CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

022408Orig1s000

CHEMISTRY REVIEW(S)

NDA 22-408

Natroba (Spinosad) Suspension 0.9%
ParaPro Pharma

Division of Dermatology and Dental Products

Zhengfang Ge, Ph.D.

Branch IV, Division of Drug Quality Assessment II
Office of New Drug Quality Assessment

Table of Contents

Chemistry Review Data Sheet

1. NDA # 22-408

2. REVIEW # 2

3. REVIEW DATE: Sep 28, 2010

4. REVIEWER: Zhengfang Ge, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
Original submission	Jan 21, 2009
Amendment 001	Feb 25, 2009
Amendment 002	Mar 10, 2009
Amendment 004	Apr 24, 2009
Amendment 005	Jun 26, 2009
Amendment 007	July 15, 2009
Amendment 008	Sep 8, 2009

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Amendment 015 (complete response)	Jul 23, 2010
Amendment 016	Sep 14, 2010
Amendment 017	Sep 23, 2010

7. NAME & ADDRESS OF APPLICANT:

Name:	ParaPro Pharamceuticals LLC
Address:	11550 North Meridian St, Suite 600 Carmel, Indiana 46032-4565
Representative:	Anson Group 11460 N. Meridian St, Suite 150 Carmel, IN 46032
Telephone:	317-580-8288

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Natroba
b) Non-Proprietary Name (USAN): Spinosad
c) CAS No: N/A
d) Code Name/# (ONDQA only): PP105
e) Chem. Type/Submission Priority (ONDQA only):

- Chem. Type: 1
- Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: 505(b)(1)

10. PHARMACOL. CATEGORY: Topical treatment of human head lice (b) (4)

11. DOSAGE FORM: Suspension

12. STRENGTH/POTENCY: Spinosad 0.9%

13. ROUTE OF ADMINISTRATION: Topical

14. Rx/OTC DISPENSED: _X_Rx ___OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

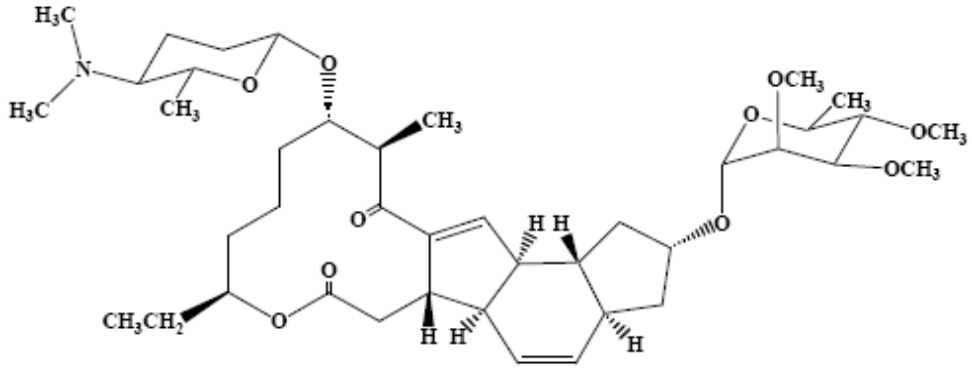
__X__Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

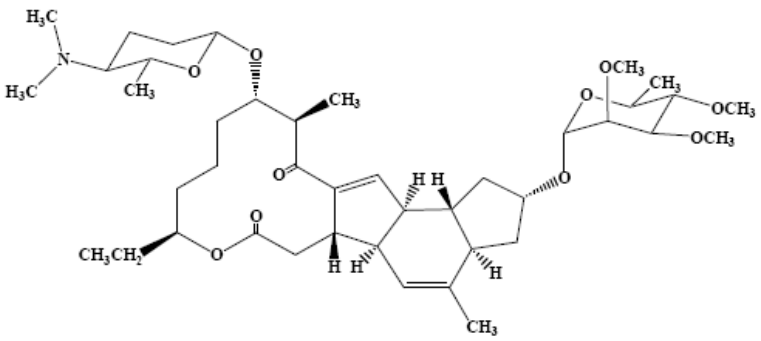
Spinosyn A: 1H-as-Indaceno[3,2-d]oxacyclododecin-7,a5-dione, 2-[(6-deoxy-2,3,4-tri-O-methyl-alpha-L-mannopyranosyl)oxy]-13-[[2R,5S,6R)-5-(dimethylamino) tetrahydro-6-methyl-2H-pyran-2-yl]oxy]-9-ethyl-2,3,3a,5a,5b,6,9,10,11,12,13,14,16a,16b-tetradecahydro-14-metyl-, (2R,3aS,5aR,5bS,9S,13S,14R,16aS,16bR)-
Spinosyn D: 1H-as-Indaceno[3,2-d]oxacyclododecin-7,15-dione, 2-[(6-deoxy-2,3,4-tri-O-methyl-alpha-L-mannopyranosyl)oxy]-13-[[2R,5S,6R)-5-(dimethylamino) tetrahydro-6-methyl-2H-pyran-2-yl]oxy]-9-ethyl-2,3,3a,5a,5b,6,9,10,11,12,13,14,16a,16b-tetradecahydro-4,14-dimetyl-, (2S,3aSR,5aS,5bS,9S,13S,14R,16aS,16bS)-

Molecular Formula, Weight and Structure:

Spinosyn A: $C_{41}H_{65}NO_{10}$ (731.461)



Spinosyn D: $C_{42}H_{67}NO_{10}$ (745.477)



17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
17795	II	Dow AgroSciences LLC	Spinosad	1	Adequate	21-Sep-2009	Reviewed by this reviewer

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
N/A		

18. STATUS:

ONDQA:

CONSULTS/ CMC RELATED REVIEWS	**RECOMMENDATION**	**DATE**	**REVIEWER**
Biometrics	Not Applicable		
EES	Acceptable	Nov 2, 2009	Office of Compliance (see section IV Attachment)
Pharm/Tox	Not Applicable		
Biopharm	Not Applicable		
LNC	Not Applicable		
Methods Validation	Not Applicable		
DMEPA	Not Applicable		

EA	Acceptable	Sep 23, 2009	See the Review #1
Microbiology	Not Applicable		

The Chemistry Review for NDA 22-408

The Executive Summary

I. Recommendations

A. 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.***

1. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

None

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

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 23-July-2010 amendment, the applicant provided a regulatory specification for the drug substance according to the Agency's request in the Complete Response letter. The specification is consistent with the one in DMF.

Drug Product:

The proposed drug product, Natroba (spinosad) suspension 0.9% w/w, is a light orange colored, slightly opaque, viscous liquid. The spinosad, the active ingredient, is completely solubilized in the formulation. 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 on benzyl alcohol as reviewed in CMC Review #1 is adequate. The applicant revised 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 by the applicant, the proposed 36 months expiation dating period is acceptable.

The applicant provided revised labeling according to the Agency's comments and the revision is acceptable from the CMC perspective.

B. Description of How the Drug Product is Intended to be Used

Natroba is indicated for the treatment of head lice *(pediculosis capitis)* infestations including lice (b) (4) in patients (b) (4).

The product will be applied to dry scalp and hair working away from scalp towards end of hair. Shake bottle well before use. Use only the amount needed to cover the scalp and hair. Leave on for 10 minutes and then rinse thoroughly with warm water. No nit combing is required

C. Basis for Approvability or Not-Approval Recommendation

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.

III. Administrative

A. Reviewer's Signature

In DFS

B. Endorsement Block

Chemist: Zhengfang Ge
Chemistry Branch Chief: Moo-Jhong Rhee

C. CC Block

ProjectManager: Down Williams
CMC Lead: Shulin Ding

11 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page

---

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

/s/

ZHENGFANG GE
09/28/2010

MOO JHONG RHEE
09/28/2010
Chief, Branch IV

Chemistry Assessment Section

Memorandum

Date: Nov 17, 2009
From: Zhengfang Ge, Ph.D., Reviewer
Through: Moo-Jhong Rhee, Ph.D., Branch Chief
To: NDA 22-408
Subject: Addendum to Review #1

The clinical division has recently approved a drug product containing benzyl alcohol (present at 5%) as an active ingredient for the treatment of head lice. This would imply that the proposed drug product in this NDA contains two active ingredients: spinosad and benzyl alcohol (b) (4) The clinical division requests the applicant to provide information to support approval of the proposed product according to the regulations for fixed-combination prescription drugs at 21 CFR 300.50, or demonstrate why the product should not be subject to these requirements. Accordingly, the following deficiencies are added/revised to those noted in the deficiencies in the Review #1 for this NDA.

Deficiency:

- If FDA determines that benzyl alcohol is a second active ingredient in TRADENAME (spinosad) Suspension, 0.9%, you will need to submit complete information on the drug substance, benzyl alcohol.
- Submit updated drug product specification which reflects the revised definitions of the “active ingredient”.

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/

ZHENGFANG GE
11/17/2009

MOO JHONG RHEE
11/17/2009
Chief, Branch III

Memorandum

Date: Nov 4, 2009
From: Zhengfang Ge, Ph.D., Reviewer
Through: Moo-Jhong Rhee, Ph.D., Branch Chief
To: NDA 22-408
Subject: Addendum to Review #1

Overall "***Acceptable"*** recommendation from the facility inspections in the manufacture of the drug substance and drug product was made by the Office of Compliance on Nov 2, 2009. However, the CMC issues listed in review #1 still remain unresolved (see review #1). Therefore, this NDA is not recommended for "***Approval***" in its present form

(b) (4)

[redacted]

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/

ZHENGFANG GE
11/04/2009

MOO JHONG RHEE
11/04/2009
Chief, Branch III

NDA 22-408

Natrova (Spinosad) Suspension 0.9%
ParaPro Pharma

Division of Dermatology and Dental Products

Zhengfang Ge, Ph.D.

Branch III, Division of Pre-Marketing Assessment II
Office of New Drug Quality Assessment

Table of Contents

Chemistry Review Data Sheet

1. NDA # 22-408

2. REVIEW # 1

3. REVIEW DATE: Sep 21, 2009

4. REVIEWER: Zhengfang Ge, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
N/A	

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original submission	Jan 21, 2009
Amendment 001	Feb 25, 2009
Amendment 002	Mar 10, 2009
Amendment 004	Apr 24, 2009
Amendment 005	Jun 26, 2009
Amendment 007	July 15, 2009
Amendment 008	Sep 8, 2009

Chemistry Review Data Sheet

7. NAME & ADDRESS OF APPLICANT:

Name:	ParaPro Pharamceuticals LLC
Address:	11550 North Meridian St, Suite 600 Carmel, Indiana 46032-4565
Representative:	Anson Group 11460 N. Meridian St, Suite 150 Carmel, IN 46032
Telephone:	317-580-8288

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Natrova
b) Non-Proprietary Name (USAN): Spinosad
c) CAS No: N/A
d) Code Name/# (ONDQA only): PP105
e) Chem. Type/Submission Priority (ONDQA only):

- Chem. Type: 1
- Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: 505(b)(1)

10. PHARMACOL. CATEGORY: Topical treatment of human head lice (b) (4)

11. DOSAGE FORM: Suspension

12. STRENGTH/POTENCY: Spinosad 0.9%

13. ROUTE OF ADMINISTRATION: Topical dermatology

14. Rx/OTC DISPENSED: _X_Rx ___OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):
_____SPOTS product – Form Completed

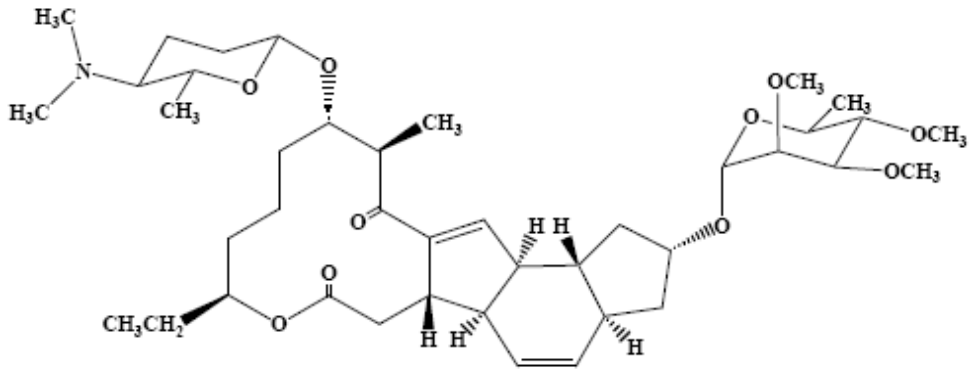
___X__Not a SPOTS product

16.CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

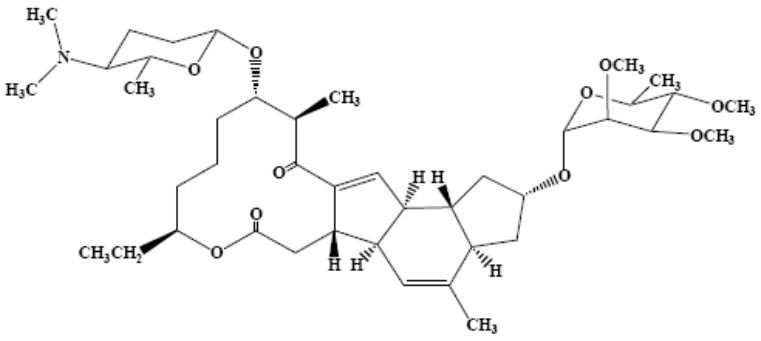
Spinosyn A: 1H-as-Indaceno[3,2-d]oxacyclododecin-7,a5-dione, 2-[(6-deoxy-2,3,4-tri-O-methyl-alpha-L-mannopyranosyl)oxy]-13-[[2R,5S,6R)-5-(dimethylamino) tetrahydro-6-methyl-2H-pyran-2-yl]oxy]-9-ethyl-2,3,3a,5a,5b,6,9,10,11,12,13,14,16a,16b-tetradecahydro-14-metyl-, (2R,3aS,5aR,5bS,9S,13S,14R,16aS,16bR)-
Spinosyn D: 1H-as-Indaceno[3,2-d]oxacyclododecin-7,15-dione, 2-[(6-deoxy-2,3,4-tri-O-methyl-alpha-L-mannopyranosyl)oxy]-13-[[2R,5S,6R)-5-(dimethylamino) tetrahydro-6-methyl-2H-pyran-2-yl]oxy]-9-ethyl-2,3,3a,5a,5b,6,9,10,11,12,13,14,16a,16b-tetradecahydro-4,14-dimetyl-, (2S,3aSR,5aS,5bS,9S,13S,14R,16aS,16bS)-

Molecular Formula, Weight and Structure:

Spinosyn A: $C_{41}H_{65}NO_{10}$ (731.461)



Spinosyn D: $C_{42}H_{67}NO_{10}$ (745.477)



17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
17795	II	Dow AgroSciences LLC	Spinosad	1	Adequate	21-Sep-2009	Reviewed by this reviewer

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
N/A		

18. STATUS:

ONDQA:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	Not Applicable		
EES	Pending		
Pharm/Tox	Not Applicable		
Biopharm	Not Applicable		
LNC	Not Applicable		
Methods Validation	Not Applicable		
DMEPA	Not Applicable		

EA	Acceptable		see review section II/B
Microbiology	Not Applicable		

The Chemistry Review for NDA 22-408

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

This NDA has not provided sufficient CMC information to assure the identity, strength, purity, and quality of the drug product (see section III List of Deficiencies on p. 52). Facilities involved are pending overall "Acceptable" recommendation from the Office of Compliance. CMC labeling issues are still pending. Therefore from a CMC perspective, this NDA is ***not*** recommended for "***Approval***" in its present form

1. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

None

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

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 makes a reference to DMF 17795 held by Dow AgroSciences LLC (Michigan, USA) for CMC information of spinosad. The DMF is reviewed and found adequate to support the NDA. The sponsor was requested to include a regulatory specification for the drug substance in the NDA in addition to reference the specification in the DMF, **the response has not been received.**

Drug Product:

The proposed drug product, (b) (4) (spinosad) suspension 0.9% w/w, is a pearl color, suspension of cetostearyl alcohol. The spinosad active ingredient is completely solubilized in the formulation. The product is packaged in a 4 ounce, white, HDPE bottle with a white, child resistant, snap top cap closure and spout.

The to-be-marketed formulation is the same formulation used in Phase 3 clinical trials and primary stability batches. The formulation contains the excipients that are compendial except ceteareth-20, FD&C Yellow #6, and stearalkonium chloride. No novel excipients are present in the formulation.

Specification for the drug product includes tests for appearance, ID, assay for Spinosyn A+D, individual A and D, individual related minor spinosyn factors, pH, viscosity, weight loss, assay for (b) (4) propyl alcohol and benzyl alcohol. The proposed acceptance criteria in the specification are generally acceptable, except for unclear definition for "related substance" and "impurities". The requested updating of the specification with clarification for the definition is still pending.

An HPLC method is used to determine the content of all the spinosyn factors and related substances including assay of the active ingredient, spinosyn A and D, and other minor spinosyn factors. According to the retention times provided by the applicant, the placebo and the spinosyn D are (b) (4) very closely and it is unclear from the chromatograms provided in the NDA whether the assay value for Spinosyn D is compromised by the placebo. The applicant was requested to provide data to assure that the strength of the drug product is not compromised by the placebo. No response has been received from the sponsor regarding this issue, which needs to be resolved before the NDA can be approved.

The applicant provided 24 months real time stability data (18 months data for the minor spinosyns) for three batches of the drug products under the proposed commercial strengths. Additional supportive stability data are also provided in the NDA. According to the submitted stability data, the drug product exhibited chemical stability during the long term stability study. No significant changes were observed in the assay and related substances. However, it was noticed that the drug product samples provided by the applicant at the time of the NDA submission was completely phase separated. It is not clear whether this is typical to the drug product. The applicant needs to provide information as to (b) (4) the storage and how long or vigorously it should be shaken to achieve a homogeneous state. The applicant needs to provide data to assure the content uniformity for the product after shaking the (b) (4) drug product before use.

During the stability studies, (b) (4) was discovered from the drug product under accelerated stability conditions, 40 C/75%RH, therefore the stability study under the accelerated condition was terminated after 2 months. Instead, stability study was conducted under the intermediate condition, 30°C/65%RH, However, stability data under intermediate condition were only provided for initial and months 12 for two stability batches which make it difficult to draw a valid conclusion (b) (4). The applicant attributed (b) (4) It also raises a question as to whether the tightness of the closure may (b) (4) The manufacture facility inspector reported that the stability samples were placed (b) (4) during the stability study. The applicant needs to provide more information on the cause (b) (4) in order to assure the quality of the drug product.

Because of the limited data at 30°C/65% and the (b) (4) problem, the applicant's proposed expiration dating period, 36 months, is not deemed acceptable, until the (b) (4) problems are satisfactorily resolved.

The applicant proposed (b) (4) as the nomenclature for the dosage form. (b) (4) is not a recommended dosage form in the Agency's dosage form database. Based on the appearance and the actual suspension of the excipient cetostearyl alcohol in the drug product, the applicant was requested to change the dosage form (b) (4) to "suspension". **No response has been received from the applicant**.

B. Description of How the Drug Product is Intended to be Used

(b) (4) is indicated for the treatment of head lice *(pediculosis capitis)* infestations (b) (4) in patients (b) (4)

The product will be applied to dry scalp and hair working away from scalp towards end of hair. Shake bottle well before use. Use only the amount needed to cover the scalp and hair. Leave on for 10 minutes and then rinse thoroughly with warm water. No nit combing is required

C. Basis for Approvability or Not-Approval Recommendation

Analytical method for assaying the drug product is not deemed fully validated. The drug product exhibits (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.

III. Administrative

A. Reviewer's Signature

In DFS

B. Endorsement Block

Chemist: Zhengfang Ge
Chemistry Branch Chief: Moo-Jhong Rhee

C. CC Block

ProjectManager: Down Williams
Pharmaceutical Assessment Lead: Shulin Ding

43 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page

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

ZHENGFANG GE
09/23/2009

MOO JHONG RHEE
09/23/2009
Chief, Branch III

MEMORANDUM

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

DATE: Sep. 17, 2009

TO: NDA 22-408 Initial Quality Assessment

FROM: Shulin Ding, Ph.D., Pharmaceutical Assessment Lead
(ONDQA Division of Pre-Marketing assessment II)

THROUGH: Moo-Jhong Rhee, Ph.D., Chief, Branch III
(ONDQA Division of Pre-Marketing assessment II)

SUBJECT: **Addendum 2: Dosage Form Recommendation**

Background

Dosage form nomenclature is one critical review issue identified for NDA 22-408 (b) (4) (spinosad) (b) (4) in the Initial Quality Assessment DFS'd on March 23, 2009. The proposed dosage form by the applicant is (b) (4) is unacceptable.

The proposed product is an orange color, suspension of cetostearyl alcohol. The active ingredient, spinosad, is completely solubilized in the formulation. Based on the flowability of the product, the formulation, the physical appearance, and the need of shaking before use, the recommendation made in the Initial Quality Assessment for dosage form is "suspension."

An addendum was added to the Initial Quality Assessment on July 17, 2009, where a change was made in the dosage form recommendation from "suspension" to "suspension*". The rationale for the change was described in the addendum.

It was brought to the attention of this reviewer after the sign-off of the Addendum that a similar case (Imodium A-D NDA 19-487/SCF-022) was discussed a few years ago in Office of New Drug Chemistry, and it was concluded that the product should be called a suspension (CMC review #1 of SCF-022) without asterisk. This conclusion is currently reflected in the Orange Book and Drugs@FDA where two dosage forms (solution and suspension) were under the brand name drug, Imodium A-D.

Reviewer's Evaluation

A review of the CMC Reviews of Imodium A-D NDA 19-487 original submission and its supplement SCF 022, Orange Book, and current approved label/labeling for Imodium A-D (NDA 19-487) confirms the following:

(1) The formulation of Imodium A-D approved in the original NDA is a solution. The reformulated one approved through Supplement SCF-022 is a suspension but the suspended particles are not the active ingredient; they are excipients. Both solution and suspension are on the U.S. market today.

(2) The dosage form "suspension" was granted to the reformulated Imodium A-D without asterisk.

Because of the existence of a precedent (Imodium A-D), this reviewer would like to reverse her recommendation of the dosage form for NDA 22-408 back to "suspension". The reviewer would also like to recommend that the physical state of the active ingredient should be captured in the text of the labeling and be a part of packaging insert for this NDA. This piece of information (b) (4) is to assist future decision-making regarding pharmaceutical equivalence.

The capture of additional information for the active ingredient(s) in label/labeling has been done in the past even for OTC Drug Facts labeling. Attached to this addendum are two OTC examples. Aleve products (NDA 20-204/SLR-032) is an NDA product. The other is a monographed astringent product. The label of the astringent product is from a technical amendment published in the Federal Register (74 FR 9759). In both cases, an asterisk is used to provide more information for the active ingredient(s).

2 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

---

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

/s/

SHULIN DING
09/17/2009

MOO JHONG RHEE
09/17/2009
Chief, Branch III

MEMORANDUM

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

DATE: April 17, 2009

TO: NDA 22-408 Initial Quality Assessment

FROM: Shulin Ding, Ph.D., Pharmaceutical Assessment Lead
(ONDQA Division of Pre-Marketing assessment II)

THROUGH: Moo-Jhong Rhee, Ph.D., Chief, Branch III
(ONDQA Division of Pre-Marketing assessment II)

SUBJECT: **Additional Comments for Dosage Form**

Background

Dosage form nomenclature is one critical review issue identified for NDA 22-408 (b) (4) in the Initial Quality Assessment DFS'd on March 23, 2009. The proposed dosage form by the applicant (b) (4) is unacceptable.

The proposed product is an orange color, suspension of cetostearyl alcohol. The active ingredient, spinosad, is completely solubilized in the formulation. Based on the flowability of the product, the formulation, the physical appearance, and the need of shaking before use, the recommendation made in the Initial Quality Assessment for dosage form is "suspension."

Reviewer's Additional Comments on Dosage Form Nomenclature

Although "suspension" is recommended as the proper dosage form for the proposed product of NDA 22-408, an asterisk to the dosage form (i.e. suspension*) is believed to be necessary in this case. The asterisk is to denote that (b) (4) an inactive ingredient (cetostearyl alcohol), and the active ingredient (spinosad) is fully solubilized in the formulation.

(b) (4)

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

/s/

Shulin Ding
4/17/2009 12:08:48 PM
CHEMIST

Moo-Jhong Rhee
4/22/2009 09:27:35 AM
CHEMIST
Chief, Branch III

Initial Quality Assessment
Branch III
Pre-Marketing Assessment Division II

OND Division:	Division of Dermatology and Dental Products
NDA:	22-408
Applicant:	ParaPro Pharmaceuticals, LLC
Stamp Date:	Jan. 22, 2009
PDUFA Date	Nov. 22, 2009
Trademark:	(b) (4)
Established Name:	Spinosad
Dosage Form:	Suspension
Route of Administration:	Topical
Indication:	Human Head Lice (b) (4)
PAL:	Shulin Ding, Ph.D.

	YES	NO
ONDQA Fileability:	☒	☐
Comments for 74-Day Letter	☒	☐

Summary and Critical Issues:

A. Summary

ParaPRO LLC is submitting a 505(b) (1) New Drug Application (NDA) for the prescription use (b) (4) The proposed indication is treatment of human head lice (b) (4)

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 makes a reference to DMF 17795 held by Dow AgroSciences LLC (Michigan, USA) for CMC information of spinosad. The DMF has never been reviewed.

The proposed drug product, (b) (4) is an orange color, suspension of cetostearyl alcohol. The spinosad active ingredient is completely solubilized in the formulation. The product is packaged in a 4 ounce, white, high density polyethylene bottle with a white, (b) (4) child resistant, snap top cap and spout. No sample size is proposed.

The to-be-marketed formulation is the same formulation used in Phase 3 clinical trials and registration stability batches. The formulation contains the following excipients: benzyl alcohol, NF; butylated hydroxytoluene, NF; ceteareth-20; cetearyl alcohol, NF; FD&C yellow #6; hexylene glycol, NF; hydrochloric acid, NF; hydroxethyl cellulose, NF; isopropyl alcohol, USP; propylene glycol, USP; sodium hydroxide, USP/NF; stearalkonium chloride; and (b) (4) water, USP. All excipients are compendial except ceteareth-20, FD&C Yellow #6, and stearalkonium chloride. No novel excipients are present in the formulation.

The designated commercial site, (b) (4) is also the manufacturing site of Phase 3 and registration stability batches. The proposed commercial production scale is approximately (b) (4)

Stability data provided in the initial submission to support an expiration dating period of 36 months at temperature below 86°F (30°C) include 24 months of long term (25°C/60% RH), 12 months of intermediate temperature (30°C/65% RH), and two months of accelerated temperature (40°C/75% RH) data from three primary batches (b) (4) Special stability data provided in the NDA to support storage/handling/shipping of the product include data from the following studies: photostability, temperature cycling, and free/thaw.

B. Critical issues for review

Dosage Form Nomenclature

- The applicant proposes (b) (4) as the dosage form. (b) (4) however, is not a dosage form recognized by the Orange Book and CDER Data Standards Manual. (b) (4)

(b) (4)

The proposed product is formulated as a suspension of cetostearyl alcohol. Its physical appearance (b) (4) and the requirement of "shaking" before use are consistent with how conventional suspensions are recognized and handled. Therefore, "suspension" is recommended by this reviewer as the dosage form for this NDA.

The fact that the suspended particles in the proposed formulation are not the active ingredient but an excipient is considered but deemed to be a non-issue. CDER Data Standards Manual states that it is the physical form of the drug product (not drug substance) to be examined in dosage form determination.

To assist the assessment of dosage form, the applicant should officially submit a representative sample to the NDA with rheograms (viscosity versus shear rate and shear stress versus shear rate).

Drug Substance

- The letter of authorization for DMF 17795 does not contain the DMF number to which the NDA makes a reference. An appropriate letter with the DMF number should be submitted to the NDA.

- Spinosad is adopted by the USAN council very recently. Its full USAN definition has not been published. The applicant describes spinosad drug substance in the General Information section of drug substance as a fermentation product primarily consist of two active components, spinosyn A and D, without giving the ratio between A and D.

- The applicant does not propose regulatory specification for drug substance. Neither does the applicant describe how the drug substance lots are received and released for drug product manufacture.

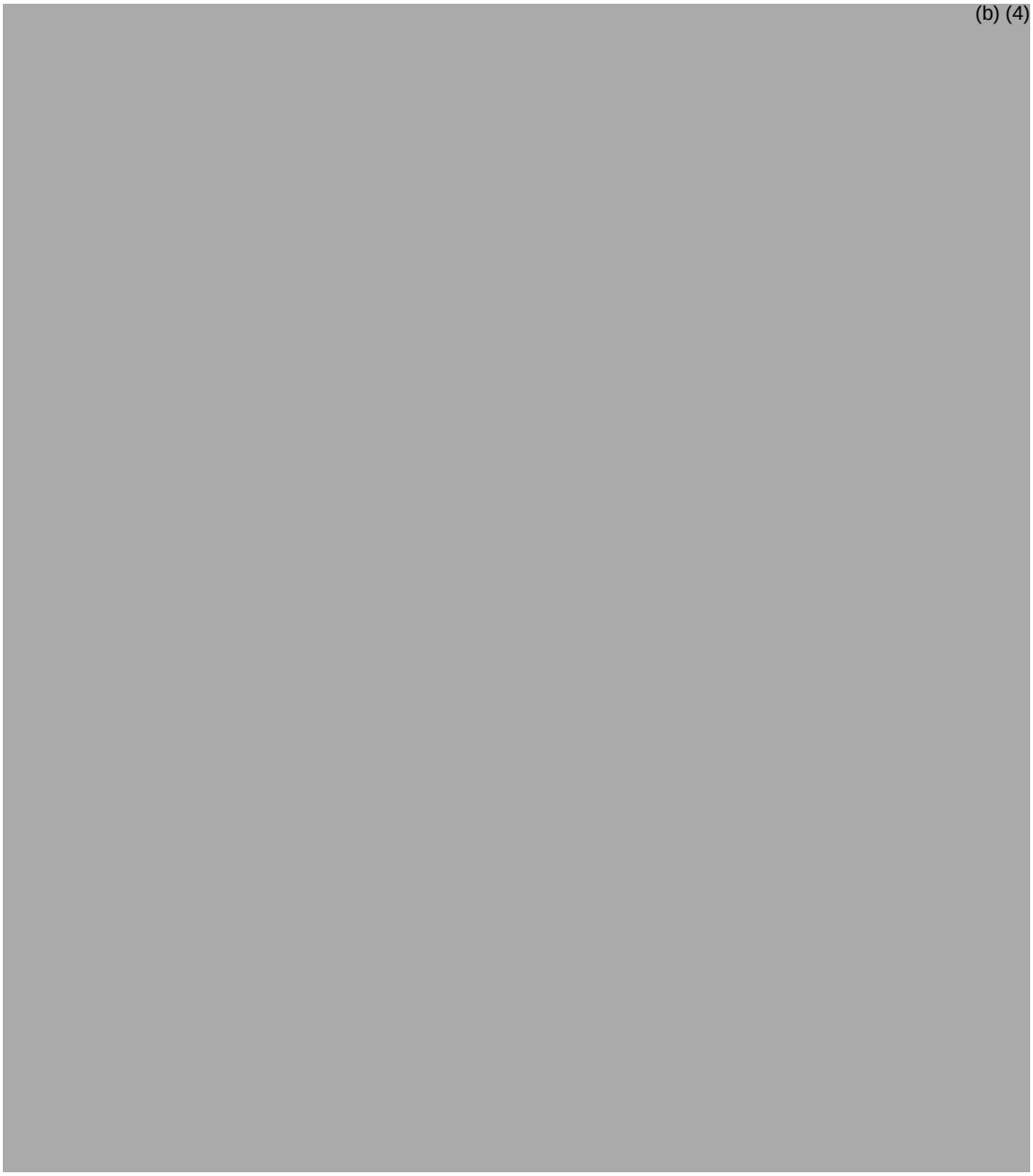
- Information for Master cell bank and working cell bank needs to be provided in the DMF and critically reviewed. Alternatively, this piece of information can be submitted by the applicant to the NDA.

Drug Product

Formulation Composition

- The table of Formulation Composition has numerous issues/deficiencies. First, the concentration of spinosad currently given in the table is a range (b) (4). This is unacceptable because this NDA proposes only one formulation and one strength for marketing. The concentration of spinosad in the Formulation Composition table of Sections 2.3.P.1 and 3.2.P.1 should be corrected to the label claim, 0.9%. Second, some functions (b) (4) assigned by the applicant to excipients are objected by Clinical because they imply claims. Third, the quantity of water used in the formulation should be "qs" (b) (4) Fourth, the grade of water is not indicated on the table. (It is USP grade per executed batch records.) Fifth, the targeted pH value should be indicated on the table since the exact amounts of hydrochloric acid and sodium hydroxide are not given. Lastly, the role of benzyl alcohol in this product is very questionable. The applicant assigns benzyl alcohol (b) (4) but benzyl alcohol at 5% is known to be safe and efficacious in killing lice. Unless the applicant can prove that benzyl alcohol (b) (4) in this product does not contribute to the efficacy, benzyl alcohol could potentially be an active ingredient.

1 Page has been Withheld in Full as B4 (CCI/TS) Immediately Following this Page



C. Comments for 74-Day Letter:

1. Provide representative samples (3 units) to the NDA with rheograms (viscosity versus shear rate and shear stress versus shear rate) to assist the assessment of dosage form.

2. Provide production forecast for five years and show calculation of EIC (Expected Introduction Concentration into the aquatic environment) for the peak year.

3. Provide a definition for spinosad drug substance. The drug substance must be defined as follows:

1) Identity and strength: The components A and D must be present with a definite ratio. Once the ratio is established, the strength can be expressed as A+D.
2) Purity: All other components are regarded as related substances and controlled per the principle described in ICH Q3A.

4 The identity and strength of the drug product must be defined per the definition of drug substance. The degradants found in the drug product must comply with the principles described in ICH Q3B.

5. Propose a regulatory specification for drug substance per the definition given above in Point 3.

6. Ensure that the tables in DMF 17795 for batch analysis and stability contain proper data to support the proposed regulatory specification. Alternatively, the tables of batch analysis and stability can be provided in the NDA.

7. Ensure that DMF 17795 contains method validation information which demonstrates that the method for the related substances is stability indicating and can adequately support the proposed related substance regulatory specification. Alternatively, the method validation information for related substances can be provided in the NDA.

8. Submit the following information for drug product toxicology batches: concentrations on components A and D individually, and related substances.

9. Propose acceptable assay specification (including method and acceptance criteria) per definition above in Points 3.1. and 4.

10. Propose acceptable Related Substances specification (including method and acceptance criteria).

11. Submit method validation information which demonstrates that the related substances method for drug product is stability indicating and can adequately support the proposed related substances specification.

12. Current method validation for drug product on assay was not carried out properly. (1) Perform forced degradation study in compliance with the principle described in ICHQ2B using all appropriate stress conditions (acid/base, heat, light, oxide, etc.) recommended by the ICH guideline. (2) Peak purity should be checked for both spinosyn A and D peaks. (3) Re-analyze method validation data and show that the method is specific, accurate, and precise for the analysis of spinosyn A and spinosyn D.

13. Provide the following test results for the caps used in the drug product container/closure system: physicochemical tests and extractables studies per USP<661>.

14. Provide the following test results for the bottles used in the drug product container/closure system: physicochemical tests per USP<661>.

D. Comments/Recommendation:

The application is fileable from the CMC perspective.

The major review issues of this NDA include dosage form, drug substance/drug product specification, drug product stability, method validation, and container/closure system. Both drug substance and drug product manufacturing sites are located in U.S. GMP inspection requests have been submitted.

Shulin Ding, Ph.D.
Pharmaceutical Assessment Lead

Moo Jhong Rhee, Ph.D.
Chief, Branch III

Filing Checklists

A. Administrative Checklists

YES	NO		Comments
x		On its face, is the section organized adequately?	
x		Is the section indexed and paginated adequately?	
x		On its face, is the section legible?	
x		Are ALL of the facilities (including contract facilities and test laboratories) identified with full street addresses and CFNs?	
x		Has an environmental assessment report or categorical exclusion been provided?	

B. Technical Checklists

1. Drug Substance Spinosad: referenced to DMF 17795

	x	Does the section contain synthetic scheme with in-process parameters?	Reference to DMF
	x	Does the section contain structural elucidation data?	Reference to DMF
	x	Does the section contain specifications?	Reference to DMF
	x	Does the section contain information on impurities?	Reference to DMF
	x	Does the section contain validation data for analytical methods?	Reference to DMF
	x	Does the section contain container and closure information?	Reference to DMF
	x	Does the section contain stability data?	Reference to DMF

2. Drug Product

x		Does the section contain manufacturing process with in-process controls?	
x		Does the section contain quality controls of excipients?	
x		Does the section contain information on composition?	
x		Does the section contain specifications?	
	x	Does the section contain information on degradation products?	This is a review issue.
x		Does the section contain validation data for analytical methods?	Yes for assay. No for RS method
x		Does the section contain information on container and closure systems?	Missing some tests per USP<661> for caps and bottles
x		Does the section contain stability data with a proposed expiration date?	
x		Does the section contain information on labels of container and cartons?	
x		Does the section contain tradename and established name?	

C. Review Issues

x		Has all information requested during the IND phases, and at the pre-NDA meetings been included?	No control on ratio of A to D.
	x	Is a team review recommended?	
x		Are DMFs adequately referenced?	LOA is w/o DMF#

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

/s/

Shulin Ding
3/23/2009 01:36:34 PM
CHEMIST

Moo-Jhong Rhee
3/23/2009 02:25:54 PM
CHEMIST
Chief, Branch III