacturing site was conducted by the Office of Compliance; the review should state that the inspection was conducted by the Office of Regulatory Affairs.

Clarification and update:

Inspections of the drug product manufacturing site resulted in issuance of a 483 to the manufacturer on July 30, 2009, and a withhold recommendation in the inspection report.

The manufacturer provided their response addressing the deficiencies articulated in the 483 to the District Office on August 31, 2009.

Based on the response, all manufacturing sites were found to be acceptable and the Office of Compliance issued a final recommendation of "acceptable" on November 2, 2009.

The remaining issues described in my initial review are unresolved and my recommendation for action (*Complete Response)* is unchanged. However, the basis for that recommendation no longer includes the need for resolution of deficiencies identified during inspection of the drug product manufacturing site.

Recommended regulatory action: *Complete Response*

The applicant needs to provide sufficient information to assure the identity, strength, purity, and quality of the drug product.

The applicant needs to address the requirements of 21CFR300.50 with regard to benzyl alcohol.

Recommended comments to the applicant:

Regulatory:
Benzyl alcohol is an approved drug for the topical treatment of head lice, and thus it appears that the product contains two active ingredients: spinosad and benzyl alcohol. Provide data to address the requirements of 21 CFR 300.50 with regard to benzyl alcohol, as well as requisite CMC and safety data for this active ingredient, or provide data to establish that benzyl alcohol is not active in the product.

Drug Substance:
In addition to cross reference to the DMF 17795, a regulatory specification for the drug substance should be submitted to the NDA.

Drug Product:

1. Include ID tests in the excipient specifications for Ceteareth-20 and Stearalkonium Chloride

2. Provide an updated drug product specification to clarify definition for "RelatedSubstances", "Impurities" and the Acceptance limit according to the agreement in the teleconference held on Aug 21, 2009 (see review in section P.5.1)

3. Based on the retention time table for the HPLC method provided in response to Q19 submitted on Aug 21, 2009, placebo (b) (4) and spinosyn D (b) (4) very closely. Provide data to demonstrate that the assay value for Spinosyn D is not compromised by the placebo peak.

4. Provide more detailed information regarding the (b) (4) drug product when stored under the accelerated condition.

5. (b) (4) was observed in the drug product samples provided to the Agency in May 2009. The following information should be provided to address the effect (b) (4) to the drug product quality:

    a. Provide data indicating when the (b) (4) starts during the storage and whether the storage condition has any effect (b) (4)

    b. Provide data to demonstrate that the content uniformity for the (b) (4) drug product is established after shaking

c. In addition to the color as proposed in the acceptance criteria for the Appearance test, the Appearance specification for the drug product should include a description for the physical form of the drug product such as lotionlike, solution-like, etc.

6. We reserve comment on the proposed labeling until the application is otherwise adequate. If you revise labeling, your response must include updated content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm.

Proprietary Name

(b) (4)

(b) (4) Submit an alternate proposed trade name for review.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22408	ORIG-1	PARAPRO PHARMACEUTICALS LLC	SPINOSAD

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/s/

JILL A LINDSTROM
11/05/2009

Summary Review for Regulatory Action

Date	November 4th, 2009
From	Susan J. Walker, M.D., F.A.A.D.
Subject	Division Director Summary Review
NDA #	22-408
Applicant Name	ParaPRO Pharmaceuticals, LLC
Date of Submission	January 23rd, 2009
PDUFA Goal Date	November 20th, 2009
Proprietary Name / Established (USAN) Name	TRADENAME/spinosad
Dosage Forms / Strength	Suspension/ 0.9%
Proposed Indication(s)	Treatment of head lice
Action/Recommended Action for NME:	*Complete Response*

Material Reviewed/Consulted OND Action Package, including:	**Names of discipline reviewers**
Medical Officer Review	Patricia Brown
Statistical Review	Lisa Kammerman
Pharmacology Toxicology Review	Jianyong Wang
CMC Review	Zhengfang Ge
Microbiology Review	NA
Clinical Pharmacology Review	Dennis Bashaw
DDMAC	NA
DSI	Roy Blay
CDTL Review	Jill Lindstrom
OSE/DMEPA	Loretta Holmes
OSE/DDRE	NA
OSE/DRISK	NA

OND=Office of New Drugs
DDMAC=Division of Drug Marketing, Advertising and Communication
OSE= Office of Surveillance and Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis
DSI=Division of Scientific Investigations
DDRE= Division of Drug Risk Evaluation
DRISK=Division of Risk Management
CDTL=Cross-Discipline Team Leader

Division Director Summary Review

1. Introduction

TRADENAME (spinosad) suspension, 0.9%, is a topical drug product for which the applicant seeks approval under Section 505 (b) (1) of the Federal Food Drug and Cosmetic Act for the topical treatment of head lice infestation in patients (b) (4). The active ingredient, spinosad, is a new molecular entity which is not marketed as a drug in the United States. There sponsor has not provided sufficient information for approval and a complete response action is recommended.

2. Background

Spinosad is a complex mixture resulting from fermentation by *Saccharopolyspora spinosa*, an acinetobacterium found in soil. Spinosyn A and spinosyn D are the active components in spinosad, and the remaining spinosyns are related compounds. Spinosad is thought to cause neural excitation in insects, and is used as an agricultural insecticide. The agency determined that the spinsad complex could be considered a single active substance and conveyed this to the sponsor on 17May2007. The sponsor has not provided sufficient information to assure the identity, strength, purity and quality of TRADENAME suspension...

Benzyl alcohol (b) (4) is a component of this drug product, (b) (4) However, after initiation of phase 3 trials for TRADENAME suspension the Agency approved 5% benzyl alcohol as an active pharmaceutical ingredient (API) for topical treatment of head lice. The applicant will need to provide information to support approval considering the regulatory obligation outlined in 21CFR 300.50.

3. CMC/Device

I concur with the conclusions of the chemistry reviewer and product quality division director that the applicant has provided insufficient information for approval in accordance with 21 CFR 314.125 (b) (1). Deficiencies include, but are not limited to:

- Failure to include in the application, a specification for acceptance of the drug substance
- Failure to comply with previous agreements on drug product impurities
- An inadequate analytical procedure for the assay of the drug product

(b) (4) was also noted in samples provided to the Agency in May 2009. Should the drug product be determined to exhibit (b) (4), it would be necessary to understand the condition of the product used in the clinical and preclinical studies, to understand the applicant's approach to resolving issues related to (b) (4) and to understand the impact on stability. (b) (4) the product was apparent under accelerated

stability conditions and this has not been adequately resolved. In addition, the dosage form nomenclature is unresolved.

Inspections have been completed for this application and a final "acceptable" recommendation has been entered into EES. A chemistry addendum in pending as of 4Nov09.

4. Nonclinical Pharmacology/Toxicology

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 applicant has provided information from 3 maximal usage trials to assess the systemic bioavailability of topical TRADENAME suspension. These studies support the use in patients down to age 4; however, the sponsor has provided inadequate information informing systemic exposure/safety in pediatric patients less than 4 years of age. Without this information, the sponsor's labeling indication would extend only down to 4 years of age. This information could be submitted as a labeling supplement. There were no additional issues that would preclude approval.

6. Clinical Microbiology

Not applicable for this application.

7. Clinical/Statistical-Efficacy

The applicant has provided sufficient information from two adequate and well-controlled trials to establish efficacy of TRADENAME suspension for the treatment of head lice. However, the sponsor has not provided adequate information to establish that the combination of spinosad and benzyl alcohol is superior to either of the monads. This application is complicated by the fact that benzyl alcohol was not an approved treatment for head lice (i.e. not classified as an active pharmaceutical ingredient) at the time the company engaged in discussions with FDA concerning their development program. The applicant identifies the function of benzyl alcohol (b) (4) for spinosad and this was determined to be a legitimate function for benzyl alcohol in this formulation. While it would be reasonable to determine if the applicant has any information to establish the individual contributions of spinosad and benzyl alcohol to the efficacy of TRADENAME suspension, the path forward for this product remains to be resolved. Potential impacts include ANDA submissions, future NDA submissions, and determination of exclusivity entitlement. The action letter should include a statement informing the applicant that with the approval of benzyl alcohol as an API,

they have an obligation to provide additional information regarding the activity of benzyl alcohol in their product.

The applicant seeks a claim for the treatment of head lice (b) (4) however, the study design precludes determination of ovicidal activity. This information was relayed to the applicant at the preNDA meeting.

8. Safety

During the development program of TRADENAME suspension 1,561 subjects were evaluated, with 1,040 exposed to TRADENAME suspension... There were no deaths for serious adverse events attributable to TRADENAME suspension. As is common with trials for head lice, the most frequently reported adverse event was application site reaction. Ocular hyperemia was reported at a rate lower than the comparator, NIX (2% vs. 3%). The review of adverse events and assessment of local tolerance did not reveal unexpected safety signals.

9. Advisory Committee Meeting

This product was not referred to an advisory committee, as there were no significant or controversial issues. The documented systemic exposure was below the level of detection and the application did not present any novel scientific issues.

10. Pediatrics

The studies conducted by the sponsor enrolled subjects 6 months of age and older. The applicant has requested a waiver in children less than 6 months of age based upon the rationale that studies are “highly impracticable since the number of subjects in this age group is very small”. A waiver is anticipated at the time of approval.

11. Other Relevant Regulatory Issues

The applicant did not identify benzyl alcohol as an active in TRADENAME suspension, and should provide information to resolve the concern that benzyl alcohol may be functioning as an additional active pharmaceutical ingredient in TRADENAME suspension.

12. Labeling

The proprietary name has not been established. Labeling discussions will occur prior to product approval.

13. Decision/Action/Risk Benefit Assessment

Regulatory Action: A Complete Response action is recommended. The action letter should include all deficiencies cited by the CMC discipline and a request for additional information establishing/refuting the status of benzyl alcohol as a potential API in this product.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22408	ORIG-1	PARAPRO PHARMACEUTICALS LLC	SPINOSAD

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/s/

SUSAN J WALKER
11/04/2009

Cross-Discipline Team Leader Review

Date	October 30 2009
From	Jill Lindstrom, MD
Subject	Cross-Discipline Team Leader Review
NDA #	22-408
Applicant	ParaPRO
Date of Submission	21 January 2009
PDUFA Goal Date	21 November 2009
Proprietary Name	TRADENAME (b) (4)
Established (USAN) names	spinosad
Dosage forms / Strength	suspension/0.9%
Proposed Indication	topical treatment of head lice infestation in patients (b) (4)
Recommended:	*Complete Response*

1. Introduction

TRADENAME (spinosad) suspension, 0.9%, is a topical drug product for which the applicant seeks approval under Section 505 (b) (1) of the Federal Food Drug and Cosmetic Act for the topical treatment of head lice infestation in patients (b) (4). The active ingredient, spinosad, is a new molecular entity which is not marketed as a drug in the United States. This memo will summarize the findings of the multi-disciplinary review team and provide the rationale for my recommended action.

Head lice infestation, pediculosis capitis, is a common and communicable condition in which the human head louse, *Pediculus humanus capitis*, infests the hairy scalp. The most prominent symptom of infestation is pruritus, and signs include lice observed on the scalp, nits attached to hair shafts, and erythema, and manifestations of excoriation such as crusting. Excoriation can result in secondary infection due to disruption in the epidermal barrier. Because the infestation is communicable, children diagnosed with the infestation may be precluded from attending school until they have received effective treatment. The therapeutic armamentarium for the treatment of head lice infestation includes approved and unapproved drug products and mechanical measures such as combing or shaving of the scalp (the latter generally reserved for very young children because of the psychological distress that can result). Approved drug products indicated for the treatment of head lice infestation include Ulesfia (benzyl alcohol) Lotion, 5%; lindane shampoo, permethrin cream rinse, pyrethrins with piperonyl butoxide solution and mousse, and malathion lotion.

Spinosad is a complex mixture resulting from fermentation by *Saccharopolyspora spinosa*, an acinetobacterium found in soil. Spinosyn A and spinosyn D are the active components in spinosad, and the remaining spinosyns are related compounds. Spinosad is thought to cause neural excitation in insects, and is used as an agricultural insecticide.

2. Background

During their development program, the applicant interacted with the Agency at three milestone meetings (pIND, EOP2, pNDA) as well as additional guidance teleconferences (four requested, three conducted, one cancelled after receipt of Agency communication). The applicant also requested and received a Special Protocol Assessment. The dates of the interactions are as follows:

Interaction type	Date	Comments
Pre-IND (pIND)	5/12/2003	
Discipline teleconference	2/9/2004	Pharmacology-toxicology
End-of-Phase 2 (EOP2)	10/31/2006	
Guidance teleconference	2/9/2007	
Guidance teleconference	4/23/2007	
Guidance teleconference (scheduled but not held)	5/21/2007	Applicant cancelled following receipt of communication dated 5/17/2007
Special Protocol Assessment (SPA)	Letter issued 7/31/07	
Pre-NDA (pNDA)	11/4/2008	

The combination policy, as articulated in 21 CFR 300.50, states that products with more than one active ingredient must demonstrate the contribution of each active ingredient to the claimed effect/s. The application for TRADENAME (spinosad) suspension, 0.9%, presents two challenges with regard to the combination policy: first, whether the drug substance, spinosad, is a single active ingredient, and second, whether benzyl alcohol is an active or an excipient. The applicant identified the first issue, whether spinosad would be considered a single active ingredient, at their pIND meeting, and it was discussed at the EOP2 meeting and subsequent guidance teleconferences; the Agency determined that the complex mixture spinosad would be considered a single active ingredient and conveyed this to the applicant in a communication dated May 17, 2007. This is further discussed in section 3, CMC, of this review.

The second issue, whether benzyl alcohol is an active, was not raised by the applicant during the development program nor directly addressed in the application. However, related topics were discussed at several points during development. In the pIND minutes, Agency comments note that, "microbial growth will be inhibited by the (b) (4) benzyl alcohol present in the finished drug product." The minutes from the EOP2 meeting reflect that, "[t]he Division raised concerns about…whether the vehicle could be active," but no specific component of the vehicle was identified. At that time, a product with benzyl alcohol as the active ingredient (Ulesfia [benzyl alcohol] lotion, 5%) was in development by another sponsor for the same indication; this information was not discussed with the applicant. A PubMed search conducted by this reviewer (search terms "benzyl alcohol AND lice," Oct 30, 2009) identified two

articles about the pedicucidal activity of benzyl alcohol with publication dates prior to the applicant's EOP2 meeting date[12].

The EOP2 meeting minutes reflect discussion of vehicle-controlled and active controlled designs. The Agency provided the following comments regarding the trial design:

At the pIND meeting 5.12.2003

> "One possible route to approval for spinosad would be to demonstrate superiority to NIX…."

At the EOP2 meeting 10.31.2006

> "The Division comments (Meeting minutes dated May 12, 2003) specified that for approval, 2 superiority trials against NIX would be required. This current study [SPN-301-07] does not include NIX."
>
> "SPN-302-07 plans to investigate 3 arms: NatrOVA 0.1%, NIX and vehicle. As there might be ethical concerns about treating subjects with vehicle, the study should be limited to two treatment arms NatrOVA and NIX."

For lice products in which the active ingredient is also used as an insecticide, the Division has historically requested active-controlled trials to ensure that the benefit of the product is meaningful and outweighs potential risks. The advice given at the pIND and EOP2 meetings reflect this position, and recommend what would be appropriate design to establish the safety and efficacy of a product with a single active. However, for a product containing two actives (such as spinosad and benzyl alcohol), a factorial design would be needed to establish the contribution of each active (e.g., TRADENAME (spinosad) suspension, vehicle plus spinosad [without benzyl alcohol], vehicle plus benzyl alcohol [without spinosad], and vehicle [without spinosad or benzyl alcohol]).

The applicant identified the function of benzyl alcohol (b) (4). The CMC review team found this function to be legitimate for the product. Reduction of benzyl alcohol (b) (4) did not result in precipitation of the API.

Ulesfia (benzyl alcohol) lotion, 5%, was approved for the topical treatment of head lice infestation in patients 6 months of age and older on April 9, 2009. In light of this action, the applicant will need to address how they have addressed the combination policy for their product, which contains benzyl alcohol (b) (4). In addition to a regulatory obligation as outlined in 21 CFR 300.50, identification of benzyl alcohol as an active has two other implications: it will ensure that any future ANDA applications based on this product

[1] Toloza AC, et. al. Fumigant and repellent properties of essential oils and component compounds against permethrin-resistant Pediculus humanus capitis (Anoplura: Pediculidae) from Argentina. J Med Entomol. 2006 Sep;43(5):889-95.

[2] Yang YC, et. al. Ovicidal and adulticidal activities of Cinnamomum zeylanicum bark essential oil compounds and related compounds against Pediculus humanus capitis (Anoplura: Pediculicidae). Int J Parasitol. 2005 Dec;35(14):1595-600. Epub 2005 Sep 15.

will contain both components, spinosad and benzyl alcohol, and it will impact the exclusivity to which the sponsor is entitled.

3. CMC

The drug substance, spinosad, is a fermentation product of *Saccharopolyspora spinosa*. Spinosad is a complex mixture of spinosyns, which are cationic amphiphilic compounds composed of large ring complexes, tertiary amines and sugars. Spinosyn A and spinosyn D are present at a ratio of 5:1 and comprise (b) (4) of the drug substance by weight; related minor spinosyns comprise an additional (b) (4) of the drug substance weight. . Because 1) spinosad is a fermentation product, 2) spinosyn A and D are present in a fixed ratio and both show evidence of activity, and 3) further purification presented significant hardship, the Agency recognized spinosad as a single active ingredient in which spinosyn A and D are the active components and the other spinosyns are related compounds (Agency communication dated May 17, 2007). Agency precedents for this determination included Dalbavancin most recently and gentamycin in the past.

The drug product, spinosad suspension, 0.9%, is a viscous peach-colored liquid which contains the active ingredient, spinosad, in a vehicle consisting of water, isopropyl alcohol, benzyl alcohol, hexylene glycol, propylene glycol, etearyl alcohol, stearalkonium chloride, ceteareth-20, hydroxyethyl cellulose, butylated hydroxytoluene, and FD&C Yellow #6. The composition is provided in the following table:

Ingredient	Percent Formula (%w/w)	Purpose
Benzyl alcohol	(b) (4)	
Butylated hydroxytoluene		
Ceteareth-20		
Cetearyl alcohol		
FD&C Yellow #6		
Hexylene glycol		
Hydroxethyl cellulose		
Isopropyl alcohol		
Propylene glycol		
Spinosad	0.9	Active ingredient
Stearalkonium chloride	(b) (4)	
Water		

Source: adapted from CMC review of NDA 22-408, Zhengfang Ge, PhD, 9/23/2009, p.17.

The drug product is packaged in white, cylindrical, 4-ounce bottles made of high-density polyethylene. The bottles have a ratchet (screw-top) neck, and are closed with a 24mm child-resistant white snap-top cap with spout. The applicant only submitted data for the 120ml size bottle.

The NDA did not contain sufficient information to assure the identity, strength, purity, and quality of the drug product. The following CMC issues were identified:

- Drug product samples submitted to the Agency developed (b) (4) The impact (b) (4) on product stability is not known.
- (b) (4) the drug product occurred under accelerated stability conditions. (b) (4)
- Drug product specifications are not adequate. A second assay is needed for drug substance identity, as in the assay the excipient peaks interfere with that for the active ingredient. In addition, the applicant has not provided specifications for impurities and related compounds.
- Agreement has not been reached on the nomenclature for the dosage form. The applicant proposed (b) (4). The applicant's product is a suspension, and the need to shake the product prior to use is consistent with the dosage form "suspension."
- Inspections of the drug product manufacturing site by the Office of Compliance resulted in issuance of a 483 and withhold recommendation.

Dr. Ge recommended *against* an approval action until these issues are resolved.

4. Nonclinical Pharmacology/Toxicology

Repeat dose dermal toxicology studies did not reveal significant dermal or systemic toxicity in rabbits (three weeks) or minipigs (four weeks). Repeat dose oral toxicology studies in rats, mice and dogs identified vacuolation and inflammation in a variety of organs, but did not reveal neurotoxicity. Spinosad was not found to be genotoxic in mutagenicity assays, and carcinogenicity studies were negative in mice and rats. Spinosad 1.8% suspension caused mild reversible irritation in the rabbit eye study, and did not induce a phototoxic reaction in mice irradiated with UVA light. Reproductive toxicity studies in rats and rabbits did not identify a teratogenic signal, and support a pregnancy category designation of Category B.

The reader is referred to the comprehensive review by Dr. Jianyong Wang for a full discussion of the nonclinical pharmacology/toxicology data. Drs. Wang and Hill did not recommend further nonclinical studies or phase 4 commitments, and recommended an *Approval* action from a pharmacological/toxicological perspective.

5. Clinical Pharmacology/Biopharmaceutics

TRADENAME (spinosad) suspension, 0.9%, is a topical product for the treatment of head lice infestestations which is intended to be applied to dry scalp and scalp hair, rinsed off after 10 minutes, and repeated in seven days if live lice are still present.

The applicant conducted three maximal usage trials to assess the systemic exposure that results from use of their product. All three trials were conducted using a formulation that contained a

two-fold higher concentration of the active ingredient than is in the to-be-marketed formulation (1.8% spinosad vs 0.9% spinosad, respectively). Because this is conservative in impact, it is acceptable. The studies are summarized in the table below:

Study	N	Age range	Disease status	Spinosad/metabolite concentration
SPN-101-04	23	21-60 years	Healthy non-infested	BLQ
SPN-103-05	14	4-15 years	Infested	BLQ
SPN-106-06	8	6-23 months	Healthy non-infested	BLQ

Source: adapted from OCPB review of NDA 22-408, CAPT E. Dennis Bashaw, PharmD; 10.6.2009, pp.8-9.

While the lack of detectable systemic levels is generally reassuring, the data is inadequate for children younger than 4 years of age due to the paucity of subjects, especially at the lower end of the age range, and the fact that those subjects did not have lice infestation. The stratum corneum, which is the major barrier to absorption of topically-administered drugs, may be disrupted in individuals infested with lice due to the inflammation that occurs at the sites at which the louse obtains a blood meal, as well as mechanical disruption caused by scratching. In addition, the surface-to-volume ratio will be greater in the youngest subjects. For these reasons, systemic exposure is likely to be greatest in this age group. (b) (4)

In addition, no data on the pharmacokinetics of benzyl alcohol were provided. This information is needed. One approach to consider would be to begin with obtainment of pharmacokinetic data for both benzyl alcohol and spinosad in subjects 6 to 23 months of age in a single study. This would provide pharmacokinetic data across the affected age range for spinosad, which is a new molecular entity, and pharmacokinetic data in the most relevant age cohort (youngest subjects) for benzyl alcohol.

No QT/QT_c study was obtained. Although spinosad is a new molecular entity, systemic exposure was below the level of detection. Because of the short application time, absence of detectable systemic exposure, and limited treatment duration, the clinical and clinical pharmacology reviewers did not think that a TQT study was warranted. Consultation was obtained from the QT-IRT team, who concurred a TQT study was not necessary.

Dr. Bashaw found that the applicant had met the requirements for approval from a clinical pharmacology perspective (b) (4)

6. Clinical Microbiology

Not applicable.

7. Clinical/Statistical- Efficacy

The applicant submitted data from two pivotal trials, Study SPN-301-07 and Study SPN-302-07, to establish the effectiveness of their product applied for 10 minutes and repeated in one week if live lice were noted at that time. These trials (301 and 302) were multi-center, prospective, randomized, double-blind, parallel group studies with three arms, TRADENAME suspension without combing, TRADENAME suspension with combing, and active control (NIX). Households were enrolled if one or more member 6 months of age or older was infested with at least 3 live lice; the youngest infested household member with at least 3 live lice was the index subject (primary efficacy cohort) and other infested household members (with at least 1 live louse) were enrolled in the secondary cohort. All subjects in a household received the same treatment. Subjects applied the requisite amount of clinical trial material, depending on hair length, for 10 minutes on day 1, and repeated the application on day 7 if live lice were still present at that time. Efficacy was assessed 14 days after the last treatment (day 14 for subjects who received only one treatment, and day 21 for subjects who received 2 treatments), and success was defined as the absence of live lice. The primary efficacy endpoint is the proportion of subjects with treatment success at 14 days after the last treatment, which is shown in the following Table:

	TRADENAME (spinosad) suspension, 0.9%		NIX	
	With nit combing	Without nit combing		P-value*
SPN-301-07	N=23 19 (82.6%)	N=91 77 (84.6%)	N=89 40 (44.9%)	<0.001
SPN-302-07	N=21 17 (81.0%)	N=83 72 (86.7%)	N=84 36 (42.9%)	<0.001

*P-value: TRADENAME (spinosad) suspension, 0.9%, w/out nit combing, vs NIX
Source: Adapted from clinical review of NDA 22-408, Dr. Patricia Brown, MD; 10.xx.2009, pp 48-9.

In both studies, the spinosad arms show similar point estimates regardless of combing, and the results are also consistent across the two pivotal trials. In both studies, TRADENAME (spinosad) suspension, 0.9%, used according to proposed labeling, is superior to NIX in the treatment of head lice infestation. Labeling should reflect that nit combing is not required.

The applicant seeks a claim for treatment of head lice (b) (4). However, the study design allowed for a second treatment after 7 days if live lice were still present. Such a study design precludes determination of ovicidal effect. In the SPA agreement letter, the agreements are framed in the context of a claim for treatment of head lice, (b) (4) Thus, the study design, population, and endpoints which were agreed upon would garner a claim for treatment of head lice infestation. The pNDA meeting minutes reflect the following comment: "The indication for the treatment (b) (4) was not pre-planned in the design phase. Results based on a *post-hoc* analysis cannot be used to establish efficacy." The applicant has

established the efficacy of their product for the treatment of head lice, (b) (4)

In summary, the applicant has established the efficacy of their product in the treatment of head lice infestation, but they have not established the contribution of individual components of the product to the claimed effect. The reader is referred to the reviews of Drs. Patricia Brown and Lisa Kammerman for a fuller discussion of the efficacy results.

8. Safety

During the development of TRADENAME suspension, 1,561 subjects were evaluated, 1,040 of whom were exposed to TRADENAME suspension. Of these, 323 subjects were enrolled in dermal safety studies, for which the dose was not reflective of anticipated labeled use. Five hundred and sixty subjects were exposed to the final to-be-marketed product, TRADENAME suspension, 0.9%, in a dose that reflected anticipated labeled use: 552 diseased subjects in the pivotal trials and 8 healthy subjects in the infant PK study. Of the 552 subjects in the pivotal trials, 400 received one application and 152 received two applications (treatment duration of 10 minutes per application).

There were no deaths or SAEs attributable to TRADNAME suspension during the development program. The most frequently reported adverse event was application site erythema (3% TRADENAME, 7% NIX), followed by ocular hyperemia (2% TRADENAME, 3% NIX); in both cases, the rate for TRADENAME suspension was lower than that for the active comparator NIX. Collection of adverse events and assessment of local tolerance did not reveal unexpected safety signals.

The reader is referred to the Clinical Review by Patricia Brown, MD, for full discussion.

9. Advisory Committee Meeting

NDA 22-408 was not presented to the Dermatology and Ophthalmology Drugs Advisory Committee because the systemic exposure to spinosad, as far as it was studied, was documented to be below the level of detection, and no concerning safety signals were identified during the development program. In addition, neither the indication nor the application presented novel issues which would have warranted advisory committee input.

10. Pediatrics

The applicant conducted their pivotal trials in subjects 6 months of age and older, the relevant population for head lice infestation (b) (4)

The applicant requested a pediatric waiver for children less than six months of age based on the rationale that studies are “are highly impracticable since the number of subjects in this age group is very small.” The application was not presented to the PeRC PREA Subcommittee in this cycle, as a *Complete Response* action is anticipated.

It is recommended that studies in children six months of age and younger be waived because of safety concerns related to benzyl alcohol, specifically that there is an increased risk of systemic absorption in children less than six months of age because of the high ratio of skin surface are to body mass and the potential for an immature skin barrier, and there is an increased risk for gasping syndrome in premature infants. This will need to be addressed in labeling. This reviewer concurs with applicant's rationale that studies would be impracticable because the number of patients aged less that 6 months is low.

As discussed in section 7 of this review (Clinical Pharmacology/Biopharmaceutics), the applicant will need to conduct a maximal usage study in children with pediculosis (b) (4)

11. Other Relevant Regulatory Issues

DSI audits were conducted and did not find deficiencies that would preclude reliance upon the data that was submitted.

The applicant did not identify benzyl alcohol as an active ingredient in their product (see Section 2 of this review). However, benzyl alcohol is the active ingredient in Ulesfia (benzyl alcohol) Lotion, 5%, which is indicated for the topical treatment of head lice. The applicant did not address the combination policy with regard to benzyl alcohol, either to fulfill the information needs articulated in 21 CFR 300.50 or to establish why this section of the regulations would not apply (e.g., that benzyl alcohol is not active in the product).

The applicant identified the role of benzyl alcohol in the product (b) (4). The formulation contains three other excipients (b) (4) (hexylene glycol, isopropyl alcohol, propylene glycol), in addition to water. The applicant did not present data to establish that benzyl alcohol was essential for (b) (4) the drug substance.

In their pivotal trials, the applicant evaluated the effectiveness of their product against an active control (NIX). This design allows a determination of the effectiveness of the product, but can not establish the contribution of individual components of the product. Hence the contribution of spinosad in the absence of benzyl alcohol is unknown; similarly, the contribution of benzyl alcohol in the absence of spinosad is unknown. The applicant conducted two phase 2 studies which included active and vehicle arms; in one of the two studies (SPN-201-05), the similar response rate between the active and vehicle arms suggests that the vehicle contains one or more active ingredient/s.

In addition to the information needs articulated in CFR 300.50, the presence of a second active results in other information needs, specifically CMC information pertaining to a second drug substance (such as specifications for benzyl alcohol), and safety data needs (such as pharmacokinetic data for benzyl alcohol).

12. Labeling

The proprietary name has not been established. (b) (4) The product is referred to as TRADENAME (spinosad) suspension, 0.9%, in this review.

The applicant submitted proposed labeling in the format that complies with the Physicians' Labeling Rule. Significant changes incorporated into revised draft labeling, following labeling review, include:

- addition of a warning about neonatal toxicity associated with benzyl alcohol exposure
- addition of a warning about use in children less than 6 months of age because of the risk for increased systemic absorption
- clarified instructions for use
- incorporation of safety and efficacy data into section 8.4, Pediatric Use

Labeling negotiations had not been conducted at the time that this review closed.

13. Recommendations/Risk Benefit Assessment

Recommended regulatory action: *Complete Response*

> The applicant needs to provide sufficient information to assure the identity, strength, purity, and quality of the drug product, and to resolve the manufacturing deficiencies that resulted in the withhold determination.
>
> The applicant needs to address the requirements of 21CFR300.50 with regard to benzyl alcohol.

Recommended comments to the applicant:

Regulatory:
Benzyl alcohol is an approved drug for the topical treatment of head lice, and thus it appears that the product contains two active ingredients: spinosad and benzyl alcohol. Provide data to address the requirements of 21 CFR 300.50 with regard to benzyl alcohol, as well as requisite CMC and safety data for this active ingredient, or provide data to establish that benzyl alcohol is not active in the product.

Drug Substance:
In addition to cross reference to the DMF 17795, a regulatory specification for the drug substance should be submitted to the NDA.

Drug Product:

1. Include ID tests in the excipient specifications for Ceteareth-20 and Stearalkonium Chloride

2. Provide an updated drug product specification to clarify definition for "RelatedSubstances", "Impurities" and the Acceptance limit according to the agreement in the teleconference held on Aug 21, 2009 (see review in section P.5.1)

3. Based on the retention time table for the HPLC method provided in response to Q19 submitted on Aug 21, 2009, placebo (b) (4) and spinosyn D (b) (4) very closely. Provide data to demonstrate that the assay value for Spinosyn D is not compromised by the placebo peak.

4. Provide more detailed information regarding (b) (4) the drug product when stored under the accelerated condition.

5. (b) (4) was observed in the drug product samples provided to the Agency in May 2009. The following information should be provided to address the effect of the (b) (4) to the drug product quality:

   a. Provide data indicating when the (b) (4) starts during the storage and whether the storage condition has any effect (b) (4)

   b. Provide data to demonstrate that the content uniformity for the (b) (4) drug product is established after shaking

   c. In addition to the color as proposed in the acceptance criteria for the Appearance test, the Appearance specification for the drug product should include a description for the physical form of the drug product such as lotionlike, solution-like, etc.

6. We reserve comment on the proposed labeling until the application is otherwise adequate. If you revise labeling, your response must include updated content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm.

Proprietary Name

(b) (4) (b) (4) (b) (4) (b) (4). Submit an alternate proposed trade name for review.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22408	ORIG-1	PARAPRO PHARMACEUTICALS LLC	SPINOSAD

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/s/

JILL A LINDSTROM
11/02/2009

CLINICAL REVIEW

Application Type	NDA
Application Number(s)	22-408
Priority or Standard	Standard
Submit Date	January 21, 2009
Received Date	January 22, 2009
PDUFA Goal Date	November 21, 2009
Division / Office	DDDP/ODE III
Reviewer Name(s)	Patricia C. Brown, MD
Review Completion Date	10/16/09
Established Name	Spinosad
(Proposed) Trade Name	(b) (4)
Therapeutic Class	Anti-lice product
Applicant	ParaPRO
Formulation(s)	Suspension, 0.9%
Dosing Regimen	One 10 minute application, if live lice seen, an additional application 1 week later
Indication(s)	Head lice
Intended Population(s)	(b) (4)

Template Version: March 6, 2009

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

Clinical:
The safety and efficacy data contained in this application would support of approval of Tradename (spinosad) Suspension, 0.9% to treat head lice in patients ages 4 years and older. However; safety data, principally data from the pharmacokinetic studies, contained in this application is insufficient to establish safety for the use of Tradename (spinosad) Suspension, 0.9% to treat head lice in pediatric patients from age 6 months to 4 years.

This informational need should be conveyed to the sponsor.

CMC:
This NDA has not provided sufficient CMC information to assure the identity, strength, purity, and quality of the drug product, Tradename (spinosad) Suspension, 0.9%, for the topical treatment of head lice in patients six months of age and older. The CMC reviewer does not recommend this NDA for approval in its present form. Significant deficiencies include the following:

a) The analytical method for assaying the drug product is not deemed fully validated.
b) When stored under accelerated conditions, the drug product (b) (4).

c) The drug product exhibits (b) (4) during storage.

To assure the identity, strength, purity, and quality of the drug product the following should be obtained:
a) Information to support validation of the analytical method for assaying the drug product
b) More detailed Information about the (b) (4) drug product under accelerated conditions, allowing identification of the cause and methods for correction
c) • Data indicating when (b) (4) starts during storage and whether the storage condition has any effect (b) (4).
• Data to demonstrate that the content uniformity for the (b) (4) drug product is established after shaking.

Additional significant deficiencies, also a basis for CMC reviewer non-approval recommendation, include:
a) The proposed dosage form nomenclature (b) (4), is not acceptable.
To Correct Deficiency; Based on the flowability of the drug product and the suspension of cetostearyl alcohol in the drug product, the sponsor should change the dosage form

nomenclature [redacted] (b) (4) to Suspension, in compliance with current Agency policy.
b) No overall "Acceptable" recommendation has been issued from the Office of Compliance.

1.2 Risk Benefit Assessment

In the United States, it is estimated that between 6 and 12 million people per year are diagnosed with *Pediculosis capitis*, head lice. The highest incidence is found in children aged 3 to 11 years. Head lice are more frequent in girls due to the tendency to have longer hair and to exchange hair care accessories.[1] Head lice are uncommon in African-Americans because anatomic differences in American lice do not allow for proper positioning of the female in order to lay eggs on coarse, curly hair.[2,3] Genetic resistance to pyrethroids and to lindane is common in the United States.[4] Available treatments without resistance documented in the United States include malathion 0.5% lotion and benzyl alcohol 5% lotion. Malathion is limited to use in children 6 years and older. There is a public health need for a product for treatment of head lice with a favorable side effect profile and approval for use in children less than 6 years of age.

Tradename (spinosad) Suspension, 0.9%, [redacted] (b) (4) has been demonstrated to be statistically superior to NIX in two well-controlled pivotal trials, SPN-301-07 and 302-07, in subjects 6 months and older. The results are robust.

Safety was evaluated in the two pivotal trials. Supportive safety data is also available from the nine other sponsor-conducted Phase 1 and 2 trials. In the clinical development program no deaths occurred and 3 SAEs, not considered related to study drug, occurred among those exposed to spinosad formulations.

In the pivotal trials, the most common adverse event reported was application site erythema, occurring in 3.1% of subjects exposed to Natrova and in 6.8% of subjects exposed to NIX. The second most common adverse event was ocular hyperemia (2.2% and 3.3% of subjects exposed to exposed to Natrova and NIX, respectively). The third most common adverse event was application site irritation (.9% and 1.5% of subjects exposed to Natrova and NIX, respectively).

[1] Jacobson CC and Abel EA. Periodic Synopsis: Parasitic Infections. Journal of the American Academy of Dermatology 2007;56:1026-43.
[2] Burkhart CN and Burkhart CG. Head lice: Scientific assessment of the nit sheath with clinical ramifications and therapeutic options. Journal of the American Academy of Dermatology 2005;53:129-133.
[3] Meinking TL et al. Chapter 83. Infestations in Dermatology e-edition, 2nd Edition: Bolognia JL and Jorizzo JL, Elsevier, Inc. © 2009.
[4] Lebwohl M, Clark L, and Levitt J. Therapy for Head Lice Based on Life Cycle, Resistance, and Safety Considerations. Pediatrics 2007;119;965-974.

Evaluation of cutaneous safety, scalp irritation (Phases 1, 2, 3) and ocular irritation (Phase 3), did not reveal clinically notable signals.

The adverse event profile observed reveals a product safe for use in children as young as 6 months. A physician intermediary is recommended because the excipient benzyl alcohol at a concentration of (b) (4) requires evaluation of the youngest patients for accurate age to avoid potentially severe adverse events associated with that moiety in small or very young infants.

While available pharmacokinetic data indicate no detectable systemic absorption in pediatric subjects having lice infestations down to 4 years of age, pharmacokinetic data are not available in lice-infested children aged 6 months to 4 years.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

At this time this is not applicable.

1.4 Recommendations for Postmarket Requirements and Commitments

At this time this is not applicable.

2 Introduction and Regulatory Background

2.1 Product Information

The sponsor, ParaPro Pharmaceuticals, LLC has submitted a 505(b)(1) application for Tradename (spinosad) Suspension, 0.9%. ParaPRO acquired the development rights for the use of spinosad from Eli Lilly and Company and the Active Pharmaceutical Ingredient (API) is prepared by Dow AgroSciences, LLC. Spinosad is a new molecular entity, derived from the fermentation of a soil actinomycete bacterium, *Saccharopolyspora spinosa*. Spinosad is composed primarily of two active ingredients, spinosyn A and spinosyn D.

Tradename (spinosad) Suspension, 0.9% is a viscous peach-colored pearlescent liquid. Spinosad .9% suspension contains 9 mg spinosad per gram in a vehicle consisting of Water, Isopropyl Alcohol, Benzyl Alcohol, Hexylene Glycol, Propylene Glycol, Cetearyl Alcohol, Stearalkonium Chloride, Ceteareth-20, Hydoroxyethyl Cellulose, Butylated Hydroxytoluene, FD&C Yellow # 6.

The sponsor-proposed indication is treatment of head lice (*Pediculus humanis capitis*) infestations including head lice (b) (4) in patients (b) (4). The product is to be applied for 10 minutes to dry scalp and hair and then rinsed off thoroughly with warm water. No nit combing is required. According to the sponsor-proposed dosage and administration, if reinfestation occurs after treatment, (b) (4) can be applied again.

The product is to be packaged in a HDPE (high density polyethylene copolymer) cylindrical design bottle (b) (4) The bottles have a 24 mm ratchet neck. The closure is a 24 mm child resistant white snap top cap and spout (b) (4) According to the sponsor, the closure (b) (4) passes child resistant senior friendly protocol.

The non-proprietary name for the proposed drug product is spinosad. (b) (4)

2.2 Tables of Currently Available Treatments for Proposed Indications

FDA approved pharmaceutical products for treatment of head lice include the following:

Table 1: Treatments for Head Lice

Treatment	Formulations	Rx/OTC			Resistance[1, 2]	Ages
Permethrin (e.g.NIX)	1% lotion	OTC			common	
Pyrethrin & piperonyl butoxide (e.g. RID)	Mousse, shampoo	OTC			common	
Benzyl alcohol	5% lotion	Rx			New product	≥ 6 months
Malthion 0.5%	Lotion	Rx			Not yet in US	≥ 6 years
Lindane 1%	Lotion, shampoo	Rx			Common	Caution on use: weights < 110 lbs

[1] Lebwohl M, Clark L, and Levitt J. Therapy for Head Lice Based on Life Cycle, Resistance, and Safety Considerations. Pediatrics 2007;119:965-974.
[2] Meinking TL et al. Chapter 83. Infestations in Dermatology e-edition, 2nd Edition: Bolognia JL and Jorizzo JL, Elsevier, Inc. © 2009.

Permethrin and pyrethrins work by impeding sodium channel closure thereby causing delayed repolarization of the neuron. This causes hyperstimulation of the nervous system, paralyzing the louse and preventing it from feeding.[1] In individuals using pyrethrin-based products, rare cases of exacerbation of asthma and even death have been reported.[2]

NDA 22-129 ULESFIA (benzyl alcohol) Lotion, 5% was approved April 9, 2009 containing 5% benzyl alcohol as the active. The indication is topical treatment of head lice infestation in patients 6 months and older. For ULESFIA, the most common adverse reactions (> 1% and more common than with placebo) are: ocular irritation, applicant site irritation, and application site anesthesia and hypoesthesia (from approved product labeling).

Malathion 0.5% and Lindane 1% are discussed in section 2.4 below.

Pharmaceutical products that are used off-label to treat head lice include oral ivermectin with a potential for neurotoxicity and trimethoprim/sulfamethoxazole with a risk of allergic rash and of Stevens Johnson syndrome.

Physical, non-pharmacologic methods for treating lice include hair removal and occlusion (petroleum jelly, olive oil, mayonnaise, etc.). Another non-pharmacologic method is nit combing. Devices have been approved for the treatment of head lice and include Lice Comb, Lockomb, Licemeister, and others.

2.3 Availability of Proposed Active Ingredient in the United States

Since the proposed active ingredient, spinosad, is a new molecular entity it is not available in the United States.

2.4 Important Safety Issues with Consideration to Related Drugs

Spinosad is a new molecular entity, derived from the fermentation of a soil actinomycete bacterium, *Saccharopolyspora spinosa*. Spinosad is an insecticide that works by causing paralysis of insects by altering the function of nicotinic and gamma butyric acid-gated ion channels resulting in prolonged over-excitation of the insect's nervous system.

Other insecticides that are FDA approved prescription products for the indication, treatment of head lice, include Lindane 1% lotion/shampoo and Malathion lotion 0.5%. Lindane is γ-benzene hexachloride. By noncompetitively inhibiting the γ-amino butyric acid (GABA) receptor which binds GABA, an inhibitory neurotransmitter, lindane causes

[1] Lebwohl M, Clark L, and Levitt J. Op.cit
[2] Wax PM and Hoffman RS. Fatality Associated with Inhalation of a Pyrethrin Shampoo. Clinical Toxicology 1994:32;457-460.

neuronal hyperstimulation with ensuing paralysis of the louse and death due to inability to feed.[1] Lindane carries a boxed warning for neurologic toxicity (PI): "Seizures and deaths have been reported following Lindane Shampoo use with repeat or prolonged application, but also rare cases following a single application according to directions. Lindane Shampoo should be used with caution infants, children, the elderly, and individuals with other skin conditions, and those who weigh < 110 lbs (59kg) as they may be at risk of serious neurotoxicity."

Malathion is an organophosphate insecticide which, after conversion to malaoxin in the louse, irreversibly inhibits acetylcholinesterase. The ensuing excess cholinergic activity causes neuronal hyperexcitability, preventing feeding. Potential risks associated with Malathion use include flammability due to the high concentration of isopropyl alcohol in the formulation. With accidental oral ingestion, cholinesterase depletion could occurr leading to severe respiratory distress. However, according to Lebwohl et al[2], reports of accidental ingestion are exceedingly rare and there are no known reports of bodily injury resulting from the isopropyl alcohol catching fire.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

Tradename (spinosad) Suspension, 0.9% was developed under commercial IND 66,657. Principal meetings are outlined in the following table:

Table 2: Principal Presubmission Regulatory Activity

Type of Meeting	Date	Objective
Pre-IND	5/12/2003	To provide general guidance on the content and format of the proposed Investigational New Drug Application under 21 CFR 312.
End of Phase 2	10/31/2006	To discuss the sponsor's plan to develop spinosad (b) (4) as a topical treatment for head lice (b) (4)
Pre-NDA	11/4/2008	To discuss the content and format of the NDA for Spinosad (b) (4) for the proposed indication of the treatment of human head lice (b) (4)

A Pre-IND meeting was held 5/12/2003. Among the issues discussed at this meeting were the following:

- Agency: Spinosad is an aqueous topical drug that is not required to be sterile prior to use. The manufacturing process involves procedures that will limit the incidence of

[1] Lebwohl M, Clark L, and Levitt J. Therapy for Head Lice Based on Life Cycle, Resistance, and Safety Considerations. Pediatrics 2007;119:965-974.
[2] Ibid

microbial contamination during production. Additionally, microbial growth will be inhibited by the (b) (4) benzyl alcohol present in the finished drug product.

- Agency: Pediatric PK studies should be done in patients with head lice infestation as the presence of scalp irritation could result in increased systemic absorption.
- Agency: One route to possible approval would be to demonstrate superiority to NIX used as labeled in 2 adequate, well controlled studies

An End of Phase 2 meeting was held 10/31/06. Areas of discussion included the following.

- In response to sponsor query, the Agency stated that the current nonclinical package appears adequate to support Phase 3 clinical studies and may be adequate to support submission of an NDA.
- In response to a sponsor inquiry, the Agency stated that the Phase 2B dose ranging study (SPN-202-06) is not acceptable as one of the two pivotal Phase 3 studies. This study was designed as Phase 2 dose ranging study and does not meet criteria (e.g. randomization, pre-specified analysis plan on handling dropouts) for a well-controlled Phase 3 trial.
- The Agency stated that under the Pediatric Research Equity Act (PREA) sponsors need to perform studies in all relevant age groups unless safety is prohibitive. The sponsor stated that no safety signal has been identified that would preclude studies in the younger age group, ages 6 to 24 months. The sponsor will include children down to 6 months of age in future studies.
- The sponsor was asked to address high vehicle response rates in the pilot dose ranging study, SPN-201-05 (22% Day 7, 89% day 14; 2 treatments) and non-concordance with vehicle response rates in dose ranging study SPN-202-06 (48.8% Day 7, 25.6% Day 14; one treatment only, nits incubated & evaluated). The sponsor stated that study SPN-210-05 included a second treatment compared with study SPN-202-06 and the criteria for success in these two studies were different. The Division raised concerns about the adequacy of efficacy assessment and whether the vehicle could be active.
- The agency stated that proposed study, SPN-302-07, plans to investigate 3 arms: NatrOVA 0.1%, NIX and vehicle. Since there might be ethical concerns about treating subjects with vehicle, the study should be limited to two treatment arms NatrOVA and NIX.

A teleconference occurred 4/23/07 to communicate a request for information to the sponsor that would aid in the determination of the applicability of the combination drug policy to Spinosad. A request was made for data to show the independent activity of Sinosyn A and Spinosyn D against lice. The sponsor subsequently submitted reports of studies that are in vitro tests of the effectiveness of the spinosyn factors at killing either cat fleas or human body lice. After reviewing these reports, the pharmacologist concluded: “The mixture of A and D appears to have insecticidal activity that is not much different from A or D alone (none of the comparisons were statistically significant) and the mixture appears to have an acceptable toxicity profile for use as an antilice treatment.”

Regarding the applicability of the combination drug policy to Spinosad, ONDQA stated in a Memorandum 5/11/07 that a viable option would be to designate the mixture of Spinosyn A

and Spinosyn D at a specified ratio as one single active ingredient. Precedents for this exist. In the Guidance Meeting Draft Reviewer Comments 5/17/07 the Agency agreed to recognize Spinosad as a single active ingredient in the sponsor's product (b) (4) "Spinosad is a naturally-derived fermentation product composed of a mixture of related compounds containing primarily Spinosyn A and D at a ratio of approximately 5:1. If Spinosad is the only active ingredient in the product, the fixed-combination drug regulations in 21 CFR 300.50 will not apply." Reviewer comments were faxed to the sponsor and the sponsor indicated that they would not need to have the previously scheduled meeting on this topic.

Regarding the protocol submitted for special clinical protocol assessment (SPA) 5/18/07, the Agency reached agreements including the following:

- The pivotal Phase 3 trials will include a third arm to further assure blinding, specifically NatrOVA with combing. This third arm does not need to be the same size as the arms for NIX or NatrOVA: the third arm would be 25% the size of the two other arms (i.e. 19 to 20 subjects per study).
- Each enrolled household will have one binary outcome (success/failure) from the primary subject. The proportion of primary subjects who are lice free will be estimated across all households.
- The safety population will include all randomized subjects who have received at least one treatment application.
- Safety laboratory data will be collected from all subjects with head lice with non-intact skin. This will be done for all qualifying pediatric age groups six months of age and above and will be done on a subset of subjects.
- It is acceptable that the youngest member of a household with three live lice be the primary subject used for evaluation.
- The protocol, specifying patient or caregiver application of the product at home, will employ anticipated labeled use.

Phase 3 study protocols were submitted 09/19, 9/28, 10/1, and 11/15/2007. Comments were faxed to sponsor on 2/11/08 and included the following:

- The sponsor should consider whether females of child-bearing potential must be required to use contraception to enroll in the phase 3 trials. The requirement to use effective contraception may be too restrictive, unless there is safety information indicating a risk.
- The agency stated that 80% is the minimum power used for designing clinical trials; therefore, the sponsor was encouraged to design the studies with higher power especially if variability was expected in the response rates for NIX. Additionally, sample size should account for drop-outs.

A Pre-NDA meeting occurred 11/4/2008. Among the issues discussed were the following:

- Although the Agency has agreed to recognize Spinosad as a single active ingredient in the proposed product, a proper control over the individual components of Spinosad

and their proportions in the mixture is necessary in order to assure strength and purity. The Agency expects that the drug product specification will include assay on individual components, and acceptance criteria will be in place on individual, total, and the ration of major components.

- The sponsor proposed the following elements for labeling for the spinosad product (b) (4) [redacted] The Agency responded that results based on a *post-hoc* analysis cannot be used to establish efficacy. In order to claim efficacy, the study design has to be pre-planned and the subjects should have the disease (b) (4) [redacted] The claim that nit combing is not required may be considered for labeling.

2.6 Other Relevant Background Information

This is a new molecular entity therefore there is no additional foreign regulatory information available at this time.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

A) Department of Scientific Investigations (DSI) inspections were requested for 4 sites with the following rationales:

Site 03 (Study 301): Robert S. Haber, MD in South Euclid, OH

- Largest treatment effect (100% success rate for the sponsor's product without nit combing arm compared to a very low success rate, 12.5%, for the NIX® arm)

Site 07 (Study 302): Mark L. Moore, MD in Indianapolis, IN

- Large treatment effect (100% with nit combing compared to a 21.4% success rate for NIX® arm)
- High, 100%, success rate for both sponsor's product arms (with and without nit combing)

Site 05 (Study 301): Dow B. Stough, MD in Hot Springs, AK

- Largest enrollment (52 subjects)
- Sponsor's product arm with nit combing had a lower response rate than sponsor's product without nit combing.

Site 09 (Study 302): Katie Shepherd, BA, PA in West Palm Beach, FL

- Largest enrollment (52 subjects) and large treatment effects, 83%, sponsor's product with and without nit combing versus 29% for NIX® arm

Final DSI reports for sites 09 (Shepherd) and 03 (Haber) were NAI, no action indicated. Final DSI reports for sites 07 (Moore) and 05 (Stough) were VAI, voluntary action indicated. After obtaining more information for sites 07 and 05, DSI concluded that the data appear acceptable in support of the respective application.

The sponsor, ParaPRO Pharmaceuticals, L.L.C., was inspected by DSI and the final report was issued 9/2/09 with the finding of no action indicated. DSI stated that: "The studies appear to have been conducted adequately, and the data submitted by the sponsor may be used in support of the respective indication."

B) The sponsor's analyses were reviewed. The review team performed independent analyses.

3.2 Compliance with Good Clinical Practices

According to the clinical study reports, the sponsor conducted the 11 studies in the clinical development program in compliance with Good Clinical Practice Regulations, 21 CFR Parts 50, 54, 56, and 312. Clinical investigations and informed consent were reviewed and approved by an Institutional Review Board prior to study initiation. Informed consent was obtained.

3.3 Financial Disclosures

The applicant submitted form FDA 3454, certifying that they, the applicant, had not entered into any financial arrangements with the clinical investigators. A list of the clinical investigators for the (b) (4) clinical development program was provided.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

Please see chemistry review by Zhengfang Ge, Ph.D.

ParaPRO acquired the development rights for the use of spinosad from Eli Lilly and Company and the Active Pharmaceutical Ingredient (API) is prepared by Dow AgroSciences, LLC.

Spinosad is a new molecular entity, derived from the fermentation of a soil actinomycete bacterium, *Saccharopolyspora spinosa*. Spinosad is composed primarily of two active ingredients, spinosyn A and spinosyn D. The other minor factors were defined as relative substance according to an agreement between the sponsor and the Agency during the filing review.

Table 3: Composition of (b) (4)

INCI Name	Target Concentration	Purpose
Benzyl Alcohol	(b) (4)	
Butylated hydroxytoluene		
Ceterareth-20		
Cetearyl alcohol		
FD&C Yellow #6		
Hexylene Glycol		
Hydrochloric Acid		
Hydroxethyl cellulose		
Isopropyl alcohol		
Propylene Glycol		
Sodium Hydroxide		
Spinosad (A+D)	0.9%	Active ingredient
Stearalkonium chloride	(b) (4)	
Water, (b) (4)		

Source: Sponsor's NDA, Section 2.3.P Drug Product, p. 2, updated in Amendment 7 dated 7/15/09, pp. 6 & 9.

The isopropyl alcohol and benzyl alcohol are included in the formulation (b) (4) of the API. Propylene and hexylene glycol are added (b) (4) properties are provided by cetostearyl alcohol and ammonyx-4. Ceteareth-20 also provides (b) (4) properties (b) (4). Hydroxyethyl cellulose is added (b) (4) Water (b) (4) The sponsor states that the formulation was intended…"to provide a level of cosmetic elegance similar to marketed hair crème rinses to …allow an easier comb out by detangling the hair ...."

Significant issues identified during the CMC review are discussed below. A number of these are not resolved and are considered deficiencies at the time of closure of this review.

1) Drug Substance:
All of the CMC information for the drug substance is cross-referenced to DMF 17795. The specification provided in the DMF was reviewed by the chemistry reviewer and appears to be acceptable.
Deficiency: There is no regulatory specification for the drug substance in the NDA.
To Correct Deficiency: A regulatory specification for the drug substance needs to be submitted to the NDA.

2) Drug Product:
Deficiency: In an amendment, responding to the 74-day letter, the sponsor agreed to redefine the drug substance as Spinosyn A+D. All of the other spinosyn factors are defined as related substance. As a result of the redefinition, the sponsor indicated that the dose strength will be (b) (4) 0.9%.
To Correct Deficiency: The sponsor needs to provide an updated drug product specification to clarify definition for "Related Substances", "Impurities" and the Acceptance limit according to the agreement in the tele-con held August 21, 2009.

Deficiency: Based on the retention time table for the HPLC method provided on August 21, 2009, placebo (b) (4) and spinosyn D (b) (4) very closely.
To Correct Deficiency: The sponsor needs to provide data to demonstrate that the assay value for spinosyn D is not compromised by the placebo peak.

Deficiency: When stored under accelerated conditions, the drug product (b) (4)
To Correct Deficiency: More detailed information is requested regarding this problem.

Deficiency: The drug product sample provided to the Agency in May 2009 showed (b) (4)
To Correct Deficiency: The following information should be provided to address the effect (b) (4) on drug product quality:
a. Provide data indicating when the (b) (4) starts during storage and whether the storage condition has any effect (b) (4).
b. Provide data to demonstrate that the content uniformity for the (b) (4) drug product is established after shaking.

3) Container/Carton Labels:
Deficiency: The proposed dosage form nomenclature, (b) (4) is not acceptable.
To Correct Deficiency: Based on the flowability of the drug product and the suspension of cetostearyl alcohol in the drug product, the sponsor should change the dosage form nomenclature (b) (4) to Suspension, in compliance with current Agency policy.

CMC Reviewer Recommendation on Approvability:
The CMC reviewer does not recommend this NDA for "***Approval***" in its present form.

The basis for this recommendation is as follows:

> Analytical method for assaying the drug product is not deemed fully validated. The drug product (b) (4) during storage. The drug product has (b) (4) problem during the accelerated conditions. Because of these issues, this NDA is not deemed to provide adequate information to assure the identity, strength, purity and quality of the drug product.
>
> It also has unacceptable nomenclature for the dosage form.
>
> No overall "Acceptable" recommendation has been issued from the Office of Compliance

Note: Due to the redefinition of the drug substance as Spinosyn A+D with all of the other spinosyn factors being defined as related substance, the dose strength of (b) (4) will be written as 0.9% in this document. For the purposes of this review the spinosad products will be written as the sponsor wrote the reports, 0.5%, 1.0%, and 2.0%. However, due to the redefinition of the drug substance it is understood that the actual concentrations studied were 0.45%, 0.9%, and 1.8%.

4.2 Clinical Microbiology

There were no significant efficacy/safety issues since (b) (4) is not an antimicrobial product.

4.3 Preclinical Pharmacology/Toxicology

The pharmacology/toxicology reviewer, Jianyong Wang, Ph.D., states that the NDA for drug product (b) (4) is approvable from a pharmacological/toxicological perspective. The reviewer does not recommend additional nonclinical studies.

In the view of the pharmacology/toxicology reviewer there are no nonclinical safety issues relevant to clinical use. Of note, administration of spinosad in the diet at up to 0.1% for 12 months did not appear to be neurotoxic in rats. Spinosad 2% suspension was not irritating to the skin of minpigs; however, it produced mild irritation in rabbit eye which was reversible with time. In mice, spinosad 2% suspension did not induce a phototoxic reaction upon irradiation with an essentially all UVA light source. In guinea pigs, spinosad did not appear to be a skin sensitizer.

The pharmacology/toxicology reviewer recommends the following labeling:

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category B.

There are no adequate and well-controlled studies with topical spinosad suspension in pregnant women. Reproduction studies conducted in rats and rabbits were negative for teratogenic effects. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

No comparisons of animal exposure with human exposure are provided in this labeling due to the low systemic exposure noted in the clinical pharmacokinetic study *[see Clinical Pharmacology (12.3)]* which did not allow for the determination of human AUC values that could be used for this calculation.

Systemic embryofetal development studies were conducted in rats and rabbits. Oral doses of 10, 50 and 200 mg/kg/day spinosad were administered during the period of organogenesis (gestational days 6 – 15) to pregnant female rats. No teratogenic effects were noted at any dose. Maternal toxicity was observed at 200 mg/kg/day. Oral doses of 2.5, 10 and 50 mg/kg/day spinosad were administered during the period of organogenesis (gestational days 7 – 19) to pregnant female rabbits. No teratogenic effects were noted at any dose. Maternal toxicity was observed at 50 mg/kg/day.

A two-generation dietary reproduction study was conducted in rats. Oral doses of 3, 10, and 100 mg/kg/day spinosad were administered to male and female rats from 10-12 weeks prior to mating through the mating, parturition, and lactation period. No reproductive/developmental toxicity was noted at doses up to 10 mg/kg/day. In the presence of maternal toxicity, increased dystocia in parturition, decreased gestation survival, decreased litter size, decreased pup body weight, and decreased neonatal survival were noted at a dose of 100 mg/kg/day.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of action

Spinosad causes neuronal excitation in insects. After periods of hyperexcitation, lice become paralyzed and die.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, mutagenesis, impairment of fertility

In an oral (diet) mouse carcinogenicity study, spinosad was administered to CD-1 mice at doses of 0.0025, 0.008, and 0.036% in the diet (approximately 3.4, 11.4, and 50.9 mg/kg/day for males and 4.2, 13.8, and 67.0 mg/kg/day for females) for 18 months. No treatment-related tumors were noted in the mouse carcinogenicity study up to the highest doses evaluated in this study of 50.9 mg/kg/day in male mice and 13.8 mg/kg/day in female mice. Female mice treated with a dose of 67.0 mg/kg/day were not evaluated in this study due to high mortality.

In an oral (diet) rat carcinogenicity study, spinosad was administered to Fischer 344 rats at doses of 0.005, 0.02, 0.05, and 0.1% in the diet (approximately 2.4, 9.5, 24.1 and 49.4 mg/kg/day for males and 3.0, 12.0, 30.1 and 62.8 mg/kg/day for females) for 24 months. No treatment-

related tumors were noted in the rat carcinogenicity study in male or female rats up to the highest doses evaluated in this study of 24.1 mg/kg/day in male rats and 30.1 mg/kg/day in female rats. Rats in the highest dose group in this study were not evaluated due to high mortality.

Spinosad revealed no evidence of mutagenic or clastogenic potential based on the results of four *in vitro* genotoxicity tests (Ames assay, mouse lymphoma L5178Y assay, Chinese hamster ovary cell chromosome aberration assay, and rat hepatocyte unscheduled DNA synthesis assay) and one *in vivo* genotoxicity test (mouse bone marrow micronucleus assay).

Oral administration of spinosad (in diet) to rats, throughout mating, gestation, parturition and lactation, demonstrated no effects on growth, fertility or reproduction, at doses up to 10 mg/kg/day *[see Pregnancy (8.1)]*

4.4 Clinical Pharmacology

Please see review by Dennis Bashaw, Pharm.D. The clinical pharmacology reviewer states that the sponsor has met the requirements under 21 CFR 320 and the application is generally acceptable form a Clinical Pharmacology standpoint. However, there is a lack of any pharmacokinetic data in lice infested subjects below the age of 4 years. Since lice infestation is accompanied by scalp inflammation and excoriation, Clinical Pharmacology recommends that if the application were to be approved on this cycle, the lower age limit for product use be (b) (4) 4 years.

4.4.1 Mechanism of Action

Spinosad causes neuronal excitation in insects. After periods of hyperexcitation, lice become paralyzed and die. The sponsor has not proposed labeling regarding mechanism of action.

4.4.2 Pharmacodynamics

The sponsor did not conduct pharmacodynamic studies.

The sponsor was asked to provide information to assess the effect of the product on cardiac repolarization and responded (4/29/09):

> Based on Guidance Document E14, the clinical evaluation of QT/QTc interval prolongation does not apply to (b) (4) since it is applied topically to the scalp for 10 minutes, and animal and human pharmacokinetic studies show no evidence of absorption or systemic exposure of spinosad.

A consult was submitted to cardiology with the following query:

> Does cardiology agree that spinosad (b) (4) does not need electrocardigraphic evaluation such as a thorough QT/QTc study? It should be

> noted that the lack of evidence of systemic exposure in humans does not prove that the product is not absorbed in humans. However, for spinosad (b) (4) systemic exposure appears not to be detectable down to low levels, (< 3 ng/mL), the product is to be applied for a short period of time (10 minutes), and the treatment course is limited (one or two treatments per episode of head lice).

The QT-IRT Review Team response was as follows:

> If you concur with the sponsor's assertion that there is no systemic exposure to spinosad and its metabolites at the clinically relevant doses, a TQT study is not needed for this product. According to the ICH E14 guideline, recommendations for a TQT study apply to new drugs having systemic bioavailability (see section I.B of ICH E14 guideline).

Evaluation of the data from the three Phase 1 PK studies conducted as part of the clinical development program, shows that there is no detectable absorption of 1% and 2 % spinosad under conditions of use. Please see also section 4.4.3 below.

4.4.3 Pharmacokinetics

The clinical development program for (b) (4) included the following three Phase 1 Human PK studies:

a) Study SPN-101-04, (22 completed) healthy adult subjects, one 10 minute application, 1.8% spinosad

b) Study SPN-106-06, (8 completed), healthy pediatric subjects, ages 6 to 24 months of age, one 10 minute application, 0.9% spinosad ((b) (4)-final formulation used)

c) Study SPN-103-05, (14 completed), pediatric subjects with head lice, 4 to 15 years of age, one 10 minute application, 1.8% spinosad

PK evaluations for the studies included assessments of spinosyn A and spinosyn D plasma concentration levels over time and derivation of PK parameters including AUC_{0-t}, C_{max}, and T_{max}. Study SPN-101-04 also included PK parameters $AUC_{0-\infty}$, $t_{1/2}$, and CL/F.

All collected samples were reported to be below the limits of quantification (< 3 ng/mL). A 10-minute topical application (spinosad 1.8%) appears not result in any detectable systemic absorption by healthy adult subjects, healthy pediatric subjects (spinosad 0.9%, (b) (4) or in pediatric subjects with head lice (spinosad 1.8%).

Assay sensitivity for lower limit of quantification (< 3 ng/mL) appears adequate. According to the clinical pharmacology reviewer, for both spinosad A and D, the LOQ (limit of quantification) was the LOD (limit of detection) as reported, the %CV for both forms at 3ng/ml was less than 7% and at the low standard it was 5%. The reviewer states that based on this we have high confidence the results are accurate.

Additional factors adding confidence in the findings of no detectable systemic absorption are the fact that spinosad is a large molecule (Spinosyn A molecular weight=731 and Spinosyn=D 745), leading to easier detection. Also treatment times are short: Proposed labeling includes 10 minute application to scalp and hair, up to 120 ml with one or sometimes two treatments.

Discussion of Adequacy of PK Data in Children:
One factor to consider is the timing of skin barrier development. Full-term infants (40 weeks gestational age) are born with a skin barrier that is comparable with that found in adults. For ultra-low birth weight infants (23-25 week gestational age), the complete development of a fully functional stratum corneum (top layer of skin considered the principal permeability barrier in mature skin and composed of protein-filled keratinocytes embedded in a layered lipid matrix) may take as long as 5 to 7 weeks after birth. For infants born later than 25 weeks gestational age but less than full term up to 2 to 4 weeks of postnatal existence is needed to achieve a fully functioning stratum corneum.[1] By six months, the age of the youngest subjects in the pharmacokinetic or pivotal studies, skin barrier function is comparable with that of adults.

The PK study SPN-106-06 involved eight healthy pediatric subjects with ages in months; 6, 9, 9, 13, 14, 19, 21, and 23. Study drug (b) (4) 0.9%) was applied directly to the scalp by site personnel for 10 minutes (± 30 seconds). Application time was measured from the end of the product application to scalp and hair. A mean of 17 grams (range 7 to 24 grams) of study drug was applied. For these subjects, scalp erythema and edema was assessed at the screening visit and on Day 1 pre-treatment, and at hours 1 and 4. No erythema or edema was seen for any of the eight subjects at any time point.

The PK study SPN-103-05 involved 14 pediatric subjects, having head lice, defined as at least 3 live lice at study entry. Ages of these subjects in years were; 4, 6, 7, 8, 9, 10, 10, 10, 10, 10, 11, 13, 13, and 15. The study drug (spinosad 1.8% Lot number: 7104-001) differed from the final to-be-marketed formulation by having twice the concentration of the API spinosad, a lesser amount of hydroxyethyl cellulose (b) (4) a slightly lesser amount of isopropanol (b) (4) and less purified water (b) (4) Study drug, spinosad 1.8%, was applied directly to the scalp by site personnel for 10 minutes (± 30 seconds).

[1] Kalia YN Nonato LB, Lund CH, Guy RH. Development of Skin Barrier Function in Premature Infants. J Invest Dermatol 1998:111:320-326.

Application time was measured from the end of the product application to scalp and hair. A mean of 30 grams (range 28 to 31 grams) of study drug was applied. For these subjects, scalp erythema and edema was assessed at the screening visit, on Day 1 (pre-treatment, and at hours 1 and 4), and on Day 7. Pre-treatment, regarding erythema; 5 subjects were assessed as having very slight erythema, 8 assessed as having well defined erythema, and one as having moderate to severe erythema. Pre-treatment, regarding edema; 5 subjects were assessed as having no edema, 5 as having very slight edema, and 4 as having slight edema. For all subjects, assessments of erythema and edema at succeeding time points either improved or stayed the same.

Patients with lice can be asymptomatic, however, pruritus is common[1]. Pruritus may take 2 to 6 weeks to develop after first exposure. This reflects an immunologic response thought to be to components of louse saliva or anticoagulant. Common findings include excoriations, erythema, pyoderma, and scaliness of the scalp and posterior neck.[2]

As discussed above, the three PK studies performed revealed no detectable systemic exposure, including use of the API, spinosad at twice (1.8%) the to-be-marketed formulation (.9%) in study SPN-101-04 (adults), and study SPN-103-05 (pediatric). However, the PK studies do not include subjects with lice infestation from 6 months to 4 years of age.

Pertinent to the issue of absorption, the clinical pharmacology reviewer reports on an in vitro study of drug penetration of human stratum corneum. Study 3787 was conducted in human cadaver skin with the formulated product used in clinical testing in humans. Concentrations of spinosad, 0.45%, .9%, and 1.8%, were exposed to the skin for 24 hours. Mean total absorption as a percentage of the applied dose in all skin layers and the receptor fluid was 15.8% including, 6.6 % in the upper corneal layer, 2.9% in the lower stratum corneum, 6.2% in the epidermal/dermal skin, and 0.02% in receptor fluid. The percentage in the receptor fluid would represent the absorbed compound. The implied conclusion is that if dermal absorption after 24 hours of contact is notably less than 1.0% in the receptor fluid, then absorption in vivo after a 10 minute application is likely to be negligible. While this study does not involve actual clinical use, the data provided is consistent with data obtained in the clinical PK studies.

Although the PK studies revealed no detectable systemic exposure, the population studied appears inadequate to support this finding in the youngest subjects, 6 months up to 4 years. Only one, SPN-103-05, of the three PK studies enrolled subjects with head lice infestation (at least 3 live lice at study entry). In this study the youngest subject was 4 years old and the next youngest was 6. Study SPN-106-06 did include

[1] Ko CJ and Elston DM. Pediculosis. Continuing Medical Education. J Am. Acad. Dermatology 2004;50:1-12.
[2] Meinking TL et al. Chapter 83. Infestations in Dermatology e-edition, 2nd Edition: Bolognia JL and Jorizzo JL, Elsevier, Inc. © 2009.

younger subjects, a total of eight from 6 to 23 months of age. However subjects in this study had no lice and no findings of scalp erythema or edema as were noted in study SPN-103-05. At the pre-IND meeting May 12, 2003, the Agency stated that:

> Pediatric PK studies should be done in patients with head lice infestation as the presence of scalp irritation could result in increased systemic absorption. This would mirror the use of the final marketed product and would be a better measure of true systemic exposure upon use since it will maximize dermal/scalp absorption.

For a new drug application, the Pediatric Research Equity Act of 2007 (PREA) requires that applicant assess the safety and effectiveness of the drug product for the claimed indication in all relevant pediatric subpopulations using age appropriate formulations. Studies must include data to support dosing and administration. For NDA 22-408, this would include relevant pharmacokinetic data for subjects having lice infestation from age 6 months up to 4 years. Additional pharmacokinetic study data will be needed. A suggested study outline follows:

Conduct an open-label study to determine the PK profile of a single treatment of Tradename (spinosad) Suspension, 0.9% in 16 subjects aged 6 months to 2 years having active lice infestation, defined as at least 3 live lice at study entry. Blood should be collected for analyses at time points that include, at a minimum, pre-application, as well as 1 and 4 hours post-application. PK evaluation should include assessments of spinosyn A and spinosyn D plasma concentration levels over time and a derivation of parameters that include AUC0-t, Cmax, and Tmax. Adverse events should be monitored and active assessment for local adverse events including ocular and scalp irritation should be performed. The study should include 8 subjects ages 6 months to <1 year and 8 subjects 1 year to < 2years.

The clinical pharmacology reviewer proposes revisions to sponsor-proposed labeling to both highlight the one study that was done in subjects with lice infestation and to indicate the proper analytical technique used. Additions are in underline and deletions are in ~~strikethrough~~.

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

Table 4: Clinical Studies: Phase 1

Protocol No. (Study Phase)	Objective	Study Design	Subject Population (Plan/Actual)	# Sites	Treatment Group(s) = # Subjects	Dosing Regimen/ Treatment Duration	Study Period
SPN-101-04 (Phase 1)	PK profile, topical & systemic tolerability following a single dose of Spinosad 2%	Open-label, single dose PK study	Healthy subjects at least 18 years of age (24/23)	1 US	Spinosad 2.0% = 23	Single application to scalp of 30 mL for 10 min.	12/4/04 to 12/21/04
SPN-102-05 (Phase 1)	Assess cumulative irritation potential of Spinosad 2% and vehicle using a 21-day study design; evaluate potential of Spinosad 2% for contact sensitization	Single-blind, vehicle-controlled, within-subject, evaluator-blind, randomized, cumulative irritation and sensitization study	Healthy subjects 18 to 65 years of age (45-Group 1, 195-Group 2 / 35-Group 1, 195-Group 2)*	1 US	Group 1 = 35 (Spinosad 2%, vehicle, [SLS] 0.1%, and NaCl 0.9%); Group 2 = 195 (Spinosad 2%, vehicle, and NaCl 0.9%)	Group 1: 21 daily spinosad applications & 1 application after 13-17 day rest period; 21 daily applications vehicle, SLS, and NaCl Group 2: 9 spinosad & NaCl applications every 48-72 hours; 1 spinosad application after 13-17-day rest	4/26/05 to 6/29/05

* 35 subjects were enrolled in Group 1, but only 34 were treated and included in the safety analysis. 195 subjects were enrolled in Group 2, but only 193 were treated and included in the safety analysis. Thus, 230 subjects were enrolled and 227 were evaluated for safety. Source: Sponsor's NDA, Integrated Summary of Safety, adapted from Table 4.1.1, pp. 20-21.

Table 5: Clinical Studies: Phase 1 (cont'd)

Protocol # (Study Phase)	Objective	Study Design	Subject Population (Plan/Actual)	# Sites	Treatment Group(s) = # Subjects	Dosing Regimen/ Treatment Duration	Study Period
SPN-103-05 (Phase 1B)	PK profile, topical tolerability following a single dose of Spinosad 2% in pediatric subjects with head lice	Open-label, single-dose PK study	Pediatric subjects 2 to 18 years of age who had head lice (12/14)	1 (US)	Spinosad 2.0% = 14	Single application to scalp of 30 mL for 10 minutes	7/13/2005 to 8/13/2005
SPN-106-06 (Phase 1B)	PK profile, topical and systemic tolerability following a single dose of Spinosad1%	Open-label, single-dose PK study	Healthy pediatric subjects 6 to 24 months of age (6/8)	1 (US)	Spinosad 1.0%= 8	Single application to scalp of 30 mL for 10 minutes	12/13/2006 to 12/17/2006
SPN-107-07 (Phase 1)	Evaluate the phototoxic potential of NatrOVA	Double-blind, single-dose, within-subject, randomized, patch study	Healthy adult subjects 18 to 65 years of age with Fitzpatrick Skin Types I, II, or III (38/38)	1 US	NatrOVA = 38 Vehicle = 38 Blank patch = 38	Single 24-hour application (patch) to back	12/5/07 to 12/13/07
SPN-108-08 (Phase 1)	Evaluate the photo-allergenic potential of NatrOVA after exposure to UV radiation	Double-blind, within-subject, randomized, patch study	Healthy adult subjects 18 to 65 years of age with Fitzpatrick Skin Type I, II, or III (65/58)	1 US	NatrOVA = 58 Vehicle = 58 Blank patch = 58	6 applic. during 3-wk induction; patches worn 24 hrs; 1 applic. during challenge phase after a 10-17-day rest	1/23/08 to 3/8/08

Source: Sponsor's NDA, Integrated Summary of Safety, adapted from Table 4.1.1, pp. 21-23.

Table 6: Clinical studies: Phase 2

Protocol # (Study Phase)	Objective	Study Design	Subject Population (Plan/Actual)	# Sites	Treatment Group(s) = # Subjects	Dosing Regimen/ Treatment Duration	Study Period
SPN-201-05 (Phase 2A)	Pilot study: determine relative efficacy & safety of different strengths of Spinosad compared to Vehicle	Single-center, investigator- & examiner-blind, four-arm, randomized, parallel dose ranging study	Subjects ≥2 years who had head lice (40/36)	1 US	Spinosad 2.0%= 10 Spinosad 1.0% = 9 Spinosad 0.5% = 8 Vehicle = 9	Two 10-minute applications to scalp	9/22/2005 to 11/4/ 2005
SPN-202-06 (Phase 2)	Evaluate safety & efficacy of different strengths of a single, 10-minute dose of Spinosad, compared to vehicle, in subjects with head lice	Multi-center, investigator-blind, three-arm, randomized, parallel dose ranging study	Subjects ≥2 years + head lice infestation of at least mild severity - at least 3 live lice (adults and/or nymphs) and nits (120/122)	4 US	Spinosad 1.0% = 39 Vehicle = 43 Spinosad 0.5% = 40	Single application to scalp	3/15/2006 to 7/1/2006
SPN-203-07 (Phase 2B)	Pilot study to compare the safety and efficacy of NatrOVA versus NIX in an Actual Use environment	Single-center, investigator- & examiner-blind, two-arm, randomized, parallel study	Subjects ≥6 months who had head lice (20/24)*	1 US	NatrOVA = 11 NIX = 12	One or two applications to scalp, as needed	3/12/2007 to 4/3/2007

* One subject in the NIX treatment group was excluded from the safety analysis.

Source: Sponsor's NDA, Integrated Summary of Safety, adapted from Table 4.1.1, pp. 24-25.

Table 7: Clinical studies: Phase 3

Protocol # (Study Phase)	Objective	Study Design	Subject Population (Plan/Actual)	# Sites	Treatment Group(s) = # Subjects	Dosing Regimen/ Treatment Duration	Study Period
SPN-301-07 (Phase 3)	Compare safety and efficacy of NatrOVA versus NIX in Actual Use environment	Multi-center, investigator- & examiner-blind, 3-arm, randomized, active controlled, parallel group study	Subjects ≥6 months with active head lice infestation Primary subjects; at least 3 live lice-adults or nymphs; secondary subjects; at least 1 live louse (Households: 171 / 203) [558 subjects]	6 US	NatrOVA with combing = 59 (57 evaluated for Safety) NatrOVA without combing = 243 (237 evaluated for Safety) NIX= 256 (246 evaluated for Safety)	One or two applications to scalp, as needed	9/25/2007 to 4/22/2008
SPN-302-07 (Phase 3)	Compare safety and efficacy of NatrOVA versus NIX in Actual Use environment	Multi-center, investigator- & examiner-blind, 3-arm, randomized, active controlled, parallel group study	Subjects ≥6 months with active head lice infestation Primary subjects; at least 3 live lice-adults or nymphs; secondary subjects; at least 1 live louse (Households: 171 / 188 [480 subjects]	6 US	NatrOVA with combing = 63 (58 evaluated for Safety) NatrOVA without combing = 203 (200 evaluated for Safety) NIX= 214 (211 evaluated for Safety)	One or two applications to scalp, as needed	9/21/2007 to 4/08/2008

Source: Sponsor's NDA, Integrated Summary of Safety, adapted from Table 4.1.1, pp. 25-26.

5.2 Review Strategy

The pivotal Phase 3 trials, SPN-301-07 and SPN-302-07, were reviewed in detail for safety and efficacy.

The safety review of the sponsor's product will focus on adverse events and systemic safety (laboratory evaluation) and local safety (cutaneous signs and symptoms at application sites). The safety database consists primarily of the pooled data from the

two pivotal trials, SPN-301-07 and SPN-302-07. Subjects in the Phase 3 trials were randomized to apply Natrova with or without nit combing. The sponsor has pooled the results of these two groups for safety analysis. The safety database also includes supportive data from the other 9 Phase 1 and 2 trials, which are discussed separately due to differences in subject populations and study design.

Special safety studies are discussed in section 7.4.5 and include:
a) SPN-102-05: repeat insult/21-day cumulative irritancy and cutaneous contact sensitization (spinosad 1.8%)
b) SPN-107-07: phototoxicity (Natrova .9%)
c) SPN-108-08: photoallergy (Natrova .9%)

5.3 Discussion of Individual Studies/Clinical Trials

Study Design:
The Phase 3 pivotal trials performed as part of the development program were of identical design. The protocol review that follows will apply to both studies unless otherwise noted.

Pivotal Phase 3 Studies:
Protocol Number: SPN-301-07
Protocol Number: SPN-302-07

Title: "A Comparative Safety and Efficacy Study Between NatrOVA® Crème Rinse 1% and NIX® Crème Rinse in Subjects ≥ 6 months of Age with *Pediculosis Capitis.*"

Study 301-07 was performed at six investigational sites in the United States and had six investigators. The first subject was enrolled September 25, 2007 and the last subject exited the study April 22, 2008.

Table 8: Investigators SPN-301-07

Site	Principal Investigator	Site Name	Location	
2	Ivy M. Muhar, MD	DMI Research	Largo, FL	
3	Robert S. Haber, MD	Haber Dermatology	South Euclid, OH	
5	Dow B. Stough, MD	Burke Pharmaceutical Research	Hot Springs, AR	
6	Lydie L. Hazan, MD	Impact Clinical trials	Beverly Hills, CA	
13	Dennis J.Ward, MD	Hill Top Research	Miamiville, OH	
14	Robert A. Lewine, MD	Hill Top Research	Scottsdale, AZ	

Source: Sponsor's NDA, Clinical Study Report for SPN-301-07, p. 29.

Table 9: Subject Enrollment by Site SPN-301-07 (ITT Population)

Analysis Center	Site	Principal Investigator	Natrova		NIX
Primary Subjects			**With Nit Combing**	**Without Nit Combing**	
1	6	Hazan	6	24	24
1	13	Ward	2	7	7
2	2	Muhar	5	19	17
3	3	Haber	2	9	8
4	5	Stough	6	24	24
5	14	Lewine	2	8	9
All Subjects					
1	6	Hazan	22	85	94
1	13	Ward	3	14	10
2	2	Muhar	8	33	41
3	3	Haber	3	22	13
4	5	Stough	16	74	74
5	14	Lewine	7	15	24

Source: Sponsor's NDA, Clinical Study Report SPN-301-07, adapted from table 10.1-3, p.63.

Study 302-07 was performed at six investigational sites in the United States and had six investigators. The first subject was enrolled September 21, 2007 and the last subject exited the study April 8, 2008.

Table 10: Investigators SPN-302-07

Site	Principal Investigator	Site Name	Location	
7	Mark L., MD	Concentrics Center for Research	Indianapolis, IN	
8	Celia Reyes-Acuna, MD	Intrinsic Research Data, Inc.	Corpus Christi, TX	
9	*Katie Shepherd, B.S.,P.A.	Lice Solutions Resource Network	West Palm Beach, FL	
10	James A. Solomon, MD, PhD	Advanced Dermatology and Cosmetic Surgery	Ormond Beach, FL	
11	Alvin A. Gabrielson, Jr., MD	Wee Care Pediatrics	Layton, UT	
12	J. Gregory Thomas, MD, FAAFP	Alegent Health Research Center	Council Bluffs, IA	

*Sub-investigators are MDs
Source: Sponsor's NDA, Clinical Study Report for SPN-302-07, p. 29.

Table 11: Subject Enrollment by Site SPN-302-07 (ITT Population)

Analysis Center	Site	Principal Investigator	Natrova		NIX
Primary Subjects			**With Nit Combing**	**Without Nit Combing**	
1	9	Shepherd	6	24	24
1	12	Thomas	1	3	4
2	7	Moore	4	14	14
3	8	Reyes-Acuna	4	15	13
4	10	Solomon	4	16	18
5	11	Gabrielson	2	11	11
All Subjects					
1	6	Shepherd	15	57	71
1	12	Thomas	4	10	15
2	7	Moore	15	46	39
3	8	Reyes-Acuna	12	39	26
4	10	Solomon	15	30	37
5	11	Gabrielson	2	21	26

Source: Sponsor's NDA, Clinical Study Report SPN-302-07, adapted from table 10.1-3, p.63.

Protocol Amendments:

1) Protocol Numbers: SPN-301-07 & SPN-302-07; Amendment Number 1, 9/12/07

- Added the exclusion criterion, "A household of more than six individuals who have head lice."
- Changed the Day 1 and Day 8 visit windows to allow +1 day flexibility.
- Made the Day 7 visit window consistent with the study schedule to state, "All enrolled subjects will return to the clinical site on Day 7 (±1 day)."
- Clarified the expected timeframe of record completion

2) Protocol Number: SPN-301-07 & SPN-302-07; Amendment Number 2, 10/18/07
The purpose of this amendment is to clarify wording regarding the process of obtaining informed consent/assent in subjects under 18 years of age.

3) Protocol Number: SPN-301-07 & SPN-302-07; Amendment Number 3, 1/22/2008
This amendment deleted the definition of non-intact scalp. The purpose was to improve the number of subjects eligible for pediatric safety lab assessments. Please also see section 7.4.2 for further discussion.

Objectives (both studies):

The primary objective of the study was to demonstrate the efficacy of Natraova, relative to NIX® Crème Rinse under actual use conditions in subjects who have been infested

with "*Pediculosis capitis" (sic)*. Efficacy assessments were made 14 days following the final product application.

The secondary objective of the study was to demonstrate the safety of Natrova based upon reported adverse events and observed skin/scalp reactions. Additional safety assessments were to include cutaneous and ocular irritation.

Study Design: These were multi-center, randomized, evaluator/Investigator-blind, three-arm, active-controlled, parallel group studies.

Number of Subjects (both studies): A sufficient number of households were screened to ensure that at least 171 households completed all phases of the study (approximately 76 primary subjects per group for the Natrova rinse without nit combing and NIX® rinse treatment groups, and 19 subjects in the Natrova rinse with nit combing treatment group).

Ages of Subjects for Inclusion: 6 months and older

Subject Population:
Primary subjects consisted of healthy males and females 6 months of age and older who were infested with *Pediculus humanis capitis*, infestation defined as at least 3 live lice present on Day 0. Subsequent household members needed only to have at least one live louse present to participate in the trial.

Inclusion Criteria (both studies):
1) Subjects who had an active head lice infestation present at Day 0. The Primary household subject was to have at least 3 live lice (adults and/or nymphs) present at baseline. Any other household members needed to only have at least one live louse.
2) Subjects were either male or female, at least 6 months of age.
3) Subjects were in good general health based on medical history.
4) Amendment 2: Each subject had an appropriately signed Informed Consent agreement. For children and adolescents, a parent (or guardian) signed an Informed Consent agreement. Each subject 12 years of age and over provided written consent. Children ages 8-11 signed a children's assent form. Children 7 years of age or less provided oral assent, if able. In the event that a child is too young to provide oral assent (i.e., if the child is 6 months of age), written consent was provided by a parent (or guardian) authorizing their child to participate in this study.
5) The subject/caregiver was able to read English or Spanish at a 7th grade level.
6) The parent or guardian within a household was willing to allow other household members to be screened for head lice. If other household members were found to have a head lice infestation, they were also to be enrolled in the study. If a member of household 15 years of age or older was unable to come to the study site for screening, they can self-determine the presence or absence of head lice and telephone a response to the study coordinator. If any infested household members 15 years or older were not

willing to enroll in the study or did not qualify for enrollment, they had to agree to use the standard course of OTC lice treatment provided by the site at home.
7) Subjects agreed not to use any other form of lice treatment during the course of the study and agreed not to use any of the excluded concomitant medications.
8) Subjects agreed not to cut or chemically treat their hair (e.g., hair color) in the period between the initial treatment and the final visit.
9) Subjects/caregiver demonstrated a clear understanding of his/her requirements for study participation and agreed to comply with study instructions.

Exclusion Criteria (both studies):
1) Individuals with history of irritation or sensitivity to pediculicides or hair care products
2) Individuals with any visible skin/scalp condition at the treatment site which, in the opinion of the investigative personnel or Sponsor, would interfere with the evaluation
3) Individuals who required treatment with topical salicylic acid, topical corticosteroids, anthralin, vitamin D analogs, retinoids, immunosuppressants, topical hair growth formulations, and topical dandruff treatments
4) Infested subjects who were previously treated with a pediculicide within the 48 hours prior to the study
5) Individuals with a condition or illness that, in the opinion of the Investigator, could compromise the objective of the protocol
6) Individuals receiving systemic or topical drugs or medication, including systemic antibiotics, which in the opinion of the investigative personnel or study monitor could interfere with the study results
7) Individuals who participated in a clinical trial within the past 30 days
8) Individuals (or, individuals from families) who, in the opinion of the Investigator, did not understand the requirements for study participation and/or could be likely to exhibit poor compliance
9) Individuals with family members who were infested with lice but were unwilling or unable to enroll in the study or to use the standard course of lice treatment
10) Females who were pregnant or nursing (Note: females of childbearing potential must have a negative urine pregnancy test prior to treatment; Day 0.) If a household had a pregnant female who had an active case of lice, the entire household was excluded from participation. If this pregnant household member did not have an active infestation, this individual was NOT to be the caregiver (one who provided treatment to other household members)
11) Sexually active females who were not using effective contraception - abstinence, vasectomized partner, oral birth control pills, birth control injections or patches, condoms with a spermicidal jelly or a diaphragm with spermicidal jelly
12) Individuals who had a history of drug abuse in the past year
13) Amendment #1: A household of more than 6 individuals who had head lice

Study Plan (both studies):
For these studies, a household was defined as a group of related or unrelated individuals living in the same dwelling, and sharing a common living space.

The primary subject within the household was determined at Day 0. The primary subject was the youngest person in the household who had three (3) live lice at screening on Day 0. All other household members needed only to have at least one live louse. Individual subjects did not need to have nits to qualify. Confirmation was made by the identification of live lice (adults or nymphs). A trained evaluator performed examinations by using an illuminated macro-magnification technique and/or good lighting. Dry-combing methods were employed to assist detection.

Households who successfully met study entrance criteria were randomized 4:4:1 respectively to receive Natrova without nit combing (approximately 76 households), NIX (approximately 76 households), or Natrova without nit combing (approximately 19 households). All members within an individual household received the same randomized treatment. After completing the Day 0 visit, subjects were dispensed study medication and were instructed to apply study medication at home per the provided Instructions for Use within 24 hours.

Instructions for Use of the test article Natrova without nit combing included the following: "Test product for use on ***DRY*** hair. … Shake Test Product bottle well just before use. Since live lice and nits live on the hair, close to the scalp, it is important to completely cover the scalp with the Test Product first, and then apply the Test Product outwards from the scalp towards the ends of the hair….The Test Product must be left on scalp and hair for 10minutes….After rinsing with warm water, shampoo the hair as usual…It is not necessary to comb out the nits (eggs) to prevent further infestation."

Household members who did not qualify but were found to be infested with lice were provided with RID® Lice Killing Shampoo. These individuals were instructed to treat with the RID® at the same time as the rest of the household to minimize the chances of this individual re-infesting household members who were participating in the study.

For the subset of pediatric subjects with non-intact scalps (25 from each of two designated sites), a blood draw was to be performed. Note that Protocol Amendment Number 3 (1/22/08) deleted the definition of non-intact scalp in order to improve the number of subjects eligible for pediatric safety lab assessments. Please also see section 7.4.2 for further discussion.

On Day 1, all subjects enrolled returned to the clinical site for evaluation of any ocular or scalp/cutaneous irritation. This evaluation was performed by a trained evaluator. Household members were also queried regarding the occurrence of any adverse events. Household members were asked if any of the treated individuals had any "eye exposure" during the treatment process. If exposure occurred, details regarding the

exposure, irritation and any concomitant treatment used (i.e., flushing eyes with water) was documented.

All enrolled subjects returned to the clinical site on Day 7 (+/- 1 day). At this visit each individual had visual lice evaluations and scalp/cutaneous irritation evaluations. Any increase in scalp irritation from baseline was documented as an adverse event. Individuals were queried as to the occurrence of any adverse events. For any household member who was found to have live lice at Day 7 (based on the trained evaluator's assessment) a second box of investigational product (the same as the one distributed on Day 0) was provided to the caregiver to take home and use according to the Instructions for Use.

On Day 8, any subject receiving a second treatment on Day 7 was to return to the clinic for evaluation of any ocular or scalp/cutaneous irritation. Household members were also be queried regarding the occurrence of any adverse events. Similarly to Day 1, household members were asked if any of the treated individuals had any "eye exposure" during the treatment process.

On Day 14 (+/- 1 day if live lice were present at the Day 7 visit or +/- 2 days if no live lice were present at the Day 7 visit), all household members enrolled in the study were to return to the clinical site for visual lice and scalp/cutaneous irritation and evaluation. Any increase in scalp irritation from baseline was documented as an adverse event. Individuals were queried as to the occurrence of any adverse events.

For those subjects who received only one treatment on Day 0, Day 14 was the final visit. If they were found to be infested with live lice, they were considered a treatment failure and provided with a standard course of therapy (RID® Lice Killing Shampoo). If they were found to be lice free, they were considered a treatment success.

For those household members who treated a second time on Day 7, if they were found to be infested with live lice, this (Day 14) was their final visit. They were considered a treatment failure and provided with a standard course of therapy (RID® Lice Killing Shampoo). If they were found to be lice free, they were scheduled for a final visit on Day 21.

For the group of pediatric subjects having pediatric safety lab assessments, another blood draw was taken.

On Day 21 (+/- 2 days), all household members who received two treatments (Days 0 and 7) were to return to the site for their final lice and scalp/cutaneous irritation evaluations. Any increase in scalp irritation from baseline was documented as an adverse event. Individuals were be queried as to the occurrence of any adverse events.

This was the final visit for all study subjects. If they were found to be infested with live lice, they were considered a treatment failure and provided with a standard course of therapy (RID® Lice Killing Shampoo). If they were found to be lice free, they were considered a treatment success.

Table 12: Schedule of Study Procedures and Evaluations

Procedure	Day 0 (Screening & Drug Dispensing)	Day 1	Day 7 (+/- 1 day)	Day 8	Day 14[a]	Day 21 (+/- 2 days)
ICF / HIPAA	X					
Visual Lice Evaluations at Clinic	X		X		X	X
Clinic Scalp Evaluations	X		X		X	X
Pregnancy Testing (UPT)	X				X[b]	X[b]
Blood draw for safety labs	X[c]				X[c]	
Demographics	X					
Medical History/Review	X	X	X	X	X	X
Inclusion/Exclusion Criteria	X					
Lice Exposure Questionnaire	X		X		X	X
Concomitant Medications	X	X	X	X	X	X
Household Randomization to Product	X					
Product Application at Home	X		X (if needed)			
AE Query	X	X	X	X	X	X
Cutaneous / Ocular Irritation Evaluation		X		X (if needed)		
Compliance Confirmation		X		X		

[a] Visit window for Day 14 is +/- 1 day if subject applies a 2nd treatment on Day 7. If subject is lice free on Day 7, the visit window for Day 14 is +/- 2 days.
[b] Urine Pregnancy Test will be conducted at the subject's final visit (Day 14 if only one treatment, Day 21 if two treatments)
[c] Blood draws will be done at two study sites on the first 25 qualifying pediatric subjects.
Source Sponsor's NDA, Clinical Study Reports for SPN-301-07 and 302-07, pp. 400 & 392, respectively

Blinding:
All study subjects were instructed not to discuss any aspects of the treatment process with the evaluators or Investigators. The investigators, site staff, and study monitors were unaware of the treatment assigned to individual households or study subjects.

All test articles were packaged in identical white boxes with two inner chambers. One chamber was for the test product. The second chamber contained lice combs, along with combing instructions if the treatment was NIX® or Natrova with nit combing. In the Natrova with no nit combing box, this chamber was empty except for a note that says "This chamber is intentionally left empty." The actual bottles of study drug were covered over with a label to prevent the subject from seeing the identity of the contents of the bottle. In order to maintain study blind, the NIX® instructions were re-typed exactly as the original Instructions for Use in the same general format as the Instructions for Use for Natrova.

During the Phase 3 studies it was discovered that the Instructions for Use indicated the identity of the test article in a footnote. The presence of this footnote was noted by the mother of a subject enrolled at Site 10 in study SPN-302-07. On October 10, 2007, the mother notified a sub-investigator who then notified Concentrics Research (the contract research organization for both studies).

When Concentrics Research became aware of the footnote, 75 households, containing 218 subjects (21% of the final study population) were enrolled in studies SPN-301-07 and 302-07. Concentrics Research notified the sponsor, ParaPRO, and the two companies reviewed language in the protocols relating to evaluator/investigator blinding and protocol deviations (sections 9.7.9 and 13.4 of the protocols). The sponsor states that after the review, it was decided that no action was necessary since the protocols and study designs included "adequate safeguards to ensure their integrity." More specifically subjects were prohibited from discussing their assigned treatments with investigators/evaluators and at all study sites a designated individual, explicitly excluded from participating in the efficacy evaluations; distributed, collected, and accounted for all assigned treatments. Subsequently an e-mail was sent to all sites on October 10, 2007 to re-emphasize the importance of adhering to the protocol requirements in regard to investigator/evaluator blinding. Also a Note to File that documented the inclusion of the treatment identity in the Instructions-for-Use was sent to each investigational site on October 10, 2007. As acknowledged by the sponsor, the two pivotal trials were conducted as investigator/evaluator-blinded rather than double-blinded trials.

Prior and Concomitant Therapy:

Subjects were instructed not to take any prescription medications (except those allowed by the protocol) without prior consultation with the Investigator unless otherwise instructed by their physician. Subjects were not allowed to use any other lice treatments (Rx, OTC, or home remedies) during their entire study participation. All medications taken during the study were documented as concomitant therapy.

Safety and Safety Monitoring:

1) Adverse Events – All Adverse Events during the study were recorded and classified on the basis of MedDRA terminology for the safety population. Adverse events were queried at all study visits.

2) Scalp/cutaneous and ocular irritation:

Scalp evaluations were conducted at Day 0, Day 7, Day 8 (if needed), Day 14, and on Day 21 (if needed). On Days 1 and 8, subjects returned to the site 24 hours after treatment for evaluation of ocular irritation.

Irritation including any erythema or edema or other condition was documented and the severity was recorded. Any increases from Baseline (Day 0) were recorded as Adverse Events. The Investigator determined the relationship to product. The scale in Table 13 was used for assessing scalp/cutaneous irritation. Ocular irritation was evaluated independently using the same scale.

Table 13: Irritation Evaluation Scale

Score	Guideline
0	No sign of irritation
1	Slight erythema
2	Noticeable erythema with slight infiltration
3	Erythema with marked edema
4	Erythema with edema and blistering

3) Safety labs were performed on selected pediatric subjects at two study sites. Each site was to collect blood from the first 25 qualifying pediatric subjects. These blood collections were done at Day 0, prior to treatment, and at Day 14.

Safety labs included:

a) Full CBC: WBC, RBC, platelet count, hemoglobin, hematocrit, and differential

b) Serum Chemistry: BUN, glucose, creatinine, sodium, potassium, chloride, AST, ALT, alkaline phosphatase, and total bilirubin.

Safety Analysis:

Safety was evaluated by tabulations of adverse events (AEs), scalp/cutaneous and ocular irritation assessments and clinical laboratory findings.

The Safety Population was composed of all randomized subjects who received at least one treatment. Confirmation that randomized subjects received at least one treatment application was based on subject reports at the post-baseline visits (e.g. reports of treatment compliance, comments, report of AEs). Subjects who did not provide at least one post-baseline evaluation were considered to be lost to follow-up and exposure to treatment along with subsequent safety outcomes for these subjects was unknown.

Subjects who refused to return to the investigational site after randomization, but who contacted the site to report having used the study medication and/or experienced at least one AE, were included in the Safety population.

Efficacy analysis:

Study Endpoints:

1) The primary efficacy endpoint was the proportion of primary subjects within the enrolled households who are lice free (without live lice) as assessed by the trained evaluator 14 days after the last treatment (i.e. Day 14 for subjects who were treated once and Day 21 for subjects who were treated twice).
2) The secondary efficacy endpoint was the proportion within each treatment group of individual household members requiring two treatments.

Study Populations:

The ITT population was the primary efficacy analysis population and the Per-Protocol population was considered supportive.

1) The intent-to-treat (ITT) population was composed of all primary subjects who were enrolled into the study and randomized to treatment.

2) The per-protocol population (PP) consisted of those ITT subjects who met the following criteria:

a) Met inclusion/exclusion criteria
b) Did not take any interfering concomitant medications
c) Attended the final visit, with the exception of a discontinuation from the study due to an adverse event related to study treatment or documented lack of treatment effect
d) Did not miss more than 1 study visit (excluding the final visit)
e) Were compliant with the dosing regimen while enrolled in the study
f) Did not receive an alternative treatment on Day 7 (different from that received on Day 0)
g) Final visit was within the visit window
h) Were not enrolled as members of two separate households although they were members of the same household

6 Review of Efficacy

Efficacy Summary

At the time of closure of this clinical review, a statistical review was not available.

Pivotal Phase 3 trials SPN-301-07 and SPN-302-07 were multi-center, randomized, evaluator/investigator-blind, three-arm, active-controlled, parallel group studies. These trials were of adequate design and sufficiently powered to study the safety and efficacy

of Natrova (.9% spinosad) when applied for 10 minutes for treatment of head lice for one application followed by a second application a week later if needed.

A majority of subjects exposed to Natrova (safety population) were Caucasian (59%) with a mean age of 16 years. A total of 19% were male and 81% were female. These demographic characteristics were similar for both Natrova and NIX treatment arms.

For the primary and non-primary ITT populations (for all three arms; Natrova with nit combing, Natrova without nit combing, Nix) a majority of the population was Caucasian (60%) with a mean age of 16.5 years. A total of 17.5% were male and 82.5 % were female. These demographic characteristics were balanced across treatment arms; Natrova with nit combing, Natrova without nit combing, and Nix.

The primary endpoint was defined as the proportion of primary subjects in the enrolled households who were lice free (no live lice, adults or nymphs) 14 days after the last treatment. The primary subjects were the youngest enrolled members of each household who had at least three live lice at study entry. In study SPN-301-07, ITT primary subjects, the proportion of subjects considered treatment successes was 82.6%, 84.6%, and 44.9% for the three respective treatment arms, Natrova with nit combing, Natrova without nit combing, and Nix. Natrova without nit combing showed statistical superiority over NIX (84.6% versus 44.9% with a p value of <.001). Using logistic regression the predicted estimated success rate for the ITT primary subjects was 89.4% in the Natrova without nit combing arm versus 44.8% in the NIX arm. Analysis of the per protocol population reveals similar treatment effects.

In study SPN-302-07, ITT primary subjects, the proportion of subjects considered treatment successes was 81.0%, 86.7%, and 42.9% for the three respective treatment arms, Natrova with nit combing, Natrova without nit combing, and Nix. Natrova without nit combing showed statistical superiority over NIX (86.7% versus 42.9% with a p value of <.001). Using logistic regression the predicted estimated success rate for the ITT primary subjects was 89.1% in the Natrova without nit combing arm versus 45.1% in the NIX arm. Analysis of the per protocol population reveals similar treatment effects.

The secondary efficacy endpoint was the proportion within each treatment group of individual household members requiring two treatments. Evaluation of the secondary endpoint was performed using ITT data from all enrolled subjects, primary and non-primary combined. In study SPN-301-07, 64% of subjects in the Natrova without nit combing arm required one treatment and 36% required two treatments. Whereas for those in the NIX arm, 35.5% required one treatment and 64.5% required two treatments. For study SPN-302-07, the results showed a similar pattern; 86% of subjects in the Natrova arm without nit combing required one treatment and 14% required two treatments. For those in the NIX arm, 40% required one treatment and 60% required two treatments.

In both pivotal studies, SPN-301-07, 302-07, results for the primary endpoint were examined in the subpopulations; gender, race, and age. While numerical variations are present, response rates for male and females are similar for both studies and both Natrova arms, with and without nit combing. The majority of subjects among the primary ITT group are Caucasian with a substantial Hispanic minority. While numerical variations are present, response rates for Caucasians and Hispanics are similar for both studies and both Natrova treatment arms. Definitive conclusions regarding response rates among the other races analyzed; Black, Asian, Native American, and other, are precluded due to small numbers. The sponsor performed subgroup analysis for age by creating two subgroups, ≤ median age and > median age. For study SPN-301-07, ITT primary population, the median ages were 9 and 6 years for the Natrova with and without nit combing arms respectively. For study SPN-302-07, ITT primary population, the median ages were 6 and 7 years for the Natrova with and without nit combing arms respectively. Response rates were similar for these two subgroups across both studies and for both Natrova treatment arms.

6.1 Indication

The sponsor-proposed indication is treatment of head lice (*Pediculus humanis capitis*) infestations (b) (4) in patients (b) (4).

6.1.1 Methods

The efficacy evaluation will focus upon a detailed review of the Phase 3 pivotal trials SPN-301-07 and SPN-302-07.

6.1.2 Demographics

Table 14: Subject Demographic Characteristics SPN-301-07: ITT Primary Subjects

	Natrova Crème rinse		**Nix Crème rinse**	**Total**
	With nit combing	***Without nit combing***		
Age (years)				
N	**23**	**91**	**89**	**203**
Mean	11	9.1	10	9.9
STD	11.6	10.1	12.8	11.5
Median	9.0	6.0	7.0	7.0
Min. to Max.	1 to 52	0 to 63	0 to 84	0 to 84

	Natrova Crème rinse		Nix Crème rinse	Total
	With nit combing	***Without nit combing***		
≤ 4 years	6 (26%)*	26 (29%)*	27 (30%)*	59 (29%)*
5 to 9 years	7 (30%)	42 (46%)	32 (36%)	81 (40%)
10 to 14 years	6 (26%)	13 (14%)	16 (18%)	35 (17%)
≥ 15 years	4 (17%)	10 (11%)	14 (16%)	28 (14%)
Gender				
Male	4 (17%)	13 (14%)	12 (14%)	29 (14%)
Female	19 (83%)	78 (86%)	77 (87%)	174 (86%)
Predominant race				
Caucasian	12 (52%)	55 (60%)	58 (65%)	125 (62%)
Black	0 (0%)	0 (0%)	1 (1%)	1 (0.5%)
Asian	1 (4%)	1 (1%)	2 (2%)	4 (2%)
Native American	1 (4%)	0 (0%)	0 (0%)	1 (0.5%)
Hispanic	8 (35%)	32 (35%)	26 (29%)	66 (33%)
Other[b]	1 (4%)	3 (3%)	2 (2%)	6 (3%)

* Percentages rounded by reviewer

[b] Examples: Caucasian and Black, White and Hispanic, Hispanic/Native American

Source: Sponsor's NDA Submission, Clinical Study report for SPN-301-07, adapted from Table 14.1.1.1, p. 121.

For study SPN-301-07, 203 subjects were enrolled in the primary ITT population. The mean age was 9.1 years for Natrova without nit combing, with a range of 0 to 63 years. Of these 26 (29%) were 4 years or younger, 42 (46%) were 5 to 9 years of age, 13 (14%) were 10 to 14 years of age, and 10 (11%) were 15 years or older. The majority of subjects were female 78 (86%) and Caucasian 55 (60%) with a substantial Hispanic minority 32 (35%). These characteristics were generally balanced across treatment arms. The All ITT population showed generally similar demographics; however, the mean age was older which might be expected based on the definition of primary ITT subjects as the youngest member of the household having three live lice.

Table 15: Subject Demographic Characteristics SPN-302-07: ITT Primary Subjects

	Natrova		Nix	Total
	With nit combing	***Without nit combing***		
Age (years)				
N	**21**	**83**	**84**	**188**
Mean	6.7	8.6	8.9	8.5
STD	4.47	9.29	10.5	9.43
Median	6.0	7.0	7.0	7.0
Min. to Max.	1 to 22	1 to 64	1 to 68	1 to 68
≤ 4 years	7 (33%)*	23(28%)*	28 (33%)*	58 (31%)*
5 to 9 years	11 (52%)	40 (48%)	34 (41%)	85 (45%)
10 to 14 years	2 (10%)	12 (15%)	13 (16%)	27 (14%)
≥ 15 years	1 (5%)	8 (10%)	9 (11%)	18 (10%)
Gender				
Male	3 (14%)	12 (15%)	6 (7%)	21 (11%)
Female	18 (86%)	71 (85.5%)	78 (93%)	167 (89%)
Predominant race				
Caucasian	13 (62%)	53 (64%)	52 (62%)	118 (63%)
Black	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Asian	0 (0%)	1 (1%)	0 (0%)	1 (0.5%)
Native American	0 (0%)	1 (1%)	0 (0%)	1 (0.5%)
Hispanic	8 (38%)	25 (30%)	28 (33%)	61 (32%)
Other[b]	0 (0%)	3 (4%)	4 (5%)	7 (4%)

* Percentages rounded by reviewer

[b] Examples: Multiracial, Mixed Caucasian/Black, Biracial, Caucasian and Hispanic

Source: Sponsor's NDA Submission, Clinical Study report for SPN-302-07, adapted from Table 14.1.1.1, p. 119.

For study SPN-302-07, 188 subjects were enrolled in the primary ITT population. The mean age was 8.6 years for Natrova without nit combing, with a range of 0 to 64 years. Of these 23 (28%) were 4 years or younger, 40 (48%) were 5 to 9 years of age, 12 (14%) were 10 to 14 years of age, and 8 (10%) were 15 years or older. The majority of subjects were female 71 (85.5%) and Caucasian 53 (64%) with a substantial Hispanic minority 25 (30%). These characteristics were generally balanced across treatment arms. The All ITT population showed generally similar demographics; however, the mean age was older which might be expected based on the definition of primary ITT subjects as the youngest member of the household having three live lice.

Assessment of baseline scalp irritation, as shown in Table 16, within studies SPN-301-07 and 302-07 reveals score that generally were balanced across treatment arms. Comparison between studies reveals somewhat higher percentages of subjects having

a score of 2 (noticeable erythema with slight infiltration) in study 301-07 as compared with study 302-07.

Table 16: Baseline Scalp Irritation Scores Pivotal Studies (Safety Population)

Treatment	**Natrova w/wo nit combing**		**Nix**	
Study	SPN-301-07	SPN-302-07	SPN-301-07	SPN-302-07
N	**294**	**258**	**246**	**211**
Scalp evaluation				
0 No sign of irritation	195 (66%)*	199 (77%)*	169 (69%)*	147 (70%)*
1 Slight erythema	55 (19%)	51 (20%)	44 (18%)	54 (26%)
2 Noticeable erythema with slight infiltration	44 (15%)	7 (3%)	33 (13%)	8 (4%)
3 Erythema with marked edema	0	1 (0.4%)	0	1 (0.5%)
4 Erythema w/ edema & blistering	0	0	0	1 (0.5%)

* Percentages rounded by reviewer

Source: Sponsor's NDA, Clinical Study Reports for Studies SPN-301-07 and 302-07, adapted from Table 11.2-2, p 71 (same table number and page both studies).

6.1.3 Subject Disposition

For study SPN-310-07, as shown in Table 17, among subjects randomized, similar percentages completed the study, 54 (92%) Natrova with nit combing, 227 (93%), Natrova without nit combing, and 230 (90%) NIX. Across the 3 treatment arms, reasons for discontinuation from the study showed similar patterns, however, a greater percentage of subjects in the NIX arm withdrew consent, 10 (4%) versus 1(2%) for Natrova with nit combing and 0 for Natrova without nit combing.

Table 17: Subject Disposition: Study SPN-301-07

	Natrova 0.9%		**NIX Crème Rinse**
	w/ nit combing	***w/o nit combing***	
# households randomized	23	91	89
# of subjects randomized	59	243	256
# of subjects completing study	54 (92%)*	227 (93%)*	230 (90%)*
# of subjects who discontinued study early	5 (9%)	16 (7%)	26 (10%)
Reasons for discontinuation from study			
Adverse event	0	0	0
Subject withdrew consent	1 (2%)	0	10 (4%)
Lost to follow-up	3 (5%)	13 (5%)	12 (5%)
Protocol violation (including lack of compliance)	1 (2%)	3 (1%)	4 (2%)
Other	0	0	0

* Calculated by reviewer as percentage of the number of subjects randomized

Source: Sponsor's NDA, Clinical Study Report for SPN-301-07, adapted from Table 14.0.2, p. 116.

Among those on NIX crème rinse who withdrew consent, reasons included: wanted to get alternative treatment for lice - 2 subjects in one family; mother did not want to continue study – 4 children in one family; mother withdrew consent because she wanted to resume breastfeeding child – 2 children in one family; and mother could not return to clinic – 2 children in one family.

For study SPN-302-07, as shown in Table 18, among subjects randomized, similar percentages completed the study, 58 (92%) Natrova with nit combing, 187 (92%), Natrova without nit combing, and 193 (90%) NIX. Across the 3 treatment arms, reasons for discontinuation from study showed similar patterns, however, a greater percentage of subjects in the NIX arm withdrew consent, 10 (6%) versus 9 (4%) for Natrova with nit combing and 0 for Natrova without nit combing. Additionally, a greater percentage in the Natrova with nit combing arm 5 (8%) were lost to follow-up as compared to 5 (2.5%) in the Natrova without nit combing and the NIX arm 5 (2%).

Table 18: Subject Disposition: Study SPN-302-07

	Natrova 0.9%		**NIX Crème Rinse**
	w/ nit combing	***w/o nit combing***	
# of households randomized	21	83	84
# of subjects randomized	63	203	214
# of subjects completing study	58 (92%)*	187 (92%)*	193 (90%)*
# of subjects who discontinued study early	5 (8%)	16 (8%)	21 (10%)
Reasons for discontinuation from study			
Adverse event	0	0	0
Subject withdrew consent	0	9 (4%)	13 (6%)
Lost to follow-up	5 (8%)	5 (3%)	5 (2%)
Protocol violation (including lack of compliance)	0	1 (0.5%)	1 (0.5%)
Other[b]	0	1 (0.5%)	2 (0.9%)

* Calculated by reviewer as percentage of the number of subjects randomized
[b] Natrova w/o nit combing – Subject 10-22-0001: "Visit 21 was inadvertently not scheduled." Nix® Crème Rinse – Subjects 10-21-0002: "Visit 21 was not done in error." and 10-21-0003: "Visit 21 not done in error."
Source: Sponsor's NDA, Clinical Study Report for SPN-302-07, adapted from Table 14.0.2, p. 114.

Those on Natrova without nit combing who withdrew consent included; withdrew consent with no other information provided (3 subjects), did not have lice any more and

did not see need to return (4 children in one family), withdrew consent because no time to continue study (1 subject), could not come in for appointment (1 subject).

Among those on NIX crème rinse, who withdrew consent, reasons included; mother can not get to clinic for study visits (1 subject), family withdrew consent after Day 7 (4 subjects), child in hospital and winter weather and no show (5 subjects in one family), mother wants to withdraw children because she knew treatment was NIX (2 subjects in one family), and 1 subject no additional information.

Table 19 displays the protocol deviations that disqualified subjects (All ITT population) for the pivotal studies, SPN-301-07 and 302-07.

Table 19: Protocol Deviations that Disqualified Subjects (Pivotal Studies: All ITT)

	Natrova				**NIX**	
	with nit combing		***w/o nit combing***			
Study	**301-07**	**302-07**	**301-07**	**302-07**	**301-07**	**302-07**
# of subjects excluded from PP analysis	9	5	62	26	95	38
Reasons for exclusion from PP analysis[a]						
Did not meet all inclusion criteria	2	0	2	0	0	0
Met an exclusion criterion	0	0	1	2	2	5
Took prohibited concomitant med.	0	0	0	0	3	1
Did not attend final visit	5	5	16	16	26	22
Missed more than one study visit	2	5	7	3	11	5
Noncompliant with treatment	7	5	20	20	31	25
Received alternate treatment on Day 8	0	0	0	0	1	4
Final visit outside of visit window	0	0	42	4	64	3
Other[b]	0	0	0	3	0	9
# of subjects excluded from safety anal.	2	5	6	3	10	3
Reasons for exclusion from safety anal.						
Did not apply study treatment	2	5	6	3	10	3
Did not supply safety data	2	5	6	3	10	3

[a] Subjects may have more than one exclusionary deviation

[b] "Other" reasons included: subjects of the same household being enrolled into different households or a subject receiving an incorrect treatment on Day 0.

Source: Sponsor's NDA submission, Clinical Study Reports for SPN-301-07, and SPN-302-07, adapted from Table 10.2-1, p. 66 (same table number and page both studies).

For study SPN-301-07, the most common protocol deviations were; non-compliance with treatment - Natrova with nit combing (7 subjects), Natrova without nit combing (20), and NIX (31); Final visit outside of treatment window - 42 Natrova without nit combing, 64 NIX; and failure to attend final visit - 5 Natrova with nit combing, 16 Natrova without nit combing, and 26 NIX. Protocol deviations among primary ITT subjects showed similar patterns.

For study SPN-302-07, in the Natrova with nit combing arm, the most common protocol deviations were failure to attend final visit (5 subjects), missed more than one study visit (5), and non-compliance with treatment (5). For both Natrova without nit combing and the NIX arms, the most common deviations were treatment non-compliance (20 and 25 subjects respectively) and failure to attend final visit (16 and 22 subjects respectively). Protocol deviations among primary ITT subjects showed similar patterns.

6.1.4 Analysis of Primary Endpoint(s)

In the pivotal Phase 3 trials, the primary efficacy endpoint was the proportion of primary subjects in the enrolled households who were lice free (no live lice, adults or nymphs) 14 days after the last treatment (Day 14 for subjects treated once and Day 21 for subjects treated twice).

The primary subjects were the youngest enrolled members of each household who had at least three live lice at study entry.

Table 20: Primary Efficacy Endpoint Analysis: Pivotal trials – ITT Primary Subjects

	Natrova				**NIX**	
	With Nit Combing		***W/O Nit Combing***			
Study	**301-07**	**302-07**	**301-07**	**302-07**	**301-07**	**302-07**
TX success/failure[a]						
N	23	21	91	83	89	84
Failure-live lice	4 (17.4%)	4 (19.0%)	14 (15.4%)	11 (13.3%)	49 (55.1%)	48 (57.1%)
Success-no live lice	19 (82.6%)	17 (81.0%)	77 (84.6%)	72 (86.7%)	40 (44.9%)	36 (42.9%)
Est. success rate[b]			89.4%	89.1%	44.8%	45.1%
95% CI estimated success rate[b]			(80.8, 94.4)	(80.4, 94.2)	(32.7, 57.5)	(33.8, 56.8)
P-value vs. Nix® [b]			<.001	<.001		

[a] 14 days after last treatment is Day 14 for subjects treated once and Day 21 for subjects treated twice
[b] Logistic regression with factors for analysis site and treatment group; CIs are presented as lower and upper bounds.
Source: Sponsor's NDA Submission, Clinical Study Reports for SPN-301-07 and SPN-302-07, adapted from Table 114.1.1-1, p. 77, and p. 76 respectively.

In study SPN-301-07, ITT primary subjects, the proportion of subjects considered treatment successes was 82.6%, 84.6%, and 44.9% for the three respective treatment arms, Natrova with nit combing, Natrova without nit combing, and Nix. Natrova without nit combing showed statistical superiority over NIX (84.6% versus 44.9% with a p value of <.001). Using logistic regression the predicted estimated success rate for the ITT primary subjects was 89.4% in the Natrova without nit combing arm versus 44.8% in the NIX arm. Analysis of the per protocol population reveals similar treatment effects.

In study SPN-302-07, ITT primary subjects, the proportion of subjects considered treatment successes was 81.0%, 86.7%, and 42.9% for the three respective treatment arms, Natrova with nit combing, Natrova without nit combing, and Nix. Natrova without nit combing showed statistical superiority over NIX (86.7% versus 42.9% with a p value of <.001). Using logistic regression the predicted estimated success rate for the ITT primary subjects was 89.1% in the Natrova without nit combing arm versus 45.1% in the NIX arm. As shown in Table 21 below, analysis of the per protocol population reveals similar treatment effects.

Table 21: Primary Efficacy Endpoint Analysis: Pivotal Trials – PP Primary Subjects

	Natrova				**NIX**	
	With Nit Combing		***W/O Nit Combing***			
Study	**301-07**	**302-07**	**301-07**	**302-07**	**301-07**	**302-07**
TX success/failure[a]						
N	18	19	70	72	59	68
Failure-live lice	1 (5.6%)	2 (10.5%)	3 (4.3%)	7 (9.7%)	27 (45.8%)	39 (57.4%)
Success-no live lice	17 (94.4%)	17 (89.5%)	67 (95.7%)	65 (90.3%)	32 (54.2%)	29 (42.6%)
Est. success rate[b]			96.9%	92.7%	46.5%	46.1%
95% CI estimated success rate[b]			(89.8, 99.1)	(84.1, 96.8)	(31.3, 62.3)	(33.2, 56.9)
P-value vs. Nix® [b]			<.001	<.001		

[a] 14 days after last treatment is Day 14 for subjects treated once and Day 21 for subjects treated twice

[b] Logistic regression with factors for analysis site and treatment group

Source: Sponsor's NDA Submission, Clinical Study Reports for SPN-301-07 and SPN-302-07, adapted from Table 14.2.4.2, p. 145, and p. 143, respectively.

6.1.5 Analysis of Secondary Endpoints(s)

The secondary endpoint was the proportion of all enrolled subjects (primary and non-primary) who required two applications of study medication. The second treatment was triggered by the assessment of the trained evaluator that live lice were present at the Day 7 visit. As shown in table 22, for study SPN-301-07, 64% of subjects in the Natrova without nit combing arm required one treatment and 36% required two treatments. Whereas for those in the NIX arm, 35.5% required one treatment and 64% required two treatments. For study SPN-302-07, the results showed a similar pattern; 86% of subjects in the Natrova arm without nit combing required one treatment and 14% required two treatments. For those in the NIX arm, 40% required one treatment and 60% required two treatments.

Table 22: Secondary Endpoint Outcomes (Pivotal Trials: All ITT Subjects)

	SPN-301-07			SPN-302-07		
	Natrova		NIX	Natrova		NIX
	w/ nit combing	*w/o nit combing*		*w/ nit combing*	*w/o nit combing*	
N	59	243	256			214
One TX	35 (59.3%)	155 (63.8%)	91 (35.5%)	51 (81%)	175 (86.2%)	85 (39.7%)
Two Tx	24 (40.7%)	88 (36.3%)	165 (64.5%)	12 (19%)	28 (13.8%)	129 (60.3%)

Source: Sponsor's NDA, Integrated Summary of Efficacy, adapted from Tables 6.2.2.2.1-2, and 6.2.2.2.1-5, pp. 79 & 81.

Regulatory background regarding secondary endpoints:
With the SPA submitted 5/18/07, the sponsor proposed two secondary endpoints:
1) the proportion within each treatment group of household members who are "lice free" 14 days after the last treatment
2) the proportion within each treatment group of individual household members requiring two treatments. (Efficacy comparisons will be made between one and two treatments.)

In the letter dated 7/31/07, the Division stated regarding the secondary endpoints: No multiplicity adjustment will be required as the first secondary endpoint will not appear in labeling.
A difficulty with the second secondary endpoint as analyzed (results shown in Table 22 above) is the use of the All ITT population. This population includes all members of each family. Results using this population are biased by the fact that there is not a large enough sample to achieve true randomization on the basis of family size. Results can be driven by the results obtained in a few large families. Results within a given family are not totally independent of each other. Additionally, All ITT subjects could enter the study with only one live louse as opposed to the three required for entry of the Primary ITT subjects. A single live louse would represent a lower bar for treatment success than three live lice. Given these difficulties, the use of these results in labeling could be misleading.

Sponsor requested labeling:
The sponsor has proposed that (b) (4) is indicated for use to treat head lice (b) (4). A second treatment is needed only if reinfestation occurs. Nit combing is not required.

The sponsor performed a *post-hoc* analysis of data for the Phase 3 trials showing the proportion of subjects with status changes, that is the proportion of subjects in each treatment group whose status changed from success at an interim visit to failure at the follow-up exit visit. According to the sponsor's Table 6.2.2.2.1-6 (Integrated Summary of Efficacy, p. 83), at most 5.6% of (b) (4) subjects versus 16.7 to 19.6 5 of NIX

subjects changed status (primary ITT subjects). The sponsor discusses more favorable figures based on All ITT subjects (4.6% of (b) (4) subjects versus 22.8 to 26.8% of NIX subjects). The sponsor also acknowledges that the cause of the status change could be reinfestation, "but given the design of these actual use studies, it is not possible to quantify this potential" (ISE, p. 82). (b) (4)

At the Pre-NDA meeting of 11/4/2008, in response to a sponsor query regarding proposed labeling, the Agency responded that results based on a *post-hoc* analysis cannot be used to establish efficacy. In order to claim efficacy, the study design has to be pre-planned and the subjects should have the disease (b) (4)

A claim for one treatment appears not to be justified based on the fact that a substantial number of subjects (non-nit combing arms) required a second treatment, in study SPN-301-07 36% and in study SPN-302-07 14%. Note that this analysis was performed on All ITT subjects as opposed to primary ITT subjects, with difficulties of interpretation as discussed above. Additionally, All ITT subjects could enter the study with only one live louse as opposed to the three required for entry of the Primary ITT subjects. A single live louse would represent a lower bar for treatment success than three live lice.

The claim that nit combing is not required is acceptable. In the pivotal trials, for the primary efficacy endpoint, success rates for treatment arms without nit combing were comparable to those with nit combing.

6.1.6 Other Endpoints

Discussion of Unintentional Disclosure of Subject Treatment to Subjects:
As mentioned in section 5.3 under blinding, the Instructions for Use indicated the identity of the test article in a footnote and therefore the pivotal trials were conducted effectively as investigator/evaluator-blinded rather than as double blinded trials. According to protocol, subjects were prohibited from discussing their assigned treatments with investigators/evaluators and at all study sites, a designated individual, who was explicitly excluded from participating in the efficacy evaluations, distributed, collected, and accounted for all assigned treatments. All subjects within the same family received the same treatment.

Knowledge of the treatment assignment might have affected subject behavior by increasing dropouts. In study SPN-301-07, in the Natrova with nit combing, Natrova without nit combing, and NIX arms, respectively, 7%, 5%, and 9% of subjects withdrew consent or were lost to follow-up. In Study SPN-302-07 those numbers were 8%, 7%, and 8% respectively. Notable differences across treatment arms for both studies are not seen.

Knowledge of treatment assignment might have affected how subjects applied treatments. For the pivotal studies compliance was assessed by subject query. For study SPN-301-07, for primary ITT subjects, in the Natrova with nit combing, Natrova without nit combing, and NIX arms, respectively, 83%, 89%, and 83% of subjects responded "Yes" at Days 7, 17, and if applicable, 21, to the question; "Has the subject continued to comply with study instructions/restrictions." For study SPN-302-07, the percentages were 91%, 90%, and 87%, respectively. Substantial differences across treatment arms are not seen.

How subjects applied treatments might affect efficacy findings, the concern would be artificially increased efficacy in Natrova arms and decreased efficacy in NIX arms. It is noted that the outcomes in the NIX treatment groups 45%, 43% (301-07, 302-07) are similar to those in more recently reported studies 55%, 46%; (Meinking et al, 2004[1] and 2007[2]) cited by the sponsor. Phase 2 studies showed generally similar results for spinosad .9%. For study SPN-201-05, two treatments were applied, nit combing was performed, evaluation occurred 7 days after the last treatment, spinosad .9% with minor formulation differences showed 100% success in a treatment arm of 9 subjects. For study SPN-202-06, subjects entered with nits as well as at least 3 live lice, one treatment was applied, nit combing was not performed, evaluation occurred 14 days after last treatment, success was defined as absence of live lice and of viable nits, spinosad .9% with minor formulation differences showed 86% success in a treatment arm of 36 subjects.

In this reviewer's opinion, although it is possible that subject knowledge of treatment may have influenced efficacy results, the degree of that influence was not likely of large enough magnitude to invalidate the finding of superiority of Natrova over NIX in the two pivotal trials.

6.1.7 Subpopulations

In both pivotal studies, SPN-301-07, 302-07, results for the primary endpoint were examined in the subpopulations; gender, race, and age.

[1] Meinking TL *et al*. Efficacy of a reduced application time of Ovide lotion (0.5% Malathion) compared to Nix crème rinse 91% permethrin) for the treatment of head lice. Pediatric Dermatology 2004;21:670-4.
[2] Meinking TL *et al*. A randomized, investigator-blinded, time-ranging study of the comparative efficacy of 0.5% malthion gel versus Ovide lotion (0.5% malthion) or Nix Crème Rinse (1% permethrin) used as labeled, for the treatment of head lice. Pediatric Dermatology. 2007;42:405-11.

Table 23: Treatment Success by Age, Gender, Race (SPN-301-07: ITT Primary)

	Natrova		Nix	
	With nit combing	**Without nit combing**		
	N = 23	N = 91	N = 89	
Variable				
Success (no live lice)				
Age category				
≤ median age	9/9 (100%)	44/54 (81.5%)	24/45 (53.3%)	
> median age	10/14 (71.4%)	33/37 (89.2%)	16/44 (36.4%)	
Gender				
Male	3/4 (75%)	12/13 (92.3%)	6/12 (50%)	
Female	16/19 (84.2%)	65/78 (83.3%)	34/77 (44.2%)	
Predominant race				
Caucasian	9/12 (75%)	53/55 (96.4%)	31/58 (53.4%)	
Black	0 (0%)	0 (0%)	0/1 (0%)	
Asian	0/1 (0%)	0/1 (0%)	1/2 (50%)	
Native American	1/1 (100%)	0/0 (0%)	0/0 (0%)	
Hispanic	8/8 (100%)	21/32 (65.6%)	8/26 (30.8%)	
Other	1/1 (100%)	3/3 (100%)	0/2 (0%)	

Source: Sponsor's NDA, Clinical Study Report for Study SPN-301-07, Table 14.2.6.1, p. 147.

Table 24: Treatment Success by Age, Gender, Race (SPN-302-07: ITT Primary)

	Natrova		Nix	
	With nit combing	**Without nit combing**		
	N = 21	N = 83	N = 84	
Variable				
Success (no live lice)				
Age category				
≤ median age	11/14 (79%)*	44/49 (90%)*	21/48 (44%)*	
> median age	6/7 (86%)	28/34 (82%)	15/36 (42%)	
Gender				
Male	3/3 (100%)	9/12 (75%)	3/6 (50%)	
Female	14/18 (78%)	63/71 (89%)	33/78 (42%)	
Predominant race				
Caucasian	11/13 (85%)	46/53 (87%)	17/52 (33%)	
Black	0 (0%)	0 (0%)	0/0 (0%)	

Asian	0/0 (0%)	1/1 (100%)	0/0 (0%)	
Native American	0/0 (0%)	0/1 (0%)	0/0 (0%)	
Hispanic	6/8 (75%)	22/25 (88%)	16/28 (57%)	
Other	0/0 (0%)	3/3 (100%)	3/4 (75%)	

* Percentages rounded by reviewer.
Source: Sponsor's NDA, Clinical Study Report for Study SPN-302-07, Table 14.2.6.1, p. 145.

While numerical variations are present, response rates for male and females are similar for both studies and both Natrova arms, with and without nit combing. The majority of subjects among the primary ITT group are Caucasian with a substantial Hispanic minority. While numerical variations are present, response rates for Caucasians and Hispanics are similar for both studies and both Natrova treatment arms. Definitive conclusions regarding response rates among the other races analyzed; Black, Asian, Native American, and other, are precluded due to small numbers. The sponsor performed subgroup analysis for age by creating two subgroups, ≤ median age and > median age. For study SPN-301-07, ITT primary population, the median ages were 9 and 6 years for the Natrova with and without nit combing arms respectively. For study SPN-302-07, ITT primary population, the median ages were 6 and 7 years for the Natrova with and without nit combing arms respectively. Response rates were similar for these two subgroups across both studies and for both Natrova treatment arms.

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

Two studies were performed to evaluate the optimal dose to be used in the pivotal Phase 3 studies.
a) SPN-201-05 conducted from September 22, 2005 to November 4, 2005
b) SPN-202-06 conducted from March 15, 2006 to July 1, 2006

The to-be-marketed formulation was not employed in these studies; minor formulation differences compared with the lots used in the Phase 3 trials were present.
For study SPN-201-05 these differences included (apart from the differing spinosad concentrations in some arms) (b) (4) hydroxylethyl cellulose versus (b) (4)) isopropyl anhydrous versus (b) (4). For study SPN-202-06 (apart from differing spinosad concentrations in some arms) the principal difference was (b) (4) propylene glycol versus (b) (4)

Study SPN-201-05:

Study SPN-201-05 was a single center, investigator/evaluator-blind, 4 arm, parallel group, vehicle-controlled trial. The 4 arms consisted of vehicle, .5% spinosad, 1.0% spinosad, and 2.0% spinosad.

Subjects were 2 years of age or older with head lice infestation defined as the presence of at least 3 live lice (adults and/or nymphs). Up to 120 ml of product was applied by investigational site personnel for 10 minutes to scalp and hair, to all assigned subjects at Day 0 and Day 7. Combing was performed.

If subjects were not infested (live lice adults or nymphs) at Day 7 and Day 14, they were considered a treatment success. If subjects were infested at Day 7, but not infested at Day 14 this was a treatment success. If subjects were not infested at Day 7, but infested at Day 14 they may have been considered a case of re-infestation. If subjects were infested at Day 7 and Day 14, they were considered a treatment failure.
A total of 36 subjects were randomized to treatment. For efficacy 35 subjects were analyzed and for safety 36 subjects were analyzed.

Table 25: Treatment Success (Lice-Free) Study SPN-201-05: ITT Population

Time point	Vehicle	Spinosad		
	0%	0.5%	1.0%	2.0%
	N=9	N=8	N=9	N=9
Day 0 Pre-Treatment	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Day 0 Before Combing	3 (33.3%)	6 (75%)	7 (77.8%)	6 (66.7%)
Day 0 After Combing	6 (66.7%)	7 (87.5%)	9 (100%)	8 (88.9%)
Day 7 Pre-treatment	2 (22.2%)	7 (87.5%)	9 (100%)	9 (100%)
Day 7 Before Combing	6 (66.7%)	8 (100%)	9 (100%)	9 (100%)
Day 7 After Combing	8 (88.9%)	8 (100%)	9 (100%)	9 (100%)
Day 14	8 (88.9%)	8 (100%)	9 (100%)	9 (100%)

Source: Sponsor's NDA, Clinical Study Report for Study SPN-201-05, Table 11.4.1-1, p. 36.

The sponsor notes that at Day 7 pre-treatment, the percent of subjects lice free for 0.5%, 1.0%, and 2.0% spinosad (87.5% [7/8], 100.0% [9/9], and 100.0% [9/9], respectively) were numerically higher than those for Vehicle Control (22.2%[2/9]). Also Day 7 pre-treatment, the percent of subjects lice free for 1.0% and 2.0% spinosad were slightly higher numerically than those for 0.5% spinosad, and no numerical difference was seen between the percent of subjects lice free for 1.0% and 2.0% spinosad.

Based on these findings the sponsor chose the 1% spinosad formulation. The comparability of this trial to the pivotal Phase 3 trials is limited by differences in trial design. Two treatments were given to all subjects. The primary endpoint was evaluated at 7 days as opposed to 14 days after the second treatment. Nit combing was performed on all subjects. As previously noted there were minor formulation differences. Note additionally the high success rate of vehicle, at Day 14, compared

with the three formulations of active. This high vehicle success rate will be discussed further in section 6.1.10.

Study SPN-202-06:

Study SPN-202-06 was a multi-center, investigator-blind, 3 arm, parallel group, vehicle-controlled trial. The 3 arms consisted of vehicle, 0.5% spinosad, and 1.0% spinosad.

Inclusion: males and females, 2 years of age and older, with at least 3 live lice (adults or nymphs) and *the presence of nits*. Product applied by investigational site personnel up to 120 ml, or until hair was saturated, for 10 minutes. Only one application, with no combing, was performed.

Seven (7) days after treatment, subjects attended an efficacy evaluation visit. During the visit, subjects who presented without live lice were scheduled for a Day 14 follow-up visit, while all other subjects were discontinued from the study as treatment failures. Subjects who then presented 14 days after treatment with no live lice were considered treatment successes while all other subjects were considered failures. At both the Day 7 and Day 14 visits, hair samples were collected from subjects who were lice-free but were observed to have potentially viable nits. After a 10-day incubation period, subjects were re-classified as failures *if the nits on their collected hairs hatched.*

The primary efficacy endpoint was the proportion of subjects free of live lice (no live lice or *viable nits-nits incubated and evaluated*) on Day 7 and Day 14 after the applied treatment.

A total of 122 subjects were enrolled of which 120 (43 - 0% spinosad, 40 - .5% spinosad, 37 - 1% spinosad) completed all phases of the study.

Table 26: Primary Efficacy Outcome: Study SPN-202-06

	Spinosad 0.5%	Spinosad 1.0%	Vehicle 0%	p-value
	N=40	N=36	N=43	
Day 7				
Success	37 (92.50%)	33 (91.67%)	21 (48.84%)	<0.0001[a], <0.0001[b]
Failure	3 (7.50%)	3 (8.33%)	22 (51.16%)	
Day 14				
Success	33 (82.50%)	31 (86.11%)	11 (25.58%)	<0.0001[a], <0.0001[b]
Failure	7 (17.50%)	5 (13.89%)	32 (74.42%)	

[a] P-value from Chi-Squared comparison of the success rate in Spinosad 0.5% to vehicle
[b] P-value from Chi-Squared comparison of the success rate in Spinosad 1.0% to vehicle
Source: Sponsor's NDA, Integrated Summary of Efficacy, Table 6.2.1.2-1, p. 57.

The proportions of successes on Day 7 in the spinosad treatment groups (1.0% - 91.67%, 0.5% - 92.50%) were similar to one another and greater than the vehicle treatment group (48.84%). At Day 14, the proportion of successes in the spinosad 1.0% treatment group was somewhat greater than the corresponding proportion in the spinosad 0.5% treatment group (86.11% versus 82.50%, respectively). The proportion of successes in both spinosad treatment groups was greater than in the vehicle treatment group (25.58%).

The Day 14 success rates show the 1.0% spinosad formulation mildly more effective than the 0.5% formulation. The success rate of vehicle compared with the two formulations of active is discordant with the success rate of the vehicle seen in study SPN-201-05. The vehicle success rate will be discussed further in section 6.1.10.

The comparability of this trial to the pivotal Phase 3 trials is limited by differences in trial design and definitions used for efficacy. One treatment was given to all subjects. Efficacy is defined based on the presence or absence of lice and of viable nits-*nits incubated and evaluated*. As previously noted there were minor formulation differences.

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

Analyses of persistence of efficacy and/or tolerance were not performed. Efficacy beyond 14 days post-treatment was not evaluated.

6.1.10 Additional Efficacy Issues/Analyses

An additional efficacy issue is distinguishing the inherent efficacy of the API spinosad from that of the vehicle, containing (b) (4) benzyl alcohol.

The Phase three pivotal trials for (b) (4) do not include vehicle arms because it has been Divisional policy that pesticides are compared against active treatment in order to establish a level of efficacy that would counterbalance the presumably greater risk of adverse events with a pesticide. (b) (4) by its mechanism of action is considered a pesticide. The trial design for (b) (4) was developed before benzyl alcohol was approved as active in ULESFIA (benzyl alcohol) Lotion 5%.

The sponsor submitted on April 26, 2007 and on May 7, 2007 reports of studies that are in vitro tests of the effectiveness of the various spinosyn factors at killing either cat fleas or human body lice. These studies were reviewed 5/23/07 by the pharmacology/toxicology reviewer, Paul C. Brown, Ph.D.

Studies included the following:
A Activity against cat fleas:
1) Study No# T9CAM0103: In vitro evaluation of the adulticidal activity of individual spinosyn factors against cat fleas, *Ctenocephalides felis,* using an artifical membrane

feeding system. Doses: The individual factors were dissolved in DMSO at a concentration of 1 ppm. Conclusions: All of the spinosyn factors (A through L) contribute to the killing of cat fleas. This study showed no difference between factors A and D in activity against cat fleas.

2) Study No# T9C060116: In vitro evaluation of the adulticidal activity of spinosyn factors A, D, A/D, G and spinosad technical against cat fleas, *Ctenocephalides felis,* using an artificial membrane feeding system. Doses: The individual factors were dissolved in DMSO and tested at a final concentration of 1 ppm. Conclusions: There is essentially no difference in potency factors A, D and mixed A+D. Spinosyn factor G appears to have lower potency than A and D.

B Activity against human body louse:
3) Study No# 349-0030B: To determine the efficacy of eight Spinosad factors against the body louse (*Pediculus humanus humanus*)
Doses: 0.01% (100ppm; clinical formulation spinosad 2% 20,000 ppm) Factors dissolved in 30% isopropanol/water solution
Methods: Lice submerged for 10 minutes in a beaker with the test material at 32 degrees C.
Findings: Vehicle (30% isopropanol solution) had no greater mortality than water. Spinosyn D corrected 24 hour mortality = 58.7; spinosyn A + D corrected 24 hour mortality = 49.5; spinosyn B corrected 24 hour mortality = 26.6; spinosyn E corrected 24 hour mortality = 1.0; other factors K,F,J,L had mortality less than that of water
The three studies outlined above suggest that spinosyn A and D, the principal elements of the (b) (4) API, have inherent insecticidal activity. The third study suggests inherent pediculicidal activity. Insofar as body lice are related to head lice, it could be inferred that spinosyn factors have inherent activity against head lice.

Additional information regarding the inherent activity of Spinosad versus vehicle may be gleaned from examination of the Phase 2 studies, SPN-201-05 and SPN-202-06. The general design of these studies is discussed in section 6.1.8 above.

In study SPN-201-05, every subject received two treatments and nit combing was performed. At Day 7, pre-treatment, 7 days after one treatment application, 2/9 subjects in the vehicle (containing (b) (4) benzyl alcohol) group were free of lice versus 7/8, 9/9, and 9/9 in the spinosad .5%, 1.0%, and 2.0% groups respectively. At Day 14, 7 days after the second treatment, 8/9 subjects in the vehicle group were lice-free versus 8/8, 9/9, and 9/9 in the spinosad .5%, 1.0%, and 2.0% groups respectively. These results suggest a strong vehicle response rate, only mildly less that for spinosad .5% which itself appears only mildly less than that for the spinosad 1.0% and 2.0% groups. These results can only be considered suggestive due to small numbers of subjects.

In study SPN-202-06, every subject received one treatment and no nit combing was performed. Efficacy; however, was defined as the proportion of subjects free of live lice (no live lice or viable nits-*nits incubated and evaluated*) on Day 7 and Day 14 after the applied treatment. At Day 14, fourteen days after the single treatment application, 11/43 (25.6%) of subjects in the vehicle group were lice/nit free versus 33/40 (82.5%) and 31/36 (86.1%) in the spinosad .5% and 1.0% groups respectively. While this study suggests a strong vehicle response rate, it appears notably less than that found in study SPN-201-05. The differences in vehicle response rate between studies SPN-201-5 and SPN-202-06 may be due to differences in design between the two studies, respectively; evaluation at Day 7 versus 14 and the use two treatments versus one. Additionally lice free in study SPN-201-05 is defined as absence of adults and/or nymphs and in study SPN-202-06 as no live lice or viable nits-*nits incubated and evaluated.*

Overall the results of studies SPN-201-05 and SPN-202-06 would seem to indicate that the API spinosad has inherent activity against lice; however, there is a considerable vehicle response rate most likely due to the presence of (b) (4) benzyl alcohol, a finding consistent with the finding of efficacy for the approved product ULESFIA (benzyl alcohol) Lotion 5%.

7 Review of Safety

Safety Summary

The principal evaluation of safety with the final-to-be-marketed formulation, occurred via the conduct of two pivotal trials, SPN-301-07 and SPN-302-07 in the United States. Supportive safety data is also available from nine other sponsor-conducted Phase1 and 2 trials.

In total, the safety database includes 1,561 subjects of whom 1,040 were exposed to spinosad at various concentrations and with variations in formulation. The sponsor states that 715 subjects were exposed to (b) (4) (API spinosad (b) (4)). This group includes a total of 104 subjects exposed in Phase 1 trials that include 96 having patch applications (SPN-107-07 & SPN-108-08) and 8 having application to healthy scalps (SPN-106-06). Subjects exposed in Phase 2 included 59 having exposure to lice-affected scalps. A total of 552 subjects were exposed in Phase 3 trials.

Of the 715 subjects the sponsor states were exposed to (b) (4) minor formulation differences were present amongst this group. Only the 552 subjects in the pivotal

Phase 3 trials (SPN-301-07 and 302-07), 8 subjects in the infant PK study (SPN-106-06) and 96 subjects in the phototoxicity (SPN-107-07) and photoallergy (SPN-108-08) trials were exposed to the final-to-be-marketed formulation; or 656/715.

Of the 552 subjects exposed to Natrova in Phase 3 trials, 400 of these had one application and 152 had two applications. Treatment time was 10 minutes and maximum product applied per treatment was 120 mL.

No deaths were reported in the 11 studies conducted in the development (b) (4) During the development program a total of 6 serious adverse events were reported. Three of these events were reported during study SPN-10-05, a repeat insult patch test/cumulative irritation study. These events included abdominal pain and nausea in one subject and considered likely related to pancreatic cancer. Dizziness noted in a second subject was considered related to vision. Two SAEs occurred in the pivotal trial SPN-301-07 in subjects randomized to NIX and included one case of application site erythema possibly related to NIX and a case of right cheek cellulitis, considered unrelated to NIX. Finally an SAE of viral gastroenteritis was reported from the pivotal trial SPN-302-07 in a subject randomized to NIX. This SAE was considered unrelated to NIX.

During the 11 studies of the clinical development program, no subjects dropped out due to an adverse event evaluated as related to use of spinosad. In both of the pivotal trials no subjects, in any of the three trial arms, dropped out due to adverse events.

In the pivotal trials, Natrova arms (with/without nit combing), 46 subjects (8.3%) reported 58 adverse events. In the NIX arms 77 subjects (16.8%) reported 91 adverse events. Thee SAEs were reported, discussed above, in the NIX arms. Among the remaining adverse events, severity was assessed as either mild or moderate with no severe events being reported.

In the pivotal trials, across study arms the most common adverse event reported was application site erythema, occurring in 3.1% (17/552) of subjects exposed to Natrova and in 6.8% (31/457) of subjects exposed to NIX. The second most common adverse event across study arms was ocular hyperemia, occurring in 2.2 % (12/552) those exposed to Natrova and in 3.3% (15/457) of those exposed to NIX. The third most common adverse event across study arms was application site irritation, occurring in .9% (5/552) of those exposed to Natrova and in 1.5% (7/457) of those exposed to NIX. Evaluation of adverse events across the development program did not reveal a safety signal regarding neurological events.

Three Phase 1 special safety studies were performed to evaluate cutaneous safety, SPN-102-5, SPN-107-07, and SPN-108-08. As studied, spinosad 2% and its vehicle were significantly less irritating than .1% SLS (positive control) but were significantly more irritating than .9% sodium chloride (negative control). There was no evidence of

induced skin sensitization to spinosad 2% or to spinosad vehicle. As studied, there was no evidence of phototoxicity for (b) (4) (to-be-marketed formulation) or to its vehicle. Also, as studied, evidence of photo-irritation or photo-sensitization that would be clinically significant under labeled conditions of use, one to two treatments and short application time, was not seen.

Cutaneous safety was also monitored by evaluation of scalp irritation (Phases 1, 2, 3) and ocular irritation (Phase 3). In Phase 1 studies, clinically significant scalp irritation was not observed. In Phase 2, formal scalp evaluations were performed in study SPN-202-06 and no statistical differences in scalp irritation were observed between the treatment groups, spinosad 0.5%, spinosad 1.0%, or vehicle. In the Phase 3 pivotal trials, mean scalp irritation scores for the Natrova treatment group declined through the course of the study and were generally lower than those for the NIX treatment group. With respect to ocular irritation, few subjects in both Natrova and NIX treatment groups exhibited signs of irritation at either Day 0 or Day 8, following treatment. Mean ocular irritation scores were lower for Natrova than for NIX after the Day 0 treatment but were mildly higher for Natrova than for NIX after the Day 8 treatment.

In the pivotal Phase 3 trials, laboratory assessments consisting of hematology and serum chemistry were performed either partially or completely on 56 subjects, 30 in Natrova treatment groups and 26 in NIX treatment groups. Clinically significant outliers are not seen. For those subjects having both Day 0 and Day 14 values, including 15 in the Natrova treatment group and 14 in the NIX treatment group, shift tables were constructed and evaluated. Notable trends or safety signals are not seen in the laboratory data gathered by the sponsor.

While available pharmacokinetic data indicate no detectable systemic absorption in pediatric subjects having lice infestations down to 4 years of age, pharmacokinetic data are not available in lice-infested children aged 6 months to 4 years.

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

The clinical development program included:

A) 6 Phase I studies principally in healthy subjects, one study in subjects with head lice
1) SPN-101-04: Spinosad 2%, healthy adult subjects, 1 application, PK
2) SPN-102-05: Spinosad 2%, healthy adult subjects 18-65, HRIPT/CI
3) SPN-103-05: Spinosad 2%, pediatric subjects with head lice, 1 application, pediatric PK

4) SPN-106-06: Spinosad 1%, healthy pediatric subjects, 1 application, infant PK, formulation - same as Phase 3
5) SPN-107-07: Spinosad 1%, healthy adult subjects 18-65, phototoxicity, formulation - same as Phase 3
6) SPN-108-08: Spinosad 1%, healthy adult subjects, photoallergy, formulation - same as Phase 3

B) 3 Phase 2 studies; 2 dose-ranging, one pilot safety and efficacy
1) SPN-201-05: Spinosad .5%, 1%, 2%, 2 applications, subjects (≥ 2 yrs) with head lice, pilot dose-ranging
2) SPN-202-06: Spinosad .5%, 1%, 1-2 applications, subjects (≥ 2 yrs) with at least 3 live lice, dose-ranging
3) SPN-203-07: Spinosad 1%, 1-2 applications, subjects (≥ 6 mo) with head lice, Phase 3 pilot

C) 2 Phase 3 studies; pivotal safety and efficacy
SPN-301-07 and SPN-302-07: Spinosad 1%, 1-2 applications, subjects (≥ 6 mo) with at least 3 live lice

The safety review of the sponsor's product will focus on adverse events and systemic safety (laboratory evaluation) and local safety (cutaneous signs and symptoms at application sites). The safety database consists primarily of the pooled data from the two pivotal trials, SPN-301-07 and SPN-302-07. Of note, subjects in the Phase 3 trials were randomized to apply Natrova with or without nit combing. The sponsor has pooled the results of these two groups for safety analysis. The safety database also includes supportive data from the other 9 Phase 1 and 2 trials, which are discussed separately due to differences in subject populations and study design.

In total the safety database includes 1,561 subjects of whom 1,040 were exposed to spinosad at various concentrations and with variations in formulation. A total of 715 subjects were exposed to (b) (4) with minor formulation differences and 656 were exposed to the final to-be-marketed formulation of (b) (4)

For all clinical studies serious adverse events and clinically important adverse events were examined. Deaths were not seen and discontinuations due to adverse events *(evaluated as related to drug product)* were not seen.

7.1.2 Categorization of Adverse Events

Adverse events were coded using the MedDRA® dictionary (version 10.1) and were tabulated by system organ class and preferred terms. For the pivotal studies SPN-301-07 and SPN-302-07 the sponsor's classification of verbatim terms to preferred terms appears acceptable.

7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

Adverse event data from the pivotal Phase 3 studies, SPN-301-07 and SPN-302-07, were pooled together. Test product, dose, mode of administration, number of treatments were the same for both studies. The sponsor also pooled together subjects who used Natrova with and without nit combing.

7.2 Adequacy of Safety Assessments

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

Table 27 shows details of treatment application in studies with subjects having active head lice infestations. In these studies treatment duration was 10 minutes for one or at most two treatments. Treatment site was scalp and amount was up to 120 ml.

Table 27: Treatment Application Details – Studies: Subjects with Active Infestations

Study	Test location	Number of Applications	Treatment per Application (Max amount)	Treatment Duration per Application
Phase 1				
SPN-103-05	Scalp	1	30mL	10 min.
Phase 2				
SPN-201-05	Scalp	2	Up to 144g (228g)	10 min.
SPN-202-06	Scalp	1	Up to 120 mL	10 min.
SPN-203-07	Scalp	1 or 2	Up to 120 mL (240 mL)	10 min.
Phase 3				
SPN-301-07	Scalp	1 or 2	Up to 120 mL (240 mL)	10 min.
SPN-302-07	Scalp	1 or 2	Up to 120 mL (240 mL)	10 min.

Source: Sponsor's NDA submission, Integrated Summary of Safety, adapted from Table 4.2-1, p. 28.

The number of subjects exposed, having active head lice infestations, included the following:
Phase 1: In study SPN-103-05, 14 subjects with head lice were exposed to spinosad 2%
Phase 2: In Phase 2 studies, 117 subjects with head lice were exposed to spinosad; 48 to 0.5%, 59 to 1.0%, and 10 to 2.0% as shown in Table 28 below.

Table 28: Summary of Subject Exposure to Treatment: Phase 2 Trials

Study	Vehicle	Spinosad 0.5%	Spinosad 1.0%	Spinosad 2.0%	NIX	Spinosad any conc
SPN-201-05	9	8	9	10	--	27
SPN-202-06	43	40	39	--	--	79
SPN-203-07	--	--	11	--	13	11
Total by Tx	***52***	***48***	***59***	***10***	***13***	***117***

Source: Sponsor's NDA submission, Integrated Summary of Safety, adapted from Table 4.2.2-1, p. 30.

Phase 3: In Phase 3, a total of 552 subjects with head lice were exposed to Natrova as shown in Table 29 below. Treatment compliance was ascertained by subject query at study visits.

Table 29: Summary of Subject Exposure to Treatment: Phase 3 Trials

	No. of Applications	Natrova	NIX	Total
Phase 3 studies		N = 552	N = 457	1009
	1	400	163	563 (56%)*
	2	152	294	446 (44%)*

* Percentages rounded by reviewer.
Source: Sponsor's NDA submission, Integrated Summary of Safety, Table 4.2.3-1, p. 31.

As shown in Table 30 following, the safety population for the Pivotal Trials included 552 subjects exposed to Natrova. The Safety Population was defined as all randomized subjects who received at least one treatment. A majority of subjects were Caucasian (59%) and female (81%). The mean age was 15.7 years old. In the United States the highest incidence of head lice is found in children aged 3 to 11 years. Head lice are more frequent in girls due to the predilection for longer hair and habits of exchanging hair care accessories.[16] Head lice affect all socioeconomic groups.[17] In African-Americans head lice are less common than in other races because anatomic differences in American lice do not allow for proper positioning of the female in order to lay eggs on coarse, curly hair.[18,19]

[16] Jacobson CC and Abel EA. Periodic Synopsis: Parasitic Infections. Journal of the American Academy of Dermatology 2007;56:1026-43.
[17] Frankowski BL and Weiner LB. Committee on School Health, Committee on Infectious Diseases. Head Lice. Pediatrics 2002;110:638-43.
[18] Burkhart CN and Burkhart CG. Head lice: Scientific assessment of the nit sheath with clinical ramifications and therapeutic options. Journal of the American Academy of Dermatology 2005;53:129-133.
[19] Meinking TL et al. Chapter 83. Infestations in Dermatology e-edition, 2nd Edition: Bolognia JL and Jorizzo JL, Elsevier, Inc. © 2009.

Table 30: Demographic Data (Pooled Pivotal Trials: Safety Population)

Treatment	**Natrova**	**NIX**	
	N=552	N=457	
Age (years)	N=552	N=457	
6 to 24 months	20 (4%)*	13 (3%)	
25 months ≤ 4 years	65 (12%)	59 (13%)	
5 to 9 years	191 (35%)	127 (28%)	
10 to 14 years	101 (18%)	95 (21%)	
≥ 15 years	174 (32%)	163 (36%)	
Median	9.0	11.0	
Mean (STD)	15.7 (14.2)	16.6 (14.5)	
Min. to Max.	0 to 66	0 to 84	
Gender	N=552	N=457	
Male	104 (19%)	73 (16%)	
Female	448 (81%)	384 (84%)	
Predominant race	N=552	N=457	U.S. Population[20]
Caucasian	325 (59%)	274 (60%)	74%
Black	0	1 (0.2%)	12.4%
Asian	6 (1%)	2 (0.4%)	4.3%
Native American	4 (0.7%)	4 (0.9%)	.8%
Hispanic	206 (37%)	166 (36%)	14.7%‡
Other†	11 (2%)	10 (2%)	

* Percentages rounded by reviewer

† Mutiracial, bi-racial, and other combinations of racial categorizations

‡ In the American Community Survey, "Hispanic or Latino" was employed as a category for ethnicity. In the Safety Summary, "Hispanic" is a category for race.

Source: Sponsor's NDA submission, Integrated Summary of Safety, adapted from Table 12-3, p. 103.

As compared with that for the U. S. population, the demographics of the population studied show a relative underrepresentation of African-Americans and a relative over representation of Hispanics. As noted above, head lice are less common in African-Americans. The over representation of Hispanic ethnicity is unlikely to affect applicability of study results to the U.S. target population.

Adequacy of Clinical Exposure:

An adequate number of subjects were exposed to Natrova (spinosad) Suspension, 0.9% at the proposed dosing regimen to assess safety for use. A total of 552 subjects

[20] U.S. Census Bureau, 2005-2007 American Community Survey, Detailed Tables – American FactFinder; B02001.Race and B03001. Hispanic or Latino Origin by Specific Origin.

in the pivotal Phase 3 trials (SPN-301-07 and 302-07), 8 subjects in the infant PK study (SPN-106-06) and 96 subjects in the phototoxicity (SPN-107-07) and photoallergy (SPN-108-08) trials were exposed to the final-to-be-marketed formulation; or 656 subjects.

In the pivotal trials, pediatric exposure in the 4 years and younger age group appears adequate (85 subjects); however, in the youngest age group 6 to 24 months (20 subjects), numbers are somewhat small. It is noted that the PK study SPN-106-06 enrolled 8 healthy subjects, aged 6 to 23 months, who were exposed to (b) (4) Because the current NDA does not include data on systemic absorption in children under age 4, additional pharmacokinetic study data will be requested. Should this data be provided, it is would provide additional safety information in the youngest age group.

Of the 552 subjects exposed to Natrova in Phase 3 trials, 400 of these had one application and 152 had two applications. Treatment time was 10 minutes and maximum product applied per treatment was 120 mL.

Topical safety was adequately evaluated in the development program and included assessment for local adverse events and three dermal safety studies. The number of subjects evaluated in the dermal safety studies was generally as recommended. Systemic safety was adequately evaluated during the course of the development program through safety laboratory testing. No clinically significant signals were identified. This might be expected since, topical application as studied in PK trials did not result in any detectable systemic absorption.

7.2.2 Explorations for Dose Response

As shown in Table 31, the clinical development program included two dose ranging studies in subjects having active head lice infestations.

Table 31: Studies with Differing Doses (Subjects with Active Lice Infestations)

Study	Vehicle	Spinosad 0.5%	Spinosad 1.0%	Spinosad 2.0%
SPN-201-05	9	8	9	10
SPN-202-06	43	40	39	--
Total by Tx	***52***	***48***	***48***	***10***

A trend to increasing rates for adverse events with increasing dose does not appear to be present in either study SPN-201-05 (Table 32) or in study SPN-202-06 (Table 33).

Table 32: Adverse Events – Study SPN-201-05

Adverse Event	Spinosad 0.5%	Spinosad 1.0%	Spinosad 2.0%	Vehicle
	N=8	N=9	N=10	N=9
Fever	1 (12.5%)	0	0	0
Burning sensation in L eye	1 (12.5%)	0	0	0

Source: Sponsor's NDA submission, Integrated Summary of Safety, Table 5.1.1-7, p. 59.

Table 33: Adverse Events – Study SPN-202-06

	Spinosad 0.5%	Spinosad 1.0%	Vehicle
Adverse Event*	N=40	N=37	N=43
GI Disorders	2 (5%)	1 (2.7%)	2 (4.7%)
Abdominal Pain	0	1 (2.7%)	0
Abdominal Pain, Upper	1 (2.5%)	0	0
Diarrhea	0	1 (2.7%)	2 (4.7%)
Nausea	0	1 (2.7%)	2 (4.7%)
Vomiting	1 (2.5%)	1 (2.7%)	2 (4.7%)
Gen Disorders & Administration Site Conditions	0	1 (2.7%)	2 (4.7%)
Pyrexia	0	0	1 (2.4%)
Application site irritation	0	1 (2.7%)	1 (2.3%)
Injury, Poisoning, & Procedural Complications	1 (2.5%)	0	0
Concussion	1 (2.5%)	0	0
Excoriation	1 (2.5%)	0	0
Nervous System Disorders	0	1 (2.7%)	2 (4.7%)
Dizziness	0	1 (2.7%)	2 (4.7%)
Respiratory, Thoracic, & Mediastinal Disorders	0	0	1 (2.3%)
Productive Cough	0	0	1 (2.3%)
Skin & Subcutaneous Tissue Disorders	1 (2.5%)	0	1 (2.3%)
Erythema	1 (2.5%)	0	1 (2.3%)

*Adverse events are sorted alphabetically by System Organ Class and preferred Term, and then by descending incidence. A subject is counted only once under Preferred Term and under overall incidence of AEs within a System Organ Class.

Source: Sponsor's NDA submission, Integrated Summary of Safety, Table 5.1.1-8, p. 60.

7.2.3 Special Animal and/or In Vitro Testing

Neurological Effects:
Neurological effects were evaluated in a 13-week neurotoxicity study in Fischer 344 rats (Study No. DERBI-4246). According to the pharmacology/toxicology reviewer, Jianyong Wang, Ph.D., under the conditions of study, essentially no neurological effects were noted.

Cardiovascular Effects:
From the Pharmacology/Toxicology Review by Jianyong Wang, Ph.D.:

> The cardiovascular safety of spinosad was not evaluated in safety pharmacology studies, and ECG was not assessed in repeat dose toxicology studies in dogs or minipigs. However, due to a very low systemic exposure to spinosad (below the limit of quantification) under the maximal use conditions in humans, no additional safety pharmacology studies are recommended at this time.

7.2.4 Routine Clinical Testing

The routine clinical testing performed was adequate to assess the safety and efficacy of use for two applications of the product one week apart.

7.2.5 Metabolic, Clearance, and Interaction Workup

The sponsor did not perform as assessment of drug-drug interactions.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

Spinosad is a new molecular entity, derived from the fermentation of a soil actinomycete bacterium, *Saccharopolyspora spinosa*. Spinosad is an insecticide that works by causing paralysis of insects by altering the function of nicotinic and gamma butyric acid-gated ion channels resulting in prolonged over-excitation of the insect's nervous system.

Preclinical testing for spinosad did not reveal a significant signal for neurological effects. Topical application as studied in the PK trials; SPN-101-04, SPN-103-05, and SPN-106-06, did not result in any detectable systemic absorption.

7.3 Major Safety Results

7.3.1 Deaths

No deaths were reported in the 11 studies conducted in the development of (b) (4).

7.3.2 Nonfatal Serious Adverse Events

During the 11 studies conducted during the development o (b) (4), 6 serious adverse events were reported as shown in Table 34 below.

Table 34: Serious Adverse Events in Clinical Development Program

Study Number	Subject No.	Treatment	Event	Dates	Relationship	
SPN-102-05	115	Patch	Abdominal pain	4/30/05 – ongoing[a]	unrelated	
	115	Patch	Nausea	5/8/05 – ongoing[a]	remote/unlikely	
	250	Patch	Dizziness	5/9/05 – ongoing	unrelated	
SPN-301-07	06-14-0002	NIX	Application site erythema	1/12/08 – 1/18/08	possibly	
	06-23-0002	NIX	Cellulitis	2/14/08 – 2/16/08	unrelated	
SPN-302-07	12-04-0004	NIX	Gastroenteritis viral	12/5/07 – 12/7/07	unrelated	

[a] Subject was diagnosed with pancreatic cancer and was lost to follow-up
Source: Sponsor's NDA Integrated Summary of Safety, 5.1.3, p. 64.

Study SPN-102-05
- Subject 115 (47 y/o female) experienced abdominal pain beginning April 30, 2005 and nausea beginning May 8, 2005. The subject was hospitalized and diagnosed with pancreatic cancer. Because the subject was lost to follow-up, both events were ongoing at the end of the study. This reviewer agrees with investigator assessment that abdominal pain was unrelated to test articles and nausea was remotely/unlikely related to test articles.
- Subject 250 (59 y/o male) experienced severe dizziness beginning (b) (6) and was admitted to the hospital for tests. Pertinent history included epilepsy. The event of dizziness was considered by the subject's doctor to be related to vision. The event was ongoing at the end of the study. This reviewer agrees with the Investigator assessment that the event of dizziness is unlikely to be related to the test articles.

Study SPN-301-07
-Subject 06-14-0002 (10y/o male) was a non-primary member of the household, was randomized to NIX, and applied the study medication twice. On Day 8 the subject presented with "slight erythema scalp", coded as application site erythema. This event occurred following the second treatment application. The event resolved without treatment or sequelae on Day 14, no further action was taken and the subject completed the study. This reviewer agrees with the assessment that this event was possibly related to NIX. The sponsor states that: "The investigator reported this as a serious AE despite the fact that it did not meet the regulatory definition of a serious event."
-Subject 06-23-0002 (5y/o female) was a non-primary member of the household, was randomized to NIX, and applied the study medication twice. On Day 14 the subject presented with "right cheek cellulitis", coded as cellulitis. The subject was hospitalized and treated with IV antibiotics. The event resolved on Day 16 with no sequelae. The subject did not have a day 21 visit. This reviewer agrees with the assessment that this event was unrelated to study medication.

Study SPN-302-07
-Subject 12-04-0004 (24 y/o female) was a non-primary member of the household, was randomized to NIX, and applied study medication once. The subject returned to the site for the Day 1 safety evaluation but did not return to the site for the Day 7 visit. It was reported by the subject's family that the subject was hospitalized (b) (6) with viral gastroenteritis (coded as infections and infestations, gastroenteritis viral). In the hospital the subject received medical treatment for hydration, pain, and nausea. The subject was released from the hospital (b) (6) and the event resolved without sequelae. The subject withdrew consent on December 7, 2007 and did not return for a follow-up study visit. The reason given for the withdrawal was poor weather conditions. This reviewer agrees with the assessment that this AE was unrelated to study medication.

7.3.3 Dropouts and/or Discontinuations

No subjects dropped out due to an adverse event *(evaluated as related)* in the 11 studies of the development program.

Dropouts:
Phase 1:
SPN-101-04: One subject was dropped because of, "…poor veins and inability to draw to draw blood samples for pharmacokinetic analysis."

SPN-102-05: Of 230 subjects enrolled, 200 completed the study. A total of 19 subjects withdrew voluntarily, mostly not returning for scheduled visits. A total of 5 subjects did

not complete due to protocol violations. A total of 6 subjects did not complete because of adverse events which included abdominal pain due to pancreatic cancer, twisted ankle, dizziness evaluated by subject's doctor as related to vision, sensitivity to skin marker, broken ankle, and fever.

Studies SPN-103-05 and SPN-106-06 had no dropouts.

SPN-107-07: Of 38 subjects enrolled, one subject failed to complete all phases of the study due to "the applicator being unable to confirm the randomization."

SPN-108-08: Of 58 subjects enrolled, 51 completed the study.
One withdrawal was listed as an adverse experience: "Subject had to use a medication which was an exclusionary medication, Dropped per P.I. AE#2." One subject requested to withdraw: "Subject started getting a bad cold and she just did not want to continue on study." Two subjects discontinued due to schedule conflicts. Two subjects did not show for scheduled study visits. One subject was dropped from study per Principal Investigator due to being in a car accident.

Phase 2:
SPN-201-05: Of 36 subjects randomized, one subject (2.0% spinosad) did not complete the study. This subject received one treatment then discontinued due to "car trouble."
SPN-202-06: Of 122 subjects enrolled, 120 completed all phases of the study. One subject withdrew due to a family emergency and one subject was dropped for refusing to return for scheduled study visits.
SPN-203-07: Of 24 subjects randomized, 23 completed the study. One subject withdrew consent. This subject discontinued the study because she was sent home from school due to school policy of no lice or nits.

Phase 3:
For additional detail see also section 6.1.3, Subject Disposition.

Study SPN-301-07:
Among subjects randomized, similar percentages completed the study, 54 (92%) Natrova with nit combing, 227 (93%), Natrova without nit combing, and 230 (90%) NIX. Across the 3 treatment arms, reasons for discontinuation from study showed similar patterns, however, a greater percentage of subjects in the NIX arm withdrew consent, 10 (4%) versus 1(2%) for Natrova with nit combing and 0 for Natrova without nit combing.

Study SPN-302-07:
Among subjects randomized, similar percentages completed the study, 58 (92%) Natrova with nit combing, 187 (92%), Natrova without nit combing, and 193 (90%) NIX. Across the 3 treatment arms, reasons for discontinuation from study showed similar

patterns, however, a greater percentage of subjects in the NIX arm withdrew consent, 10 (6%) versus 9 (4%) for Natrova with nit combing and 0 for Natrova without nit combing. Additionally, a greater percentage in the Natrova with nit combing arm 5 (8%) were lost to follow-up as compared to 5 (2.5%) in the Natrova without nit combing and the NIX arm 5 (2%).

7.3.4 Significant Adverse Events

Significant adverse events noted during the pivotal, Phase 3 trials included two pregnancies; details are shown in Table 35 below.

Table 35: Significant Adverse Events in Pivotal Trials

Study	Subject #	Treatment	Event	Dates	Relationship	
SPN-301-07	06-06-0003	NIX	Pregnancy	NA[a]	Unrelated	
SPN-302-07	09-40-0004	NIX	Pregnancy	12/20/07-1/15/08	Unrelated	

[a]The pregnancy was not recorded as an AE and onset and resolution dates were not provided
Source: Sponsor's NDA, Integrated Summary of Safety, 5.1.4, p. 65.

Study SPN-301-07
- Subject 06-06-0003 (29 y/o Hispanic female) entered the study on November 5, 2007 and reported no recently resolved or ongoing medical conditions. The subject was a non-primary member of the household and was randomized to NIX. On Day 14 the subject presented with live lice and reported she was 8 months pregnant. No urine pregnancy test was conducted at study entry or study exit. The subject left the study prior to being dispensed Rid. The subject subsequently reported delivery of a healthy infant.

Study SPN-302-07
- Subject 09-40-0004 (29 y/o Hispanic female) entered the study on November 28, 2007 and reported no recently resolved or ongoing medical conditions. The subject was a non-primary member of the household and was randomized to NIX. On Day 7 the subject presented with live lice and was dispensed a second course of treatment. At the Day 14 and 21 follow-up visits the subject was lice free and considered a treatment success. The subject had a negative urine pregnancy test upon entry; however, the pregnancy test was not done on the Day 21 (exit) visit, December 19, 2007. The subject did return to the site one day later for pregnancy testing, with a positive result. The subject had a non-complicated, elective, surgical abortion on January 15, 2008.

7.3.5 Submission Specific Primary Safety Concerns

(b) (4) is a mixture of factors, primarily Spinosyn factor A (b) (4)) and Spinosyn factor D (b) (4)). As assessed by the pharmacology/toxicology reviewer, spinosad causes neuronal excitation in insects. After periods of hyperexcitation, lice become paralyzed and die. (b) (4) therefore has the potential for neurological adverse events.

The excipient benzyl alcohol is present at a (b) (4) concentration. Benzyl alcohol is an antimicrobial preservative used in cosmetics, food, and pharmaceutical formulations including oral and parenteral preparations, the typical concentration being 1% v/v. Benzyl alcohol (b) (4) v/v solutions have some local anesthetic properties which are utilized in some parenterals, cough products, ophthalmic solutions, ointments, and aerosol sprays.[21] The Cosmetic Ingredient Review Expert Panel concluded that benzyl alcohol is safe for use in hair dyes at concentrations up to (b) (4).[22]
NDA 22-129 ULESFIA (benzyl alcohol) Lotion, 5% was approved April 9, 2009 containing 5% benzyl alcohol as the active. The indication is topical treatment of head lice infestation in patients 6 months and older. For ULESFIA, the most common adverse reactions (> 1% and more common than with placebo) are: ocular irritation, applicant site irritation, and application site anesthesia and hypoesthesia (from product labeling).

Benzyl alcohol used as preservative in saline flush solutions has been associated with 16 neonatal deaths. The deaths occurred in pre-term neonates weighing 2500 grams who had central intravascular catheters flushed periodically each day with bacteriostatic saline containing 9 mg/ml benzyl alcohol. Estimates of daily intake of benzyl alcohol ranged from 99 to 405 mg/kg/day.[23]

The clinical pattern referred to as the “gasping syndrome” is characterized by the deterioration of multiple organ systems and eventual death. The typical course included gradual neurologic deterioration, severe metabolic acidosis, gasping respiration, hematologic abnormalities, skin breakdown, hepatic and renal failure, hypotension, and cardiovascular collapse.[24] Other symptoms can include seizures and intracranial hemorrhages. Blood and urine of affected infants reveal high levels of benzyl alcohol or its metabolites.[25]

[21] Storey RA . Monograph: Benzyl Alcohol in Rowe RC, Shesky PJ, and Quinn ME . Editors: Pharmaceutical Excipients, London: Pharmaceutical Press.Electronic version, 2009.
[22] Nair B. Final Report on the Safety Assessment of Benzyl Alcohol, Benzoic Acid, and Sodium Benzoate. Int. Journal of Toxicology 2001;20(Suppl. 3):23-50.
[23] Neonatal Deaths Associated with Use of Benzyl Alcohol – United States: CDC; MMWR 1982; 31:290-291.
[24] Gershank J *et al*. The Gasping Syndrome and Benzyl Alcohol Poisoning. New England J Med 1982;307:1384-1388.
[25] Neonatal Deaths Associated with Use of Benzyl Alcohol – United States: CDC; Op.cit.

Delayed-type hypersensitivity reactions, i.e. allergic contact dermatitis, have been reported to benzyl alcohol as a preservative in antibiotic and antifungal creams, topical corticosteroids, and sclerosing agents.[26] Additionally, following parenteral administration of benzyl alcohol preserved products, contact dermatitis has been seen as well as more generalized allergic symptoms including nausea, fatigue, or angioedema.[27]

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

Phase 1:

1) SPN-101-4: This was a single treatment pharmacokinetic and tolerance study (spinosad 2%) in healthy adult subjects, with 23 subjects exposed (22 completed the study). Exposure consisted of one 10 minute application with a maximum amount of 30 ml of spinosad 2%. A total of two subjects experienced two adverse events. Subject # 113 reported cold symptoms that were considered by the investigator to be mild and unrelated to study drug. Subject 105 experienced a TSH value within normal limits at screening, then elevated on days 5 and 7, within normal limits at day 15, elevated at day 27, within normal limits day 41, and elevated at day 57. The investigator considered the fluctuating TSH results to represent a pre-existing sub-clinical hypothyroidism. The subject was referred to a physician for follow-up.

2) SPN-102-05: This was a cumulative irritation and contact sensitization study in which 227 subjects were divided into two groups: Group 1, including 34 subjects, who received topical applications of spinosad 2%, vehicle, SLS, and sodium chloride; Group 2, including 193 subjects, who received topical applications of spinosad 2.0% and vehicle. In Group 1 subjects received exposure to 22 applications of 0.2mL spinosad 2% and in Group 2 subjects received 10 applications of spinosad 2%. Duration of exposure per application was 24 to 72 hours. A total of 80 adverse events were experienced by 57 (25%) subjects. Of the 80 adverse events, 32 were considered mild, 37 considered moderate, and 11 severe. Severe events include urinary tract infection, dizziness (see subject # 250 below), tubal ligation, stomach flu, arthritis pain in leg, tooth extracted, genital area infection (fungus), increased high blood pressure, broken ankle, whiplash neck to waist, and abscess on thumb. These were all considered unrelated to test articles.

[26] Amado A and Jacob SE. Benzyl Alcohol Preserved Saline used to Dilute Injectables Poses a risk of Contact Dermatitis in Fragrance-Sensitive Patients [letter]. Dermatol Surg 2007;33:1396-1397.
[27] "Inactive" Ingredients in Pharmaceutical Products (RE5046); American Academy of Pediatrics, Pediatrics, Policy statement, Vol. 76, No. 4; October, 1985, p. 635-643.

- Subject 250 (59 y/o male) experienced severe dizziness beginning (b) (6) and was admitted to the hospital for tests. This event was also assessed as a SAE. Pertinent history included epilepsy. The event of dizziness was considered by the subject's doctor to be related to vision. The event was ongoing at the end of the study. The investigator assessed this event as unrelated to test articles and this reviewer agrees with this assessment.

A total 11 adverse events were considered remote/unlikely to be related, 2 were considered possibly related, and one was considered highly probably related. The possibly related adverse events were itching on the upper and lower arms of subject 304 and a fever reported by subject 392. These events resolved without need for medication. The highly probably related adverse event was a moderate bruise on the arm of subject 265. The bruise lasted for 17 days and resolved on its own.

3) SPN-103-05: This was a single treatment PK and tolerance study in pediatric subjects (ages 2 to 18 years) and having at least 3 live lice. A total of 14 subjects were enrolled into this study and all received approximately 30 mL of 2% spinosad applied topically on the scalp for 10 minutes. One adverse event was reported in subject #112 consisting of a fever assessed as mild in severity and unrelated to test article application since it occurred after the screening visit but resolved before product application.

4) SPN-106-06: This was a single treatment PK and tolerance study in pediatric subjects (6 to 24 months of age) in good general health (no head lice). A total of 8 subjects received approximately 30 mL of (b) (4) (to-be-marketed formulation) applied topically to the scalp for 10 minutes. Two adverse events were reported, nasal congestion and low grade fever, both assessed as mild and unrelated to product application.

5) SPN-107-07: This was a study performed to evaluate the phototoxic potential of (b) (4) (to-be-marketed formulation) in which 38 subjects received exposure to a patch containing 0.2mL of product for one 24 hour application. Two adverse events were experienced by two subjects. Subject # 16 experienced a sore throat rated as of moderate severity and resolving without sequelae. Subject #22 experienced a headache for one day, rated as moderate in severity, and resolving without sequelae. Both of these adverse events were not considered related to the test articles by the principal investigator.

6) SPN-108-08: This was a study to evaluate the photoallergic potential of (b) (4) (to-be-marketed formulation) in which 58 healthy volunteers were exposed to patches containing 0.2mL of product for seven 24 hour applications. A total of 35 adverse events were reported by 20 subjects during the course of the study. Of the 35 adverse events; 14 were considered mild, 20 were considered moderate, and 1 was considered severe by the Principal Investigator. There were no serious adverse events. The

severe adverse event was reported by subject # 27 as pain from a herniated disc (subject was in car accident). The moderate adverse events were experienced by 11 subjects as follows: knee pain, headache / bladder infection, chest congestion, headache / runny nose / coughing, earache, nasal congestion, tonsillitis, vomiting, menstrual cramps, coughing / fever / bronchitis, and headache / coughing / runny nose. The mild adverse events were experienced by 10 subjects as follows: chest congestion, nasal congestion, headache, aches in shoulder, weak (body aches), nasal congestion/coughing, sore throat/coughing/nasal congestion, nasal congestion, nausea, and runny nose/sore throat. The Principal Investigator considered all of the adverse events not related to test articles.

Phase 2:

1) SPN-201-05: This was a dose-ranging study (subjects having at least 3 live lice) wherein 8 subjects were exposed to 0.5% spinosad, 9 to 1.0% spinosad (minor formulation differences from (b) (4), 10 to 2.0% spinosad and 9 to vehicle. Treatments were applied by investigational site personnel. Treatment time was 10 minutes and two treatments were applied except for one subject in the 2.0% spinosad group who received one treatment. Approximately 85 grams of product were applied per subject at each application. The sponsor reports that 2 subjects (one each in the 1.0% and 2.0% spinosad groups) had treatment-emergent erythema and one subject (0.5% spinosad group) had treatment-emergent erythema and edema. These events are suggestive of contact dermatitis. The sponsor then goes on to report that two subjects (0.5% spinosad group) experienced two adverse events. One subject reported mild fever which was assessed as not related to study medication. Another subject reported mild burning sensation in the left eye. The sponsor reports, for the burning sensation, the product was washed out of the left eye with a towel and the sensation lasted about two minutes. In the study report under section 12.2.2 it is stated that this event was not related to study medication. However under section 12.2.1 of the study report and in the ISS (p. 48) it is stated that the relationship to study medication was not reported. This reviewer's opinion is that the description of the event is suggestive of a relationship between use of the product and mild burning sensation in the eye.

2) SPN-202-06: This was a dose-ranging study (subjects having at least 3 live lice) wherein 40 subjects were exposed to spinosad 0.5%, 39 were exposed to spinosad 1.0% (minor formulation differences from (b) (4) and 43 were exposed to vehicle. Treatments were applied by investigational site personnel. Treatment time was 10 minutes and one treatment was applied. Maximum treatment was up to 120 mL of product. A total of 23 adverse events, shown below, were experienced by 11 (9%) subjects during the study.

1.0 % spinosad:

Subject 201 (F 33yo) increase in scalp irritation: mild - possibly related
Subject 513 (F 6yo) abdominal cramps, nausea, vomiting, diarrhea, dizziness: all assessed as mild and unrelated

0.5% spinosad:
Subject 111 (F 35) vomiting (single episode): mild – possibly related
Subject 301 (F 7) concussion: moderate – unrelated, facial abrasions: mild – unrelated
Subject 313 (F 4) noticeable erythema with slight infiltration: moderate - related
Subject 330 (F 13) stomach ache: mild – unrelated

Vehicle:
Subject 206 (F 6) increased scalp irritation: moderate – unrelated
Subject 306 (F 7) noticeable erythema with slight infiltration (nape of neck):Mild – related
Subject 512 (F 2) nausea, vomiting, diarrhea, fever, dizziness: mild – unrelated
Subject 515 (F 25) nausea, vomiting, diarrhea, dizziness: mild – unrelated
Subject 537 (F 5) productive cough: mild – unrelated

Examined across the 3 treatment groups, 4 adverse events were considered possibly related or definitely related to test article application. These included a case of increase in scalp irritation in the 1% group and 2 cases of noticeable erythema with slight infiltration, one in the .5% group and one in the vehicle group. A single episode of vomiting in a 35 y/o female (subject 111 exposed to 0.5% spinosad) was assessed as possibly related. No actions were taken for this event and the episode resolved without sequelae.

The case of increased scalp irritation in subject 206 (vehicle), assessed as unrelated, had associated comments noting that itching did not increase after treatment; however the subject still had live lice which led to continuous scratching.

3) SPN-203-07: This was an actual use pilot study (subjects having head lice infestation of at least mild severity: defined as presence vs absence of head lice) in 24 subjects ages 6 months and older. A total of 11 (of these 10 had 1 treatment and one had two treatments) subjects were exposed to 1.0% spinosad (in ISS described as (b) (4) however minor formulation difference). A total of 12 subjects were exposed to NIX (one had one treatment and 11 had two treatments) and included in the safety population. (One Nix subject who discontinued from the study was excluded from the ITT and safety populations because of lack of post-treatment safety and efficacy evaluations.) Treatments were applied by subject or caregiver at home according to instructions for use. Maximum amount applied was planned as 240mL and treatment time was planned to be 10 minutes.

Spinosad 1.0% AEs:
One subject had fever and strep throat: mild, assessed as not related to study medication. The fever and strep throat were treated with drug therapy.

NIX AEs:
One subject had dehydration: severe, assessed as not related to study medication. This subject went to the hospital where she received water and Gatorade and later followed up with her pediatrician.

Phase 3:
In the pivotal trials, Natrova arms (with/without nit combing), 46 subjects (8.3%) reported 58 adverse events. In the NIX arms 77 subjects (16.8%) reported 91 adverse events. Three SAEs were reported, discussed in section 7.3.2, in the NIX arms. Among the remaining adverse events, severity was assessed as either mild or moderate with no severe events being reported.

In the pivotal trials, across study arms the most common adverse event reported was application site erythema, occurring in 3.1% (17/552) of subjects exposed to Natrova and in 6.8% (31/457) of subjects exposed to NIX. The second most common adverse event across study arms was ocular hyperemia, occurring in 2.2 % (12/552) of those exposed to Natrova and in 3.3% (15/457) of those exposed to NIX. The third most common adverse event across study arms was application site irritation, occurring in .9% (5/552) of those exposed to Natrova and in 1.5% (7/457) of those exposed to NIX.

Table 36: Adverse Events Pivotal Trials (Incidence ≥ 1% in at Least One Tx Group)

Adverse Event[a]	Natrova With/Without Nit combing N=552	Nix N=457
Eye disorders	12 (2.2%)	20 (4.4%)
Ocular hyperemia	12 (2.2%)	15 (3.3%)
General disorders and administration site conditions	25 (4.5%)	41 (9.0%)
Application site erythema	17 (3.1%)	31 (6.8%)
Application site irritation	5 (0.9%)	7 (1.5%)
Infections and infestations	5 (0.5%)	10 (2.2%)
Skin and subcutaneous tissue disorders	3 (0.5%)	5 (1.1%)

[a] Counts reflect numbers of subjects reporting one or more adverse events classified to MedDRA system organ class and preferred term. Subjects are counted only once at each level of summarization (system organ class or preferred term.
Source: Sponsor's NDA Submission, Integrated Summary of Safety, adapted from Table 12-12, p.138.

Other clinically pertinent, less common adverse reactions (less than 1% but more than 0.1%) include; application site dryness, application site exfoliation, alopecia, dry skin, and erythema. Please see Table 37 for a summary of adverse events

Table 37: Summary of Adverse Events (Pivotal Trials: Safety Population)

Adverse Event* *MedDRA Preferred Term*	**Natrova with/without nit combing**	**NIX**	
	N=552 (%)	N=457 (%)	
Ear pain	1 (0.2)	1 (0.2)	
Eye irritation	0	4 (**0.9**)†	
Eye pruritus	0	1 (**0.2**)	
Lacrimation increased	0	1 (**0.2**)	
Occular hyperemia	12 (2)	15 (**3**)	
Diarrhea	1 (0.2)	2 (**0.4**)	
Gastroesophageal reflux disease	1 (0.2)	0	
Nausea	0	1 (**0.2**)	
Stomach discomfort	1 (**0.2**)	0	
Vomiting	1 (**0.2**)	0	
Application site discoloration	0	1 (**0.2**)	
Application site dryness	1 (**0.2**)	0	
Application site erythema	17 (3)	31 (**7**)	
Application site exfoliation	1 (**0.2**)	0	
Application site irritation	5 (0.9)	7 (**2**)	
Application site scab	0	1 (**0.2**)	
Pyrexia	1 (0.2)	1 (0.2)	
Cellulitis	0	1 (**0.2**)	
Ear infection	0	1 (**0.2**)	
Gastroenteritis viral	0	1 (**0.2**)	
Influenza	1 (**0.2**)	0	
Nasopharyngitis	2 (0.4)	2 (0.4)	
Otitis media	1 (0.2)	0	
Pharyngitis streptococcal	0	1 (**0.2**)	
Upper respiratory tract infection	1 (0.2)	4 (**0.9**)	
Skin laceration	1 (**0.2**)	0	
Fibromyalgia	0	1 (**0.2**)	
Dizziness	1 (**0.2**)	0	
Headache	1 (0.2)	1 (0.2)	
Syncope	0	1 (**0.2**)	
Chronic Obstructive Pulmonary Dz	0	2 (**0.4**)	
Cough	1 (0.2)	1 (0.2)	
Pharyngolaryngial pain	1 (**0.2**)	0	
Alopecia	1 (**0.2**)	0	
Dry skin	1 (0.2)	1 (0.2)	
Erythema	1 (0.2)	4 (**0.9**)	

* Counts reflect number of subjects reporting one or more adverse events classified to MedDRA (Version 10.1) preferred term. Subjects are counted only once at each level of summarization (for this table, preferred term).

† Figures are in bold where percentage exceeds that of other treatment group.

Source: Sponsor's NDA, Clinical Study Reports for studies SPN-301-7 and 302-07, adapted from Tables 14.3.1.2.2, pp. 160-161 and 162-163, respectively.

Active Assessments:
Scalp Irritation and Ocular Irritation:

Cutaneous safety was also monitored by evaluation of scalp irritation (Phases 1, 2, 3) and ocular irritation (Phase 3). In Phase 1 studies, clinically significant scalp irritation was not observed. In Phase 2, formal scalp evaluations were performed in study SPN-202-06 and no statistical differences in scalp irritation were observed between the treatment groups, spinosad 0.5%, spinosad 1.0%, or vehicle.

Phase 3:

In the pivotal Phase 3 trials the scale shown in Table 38 was used to evaluate both scalp and ocular irritation.

Table 38: Irritation Evaluation Scale (Scalp and Ocular)

Score	Descriptor
0	No sign of irritation
1	Slight erythema
2	Noticeable erythema with slight infiltration
3	Erythema with marked edema
4	Erythema with edema and blistering

Source: Sponsor's NDA, Integrated Summary of Safety, Table 7.3-1, p. 90.

In the Phase 3 pivotal trials, as shown in Table 39, mean scalp irritation scores for the Natrova treatment group declined through the course of the study and were generally lower than those for the NIX treatment group.

Table 39: Summary of Scalp Irritation

	Score	0	1	2	3	4
Treatment	N					
Day 0						
Natrova	552	394 (71%)*	106 (19%)	51 (9%)	1 (0.2%)	0
Nix	457	316 (69%)	98 (21%)	41(9%)	1 (0.2%)	1 (0.2%)
Day 1						
Natrova	549	412 (75%)	106 (19%)	31 (6%)	0	0
Nix	454	351 (77%)	73 (16%)	29 (6%)	1 (0.2%)	0
Day 7						
Natrova	541	438 (81%)	89 (16%)	14 (3%)	0	0
Nix	436	337 (77%)	80 (18%)	18 (4%)	1 (0.2%)	0

	Score	0	1	2	3	4
Day 8						
Natrova	151	134 (89%)	12 (8%)	5 (3%)	0	0
Nix	285	228 (80%)	48 (17%)	9 (3%)	0	0
Day 14						
Natrova	527	482 (92%)	41 (8%)	4 (0.8%)	0	0
Nix	426	367 (86%)	56 (13%)	3 (0.7%)	0	0
Day 21						
Natrova	105	101 (96%)	4 (4%)	0	0	0
Nix	141	131 (93%)	10 (7%)	0	0	0

* Percentages rounded by reviewer
Source: Sponsor's NDA, Integrated Summary of Safety, adapted from Table 12.5, p.107.

As shown in Table 40, with respect to ocular irritation, few subjects in both Natrova and NIX treatment groups exhibited signs of irritation at either Day 0 or Day 8, following treatment.

Table 40: Summary of Ocular Irritation

	Score	0	1	2	3	4
Treatment	N					
Day 1						
Natrova	549	541 (98%)*	8(2%)	0	0	0
Nix	454	439 (97%)	14(3%)	1(0.2%)	0	0
Day 8						
Natrova	151	145 (96%)	6 (4%)	0	0	0
Nix	285	277 (97%)	7 (3%)	1 (0.4%)	0	0

* Percentages rounded by reviewer
Source: Sponsor's NDA, Integrated Summary of Safety, adapted from Table 12.6, p.109.

In the pivotal trials, 14 subjects in the Natrova treatment group experienced ocular irritation. For 11 of these subjects it is explicitly stated in listing 16.2.7.3 that the event resolved without sequelae. In one case (SPN 301; subject 6-01-0001) the outcome is listed as unknown in listing 16.2.7.3. This subject had an assessment of ocular irritation at Day 1 with a finding of slight erythema. This subject withdrew from the study, listed as lost to follow-up. A narrative provided by the sponsor indicates; however, that at the time of study discontinuation the reported AE was not ongoing.

In trial SPN-302-07, two subjects (09-02-0002 and 09-03-0001) were identified as having an evaluation for ocular irritation at Day 1 with a finding of slight erythema. Both

subjects did have scalp evaluations at day 14. Neither of these subjects are listed (16.2.7.3) as having had adverse events. In response to an information request, the sponsor stated (7/15/09) that for both of these subjects the irritation did resolve without sequelae. The sponsor also clarified that only if eye irritation was greater than mild (a score greater than 1 on the irritation evaluations scale) was it recorded as an adverse event, per protocol flow chart (section 9.5.1 of protocol).

7.4.2 Laboratory Findings

Phase 1:
Clinical laboratory evaluations were performed in four of the six Phase 1 studies: (SPN-101-04, SPN-102-05, SPN-103-05, and SPN-106-06). In study SPN-102-05, laboratory evaluations were performed only upon screening to confirm eligibility. This study will not be discussed further.

SPN-101-04: This was a single treatment PK and tolerance study (spinosad 2%) in healthy adult subjects, with 22 completing the study. Laboratory evaluations included serum chemistry, hematology, and urinalysis at screening, 48-hours post-treatment (day 3), and at day 7. Thyroid function tests were also performed at screening, days 3, 5 and 7. Laboratory value changes considered clinically significant were noted in subject # 105 (25 y/o female), who had a TSH within normal limits at screening, elevated on days 5 and 7, within normal limits day 15, above normal day 27, within normal day 41, and then above normal day 57. The investigators considered these fluctuating TSH values consistent with a pre-existing sub-clinical hypothyroidism. The subject was referred to a physician for follow-up.

SPN-103-05: This was a single treatment PK and tolerance study (spinosad 2%) in pediatric subjects (ages 2 to 18 years) having at least 3 live lice. A total of 14 subjects completed the study. Laboratory evaluations included serum chemistry, hematology, urinalysis, and thyroid function tests pre-treatment and post-treatment (Day 7). Table 41 summarizes the shifts from normal at pre-treatment to either high or low at Day 7.

Table 41: Shifts in Laboratory Test Results Study SPN-103-05

Type of Shift	Laboratory Test	Frequency	Subject Number
Normal Screen, High day 7	Absolute Eosinophils	1	102
	ALT	1	102
	Triglycerides	1	102
	Cholesterol, Total	2	103, 114
	MCV	1	114
	Total T3	1	103
	Glucose	1	101

Type of Shift	Laboratory Test	Frequency	Subject Number
Normal Screen, Low Day 7	Urea Nitrogen (BUN)	1	110
	TSH	1	108
	Absolute Lymphocytes	1	109
	Hematocrit	1	104
	White Blood Cell Count	2	109, 113

Source: Sponsor's NDA Submission, Clinical Study Report for Study SPN-103-05, adapted from Table 12.4.2.2, p.138. Changes to this table were made, by the reviewer, based on Table 14.2.6 and Post-Text Listing 16.4.17 from the Clinical Study Report for Study SPN-103-05.

Note that no more than two subjects had changes in any individual laboratory value. Changes were considered not clinically significant except for the total T3 value in subject 103 on Day 7. Subject 103 was a ten year old female who had a total T3 of 206 prior to treatment (reference range 123-211). On Day 7 the total T3 was 246. When repeated four days later, the total T3 value was 225 which was not considered clinically significant.

SPN-106-06: This was a single treatment PK and tolerance study (b) (4) 0.9%) in pediatric subjects (6 to 24 months of age) in good general health (no head lice). A total of 8 subjects completed the study. Laboratory evaluations performed included full CBC and serum chemistry at screening visit and at the conclusion of Day 1 (4 hours post-treatment). The clinical study report for SPN-106-06 states that the normal ranges for each of the laboratory parameters were not appropriately adjusted by the clinical lab for the age of the pediatric population in this study. Therefore some values were flagged as being out of the normal range. According to the study report, the Investigator reviewed the results and determined that the reported values were within range for all subjects. Copies of these laboratory reports with investigator annotations are provided in the clinical study report for SPN-106-06 and have been examined by this reviewer. Significant laboratory safety trends are not seen for study SPN-106-06.

Phase 2:
No clinical laboratory evaluations were performed in the Phase 2 studies.

Phase 3:
Regulatory background regarding lab studies:

- At the End of Phase 2 meeting of October 31, 2006 the Division stated that, "…laboratory data from subjects infested with head lice with non-intact skin will be needed for all pediatric age groups."
- In the SPA letter dated 7/31/2007 the Division stated:

> Safety laboratory data will be collected from all subjects with head lice with non-intact skin. This will be done for all qualifying pediatric age groups six months of age and above. This will be done with a subset of subjects. Specifically, two of the six sites for each study will conduct these safety laboratory data studies.

> Further, the first 25 qualifying subjects per designated site will be evaluated for safety laboratory data.

- In protocols SPN-301-07, Amendment Number 2, 10/18/07, serial # 50 and SPN-302-07, Amendment Number 2, 10/18/07, serial # 51, the sponsor stated:

> Two study sites will be chosen to collect blood specimens from pediatric subjects with nonintact scalps for safety labs. These blood collections will be done at Day 0, prior to treatment and at Day 14. Each site will collect these blood samples from the first 25 qualifying pediatric subjects. A non-intact scalp is defined as: 1) raised welts or inflammation indicating a recent lice "bite" (similar to a mosquito bite); and/or 2) evidence of broken skin resulting from the discomfort and scratching of the scalp due to the presence of lice.
>
> Safety labs will include:
> Full CBC: White blood cell (WBC), Red blood cell (RBC), platelet count, hemoglobin, hematocrit and differential counts.
> Serum Chemistry: blood urea nitrogen, glucose, creatinine, sodium, potassium, chloride, aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase and total bilirubin

In a review dated 1/18/08, the clinical reviewer stated that this was acceptable in terms of the SPA agreement.

In the current NDA submission (ISS), the applicant states that during the Investigator meeting on 9/11/2007 the sites chosen to perform safety laboratory studies were instructed that a non-intact scalp was equivalent to a scalp assessment score of 2 or greater (noticeable erythema with slight infiltration). The applicant estimated that each study would complete approximately 50 pediatric safety laboratory evaluations.

The estimated total of 100 pediatric safety laboratory evaluations was not achieved. The applicant states that the original designated draw sites for SPN-301-07 were Site 01 (Nolan) and Site 02 (Muhar); for SPN-302-07 the sites were Site 07 (Moore) and Site 08 (Reyes-Acuna). For both studies subject enrollment began 9/21-25/07. As of early November 2007, the applicant states that very few subjects had been enrolled with a scalp irritation score of 2.

On 11/26/07, to increase the opportunity for qualifying blood draw subjects, the contract research organization (Concentrics Research), informed the 4 blood draw sites that the scalp assessment score for eligibility was lowered from 2 (noticeable erythema with slight infiltration) to 1 (slight erythema). At this time site 01 had not enrolled any subjects and site 02 was finding very few scalp assessment scores greater than 0. Site 07 had completed the majority of their enrollment without finding subjects eligible for safety laboratory assessment and site 08 was finding few scalp assessment scores greater than 0.

On 12/11/07, two sites were added to SPN-301-07 and designated as pediatric safety laboratory sites, Site 13 (Ward) and Site 14 (Lewine). On 1/3/08 Site 01 (Nolan) was closed due to lack of enrollment.

On 1/10/08, two of the existing sites in SPN-302-07 were added as blood draw sites, Site 11 (Gabrielson) and Site 12 (Thomas).

On 1/22/08, a protocol amendment was approved that deleted the requirement for non-intact scalp for blood draws thus allowing all enrolled pediatric subjects to have safety laboratory evaluations. By the time this amendment became effective, sites 07 and 08 (Study SPN-302-07) had completed enrollment.

This reviewer finds that a total of 56 subjects had partial or complete laboratory testing performed (53 in SPN-301-07 and 3 in SPN-302-07). This number included 30 subjects in the NatrOVA treatment group and 26 in the NIX treatment group. The numbers were confirmed by the sponsor's response (7/15/09) to an information request.

For both SPN-301-07 and 302-07, Laboratory assessments were conducted on Days 0 and 14; laboratory tests included hematology (WBC, RBC, platelet, hemoglobin, hematocrit, basophils, neutrophils, eosinophils, lymphocytes, and monocytes) and serum chemistry (BUN, glucose, creatinine, sodium, potassium, chloride, AST, ALT, ALP, and total bilirubin). Reference ranges used were consistent with those used in general clinical practice.

For study SPN-301-07, in the Natrova group, 12 subjects had laboratory assessments performed at screening, but not at Day 14, and 3 subjects had laboratory assessments only at Day 14. The Natrova group in this study included 15 subjects having laboratory assessments at Day 0 and at Day 14 (ages 4, 5, 5, 6, 6, 6, 8, 9, 9, 10, 10, 10, 11, 12, 12, & 15). Amongst these subjects, the applicant used the National Cancer Institute Common Technology Criteria for Adverse Events, Grade 2 as the threshold for concern. This reviewer also examined the laboratory findings for this study and did not find clinically significant outliers.

Using the threshold for concern, 2 subjects were identified:
1) Subject 13-05-0001 (6 y/o female in the Natrova without nit combing group) had neutrophils of 1.4 x 10^3/mm^3 on Day 14 (laboratory reference range: 1.5 to 8.5 x 10^3/mm^3 and Grade 2 threshold: 1.0 to 1.5 x 10^3/mm^3). At Day 0 the subject had neutrophils of 4.6 x 10^3/mm^3. The Investigator did not consider the findings clinically significant. This subject showed no other hematology values outside of reference range either at Day 0 or at Day 14.

2) Subject 13-12-0003 (12 y/o female in the Natrova without nit combing group) had ALT of 56 U/L at Day 0 (laboratory reference range 5 to 20 U/L). The Grade 2 threshold

was greater than 2.5 x the upper limit of normal to 5 x the upper limit of normal. On Day 14 this subject's ALT was 43 U/L, which no longer met the Grade 2 threshold for concern. The Investigator did not consider the Day 0 ALT to be clinically significant.

Also for study SPN-301-07, in the NIX group, 7 subjects had laboratory assessments performed at screening, but not at Day 14, and 5 subjects had laboratory assessments only at Day 14. The NIX group in this study included 11 subjects having laboratory assessments at Day 0 and at Day 14 (ages 4, 7, 8, 8, 9, 10, 10, 10, 11, 11 & 16). Amongst these subjects, the applicant used the National Cancer Institute Common Technology Criteria for Adverse Events, Grade 2 as the threshold for concern and no subjects were identified as having achieved this threshold.

For study SPN-302-07, only 3 subjects (ages 5, 7 & 7) had laboratory assessments. All 3 were randomized to the NIX treatment group and had laboratory assessments at Day 0 and at Day 14. Amongst these subjects, the applicant used the National Cancer Institute Common Technology Criteria for Adverse Events, Grade 2 as the threshold for concern and no subjects were identified as having achieved this threshold.

For examination of laboratory values, the applicant constructed shift tables, comparing Day 0 with Day 14 values, for the 25 laboratory parameters measured. Subjects included are 15 in the Natrova treatment group (one of these having missing chemistry values at Day 14) and 14 in the NIX treatment group (for NIX the subjects are pooled across the two studies SPN-301-07 and SPN-302-07).

For 15 laboratory parameters either no shifts were seen from Day 0 to Day 14 (13/15 subjects) or shifts to improved status (e.g. ANL Day 0 to WNL Day 14) were seen (2/15 subjects). For 10 laboratory parameters, shifts were seen to a more abnormal status in some subjects. Table 42, following, shows shift tables for those parameters wherein a more abnormal status was seen at Day 14 as compared with Day 0.

Table 42: Laboratory Value Shift Tables Pivotal Studies

		Natrova				NIX		
		Day 14				Day 14		
	Day 0	**BNL***	**WNL†**	**ANL‡**		**BNL**	**WNL**	**ANL**
ALT (U/L)	BNL	0	0	0		0	0	0
	WNL	0	10	***1*****		0	12	0
	ANL	0	2	1		0	0	2
Bilirubin, total (mg/dl)	BNL	3	2	0		4	3	0
	WNL	***2***	7	0		0	7	0
	ANL	0	0	0		0	0	0
BUN (mg/dl)	BNL	0	0	0		0	0	0
	WNL	0	8	***4***		0	10	***1***
	ANL	0	0	2		0	2	1
Creatinine (mg/dl)	BNL	7	2	0		7	3	0
	WNL	***2***	3	0		0	4	0
	ANL	0	0	0		0	0	0
Glucose (mg/dl)	BNL	0	0	0		0	0	0
	WNL	0	12	***1***		0	14	0
	ANL	0	1	0		0	0	0
Hematocrit (%)	BNL	0	0	0		0	0	0
	WNL	0	14	***1***		0	14	0
	ANL	0	0	0		0	0	0
Lymphocytes ($10^3/mm^3$)	BNL	0	0	0		0	0	0
	WNL	***1***	14	0		0	14	0
	ANL	0	0	0		0	0	0
Neutrophils, Total ($10^3/mm^3$)	BNL	0	0	0		0	0	0
	WNL	***1***	12	***1***		0	14	0
	ANL	0	0	1		0	0	0
Platelets ($10^3/mm^3$)	BNL	0	0	0		0	0	0
	WNL	0	13	***2***		0	12	0
	ANL	0	0	0		0	1	1
White Blood Cells ($10^3/mm^3$)	BNL	0	1	0		0	0	0
	WNL	***1***	11	***2***		0	14	0
	ANL	0	0	0		0	0	0

BNL* = below normal lower limit; WNL† = within normal limits; ANL‡ = above normal upper limit

** Values in bold and italic are those shifting to more abnormal status.
Source: Sponsor's NDA Submission, Integrated Summary of Safety, adapted from Table 6.3-2, pp.76-77. Changes to this table were made, by the reviewer, based on Table 12-16, Integrated Summary of Safety, pp. 148-152.

Examination of Table 42 reveals more changes to abnormal status in those subjects treated with Natrova; however the distribution amongst the laboratory values appears generally random. Shifts outside of normal range, as examined by this reviewer are generally of small magnitude. One value, BUN showed 4 subjects in the Natrova group having shifts from WNL to ANL going from Day 0 to Day 14, while one NIX subject experienced a shift from WNL to ANL. As shown in Table 43, the values seen in these shifts were not extreme, all being below 20 mg/dL.

Table 43: Values (BUN and Creatinine) for Subjects Shifting WNL to ANL

Subject	**Age/Sex**	**Day 0**		**Day 14**		**Ref. range (**mg/dL)	
Natrova		BUN mg/dL	Creat mg/dL	BUN	Creat	BUN	Creat
14-01-0004	10/F	13.4	.44 L	18.8 H	.50 L	5-16	.6-1.0
13-05-0001	6/F	11.5	.44 L	16.2 H	.52	3.9-14	.5-0.8
13-10-0002	18/F	13.4	.57	19.0 H	.66	3.9-16	.5-.9
14-09-0001	6/F	10.4	.38 L	15.1 H	.41 L	3.9-14	.5-.8
Nix							
07-08-0001	7/F	15.1	.49 L	16.2 H	.64	3.9-16	.5-.9

Source: Sponsor's NDA, Clinical Study report SPN-301-07, Listing 16.2.8.2, pp. 2440-2498.

In the opinion of this reviewer, notable trends or safety signals are not seen in the laboratory data gathered by the applicant. Although the small numbers of subjects tested renders this conclusion less definitive, the conclusion is supported by the lack of a clinically significant laboratory signal in study SPN-103-05, a PK study in subjects ages 2 to 18 years and having at least 3 live lice at study entry.

7.4.3 Vital Signs

Vital signs (pulse, blood pressure, temperature) were measured in studies SPN-101-04, 102-05, 103-05, and 106-06. Clinically significant changes in vital signs were not seen.

No vital signs were measured in Phase 2 or Phase 3 studies.

7.4.4 Electrocardiograms (ECGs)

ECGs were performed only in studies SPN-101-04 and 102-05. In SPN 101-04, ECGs were performed upon all subjects, healthy adult volunteers, at entry and exit. One subject had an abnormal ECG upon entry however all subjects had normal ECGs upon exit. In SPN-102-05, ECGs were performed only at entry on study subjects, healthy

adult volunteers. The sponsor reports that clinically significant abnormalities were not seen.

A thorough QT/QTc study was not required due to the fact that in PK studies systemic absorption was not detected. Please see section 4.4.2.

7.4.5 Special Safety Studies/Clinical Trials

Phase 1 Dermal Safety Studies

A total of 3 special safety studies were performed, one performed with spinosad 2% and two with the to-be-marketed formulation. These included a contact irritancy and contact allergy study SPN-102-05, a contact photoirritancy study SPN-107-07, and a contact photoallergy study SPN-108-08.

Study SPN-102-05: "A Combined Skin Irritation and Sensitization Study of ParaPro Spinosad Topical Crème Rinse (2%) and ParaPro Placebo Crème Rinse (Drug Free) in Healthy Adult Subjects"

The purpose of this study was to determine the irritation and contact sensitization potential of repeated applications of spinosad 2% and vehicle versus a positive and negative control in healthy adult human subjects. The study was performed in compliance with Good Clinical Practice, April 26, 2005 to June 29, 2005.

This was a single-center, evaluator-blinded, intra-individual randomized, vehicle-controlled trial. A total of 230 healthy adult subjects were enrolled including, 35 in group 1 and 195 subjects in group 2. Of 227 subjects treated, 160 (70%) were female and 67 (30%) were male. Subjects were 18 to 65 years old. Female subjects were ineligible if they were pregnant or nursing.

Test articles included spinosad 2%, spinosad vehicle, 0.1% aqueous sodium lauryl sulfate (positive irritant control), and 0.9% aqueous sodium chloride (negative control).

Test articles were applied to a non-woven cotton pad (0.2 ml). Please see Table 44, following:

Table 44: Group Assignment and Treatment (Study SPN-102-05)

Induction Phase			
	Test Product	Patch type	Quantity per Patch
Group 1	ParaPro Spinosad Cream Rinse 2%	Semi-occlusive*	0.2 ml
	ParaPro Vehicle Cream Rinse	Semi-occlusive	0.2 ml
	Positive Control (0.1% SLS)	Occlusive†	0.2 ml
	Negative Control (0.9%) sodium chloride	Occlusive	0.2 ml
Group 2	ParaPro Spinosad Cream Rinse 2%	Semi-occlusive	0.2 ml
	Negative Control (0.9%) sodium chloride	Semi-occlusive	0.2 ml
Rest Phase Group 1 and 2: no product application			
Challenge Phase			
All Subjects	ParaPro Spinosad Cream Rinse 2%	Semi-occlusive	0.2 ml
	Negative Control (0.9%) sodium chloride	Semi-occlusive	0.2 ml

*Semi-occlusive: a nonwoven cotton pad (Webril®) held to the skin on all sides by a strip of hypoallergenic tape (Micropore™)
†Occlusive: a nonwoven cotton pad (Webril®) held to the skin on all sides by a strip of hypoallergenic tape (Blenderm™)
Source: Sponsor's NDA Submission, Clinical Study Report for Study SPN-102-05, 16.1.1, Table 2, p. 63.

The sponsor notes that (b) (4) is designed for a 10-minute open application followed by a rinse off procedure. Thus the 2% spinosad test article was tested under semi-occlusive patching conditions.

Subjects in Group 1 received 21 induction applications (24 ± 1 hr) once daily by site personnel Day 2 through 22. Patches were applied to subject's backs according to a randomization scheme.

Subjects in Group 2 received nine induction applications by site personnel, three times a week (48± 2 hours Monday and Wednesday and 72 ± 4 hours on Fridays).

Skin assessments for irritation were done at least 15 minutes after removal. Skin assessments were also done immediately prior to patch reapplication.

(Each test article was repeatedly applied to the same site unless a strong reaction was exhibited. Test articles that exhibited a strong reaction were moved to an adjacent site twice and then discontinued if a third strong reaction developed.)

For both groups, a rest phase lasted from 13 to 17 days. This was followed by the challenge phase wherein both groups received one 48 hour application of the 2% test article to naïve sites. Skin reactions were evaluated at least 15 minutes, and at 24 ± 1 hr, 48 ± 2 hrs, and at 72 ± 4 hours after patch removal.

For Group 1, irritation during induction was measured using the Berger and Bowman scoring scale. This scale is given as an example in the FDA Guidance cited by the applicant.[28] The categories used appear to be clinically distinct.

Irritation - numeric grades:
0 No evidence of irritation
1 Minimal erythema, barely perceptible
2 Definite erythema, readily visible; or minimal edema; or minimal papular response
3 Erythema and papules
4 Definite edema
5 Erythema, edema and papules
6 Vesicular eruption
7 Strong reaction spreading beyond the test site

Irritation – letter grades
A Slight glazed appearance
B Marked glazing
C Glazing with peeling and cracking
F Glazing with fissures
G Film of dried serous exudate covering all or portion of the patch site
H Small petechial erosions and/or scabs

During the challenge phase for Group 1 and for both the induction and challenge phase for Group 2 a scale developed by Hill Top Research was used to assess skin sensitization:

Skin Inflammatory Responses - Numeric grades:
0 No visible reaction and/or erythema
+ Slight, confluent or patchy erythema
1 Mild reaction macular erythema (faint, but definite pink)
2 Moderate reaction - macular erythema (definite redness, similar to a sunburn)
3 Strong to severe reaction - macular erythema (very intense redness)

[28] Skin Irritation and Sensitization Testing of Generic Transdermal Drug Products. U.S. Department of Health and Human Services, Food and Drug Administration, CDER, December 1999. A subsequent Draft Guidance on Lidocaine (May 2007) states that the prior Guidance has been withdrawn and is currently under revision.

Skin Reaction – Letter Grades

E Edema – swelling, spongy feeling when palpated
P Papule – red, solid, pinpoint elevation
V Vesicle – small elevation containing fluid
B Bulla reaction – fluid-filled lesion (blister)
S Spreading – evidence of the reaction beyond the Webril pad area
W Weeping – result of a vesicular or bulla reaction – serous exudate
I Induration – solid, elevated, hardened, thickened skin

Skin Superficial Effects - Letter Grades

g Glazing
y Peeling
c Scab, dried film of serous exudate of vesicular or bulla reaction
d Hyperpigmentation (reddish-brown discoloration of test site)
h Hypopigmentation (loss of visible pigmentation at test site)
f Fissuring – grooves in the superficial layers of the skin

Results:

A total of 230 subjects were enrolled in this study. A total of 227 subjects were treated. Thirty subjects withdrew. A total of 19 subjects withdrew voluntarily, mostly not returning for scheduled visits and a total of 5 subjects did not complete due to protocol violations. A total of 6 subjects did not complete because of adverse events. These included abdominal pain due to pancreatic cancer, twisted ankle, dizziness evaluated by subject's doctor as related to vision, sensitivity to skin marker, broken ankle, and fever.

Adverse events:

The safety population, 227, included all randomized subjects who received patches in both study groups. A total of 80 adverse events were experienced by 57 subjects. Of the 80 adverse events, 32 were considered mild, 37 considered moderate, and 11 severe. Severe events include urinary tract infection, dizziness (see SAE below), tubal ligation, stomach flu, arthritis pain in leg, tooth extracted, genital area infection (fungus), increased high blood pressure, broken ankle, whiplash neck to waist, and abscess on thumb. These were all considered unrelated to test articles.

Please see sections 7.3.2 and 7.4.1 for further discussion of adverse events.

Irritation Results:

Cumulative irritation scores included the actual patch test scores recorded following visual evaluation of the test sites during the induction phase for only Group 1. Scores were reported as a combination of numerical and letter scores. After letter scores were converted to numeric scores, the Friedman rank sum test was used to analyze the transformed skin irritation scores. The per-protocol population (n=20) for the Friedman rank sum analysis for Group 1 included all randomized subjects who did not miss a visit and did not have any patches removed due to reactions unrelated to the test article.

Table 45: Summary of Total Irritation and rank Scores (Group 1: Per Protocol)

	Spinosad 2%		Vehicle		0.1% SLS*		0.9% NaCl†	
Subject #	Total Irritation	Rank	Total Irritation	Rank	Total Irritation	Rank	Total Irritation	Rank
101	24	3	20	2	39	4	4	1
102	26	3	24	2	39	4	13	1
103	6	2	3	1	33	4	37	3
104	35	2	22	1	44	4	37	3
105	36	3	36	3	48	4	32	1
106	41	3	38	2	44	4	25	1
108	13	1	30	2	42	4	31	3
109	27	3	24	2	39	4	13	1
110	32	3	25	2	39	4	11	1
111	7	2	16	3	33	4	3	1
112	35	3	29	2	45	4	17	1
114	40	2	42	4	41	3	21	1
118	11	2	29	3	43	4	11	2
124	12	2	13	3	31	4	2	1
125	11	1	28	3	40	4	14	2
126	16	2	11	1	46	4	35	3
128	21	3	19	2	43	4	15	1
130	23	3	21	2	38	4	16	1
131	34	3	34	3	44	4	19	1
132	16	2	28	3	40	4	16	2

*0.1% SLS = positive control
†0.9% Sodium Chloride = negative control
Source: Sponsor's NDA Submission, Clinical Study Report for Study SPN-102-05, Table 14.2.6.1, p. T14.2-46.

For Group 1, the 21-day cumulative irritation score was the primary comparative endpoint. Table 46 summarizes cumulative irritation scores and the Friedman rank sum analysis for Group 1:

Table 46: Cumulative Irritation – Comparative Analysis (Study SPN-102-05)

Treatment	Average 21-Day Cumulative Irritation Score	Average within Subject Rank	Significant Comparisons
A: ParaPro Spinosad 2% Crème rinse	23.30	2.30	C vs. A,B,D A,B vs. D
B: ParaPro vehicle Crème Rinse	24.60	2.25	
C: 0.1% SLS (positive control)	40.55	3.95	
D: 0.9% Sodium Chloride (neg. control)	17.10	1.50	

Source: Sponsor's NDA Submission, Clinical Study Report for Study SPN-102-05, Table 14.2.6.2, p. T14.2-47.

Conclusion for induction phase:
Under the conditions of this study, spinosad 2%, vehicle, and sodium chloride are significantly less irritating than .1% SLS. Additionally, spinosad 2% and vehicle are significantly more irritating than .9% sodium chloride.

The applicant also performed an analysis wherein the scores for each test material were normalized for a base of 10 subjects. An historically derived category scale based on the magnitude of the base 10 total score was employed to classify the normalized scores into the following: mild, probably mild, possibly mild, experimental cumulative irritant, or experimental primary irritant. According to the Hill Top Research study report, this system was developed through experience with cosmetic articles, emphasizing the comparative evaluation of relatively mild test articles and attempting to predict the responsiveness of a typical subject. The results of this analysis are shown in the following table:

Table 47: Base 10 Cumulative Irritation Categorizations (Study SPN-102-05)

Treatment	Base 10 Score	Categorization
Spinosad 2.0%	225.0	Class 3 (possibly mild in normal use)
Placebo	236.3	Class 3 (possibly mild in normal use)
SLS	414.6	Class 3 (possibly mild in normal use)
Sodium Chloride	176.3	Class 2 (probably mild in normal use)

Source: Sponsor's NDA Submission, Integrated Summary of Safety, Table 7.1.4-4, p. 81.

Under the conditions of this study, spinosad 2%, its vehicle, and .1% SLS are categorized as class 3, evidence of a moderate potential for mild cumulative irritation. The .9% sodium chloride was categorized as Class 2, evidence of a slight potential for very mild cumulative irritation.

Sensitization Results:
A total of 200 subjects completed the challenge phase of the study. The numeric scale used to grade inflammatory responses was described earlier. Results for the challenge phase are shown in Tables 48 and 49 following:

Table 48: Frequency Distribution of Challenge Scores Group 1 (Study SPN-102-05)

		Evaluation							
		15 Minutes Post		24 Hors Post		48 Hours Post		72 Hours Post	
Treatment	Score	Num	%[1]	Num	%[1]	Num	%	Num	%[1]
Spinosad 2%	+	3	11	0	0	1	4	0	0
	0	25	89	28	100	27	96	27	96
	1	0	0	0	0	0	0	0	0
	unknown	0	0	0	0	0	0	1	4
Vehicle	+	3	11	0	0	0	0	0	0
	0	25	89	28	100	28	100	27	96
	1	0	0	0	0	0	0	0	0
	unknown	0	0	0	0	0	0	1	4

[1]Percentages rounded by reviewer
Source: Sponsor's NDA Submission, Clinical Study Report for Study SPN-102-05, Table 14.2.10.2, p. T14.2-63.

Table 49: Frequency Distribution of Challenge Scores Group 2 (Study SPN-102-05)

		Evaluation							
		15 Minutes Post		24 Hors Post		48 Hours Post		72 Hours Post	
Treatment	Score	Num	%[1]	Num	%[1]	Num	%[1]	Num	%[1]
Spinosad 2%	+	9	5	3	2	2	1	0	0
	0	160	90	169	98	168	98	169	99
	1	8	5	1	.6	2	1	0	0
	unknown	0	0	0	0	0	0	1	.6
Vehicle	+	13	7	1	.6	1	.6	0	0
	0	156	88	171	99	171	99	169	99
	1	8	5	1	.6	0	0	0	0
	unknown	0	0	0	0	0	0	1	.6

[1]Percentages rounded by reviewer
Source: Sponsor's NDA Submission, Clinical Study Report for Study SPN-102-05, Table 14.2.11.2, p. T14.2-88.

Conclusion Sensitization Phase:
This reviewer agrees with the investigator that, under the conditions of this study, there was no evidence of induced skin sensitization to spinosad 2% or to spinosad vehicle.

Study SPN-107-07: "An Evaluation of the Phototoxic Potential of NatrOVA® Crème Rinse – 1% in Healthy Volunteers"

The purpose of this study was to evaluate the phototoxic potential of NatrOVA Crème Rinse 1% in healthy adult human subjects. This study was conducted in accordance with 21 CFR Parts 50, 54, 56, and 312. Study dates were December 5, 2007 to December 13, 2007.

This was a single center, intra-individual comparison, randomized, vehicle-controlled, double-blind trial that enrolled 38 healthy adult volunteers (13 male and 25 female). Subjects were between 18 and 65 years of age and had skin phototypes I, II, or III on the 4-point Fitzpatrick scale. Female subjects were ineligible if they were pregnant, nursing, or planning a pregnancy. Test articles included spinosad 1% crème rinse and spinosad 1% vehicle crème rinse.

Table 50: Patch Test Articles (Study SPN-107-07)

Sponsor Code/HTR[1] Code	Patch Type	Concentration	Method and Quantity of Application to Patch
Vehicle /HTR Code A	Semi-Occlusive[2]	Neat	0.2 ml
Natrova /HTRCode B	Semi-Occlusive	Neat	0.2 ml
Blank Patch/HTR Code C	Semi-Occlusive	n/a	n/a

[1]HTR = Hill Top Research
[2]Semi-occluded using a non-woven cotton pad (Webril®) held to the skin on all sides by a strip of hypoallergenic tape (Micropore™)
Source: Sponsor's NDA Submission, Clinical Study Report for Study SPN-107-07, 9.4.4, p. 18.

For each subject the Minimal erythema Dose (MED) of UVA/UVB was determined at screening. For each subject, unprotected naïve skin was exposed to a series of 5 UVA/UVB exposures each 25 % greater than the previous dose. The lowest dose was approximately 0.5 MED and was based on skin type. The MED was determined to be the smallest dose of energy that produced uniform redness to the borders of the exposure site at 22 to 24 hours after irradiation.

For determination of phototoxicity, subjects were exposed to two sets of patches, each set containing one patch each as follows; Natrova, vehicle cream rinse, and blank. One set of patches was placed on one side of the spine and the other set was placed on the other side of the spine. Patches were applied to the subject within 15-30 minutes of test article dispensing to the patch. At approximately 24 (+ 1) hours after application, one set of patches, determined by study randomization, was removed and test sites were irradiated. Within 10 minutes of patch removal, the test sites were irradiated with 16 Joules/cm^2 of UVA irradiation. The sites were then irradiated with 0.75 MED of UVB/UVA. Subjects served as their own control. Non-irradiated sites were used as controls to assess non-phototoxic reactions (the test article's inherent irritation

potential). The same individual conducted all evaluations of the test sites during the course of the study. This individual was also blinded as to treatment assignments and any previous scores.

Local responses were scored according to the scales that follow. Scores represented the presence of clinically significant effects, involving at least 25% of the test site.

Erythema Grading Scale:
0 No visible reaction and/or erythema
0.5 Slight, confluent or patchy erythema
1 Mild erythema (pink)
2 Moderate erythema (definite redness)
3 Strong erythema (very intense redness)

For Reaction Grading Scale and Superficial Effects Grading Scale please see write-up of study SPN-102-05.

Results:
A total of 38 subjects were enrolled in the study and 37 completed all phases of the study. One subject (#38) was dropped from the study after patching because the randomization assignment could not be confirmed.

Adverse Events:
Two adverse events were experienced by two subjects. Subject # 16 experienced a sore throat rated as of moderate severity and resolving without sequelae. Subject #22 experienced a headache for one day, rated as moderate in severity, and resolving without sequelae. Both of these adverse events were not considered related to the test articles by the principal investigator.

Phototoxicity Results:
As shown in Table 51, at the irradiated sites for Vehicle, Natrova, and Blank, the highest ratings were 1, mild erythema, and the pattern of erythema grade scores was similar. For all three, erythema peaked at 24 hours after irradiation. The majority of subjects, at the irradiated sites for all 3 test articles, experienced no visible erythema.

At the non-irradiated sites, for all three test articles, at least 94% of subjects experienced no visible reactions at any post-exposure time point.

Table 51: Phototoxicity Outcomes by Treatment, Time Point, & Erythema Grade

	Erythema Grade N(%[1])				
	0	0.5	1	2	3
Vehicle Non-Irradiated					
1 Hour	37 (100%)	0	0	0	0
24 Hour	36 (100%)	0	0	0	0
48 Hour	35 (95%)	2 (5.4%)	0	0	0
72 Hour	35 (95%)	2 (5.4%)	0	0	0
Vehicle UV Irradiated					
1 Hour	26 (70%)	9 (24%)	2 (5.4%)	0	0
24 Hour	21 (58%)	14 (39%)	1 (2.8%)	0	0
48 Hour	24 (65%)	13 (35%)	0	0	0
72 Hour	28 (76%)	9 (24%)	0	0	0
Natrova Non-Irradiated					
1 Hour	36 (97%)	1 (2.7%)	0	0	0
24 Hour	34 (94%)	2 (5.6%)	0	0	0
48 Hour	36 (97%)	1 (2.7%)	0	0	0
72 Hour	36 (97%)	1 (2.7%)	0	0	0
Natrova UV Irradiated					
1 Hour	26 (70%)	9 (24%)	2 (5.4%)	0	0
24 Hour	26 (72%)	9 (25%)	1 (2.8%)	0	0
48 Hour	26 (70%)	11 (30%)	0	0	0
72 Hour	26 (70%)	11 (30%)	0	0	0
Blank Non-Irradiated					
1 Hour	36 (97%)	1 (2.7%)	0	0	0
24 Hour	36 (100%)	0	0	0	0
48 Hour	37 (100%)	0	0	0	0
72 Hour	37 (100%)	0	0	0	0
Blank UV Irradiated					
1 Hour	29 (78%)	6 (16%)	2 (5.4%)	0	0
24 Hour	24 (67%)	10 (28%)	2 (5.6%)	0	0
48 Hour	23 (62%)	14 (38%)	0	0	0
72 Hour	28 (76%)	9 (24%)	0	0	0

[1]Percentages rounded by reviewer.

Source: Sponsor's NDA Submission, Integrated Summary of Safety, Table 7.1.5-2, p. 83.

Conclusion: This reviewer agrees with the investigator that under the conditions of the study phototoxic activity was not observed from any of the subjects after UV exposure.

Study SPN-108-08: "An Evaluation of the Photoallergy Potential of Natrova® Crème Rinse – 1% in Healthy Volunteers"

The purpose of this study was to determine the photoallergic potential of Natrova compared to its vehicle in healthy adult human subjects. The study was conducted in accordance with 21 CFR Parts 50, 54, 56, and 312. Study dates were January 23, 2008 to June 19, 2008.

This was a single-center, intra-individual comparison, randomized, vehicle-controlled, double-blinded study that enrolled 58 healthy adult volunteers (44 females and 14 males). Subjects were between 18 and 65 years of age and had skin phototypes I, II, or III on the 4-point Fitzpatrick scale. Female subjects were ineligible if they were pregnant, nursing, or planning a pregnancy. Test articles included Natrova 0.9% and Natrova vehicle cream.

Table 52: Patch Test Study Articles (Study SPN-108-08)

Sponsor Code/HTR[1] Code	Patch Type	Concentration	Method and Quantity of Application to Patch
Vehicle /HTR Code B	Semi-Occlusive[2]	Neat	0.2 ml
Natrova /HTRCode C	Semi-Occlusive	Neat	0.2 ml
Blank Patch/HTR Code A	Semi-Occlusive	n/a	n/a

[1]HTR = Hill Top Research
[2]Semi-occluded using a non-woven cotton pad (Webril®) held to the skin on all sides by a strip of hypoallergenic tape (Micropore™)
Source: Sponsor's NDA Submission, Clinical Study Report for Study SPN-108-08, 9.4.4, p. 19.

The duration of this study was approximately 6 weeks plus a 2 to 3 day screening period. The study included screening, induction, rest, and challenge phases. A re-challenge phase was not needed.

For each subject the Minimal erythema Dose (MED) of UVA/UVB was determined at screening. For each subject, unprotected naïve skin was exposed to a series of 5 UVA/UVB exposures each 25 % greater than the previous dose. The lowest dose was approximately 0.5 MED and was based on skin type. The MED was determined to be the smallest dose of energy that produced uniform redness to the borders of the exposure site at 22 to 24 hours after irradiation.

Induction Application 1 occurred within 5 days of MED determination. The induction phase consisted of six 24-hour applications of 2 sets of test patches, each set containing one patch each; Natrova 0.9%, vehicle cream rinse, and blank. One set of patches was placed on one side of the subject's spine and the other set was placed on the other side of the spine. Patches were applied to the subject within 15-30 minutes of test article dispensing to the patch. At approximately 24 ($\pm$ 2) hours after application, one set of patches, determined by study randomization, was removed and test sites

were irradiated within 10 minutes of patch removal with 2.0 MED of UVB/UVA. Subjects served as their own control. All test sites were evaluated immediately prior to the next application. (Each test article was repeatedly applied to the same site unless a strong reaction was exhibited. Test articles that exhibited a strong reaction were moved to an adjacent site twice and then discontinued if a third strong reaction developed.) Patches were applied and removed by a trained technician. Test articles were supplied in a manner that maintained blinding regarding product identity. Study personnel conduction evaluations were blinded to both treatment and previous scores throughout the study.

The rest period for this study was approximately 10 to 17 days.

The challenge phase consisted of a single 24-hour application of 2 sets of the same test patches (Natrova 0.9%, vehicle cream rinse, blank) to naïve sites on the subject's back. For evaluation of photoallergy, one set of the test sites was exposed to 0.75 MED of UVB/UVA and 16 Joules/cm^2 of UVA radiation. The non-irradiated patch sites were used as controls to assess non-photoallergy reactions. After the final patch was removed, test sites were evaluated at 1 ($\pm$ 0.25), 24 ($\pm$ 1), 48 ($\pm$ 2), and 72 ($\pm$ 2) hours.

Local responses were scored according to the scales that follow. Scores represented the presence of clinically significant effects, involving at least 25% of the test site.

Erythema Grading Scale:
0 No visible reaction and/or erythema
0.5 Slight, confluent or patchy erythema
1 Mild erythema (pink)
2 Moderate erythema (definite redness)
3 Strong erythema (very intense redness)

For Reaction Grading Scale and Superficial Effects Grading Scale please see write-up of study SPN-102-05.

Results:
A total of 58 subjects were enrolled in the study and 51 completed all phases of the study. Seven subjects were discontinued from the study. One of these was listed as an adverse experience: "Subject had to use a medication which was an exclusionary medication, Dropped per P.I. AE#2." One subject requested to withdraw: "Subject started getting a bad cold and she just did not want to continue on study." Two subjects discontinued due to schedule conflicts. Two subjects did not show for scheduled study visits. One subject (# 27) was dropped from study per Principal Investigator. This subject was dropped due to being in a car accident and receiving a steroid injection for inflammation of a herniated disc aggravated by being in the car accident.

Adverse Events:
Please see section 7.4.1 for a discussion of adverse events.

Irritation Assessment: Induction Phase:
As shown in Table 53, no erythema was seen in any of the non-irradiated sites for all three test articles. For the irradiated sites, the pattern for the 3 test articles (Natrova, vehicle, Blank) is similar. More erythema is seen in earlier visits, 3 through 7. In visits 9 through13, a majority of subjects in almost all cases (except 49%, visit 9 vehicle in Table 53) show no erythema. For those that do show erythema, it decreases over visits 9 to 13. Low numbers of subjects, 7% or less, show erythema grades 2 and 3. The numbers of these subjects also decrease over time going to 0 by visit 13, except for one subject in the Natrova UV irradiated group.

Table 53: Induction Phase Results (Study SPN-108-08)

	Erythema Grade N (%)*				
	0	**0.5**	**1**	**2**	**3**
Vehicle Non-Irradiated					
Visit 3	56 (100%)	0	0	0	0
Visit 5	57 (100%)	0	0	0	0
Visit 7	56 (100%)	0	0	0	0
Visit 9	55 (100%)	0	0	0	0
Visit 11	55 (100%)	0	0	0	0
Visit 13	54 (100%)	0	0	0	0
Vehicle UV Irradiated					
Visit 3	13 (23%)	10 (18%)	9 (16%)	24 (43%)	0
Visit 5	12 (21%)	6 (11%)	15 (26%)	21 (37%)	3 (5%)
Visit 7	16 (29%)	8 (14%)	14 (25%)	16 (29%)	2 (4%)
Visit 9	27 (49%)	7 (13%)	16 (29%)	4 (7%)	1 (2%)
Visit 11	41 (75%)	3 (5%)	11 (20%)	0	0
Visit 13	46 (85%)	2 (4%)	6 (11%)	0	0
Natrova Non-Irradiated					
Visit 3	56 (100%)	0	0	0	0
Visit 5	57 (100%)	0	0	0	0
Visit 7	56 (100%)	0	0	0	0
Visit 9	55 (100%)	0	0	0	0
Visit 11	55 (100%)	0	0	0	0
Visit 13	54 (100%)	0	0	0	0

	Erythema Grade N (%)*				
	0	**0.5**	**1**	**2**	**3**
Natrova UV Irradiated					
Visit 3	13 (23%)	10 (18%)	9 (16%)	24 (43%)	0
Visit 5	14 (25%)	5 (9%)	15 (26%)	22 (39%)	1 (2%)
Visit 7	13 (23%)	8 (14%)	14 (25%)	19 (34%)	2 (4%)
Visit 9	30 (55%)	7 (13%)	14 (25%)	3 (6%)	1 (2%)
Visit 11	41 (75%)	3 (6%)	10 (18%)	0	1 (2%)
Visit 13	46 (85%)	1 (2%)	6 (11%)	0	1 (2%)
Blank Non-Irradiated					
Visit 3	56 (100%)	0	0	0	0
Visit 5	57 (100%)	0	0	0	0
Visit 7	56 (100%)	0	0	0	0
Visit 9	55 (100%)	0	0	0	0
Visit 11	55 (100%)	0	0	0	0
Visit 13	54 (100%)	0	0	0	0
Blank UV Irradiated					
Visit 3	17 (30%)	9 (16%)	6 (11%)	24 (43%)	0
Visit 5	21 (37%)	4 (7%)	13 (23%)	18 (32%)	1 (2%)
Visit 7	22 (39%)	4 (7%)	12 (21%)	18 (32%)	0
Visit 9	34 (62%)	5 (9%)	13 (24%)	2 (4%)	1 (2%)
Visit 11	44 (80%)	3 (6%)	7 (13%)	1 (2%)	0
Visit 13	52 (96%)	1 (2%)	1 (2%)	0	0

*Percentages rounded by reviewer.
Source: Sponsor's NDA Submission, Integrated Summary of Safety, Table 7.1.6-2, p. 86.

Challenge Phase Results:
As shown in Table 54, Non-irradiated sites showed in the vast majority of cases no erythema. Only one subject showed mild erythema for all three test articles (Natrova, vehicle, blank) at 1 hour. For the irradiated sites, a majority of subjects showed no erythema. For the three test articles (Natrova, vehicle, blank) a similar pattern was seen with regard to grade 1 erythema, low numbers of subjects that decreased over the span of readings from 1 to 72 hours. One subject was reported to show erythema grades 2 or 3 for each of the three test articles (Natrova, vehicle, blank).

Table 54: Photo-Allergy Challenge Phase Results (Study SPN-108-08)

	Erythema Grade N(%)*				
	0	0.5	1	2	3
Vehicle Non-Irradiated					
1 Hour	50 (98%)	0	1 (2%)	0	0
24 Hour	51 (100%)	0	0	0	0
48 Hour	51 (100%)	0	0	0	0
72 Hour	51 (100%)	0	0	0	0
Vehicle UV Irradiated					
1 Hour	46 (90%)	2 (4%)	2 (4%)	1(2%)	0
24 Hour	33 (65%)	8 (16%)	10(20%)	0	0
48 Hour	40 (78%)	7 (14%)	3 (6%)	0	1 (2%)
72 Hour	44 (86%)	4 (8%)	2 (4%)	0	1 (2%)
Natrova Non-Irradiated					
1 Hour	50 (98%)	0	1 (2%)	0	0
24 Hour	51 (100%)	0	0	0	0
48 Hour	51 (100%)	0	0	0	0
72 Hour	51 (100%)	0	0	0	0
Natrova UV Irradiated					
1 Hour	47 (92%)	1 (2%)	3 (6%)	0	0
24 Hour	34 (67%)	9 (18%)	7 (14%)	0	1 (2%)
48 Hour	44 (86%)	6 (12%)	0	1 (2%)	0
72 Hour	45 (88%)	5 (10%)	0	1 (2%)	0
Blank Non-Irradiated					
1 Hour	50 (98%)	0	1 (2%)	0	0
24 Hour	51 (100%)	0	0	0	0
48 Hour	51 (100%)	0	0	0	0
72 Hour	51 (100%)	0	0	0	0
Blank UV Irradiated					
1 Hour	45 (88%)	4 (8%)	2 (4%)	0	0
24 Hour	38 (75%)	6 (12%)	7 (14%)	0	0
48 Hour	44 (86%)	6 (12%)	0	1 (2%)	0
72 Hour	47 (92%)	3 (6%)	0	1 (2%)	0

*Percentages rounded by reviewer.

Source: Sponsor's NDA Submission, Integrated Summary of Safety, Table 7.1.6-2, p. 86.

Conclusions:

A. Photo-Irritation/Induction Phase: The sponsor has concluded that under the conditions of this study: "Natrova cannot be considered significantly more irritating to UV irradiated skin than either a blank patch or a vehicle patch." The use of the term

"significantly" may be misleading in this case since statistics were not applied to these results. It may be more accurate to state that under the conditions of this study, Natrova cannot be considered markedly more irritating to UV irradiated skin than either a blank patch or a vehicle patch. (There may be evidence in this study of rare photo-irritation for Natrova. However when the product is used as labeled, only one or two treatments and short application time, the clinical importance of this appears limited.)

B. Photo-Allergy/Challenge Phase: The sponsor states that none of the subjects in this study were considered to have experienced photo-allergic reactions. It may be more accurate to state that under the conditions of this study it is unlikely that any of the subjects experienced photo-allergic reactions. (There may be evidence in this study for rare photo-sensitization for vehicle. However when the product is used as labeled, only one or two treatments and short application time, the clinical importance of this appears limited.)

7.4.6 Immunogenicity

This is not applicable since the drug is not a therapeutic protein.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

Please see section 7.2.2.

7.5.2 Time Dependency for Adverse Events

Most subjects experienced adverse events at the time of or shortly (days) after product application.

7.5.3 Drug-Demographic Interactions

In response to an information request (6/26/09), the sponsor provided information (7/15/09) regarding sub-group analyses for adverse events by age, race, and sex.

Table 55: Adverse Event Subgroup Analysis (Age)

Age	(b) (4) with & without nit combing	NIX
≤ 24 months	N = 20	N = 13
Any adverse event	6 (30%)	2 (15%)
Local adverse event*	4 (20%)	1 (8%)
25 months to 12 years	N = 327	N = 249
Any adverse event	26 (8%)	45 (18%)
Local adverse event	18 (6%)	35 (15%)
13 to 16 years	N = 44	N = 49
Any adverse event	6 (14%)	11 (22%)
Local adverse event	4 (10%)	10 (20%)
≥ 17 years	N = 160	N = 146
Any adverse event	17 (11%)	30 (21%)
Local adverse event	14 (9%)	21 (14%)
Other Age Groupings		
≤ median age (9 years)	N = 300	N = 219
Any adverse event	29 (10%)	41 (19%)
Local adverse event	19 (6%)	30 (14%)
> median age	N = 251	N = 238
Any adverse event	26 (10%)	44 (18%)
Local adverse event	19 (8%)	36 (15%)
6 months to 12 years	N = 347	N = 262
Any adverse event	32 (9%)	47 (18%)
Local adverse event	21 (6%)	35 (14%)
> 12 years	N = 204	N =146
Any adverse event	23 (11%)	41 (21%)
Local adverse event	17 (8%)	31 (16%)

* Local adverse events are defined, by the reviewer, for this analysis as any (MedDRA) preferred term under the system organ class of eye disorders, all preferred terms related to application site, and all preferred terms under the system organ class, skin and subcutaneous disorders. Counts, provided by the sponsor, reflect numbers of subjects reporting one or more adverse events classified to MedDRA (Version 10.1). Subjects are counted only once at each level of summarization; in this case preferred terms.

Source: Sponsor's NDA, Submission dated July 15, 2009, compiled by reviewer from listings in Table 14.3.1.2.2.1, pages 1 to 22.

For (b) (4) in general, the frequency of adverse events both total and local is similar across the age groupings, as shown in Table 55. Although in the youngest age group,

less than or equal to 24 months, the percentage of adverse events appears higher, small numbers preclude a definitive conclusion. All of the adverse events for (b) (4) in this age group were classified as mild. The local adverse events included; subject 6-17-0001, having ocular hyperemia, considered possibly related, resolved; subjects 14-01-0001 and 14-01-0002, having application site erythema, considered unrelated, resolved; and subject 14-01-0002 having erythema, considered unrelated, and ongoing. The non-local adverse events included subject 7-29-0001 having nasopharyngitis and subject 14-01-0001 having a skin laceration.

Table 56: Adverse Event Subgroup Analysis (Gender & Race/Ethnicity)

	(b) (4) with and without nit combing	NIX
Gender		
Male	N = 104	N = 73
Any adverse event	12 (12%)	11 (15%)
Local adverse event*	10 (10%)	11 (15%)
Female	N = 448	N = 384
Any adverse event	42 (9%)	77 (70%)
Local adverse event	29 (6%)	55 (14%)
Race/Ethnicity†		
Caucasian	N = 325	N = 274
Any adverse event	25 (8%)	48 (18%)
Local adverse event	14 (4%)	33 (12%)
Hispanic		
Any adverse event	27 (13%)	35 (21%)
Local adverse event	23 (11%)	30(18%)

* Local adverse events are defined, by the reviewer, for this analysis as any (MedDRA) preferred term under the system organ class of eye disorders, all preferred terms related to application site, and all preferred terms under the system organ class, skin and subcutaneous disorders. Counts, provided by the sponsor, reflect numbers of subjects reporting one or more adverse events classified to MedDRA (Version 10.1). Subjects are counted only once at each level of summarization; in this case preferred terms.

† The numbers of events reported for the races; Black, Native American, and Asian were too small to adequately explore adverse event rates in these groups.

Source: Sponsor's NDA, Submission dated July 15, 2009, compiled by reviewer from listings in Table 14.3.1.2.2.1, pages 1 to 22.

As shown in Table 58, for (b) (4) the frequency of adverse events, both total and local, is similar across the subgroups of gender (male versus female) and of race/ethnicity (Caucasian versus Hispanic).

7.5.4 Drug-Disease Interactions

No formal analyses were performed for drug-disease interactions with this topical drug product.

7.5.5 Drug-Drug Interactions

No formal analyses were performed for drug-drug interactions with this topical drug product.

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

Human carcinogenicity was not assessed as part of the clinical development program. Controlled clinical trials were too short to allow for evaluation of carcinogenicity.

7.6.2 Human Reproduction and Pregnancy Data

No studies in pregnant women were performed as part of the development program. During the clinical development program a total of two cases of pregnancy were reported in subjects exposed to (b) (4) For more information regarding these subjects please see section 7.3.4.

7.6.3 Pediatrics and Assessment of Effects on Growth

The pivotal trials included children 6 months of age and older and the original NDA application did not include a waiver for pediatric studies for children less than 6 months of age. The 74 day letter (4/6/09) requested submission of a pediatric assessment as required by the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c).

In response to the above request, on 9/8/09 the sponsor submitted a request for a waiver of pediatric use (0 to 6 months) for (b) (4) (spinosad, 0.9%) Suspension per 21 CFR 201.23(c)(2)(i)(B) and (C)ii. The sponsor states that (b) (4) is not likely to be used in a substantial number of subjects in the 0 to 6 month age group, and clinical studies in this age group are highly impracticable since the number of subjects in this age group is very small. Literature published on the prevalence of lice in the pediatric patient population indicates that the majority of cases of lice occur in patients ranging in age from 3 to 11 or 12 years old. Because of a lack of substantial need for lice treatment in the age group 0 to 6 months, this reviewer agrees that a waiver for this population is appropriate.

Assessment of effect on growth was not performed as part of the clinical development program. The pivotal studies involved, at most, two applications of study drug one week apart.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

Overdose:
Overdose appears unlikely since (b) (4) is applied topically at most twice per lice episode and has minimal systemic absorption. Overdose was not reported as an adverse in event in the clinical development program.
Drug Abuse:
No instances of drug abuse were reported in the clinical development program. The sponsor states that there is no evidence of dependency effects associated with spinosad (the API in (b) (4)).

Withdrawal and Rebound:
No instances of withdrawal or rebound were reported in the safety database.

7.7 Additional Submissions / Safety Issues

The sponsor, ParaPRO did not submit a 120 day safety update. The sponsor states in the Amendment dated, 9/8/2009, that: "None is required since all the clinical data, including the safety data, were submitted when the e-CTD was submitted on 22 January 2009. At this time no clinical studies are underway and no other clinical studies are planned."

8 Postmarket Experience

The sponsor's drug product, (b) (4) is not marketed in any country at this time.

9 Appendices

9.1 Literature Review/References

Literature references are cited in the body of the review.

9.2 Labeling Recommendations

Assessment of labeling is ongoing at the time of this review.

9.3 Advisory Committee Meeting

No Advisory Committee was convened in response to this application.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22408	ORIG-1	PARAPRO PHARMACEUTICALS LLC	SPINOSAD

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

/s/

PATRICIA C BROWN
10/16/2009

JILL A LINDSTROM
10/30/2009

CLINICAL FILING CHECKLIST FOR NDA

NDA/BLA Number: 22-408 **Applicant: ParaPRO Pharmaceuticals** **Stamp Date: 1/22/09**

Drug Name: Spinosad (b) (4) **NDA Type: Standard**

On initial overview of the NDA/BLA application for filing:

	Content Parameter	Yes	No	NA	Comment
FORMAT/ORGANIZATION/LEGIBILITY					
1.	Identify the general format that has been used for this application, e.g. electronic CTD.	eCTD			
2.	On its face, is the clinical section organized in a manner to allow substantive review to begin?	X			
3.	Is the clinical section indexed (using a table of contents) and paginated in a manner to allow substantive review to begin?				It is navigable. There is an index for each study report. No overall index.
4.	For an electronic submission, is it possible to navigate the application in order to allow a substantive review to begin (*e.g.*, are the bookmarks adequate)?	X			
5.	Are all documents submitted in English or are English translations provided when necessary?	X			
6.	Is the clinical section legible so that substantive review can begin?	X			
LABELING					
7.	Has the applicant submitted the design of the development package and draft labeling in electronic format consistent with current regulation, divisional, and Center policies?	X			
SUMMARIES					
8.	Has the applicant submitted all the required discipline summaries (*i.e.*, Module 2 summaries)?	X			
9.	Has the applicant submitted the integrated summary of safety (ISS)?	X			
10.	Has the applicant submitted the integrated summary of efficacy (ISE)?				
11.	Has the applicant submitted a benefit-risk analysis for the product?	X			
12.	Indicate if the Application is a 505(b)(1) or a 505(b)(2). If Application is a 505(b)(2) and if appropriate, what is the reference drug?	505(b)(1)			
DOSE					
13.	If needed, has the applicant made an appropriate attempt to determine the correct dosage and schedule for this product (*i.e.*, appropriately designed dose-ranging studies)? Study Number: SPN-202-06 Study Title: Efficacy and Safety of Different Strengths of Spinosad topical Creme Rinse (0.0%, 0.5%, or 1.0%) Sample Size: 43,40,37 Arms: 3 Location in submission: 5.3.5.1.1	X			
EFFICACY					
14.	Do there appear to be the requisite number of adequate and well-controlled studies in the application?	X			

CLINICAL FILING CHECKLIST FOR NDA

	Content Parameter	Yes	No	NA	Comment
	Pivotal Study #1 SPN-301-07 Indication: treatment of head lice Pivotal Study #2 SPN-302-07 Indication: treatment of head lice				
15.	Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?	X			
16.	Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints.	X			
17.	Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission?			X	
SAFETY					
18.	Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division?	X			
19.	Has the applicant submitted adequate information to assess the arythmogenic potential of the product (*e.g.*, QT interval studies, if needed)?		X		ECG's performed only in SPN-101-04 & SPN-102-05
20.	Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product?			X	
21.	For chronically administered drugs, have an adequate number of patients (based on ICH guidelines for exposure[1]) been exposed at the dose (or dose range) believed to be efficacious?			X	
22.	For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division?	X			
23.	Has the applicant submitted the coding dictionary[2] used for mapping investigator verbatim terms to preferred terms?	X			
24.	Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs?	X			
25.	Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)?	X			Also have narratives for all discontinued subjects

[1] For chronically administered drugs, the ICH guidelines recommend 1500 patients overall, 300-600 patients for six months, and 100 patients for one year. These exposures MUST occur at the dose or dose range believed to be efficacious.

[2] The "coding dictionary" consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

CLINICAL FILING CHECKLIST FOR NDA

	Content Parameter	Yes	No	NA	Comment
OTHER STUDIES					
26.	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?	X			
27.	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (*e.g.*, label comprehension, self selection and/or actual use)?			X	
PEDIATRIC USE					
28.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?		X		
ABUSE LIABILITY					
29.	If relevant, has the applicant submitted information to assess the abuse liability of the product?			X	
FOREIGN STUDIES					
30.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?			X	
DATASETS					
31.	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?				STATS
32.	Has the applicant submitted datasets in the format agreed to previously by the Division?				"
33.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?				"
34.	Are all datasets to support the critical safety analyses available and complete?				"
35.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?				"
CASE REPORT FORMS					
36.	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?	X			
37.	Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?	X			Subjects who withdrew are included.
FINANCIAL DISCLOSURE					
38.	Has the applicant submitted the required Financial Disclosure information?		X		No form 3454
GOOD CLINICAL PRACTICE					
39.	Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?	X			

IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE? Yes

If the Application is not fileable from the clinical perspective, state the reasons and provide comments to be sent to the Applicant.

CLINICAL FILING CHECKLIST FOR NDA

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

A) Filing review issue:

Insufficient information has been provided to assess the effect of the product on cardiac repolarization.

B) The following information request should be included in the 74 day letter:

a) information to assess the effect of the product on cardiac repolarization

b) a pediatric assessment

c) a completed form FDA 3454 attesting to the absence of financial interests and arrangements as described in 21 CFR 54.4 paragraph (a)(3)

Patricia C. Brown, M.D.	3/20/09
Reviewing Medical Officer	Date
Jill Lindstrom	see sign-off date
Clinical Team Leader	Date

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

/s/

Patricia Brown
3/20/2009 10:56:46 AM
MEDICAL OFFICER

Jill Lindstrom
3/20/2009 11:06:19 AM
MEDICAL OFFICER