CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

022408Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

EXCLUSIVITY SUMMARY

NDA # 022408 SUPPL # HFD # 540

Trade Name Natroba

Generic Name spinosad

Applicant Name ParaPRO, LLC

Approval Date, If Known

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES ☒ NO ☐

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3,SE4, SE5, SE6, SE7, SE8

505(b)(1)

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES ☒ NO ☐

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

d) Did the applicant request exclusivity?

YES ☐ NO ☒

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

e) Has pediatric exclusivity been granted for this Active Moiety?

YES ☐ NO ☒

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES ☐ NO ☒

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES
(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES ☐ NO ☒

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES ☐ NO ☐

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered “NO” for original approvals of new molecular entities.)
IF “YES,” GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a)

is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES ☐ NO ☐

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES ☐ NO ☐

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES ☐ NO ☐

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES ☐ NO ☐

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES ☐ NO ☐

If yes, explain:

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES ☐ NO ☐

Investigation #2 YES ☐ NO ☐

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES ☐ NO ☐

Investigation #2 YES ☐ NO ☐

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1 !
!
IND # YES ☐ ! NO ☐
! Explain:

Investigation #2 !
!
IND # YES ☐ ! NO ☐
! Explain:

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1	!
	!
YES ☐	! NO ☐
Explain:	! Explain:

Investigation #2	!
	!
YES ☐	! NO ☐
Explain:	! Explain:

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES ☐ NO ☐

If yes, explain:

==========

Name of person completing form: Dawn Williams, B.S.N.
Title: Regulatory Health Project Manager
Date: October 19, 2010

Name of Office/Division Director signing form: Susan J. Walker, M.D., F.A.A.D.
Title: Director, DDDP

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05

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/s/

DAWN WILLIAMS
12/21/2010

SUSAN J WALKER
12/28/2010

ParaPRO ANSON GROUP

9 April 2009

Module 1.3.3

Debarment Certification

ParaPRO hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application.

O. Reed Tarwater, Ph.D., RAC
Director, Anson Group and Regulatory Consultant to ParaPRO

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Silver Spring, MD 20993

NDA 022408

PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE

ParaPRO Pharmaceuticals, LLC
11550 North Meridian Street
Suite 600
Carmel, Indiana 46032-4565

ATTENTION: William H. Culpepper, III
President

Dear Mr. Culpepper:

Please refer to your New Drug Application (NDA) resubmission dated July 23, 2010, received July 26, 2010, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Spinosad Suspension, 0.9%.

We also refer to your July 23, 2010 correspondence, received July 26, 2010, requesting review of your proposed proprietary name, Natroba.

We have completed our review of the proposed proprietary name, Natroba, and have concluded that it is vulnerable to name confusion that could lead to medication errors with a proposed proprietary name for a pending application. 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.

If you wish to continue to pursue the proposed name Natroba at this time, we will re-review your name 90 days prior to the approval of the NDA. If **any** of the proposed product characteristics as stated in your July 23, 2010 submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Janet Anderson, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-0675. For any other information regarding this application, contact the Office of New Drugs (OND) Regulatory Project Manager, Dawn Williams, at (301) 796-5376.

Sincerely,

{See appended electronic signature page}

Denise P. Toyer, Pharm.D.
Deputy Director
Division of Medication Error Prevention and Analysis
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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

/s/

DENISE P TOYER
10/22/2010

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

TO *(Office/Division)*: DDMAC

FROM (*Name, Office/Division, and Phone Number of Requestor)*: DDDP
Dawn Williams, RPM; 6-5376
Trish Brown, Clinical Reviewer; 6-0857

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
August 19, 2010		022408	Pending NDA Resubmission	July 26, 2010

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
spinosad suspension, 0.9%	Standard	Pediculicide/Lice Agent (4020140)	September 1, 2010

NAME OF FIRM: ParaPRO, Pharmaceuticals

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE / ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE-NDA MEETING
- ☐ END-OF-PHASE 2a MEETING
- ☐ END-OF-PHASE 2 MEETING
- ☐ RESUBMISSION
- ☐ SAFETY / EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☒ OTHER *(SPECIFY BELOW)*:

II. BIOMETRICS

- ☐ PRIORITY P NDA REVIEW
- ☐ END-OF-PHASE 2 MEETING
- ☐ CONTROLLED STUDIES
- ☐ PROTOCOL REVIEW
- ☐ OTHER (SPECIFY BELOW):
- ☐ CHEMISTRY REVIEW
- ☐ PHARMACOLOGY
- ☐ BIOPHARMACEUTICS
- ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE 4 STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL - BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG SAFETY

- ☐ PHASE 4 SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE, e.g., POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ NONCLINICAL

COMMENTS / SPECIAL INSTRUCTIONS: Please review and make recommendations on the PI for NDA 22-408, spinosad suspension, 0.9%. Please determine whether the PI has any language that could be promotional in nature.
eRoom Location of the label:
http://eroom.fda.gov/eRoom/CDER3/CDERDivisionofDematologyandDentalProducts/0_18816
When a reviewer assignment has been made, please advise me of his/her name so that I can forward the meeting invitiations.
Thank you!

SIGNATURE OF REQUESTOR
Dawn Williams, RPM

METHOD OF DELIVERY (Check one)
☒ DARRTS ☒ EMAIL ☐ MAIL ☐ HAND

PRINTED NAME AND SIGNATURE OF RECEIVER

PRINTED NAME AND SIGNATURE OF DELIVERER

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

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/s/

DAWN WILLIAMS
08/25/2010

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

TO *(Office/Division)*: DRISK

FROM (*Name, Office/Division, and Phone Number of Requestor)*: DDDP
Dawn Williams, RPM; 6-5376
Trish Brown, Clinical Reviewer; 6-0857

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
August 19, 2010		022408	Pending NDA Resubmission	July 26, 2010

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
spinosad suspension, 0.9%	Standard	Pediculicide/Lice Agent (4020140)	September 1, 2010 (Date of the 2nd Labeling Meeting)

NAME OF FIRM: ParaPRO Pharmaceuticals

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE / ADDITION
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- ☐ END-OF-PHASE 2a MEETING
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- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☒ OTHER *(SPECIFY BELOW)*:

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- ☐ POISON RISK ANALYSIS

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- ☐ NONCLINICAL

COMMENTS / SPECIAL INSTRUCTIONS: Please review the Patient Information section of the PI. We are targeting action on this NDA Resubmission on November 16, 2010.
The eRoom Location of the Label:
http://eroom.fda.gov/eRoom/CDER3/CDERDivisionofDematologyandDentalProducts/0_18816
Please provide me with the name of the assigned reviewer so that I can forward the labeling meeting invitations to him/her. Thank you!

SIGNATURE OF REQUESTOR
Dawn Williams, RPM

METHOD OF DELIVERY (Check one)
☒ DARRTS ☒ EMAIL ☐ MAIL ☐ HAND

PRINTED NAME AND SIGNATURE OF RECEIVER

PRINTED NAME AND SIGNATURE OF DELIVERER

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

TO *(Office/Division)*: DMEPA

FROM (*Name, Office/Division, and Phone Number of Requestor)*: DDDP
Dawn Williams, RPM; 6-5376
Trish Brown, Clinical Reviewer; 6-0857

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
August 19, 2010		022408	Pending NDA Resubmssion	July 26, 2010

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
spinosad suspension, 0.9%	Standard	Pediculicide/Lice Agent (4020140)	September 1, 2010 (second labeling meeting date)

NAME OF FIRM: ParaPRO Pharmaceuticals

REASON FOR REQUEST

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- ☐ END-OF-PHASE 2 MEETING
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- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☒ OTHER *(SPECIFY BELOW)*:

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- ☐ NONCLINICAL

COMMENTS / SPECIAL INSTRUCTIONS: Please review the attached Package Insert (PI and PPI) and carton and container labels. Labeling meetings have been scheduled for March 11 and 23, 2010. This is an electronic submission.
eRoom Location of Labeling for PI:
http://eroom fda.gov/eRoom/CDER3/CDERDivisionofDematologyandDentalProducts/0_18816
eRoom Location of Carton and Container Labels:
http://eroom fda.gov/eRoom/CDER3/CDERDivisionofDematologyandDentalProducts/0_189cb
We are targeting action on this NDA on November 16, 2010.
Once a reviewer assignment has been made, please provide me with his/her name so that I can forward the labeling meeting invitations.
Thank you!

SIGNATURE OF REQUESTOR	METHOD OF DELIVERY (Check one)
Dawn Williams, RPM	☒ DARRTS ☒ EMAIL ☐ MAIL ☐ HAND
PRINTED NAME AND SIGNATURE OF RECEIVER	PRINTED NAME AND SIGNATURE OF DELIVERER

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

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/s/

DAWN WILLIAMS
08/25/2010

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

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/s/

DAWN WILLIAMS
08/25/2010

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

TO *(Office/Division)*: Pediatric and Maternal Health Staff	FROM (*Name, Office/Division, and Phone Number of Requestor)*: DDDP Dawn Williams, RPM; 6-5376 Trish Brown, Clinical Reviewer; 6-0857

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
August 16, 2010		022408	Pending Resubmission	July 26, 2010

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
(spinosad) Suspension, 0.9%		Pediculicide/Lice Agent (Topical) 4020140	Meetings scheduled for August 26, 2010, and September 1, 2010

NAME OF FIRM: ParaPRO Pharmaceuticals, LLC

REASON FOR REQUEST

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- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☒ OTHER *(SPECIFY BELOW)*:

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- ☐ PROTOCOL REVIEW
- ☐ OTHER (SPECIFY BELOW):
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- ☐ PHARMACOLOGY
- ☐ BIOPHARMACEUTICS
- ☐ OTHER (SPECIFY BELOW):

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- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ NONCLINICAL

COMMENTS / SPECIAL INSTRUCTIONS:

The sponsor, 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. Spinosad is used as an agricultural insecticide and is thought to act in lice by causing neuronal excitation followed by paralysis and death. The initial application was reviewed, and the action taken was a Complete Response on November 18, 2009. Among the reasons for the complete response was:

"(b) (4) provide pharmacokinetic data for spinosad, as well as for benzyl alcohol, in lice-infested pediatric subjects aged 6 – 24 months."

The applicant requested a pediatric waiver for children less than 6 months of age based on the rationale that studies are “highly impractical since the number of subjects in this age group is very small.’’ The application was not presented to the PeRC PREA subcommittee because of the Complete Response action.

The applicant provided a resubmission for the spinosad product on July 26, 2010.
DDDP now requests the consultative opinion of the pediatric and maternal health staff regarding pediatric labeling for the spinosad drug product.

If you have any questions regarding this consult, please feel free to contact the Medical Officer, Trish Brown, or me at the numbers listed above.

Once an assignment has been made, please provide me with the name so that I can forward him/her the meeting invitations.

Thank you!

SIGNATURE OF REQUESTOR Dawn Williams, RPM	METHOD OF DELIVERY (Check one) ☒ DARRTS ☒ EMAIL ☐ MAIL ☐ HAND
PRINTED NAME AND SIGNATURE OF RECEIVER	PRINTED NAME AND SIGNATURE OF DELIVERER

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

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/s/

DAWN WILLIAMS
08/17/2010

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

TO *(Office/Division)*: Pediatric and Maternal Health Staff-MHT	FROM (*Name, Office/Division, and Phone Number of Requestor)*: DDDP Dawn Williams, RPM; 6-5376 Trish Brown, Clinical Reviewer; 6-0857

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
August 16, 2010		022408	Pending Resubmission	July 26, 2010

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
(spinosad) Suspension, 0.9%		Pediculicide/Lice Agent (Topical) 4020140	Meetings scheduled for August 26, 2010, and September 1, 2010

NAME OF FIRM: ParaPRO Pharmaceuticals, LLC

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE / ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE-NDA MEETING
- ☐ END-OF-PHASE 2a MEETING
- ☐ END-OF-PHASE 2 MEETING
- ☐ RESUBMISSION
- ☐ SAFETY / EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☒ OTHER *(SPECIFY BELOW)*:

II. BIOMETRICS

- ☐ PRIORITY P NDA REVIEW
- ☐ END-OF-PHASE 2 MEETING
- ☐ CONTROLLED STUDIES
- ☐ PROTOCOL REVIEW
- ☐ OTHER (SPECIFY BELOW):
- ☐ CHEMISTRY REVIEW
- ☐ PHARMACOLOGY
- ☐ BIOPHARMACEUTICS
- ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE 4 STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL - BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG SAFETY

- ☐ PHASE 4 SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE, e.g., POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ NONCLINICAL

COMMENTS / SPECIAL INSTRUCTIONS:

The sponsor, 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. Spinosad is used as an agricultural insecticide and is thought to act in lice by causing neuronal excitation followed by paralysis and death. The initial application was reviewed, and the action taken was a Complete Response on November 18, 2009. Among the reasons for the complete response was:

"(b) (4) provide pharmacokinetic data for spinosad, as well as for benzyl alcohol, in lice-infested pediatric subjects aged 6 – 24 months."

The applicant requested a pediatric waiver for children less than 6 months of age based on the rationale that studies are “highly impractical since the number of subjects in this age group is very small.’’ The application was not presented to the PeRC PREA subcommittee because of the Complete Response action.

The applicant provided a resubmission for the spinosad product on July 26, 2010.
DDDP now requests the consultative opinion of the pediatric and maternal health staff regarding pediatric labeling for the spinosad drug product.

Please review and provide comments/recommendations on the pregnancy and nursing mothers section of this labeling (contains benzyl alcohol).

If you have any questions regarding this consult, please feel free to contact the Medical Officer, Trish Brown, or me at the numbers listed above.

Once an assignment has been made, please provide me with the name so that I can forward him/her the meeting invitations.

Thank you!

SIGNATURE OF REQUESTOR Dawn Williams, RPM	METHOD OF DELIVERY (Check one) ☒ DARRTS ☒ EMAIL ☐ MAIL ☐ HAND
PRINTED NAME AND SIGNATURE OF RECEIVER	PRINTED NAME AND SIGNATURE OF DELIVERER

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

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/s/

DAWN WILLIAMS
08/25/2010

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Silver Spring, MD 20993

NDA 022408

PROPRIETARY NAME REQUEST WITHDRAWN

ParaPRO Pharmaceuticals, LLC
11550 North Meridian Street, Suite 600
Carmel, Indiana 46032-4565

ATTENTION: William H. Culpepper, III
President

Dear Mr. Culpepper:

Please refer to your New Drug Application (NDA) dated January 21, 2009, received January 22, 2009, submitted under section 505(b) of the Federal Food, Drug and Cosmetic Act for Spinosad Topical Suspension, 0.9%.

We acknowledge receipt of your June 14, 2010, correspondence, on June 14, 2010, notifying us that you are withdrawing your May 25, 2010, request for a review of the proposed proprietary name Natroba, (b) (4). This proposed proprietary name request is considered withdrawn as of June 14, 2010.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, call Janet L. Anderson, Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-0675. For any other information regarding this application, contact the Office of New Drugs (OND) Regulatory Project Manager, Dawn Williams at (301) 796-5376.

Sincerely,

{See appended electronic signature page}

Carol Holquist, RPh
Director
Division of Medication Error Prevention and Analysis
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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

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/s/

CAROL A HOLQUIST
07/12/2010

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 022408

MEETING MINUTES

ParaPRO Pharmaceuticals, LLC
Attention: O. Reed Tarwater, Ph.D., RAC
Senior Regulatory Consultant
11460 N. Meridian Street, Suite 150
Carmel, IN 46032

Dear Dr. Tarwater:

Please refer to your New Drug Application (NDA submitted under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act for TRADENAME (spinosad) Suspension, 0.9% for the treatment of head lice (b) (4) in patients (b) (4)

We also refer to the meeting between representatives of your firm and the FDA on March 25, 2010. The purpose of the meeting was to discuss whether ParaPRO's product contains two active ingredients, spinosad and benzyl alcohol.

A copy of the official minutes of the meeting is attached for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Dawn Williams, Regulatory Project Manager, at (301) 796-5376.

Sincerely,

{See appended electronic signature page}

Susan J. Walker, M.D., F.A.A.D.
Director
Division of Dermatology and Dental Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosure

Meeting Minutes

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type: Type A
Meeting Category: Post-Action Meeting

Meeting Date and Time: March 25, 2010, 10:00 AM
Meeting Location: FDA White Oak Campus, Building 22, Room 1309

Application Number: NDA 022408
Product Name: TRADENAME (spinosad) Suspension, 0.9%
Indication: Treatment of head lice (b) (4) in patients (b) (4)

Sponsor/Applicant Name: ParaPRO Pharmaceuticals, LLC

Meeting Chair: Susan Walker, M.D.
Meeting Recorder: Dawn Williams, B.S.N.

FDA ATTENDEES
Julie Beitz, M.D., Director, ODE III
Susan Walker, M.D., F.A.A.D., Director, DDDP
Patricia Brown, M.D., Clinical Reviewer, DDDP
Barbara Hill, Ph.D., Pharmacology Supervisor, DDDP
Jianyong Wang, Ph.D., Pharmacology Reviewer, DDDP
Shulin Ding, Ph.D., Pharmaceutical Assessment Lead, DPA II, Branch III
Zhengfang Ge, Ph.D., Product Quality Reviewer, DPA II, Branch III
Dennis Bashaw, Pharm.D., Director, DCP III
Mohamed Alosh, Ph.D., Biostatistics Team Leader, DB III
Kathy Fritsch, Ph.D., Biostatistics Reviewer, DB III
Carin Kim, Ph.D., Biostatistics Reviewer, DB III
Michael Bernstein, J.D., Supervisory Regulatory Counsel, DRP
Donna Katz, J.D., Associate Chief Counsel, OCC
Maria Walsh, M.S.N., Acting ADRA, ODE III
Barbara Gould, M.B.A.H.C.M, Chief, Project Management Staff, DDDP
Dawn Williams, B.S.N., Regulatory Health Project Manager, DDDP

SPONSOR ATTENDEES
Bill Culpepper, President, ParaPRO Pharmaceuticals
William Kozarek, Ph.D., Senior CMC Consultant, Anson Group
John Quiring, Ph.D., President and CEO, QST Consultations
Suzanne O'Shea, Counsel, Baker and Daniels
Reed Tarwater, Ph.D., Director, Anson Group

1.0 Regulatory Correspondence History (includes Regulatory History of past correspondences/interactions)

We have sent the following correspondences:

- November 18, 2009 Complete Response Letter

We have received the following correspondences:

- A letter dated December 29, 2009 from Suzanne O'Shea and Daniel Carmichael of Baker Daniels to Dr. Julie Beitz requesting a Type A meeting to discuss ParaPRO's response to the Complete Response Letter
- ParaPRO's Briefing Document dated January 22, 2010 for a Type A Meeting

Comments

We believe that the activity of the spinosad component of the ParaPRO product may be supported by the phase 2 clinical trial experience (SPN-202-06).

We have not yet reached a consensus on whether benzyl alcohol, present (b) (4) in the ParaPRO product, is an active ingredient. Some of the issues that we have been discussing and would like further clarity from you are:

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 benzyl alcohol be (b) (4) in this product cannot be the sole basis for determining that the benzyl alcohol is an inactive ingredient.

Meeting Discussion:
Sponsor committed to submitting the following existing information to support that benzyl alcohol is a formulation necessity including items such as:

- (b) (4) of spinosad (b) (4)
- pH (b) (4) profile
- formulation development data (b) (4) and pH, etc.
- formulation issues related to cosmetic acceptability

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. a 22% and 89% treatment success rate for the vehicle in phase 2 study SPN-201-05 at days 7 and 14, respectively;
    b. 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 sponsor 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 sponsor 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.

Meeting Discussion:
The sponsor presented a hand-out at the meeting, and they will amplify this information in a formal submission to the pending NDA.

Responses to your remaining questions, except for Question 9, cannot be provided until we determine whether benzyl alcohol is or is not an active ingredient in your product.

Question 9:
Does the FDA agree that the specifications for Ammonyx4 (b) (4) are adequate?

Response:
Yes, the specifications for Ammonyx4 (b) (4) are acceptable.

Meeting Discussion:
The sponsor inquired about the acceptability of spinosad drug substance specification. The Agency responded that the spinosad specification submitted in the briefing package is acceptable.

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

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/s/

SUSAN J WALKER
04/09/2010

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

TO *(Office/Division)*: DDMAC- Andy Haffer	FROM (*Name, Office/Division, and Phone Number of Requestor)*: DDDP Dawn Williams, RPM 6-5376

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
September 21, 2009		22-408	PI	September 18, 2009

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
spinosad	Standard		October 5, 2009

NAME OF FIRM: ParaPRO, Pharmaceuticals

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE / ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE-NDA MEETING
- ☐ END-OF-PHASE 2a MEETING
- ☐ END-OF-PHASE 2 MEETING
- ☐ RESUBMISSION
- ☐ SAFETY / EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☒ OTHER *(SPECIFY BELOW)*:

II. BIOMETRICS

- ☐ PRIORITY P NDA REVIEW
- ☐ END-OF-PHASE 2 MEETING
- ☐ CONTROLLED STUDIES
- ☐ PROTOCOL REVIEW
- ☐ OTHER (SPECIFY BELOW):
- ☐ CHEMISTRY REVIEW
- ☐ PHARMACOLOGY
- ☐ BIOPHARMACEUTICS
- ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE 4 STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL - BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG SAFETY

- ☐ PHASE 4 SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE, e.g., POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ NONCLINICAL

COMMENTS / SPECIAL INSTRUCTIONS: Please review and make recommendations on the PI for NDA 22-408, (b) (4) (spinosad) Suspension, 0.9%. Please determine whether the PI has any language that could be promotional in nature.

Thanks!

SIGNATURE OF REQUESTOR	METHOD OF DELIVERY (Check one)
Dawn Williams, RPM	☒ DARRTS ☒ EMAIL ☐ MAIL ☐ HAND
PRINTED NAME AND SIGNATURE OF RECEIVER	PRINTED NAME AND SIGNATURE OF DELIVERER

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

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/s/

DAWN WILLIAMS
09/21/2009

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 22-408 **INFORMATION REQUEST**

ParaPRO Pharmaceuticals, LLC
c/o Anson Group
Attention: Reed Tarwater, Ph.D., RAC
Director
11460 N. Meridian St., Suite 150
Carmel, IN 46032

Dear Dr. Tarwater:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for (b) (4) (spinosad) Suspension 0.9%, for treatment of human head lice (b) (4).

We also refer to your submissions dated June 29, July 9, July 16, and August 21, 2009.

We are reviewing the CMC sections of your submissions and have the following comments and information requests. We request a written response by close of business September 11, 2009 in order to continue our evaluation of your NDA.

Drug Substance:

- In addition to cross reference DMF 17795, submit a specification for the drug substance to the NDA.

Drug Product:

1. The proposed weight loss acceptance criteria (b) (4) is considered significant according to ICH Q1A, tighten the acceptance criteria for weight loss to NMT (b) (4) supported by your stability results.

2. Based on the retention time table for the HPLC method provided in response to Q19 submitted on August 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.

3. Provide more detailed information regarding the (b) (4) drug product when stored under accelerated condition. Explain why only one of the primary stability batches was studied for the stabilities under intermediate condition between initial and month 12, but the other two batches only tested at initial and month 12.

4. It is discovered that the drug product sample provided to the Agency is (b) (4) (b) (4). Provide manufacture date of the sample product and explain if this is common to the drug product.

5. Send additional drug product samples from the primary batches.

Container/Carton Labels:

1. The proposed dosage form nomenclature (b) (4) is not acceptable. Based on the flowability of the drug product and the (b) (4) cetostearyl alcohol in the drug product, you should change the dosage form nomenclature (b) (4) to **Suspension**, which is in compliance with the Agency's current policy.

2. The strength of the drug product should be revised to 0.9% and should be moved out of the parentheses. The drug product should be expressed as (b) (4) (spinosad) Suspension 0.9%.

3. The storage condition should be expressed as Store at 25°C (77°F); excursions permitted to 15° to 30°C (59° to 86°F).

4. "Shake well before use" should be moved to more prominent location.

5. Provide updated mock-up of container/carton labels.

If you have any questions, call me at (301) 796-5376.

Sincerely,

{See appended electronic signature page}

Dawn Williams, RN, BSN
Regulatory Health Project Manager
Division of Dermatology and Dental Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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

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/s/

DAWN WILLIAMS
09/03/2009

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 22-408 **(E) CAC – FINAL REPORT**

ParaPRO Pharmaceuticals, LLC
c/o Anson Group
Attention: Reed Tarwater, Ph.D., RAC
Director
11460 N. Meridian St., Suite 150
Carmel, IN 46032

Dear Dr. Tarwater:

Please refer to your new drug application for (b) (4) (spinosad) Suspension 0.9%, for the treatment of head lice (b) (4) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act.

Our Executive Carcinogenicity Assessment Committee (Exec CAC) reviewed your oral mouse and rat carcinogenicity study reports on August 18, 2009. As requested in your July 7, 2009 submission, a copy of the final Exec CAC minutes regarding (b) (4) is enclosed.

The recommendations made by the Exec. CAC are advisory in nature and should not be interpreted as a measure of the approvability of any application for this product.

If you have any questions, call Dawn Williams, Regulatory Project Manager, at (301)796-5376.

Sincerely,

{See appended electronic signature page}

Barbara Hill, Ph.D.
Pharmacology Supervisor
Division of Dermatology and Dental Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosure

Executive CAC
Date of Meeting: August 18, 2009

Committee: David Jacobson-Kram, Ph.D., OND IO, Chair
Paul Brown, Ph.D., OND, IO, Member
Todd Bourcier, Ph.D., DMEP, Alternating Member
Barbara Hill, Ph.D., DDDP, Supervisor
Jianyong Wang, Ph.D., DDDP, Presenting Reviewer

Author of Draft: Jianyong Wang, Ph.D.

The following information reflects a brief summary of the Committee discussion and its recommendations.

NDA #: 22-408
Drug Name: (b) (4) Spinosad)
Sponsor: ParaPRO Pharmaceuticals, Carmel, Indiana

Background:

(b) (4) spinosad) is developed by the sponsor to treat head lice infestation. The proposed use of this drug product is a single topical treatment (up to 120 mL, which contains 1200 mg spinosad) on scalp and hair for 10 minutes then the drug product will be rinsed off with warm water. Clinical pharmacokinetic studies have shown that systemic exposure to spinosad/spinosad metabolites is very low (below the limit of quantification: 3 ng/mL) under maximal use conditions of the drug product. Usually carcinogenicity studies are not considered necessary to support the development of a drug product for an acute indication. However, spinosad is used as an agricultural insecticide and two oral carcinogenicity studies have been conducted to support that use. The study protocols of the two carcinogenicity studies were not submitted to the Agency for evaluation. The two oral carcinogenicity study reports were submitted to the NDA for review.

Mouse Carcinogenicity Study:

In an 18-month oral mouse carcinogenicity study, doses (in diet) of 0, 0.0025, 0.0080, and 0.0360% of spinosad (0, 3.4, 11.4, and 50.9 mg/kg/day for males and 0, 4.2, 13.8, and 67.0 mg/kg/day for females) were given to CD-1 mice. There were no significant treatment-related findings in low or middle dose group mice. Due to a high mortality rate, high dose females were terminated early on Day 455. Body weights were lower in high dose males (3-11.2%) and females (4.6-11.1%), compared with control. Spleen weights were higher in high dose males and females at the 3 months sacrifice only, which was consistent with the histological finding of increased extramedullary hematopoiesis noted in spleen. Thickening of the glandular portion of stomach was noted in the majority of high dose animals. Histologically, increase in vacuolation in various tissues, sinus histiocytosis in lymph nodes, skeletal muscle myopathy, chronic inflammation and hyperplasia of the glandular mucosa of stomach, and hyperplasia and

hyperkeratosis of the nonglandular mucosa of stomach, were noted in high dose males and females. There were no significant neoplastic findings according to the Haseman-Lin-Rahman criteria. High dose females were not included in the neoplastic findings statistical evaluation due to early termination.

The NOAEL is considered to be the middle dose in the study, 0.008% of spinosad. The high dose (0.036%) reached the MTD in males and exceeded the MTD in females, while the middle dose is below the MTD in females. It would be preferable to have a dose between 0.036% and 0.008% in females. However, the overall study design appears acceptable.

Rat Carcinogenicity Study:

In a 2-year oral rat carcinogenicity and chronic toxicity study, doses (in diet) of 0, 0.005, 0.02, 0.05, and 0.10% of spinosad (0, 2.4, 9.5, 24.1 and 49.4 mg/kg/day for males and 0, 3.0, 12.0, 30.1 and 62.8 mg/kg/day for females) were given to Fischer 344 rats. Due to a high mortality rate, high dose males and females were terminated early on Days 714 and 611, respectively. Body weights were lower in high dose males (3-17.8%) and females (2.1-9.9%), compared with control. Gross pathology and histology were not evaluated in high dose males and females at 24-month sacrifice due to early termination. An increase in organ weights was noted in heart, kidney, liver, spleen, and thyroid gland in high dose animals. An increase in organ weights was also noted in heart (male), kidney (female), thyroid gland in animals at 0.05% dose, to a lesser degree compared to high dose group. At the 12 months sacrifice, histological findings noted in high dose group included: heart degeneration, vacuolation in kidney (females), skeletal muscle degeneration, slight aggregation of reticuloendothelial cells in liver, spleen, and mesenteric lymph nodes, slight increase of extramedullary hematopoesis in spleen (females), slight subacute to chronic inflammation in lung, degeneration/regeneration of the glandular mucosa of stomach, vacuolation and subacute to chronic inflammation in thyroid gland. Similar findings were also observed in the liver, mesenteric lymph node, and thyroid gland of females at 0.05% dose and the thyroid gland of males at 0.05% dose. At the 24-month sacrifice, histological findings noted in animals at 0.05% dose included: vacuolation, subacute to chronic inflammation, and necrosis of thyroid gland, slight subacute to chronic inflammation in lung (females), and slight aggregation of reticuloendothelial cells in lymph nodes. Vacuolation in thyroid glands was also noted in a number of male and female rats at 0.02% dose. There were no significant neoplastic findings according to the Haseman-Lin-Rahman criteria. High dose males and females were not included in the neoplastic findings statistical evaluation due to early termination.

The NOAEL is considered to be the low dose of the study, 0.005% of spinosad, considering histological findings in animals at 0.02% dose. The high dose (0.10%) exceeded the MTD in both males and females, indicated by high mortality and toxicity. The second high dose (0.05%) produced some toxicity in both male and female rats, indicated by organ weight increase and histological findings (mainly in thyroid gland, lung, and lymph nodes). This study is considered adequate for testing oral carcinogenicity of spinosad in rats.

Executive CAC Recommendations and Conclusions:

1) 18-month oral (diet) mouse carcinogenicity study:

- The Committee concluded that the study was acceptable, noting no prior FDA concurrence.
- The Committee concluded that the study was negative for drug-related neoplasms.

2) 2-year oral (diet) rat carcinogenicity study:

- The Committee concluded that the study was acceptable, noting no prior FDA concurrence.
- The Committee concluded that the study was negative for drug-related neoplasms.

David Jacobson-Kram, Ph.D.
Chair, Executive CAC

cc:\
/Division File, DDDP
/B. Hill, Supervisor, DDDP
/J. Wang, P/T reviewer, DDDP
/D. Williams, Project Manager, DDDP
/A. Seifried, OND IO

Linked Applications	Submission Type/Number	Sponsor Name	Drug Name / Subject
NDA 22408	ORIG 1	PARAPRO PHARMACEUTICALS LLC	SPINOSAD

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/s/

ADELE S SEIFRIED
08/19/2009

DAVID JACOBSON KRAM
08/20/2009

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

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/s/

DAWN WILLIAMS
09/03/2009

BARBARA A HILL
09/03/2009

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 22-408 **INFORMATION REQUEST LETTER**

ParaPRO Pharmaceuticals, LLC
c/o Anson Group
Attention: Reed Tarwater, Ph.D., RAC
Director
11460 N. Meridian St., Suite 150
Carmel, IN 46032

Dear Dr. Tarwater:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for [redacted] (b) (4), indicated for treatment of human head lice [redacted] (b) (4).

We also refer to your submissions dated March 30 and April 24, 2009.

We are reviewing the Clinical and CMC sections of your submissions and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

Chemistry, Manufacturing and Controls

Drug Substance:

1. Provide a regulatory specification for the drug substance in this NDA.

2. Clarify if acceptance tests are conducted at the manufacturer of the drug products and provide acceptance specification.

3. In the response to the 74-day letter, you provided total of minor spinosyn components for the pre-clinical and clinical batches of the drug substance, please also provide data for the individual minor components and other impurities.

4. A list of deficiencies for DMF 17795, cross-referenced for the drug substance in this NDA, has been communicated to the DMF holder. The deficiencies need to be resolved before this NDA may be approved.

Drug Product:

For components/composition:

5. Correct the components/composition of the formulation to reflect the changes of the Spinosad definition from total spinosyns to spinosyns (A+D) and the drug product strength (b) (4) to 0.9%.

6. In addition to the weight percentages (% w/w) provided in the formulation table for the drug product, please provide a column for the quantitative amount in weight for each component. The amount of the drug substance should reflect the actual amount of the spinosyns (A+D) contained in the drug substance.

7. Delete strengths (b) (4) in the formulation table, since only 0.9% is the proposed drug product for this NDA.

8. Since sodium hydroxide and hydrochloric acid are used to adjust the pH of the product, indicate the range of the pH in the formulation table and change water quantity from (b) (4) to q.s. Add the quality of the water to the formulation table.

9. For the formulation ingredients cetearyl alcohol, hexylene & propylene glycol, and stearalkonium chloride you have assigned the following functions, respectively; (b) (4). You are requested to assign functions to these ingredients based on the physicochemical properties of the ingredients, not how the ingredients act on skin or hair.

For Batch Formula:

10. The spinosad concentration in the batch formula needs to be changed as a consequence of the Spinosad definition change. The amount of the drug substance should reflect the actual amount of spinosyns (A+D) contained in the drug substance batches.

For Control of excipients:

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

For Specification:

12. Revise assay specification from total spinosad to the Spinosyns (A+D). Provide specification for the ratio of factor A/D or individual specifications for factor A and D.

13. Provide specification for related substances including total of minor spinosyns, individual minor spinosyns, and any other related substance/degradation products. The acceptance criteria for the minor spinosyns should be a range rather than a limit. The acceptance criteria should be supported by the batch results.

14. In addition to the ID test using HPLC retention time as proposed, provide a secondary identity test using a different technology such as UV/Vis.

15. Add an upper limit for the acceptance criterion of the viscosity specification.

16. Remove the term of (b) (4) in the acceptance criterion for the specificity gravity. The acceptance criterion should read (b) (4)".

17. Weight loss was discovered during stability studies, however, no acceptance criterion was provided in the drug product specification. Provide a justification for this omission.

18. The specification for the appearance is proposed as (b) (4) Revise your specification to better describe the appearance.

For analytical methods used for Assay and related substances:

19. The sample chromatogram, provided in validation report for method TM 05-0189, appendix B, contains 20 peaks and the peak assignments are very difficult to read. There are only 11 retention times provided in the table of the method procedure. Clarify the difference, and provide a sample chromatogram with better quality and a table with the peak assignments.

20. It is noted that two methods, including methods TM 04-0014 and TM 05-0819, have been used for assay and related substance testing during the drug product development. Submit to your pending NDA, a table listing the drug product batches along with the analytical methods. Provide data including assay and related substances to demonstrate these two methods are comparable.

21. Your validation result for method TM 05-0189 only contains validation for Spinosyn A and D. Provide complete validation results for other minor spinosyn components (e.g. each individual peak of the spinosyn factor or mixture of several spinosyn factors) and other impurities/degradation products.

22. In addition to the stress study using HCl for the validation of assay method, provide data for stress studies under basic and oxidation conditions since both conditions may cause degradation as shown in the drug substance degradation pathway.

For Batch Analyses:

23. Provide a table of spinosyn (A+D), A/D or individual A and D, and minor spinosyn factors (total and each individual) for your batch analysis results. Your calculation of these components should reflect the dose strength change (b) (4) 0.9%.

24. The COAs for the pre-clinical batches F-621-062, F-621-069 and F-621-075 include (b) (4) unknown impurities (b) (4). However, these impurities are not reported in the clinical batches. Clarify whether they were not detected or the

tests were not conducted in the clinical batches. Clarify the difference since the formulations remained unchanged.

For Stability:

25. Revise your stability data for assay results to reflect the changes of the Spinosad definition from total spinosyns to spinosyns (A+D) and the label claim (b) (4) to 0.9%.

26. It is indicated in section P.3.5 Process Validation/Evaluation, that (b) (4) scale is at least (b) (4) of the commercial batch. However your batch formula and stability commitment indicated that full scale drug production is (b) (4). Confirm that (b) (4) is deemed full scale. Otherwise, your post approval stability commitment should include stability studies for the 1st three batches of the commercial drug products.

27. Provide stability commitment and stability protocol for one batch of the drug product each year post-approval.

28. In addition to the committed stability studies, amend your post-approval commitment to include the following:

    If any batches are found to fall outside of the approved specifications, the batch will be withdrawn from the market and FDA will be notified. If the deviation is a single occurrence that does not affect the safety and efficacy of the drug product, justification for the continued distribution of the batch will be discussed with the Agency. The change or deterioration in the distributed drug will be reported under 21CFR 314.81(b)(i)(ii).

For Environment Assessment:

29. For your categorical exclusion of the environment assessment, demonstrate that the estimated concentration of the substance at the point of entry into the aquatic environment (EIC) will be below 1 part per billion.

For Drug Product Samples:

30. Confirm that the samples you sent to the Agency in May 2009 are packaged in the to-be-marketed container/closure system. Otherwise, provide representative drug product samples in the commercial package (3 units) to the pending NDA.

Statistical

31. Provide complete statistical datasets for the Phase 2 trial, SPN 201-05.

Clinical

32. Identify those subjects having either partial or complete laboratory assessments in pivotal trials, SPN-301-07 and 302-07.

33. In trial SPN-302-07, two subjects 09-02-0002 and 09-03-0001 are identified as having experienced ocular irritation. These two subjects were not included as having had adverse events, listing 16.2.7.3. Provide the outcome for both of these subjects (i.e. Did the irritation resolve? Were there sequelae?), and clarify why these events were not coded as adverse events.

34. Provide sub-group analysis for adverse events by age, race, and sex for the pooled pivotal trials, SPN-301-07 and 302-07.

If you have any questions, call Dawn Williams, Regulatory Project Manager, at (301) 796-0155.

Sincerely,

{See appended electronic signature page}

Barbara Gould, M.B.A.H.C.M.
Chief, Project Management Staff
Division of Dermatology and Dental Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

Barbara Gould

6/26/2009 11:37:19 AM

FDA Facsimile Memorandum

Date: June 19, 2009

To: Reed Tarwater, Ph.D., RAC

From: Catherine Carr, MSc., Regulatory Project Manager

Subject: NDA 22-408/Spinosad/Pharm/Tox Information Request

Dear Dr. Tarwater:

It has been recently determined that you should submit the final study reports for the 18-month carcinogenicity study conducted in mice and the 2-year carcinogenicity study conducted in rats to NDA 22-408. The data from these two nonclinical carcinogenicity studies needs to be reviewed to assure that the carcinogenicity wording proposed for the Spinosad label is accurate.

The study reports should be submitted in a format that can be analyzed by CDER statisticians. Information on providing electronic data can be found at http://www.fda.gov/cder/regulatory/ersr/ectd.htm. The specific format (table) for submission of tumor data of two-year carcinogenicity studies can be found at http://www.fda.gov/cder/regulatory/ersr/Studydata.pdf. Guidance on statistical aspects of carcinogenicity studies can be found in the draft guidance entitled "Statistical Aspects of the Design, Analysis, and Interpretation of Chronic Rodent Carcinogenicity Studies of Pharmaceuticals", which is available at http://www.fda.gov/cder/guidance/815dft.htm.

The final study reports for the two carcinogenicity studies with the appropriate electronic data sets should be submitted to the NDA by COB on June 25, 2009.

If you have any questions regarding this fax, please feel free to give me a call.

Thank you.

Catherine Carr, MSc
Regulatory Health Project Manager
Food and Drug Administration
Division of Dermatology and Dental Products (DDDP)
White Oak, Bldg 22, Room 5175
10903 New Hampshire Avenue
Silver Spring, MD 20993
Tele: (301) 796-2311
Fax: (301) 796-9894/9895

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/s/

Catherine Carr
6/19/2009 04:48:41 PM
CSO

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

TO *(Office/Division)*:	FROM (*Name, Office/Division, and Phone Number of Requestor)*:
Division of Cardiorenal Products, Attn: Edward Fromm	Catherine Carr, Division of Dermatology and Dental Produts, 301-796-2311

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
June 1, 2009		22-408	Original NDA	January 21, 2009

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
Spinosad			June 19, 2009

NAME OF FIRM: ParaPRO Pharma

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE / ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE-NDA MEETING
- ☐ END-OF-PHASE 2a MEETING
- ☐ END-OF-PHASE 2 MEETING
- ☐ RESUBMISSION
- ☐ SAFETY / EFFICACY
- ☒ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☐ OTHER *(SPECIFY BELOW)*:

II. BIOMETRICS

- ☐ PRIORITY P NDA REVIEW
- ☐ END-OF-PHASE 2 MEETING
- ☐ CONTROLLED STUDIES
- ☐ PROTOCOL REVIEW
- ☐ OTHER (SPECIFY BELOW):
- ☐ CHEMISTRY REVIEW
- ☐ PHARMACOLOGY
- ☐ BIOPHARMACEUTICS
- ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE 4 STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL - BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG SAFETY

- ☐ PHASE 4 SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE, e.g., POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ NONCLINICAL

COMMENTS / SPECIAL INSTRUCTIONS:

The sponsor, ParaPRO, submitted NDA 22-408 for Spinosad (b) (4) January 22, 2009, and the 10 month goal date is November 20, 2009. The proposed indication is, treatment of head lice infestations (b) (4) in patients (b) (4). This product is a new molecular entity, derived from the fermentation process of a rare, naturally occurring soil actinobacterium, Saccharopolyspora spinosa. According to the sponsor, research has been performed upon spinosad as a treatment for chewing and sucking lice infestations on sheep and on dairy and beef cattle.

Human PK studies included the following:
a) Study SPN-101-04, (22 completed) healthy adult subjects, one 10 minute application, 2% spinosad
b) Study SPN-106-06, (8 completed), healthy pediatric subjects, ages 6 to 24 months of age, one 10 minute application, 1% spinosad (NatrOVA 1%)
c) Study SPN-103-05, (14 completed), pediatric subjects with head lice, 4 to 15 years of age, one 10 minute application, 2% spinosad

All collected samples were reported to be below the limits of quantification (< 3 ng/mL) and no analyses of spinosad and/or spinosad metabolites could be performed. The sponsor has concluded that a 10-minute topical application (spinosad 2.0%) did not result in any systemic absorption by healthy adult subjects, healthy pediatric subjects (spinosad 1%, NatrOVA), or in pediatric subjects with head lice (spinosad 2%). Proposed labeling includes 10 minute application to scalp and hair, up to 120 ml with one or sometimes two treatments.

No nonclinical cardiovascular safety pharmacology studies were submitted. EKG evaluation was not performed in the toxicology studies in dogs. An HERG assay was not conducted. When queried about the lack of nonclinical cardiovascular safety pharmacology studies, the sponsor has responded (4/24/09):

Human PK studies have shown no measurable systemic exposure after use of (b) (4) as intended. Since there are no systemic levels of spinosad following topical administration in humans, it is clear that the topical use of this compound will not result in adverse pharmacological or toxicological effects in humans. Therefore, cardiovascular safety pharmacology and toxicokinetic data are not relevant.

DDDP Question to Cardiology:
An NME such as spinosad (b) (4)), as per Guidance E14 "Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs," would be expected to receive a clinical electrocadiographic evaluation beginning early in clinical development, typically a thorough QT/QTc study. The sponsor was asked to provide information to assess the effect of the product on cardiac repolarization and responded (4/29/09):

Guidance Document E14 Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs states that, "The recommendations contained in this document are generally applicable to new drugs having systemic bioavailability, but may not apply to products with highly localized distribution and those administered topically and not absorbed."

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.

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).

Notes: In the clinical development program for spinosad (b) (4) 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 were reported to have normal ECGs upon exit. In SPN-102-05, ECGs were performed only at entry on study subjects, healthy adult volunteers.

*Reviewer note: A study (DERBI-44495), using radiocarbon labeled spinosyn A, in rats, revealed systemic absorption of approximately 1% of the topically applied dose at 24 hours after one application.

The Mid-Cycle meeting is scheduled for June 19, 2009. Cardio Reviewer's attendance is requested

SIGNATURE OF REQUESTOR .Catherine Carr, Regulatory Project Manager	METHOD OF DELIVERY (Check one) ☒ DFS ☒ EMAIL ☐ MAIL ☐ HAND
PRINTED NAME AND SIGNATURE OF RECEIVER	PRINTED NAME AND SIGNATURE OF DELIVERER

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/s/

Catherine Carr

6/1/2009 10:35:40 AM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 22-408

PROPRIETARY NAME REQUEST
- CONDITIONALLY ACCEPTABLE

ParaPRO Pharmaceuticals, LLC
c/o Anson Group
11460 N. Meridian Street, Suite 150
Carmel, Indiana 46032

ATTENTION: Reed Tarwater
Director, Anson Group, and
Regulatory Consultant to ParaPRO

Dear Mr. Tarwater:

Please refer to your New Drug Application (NDA) dated January 21, 2009, received January 22, 2009, submitted under section 505(b) of the Federal Food, and Cosmetic Act for Spinosad (b) (4)

We also refer to your February 25, 2009, correspondence, received February 26, 2009, requesting review of your proposed proprietary name, (b) (4) We have completed our review of the proposed proprietary name, (b) (4)

If **any** of the proposed product characteristics as stated in your February 25, 2009 submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, call Janet L. Anderson, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-0675. For any other information regarding this application contact the Office of New Drugs (OND) Regulatory Project Manager.

Sincerely,

{See appended electronic signature page}

Carol Holquist, RPh.
Director
Division of Medication Error Prevention and Analysis
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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/s/

Denise Toyer
5/27/2009 05:30:17 PM
signing for Carol Holquist, Director DMEPA

DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service
Food and Drug Administration
Rockville, MD 20857

FILING COMMUNICATION

NDA 22-408

ParaPro Pharmaceuticals, LLC
Attention: O. Reed Tarwater, Ph. D., RAC
Senior Regulatory Consultant
11460 N. Meridian Street, Suite150
Carmel, IN 46032

Dear Dr. Tarwater:

Please refer to your new drug application (NDA), dated January 21, 2009, received January 22, 2009, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for TRADENAME (spinosad) (b) (4)

We also refer to your submission dated March 30, 2009.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR 314.101(a), this application is considered filed 60 days after the date we received your application. The review classification for this application is **Standard**. Therefore, the user fee goal date is November 22, 2009.

We are reviewing your application according to the processes described in the Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, mid-cycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing commitment requests by October 7, 2009.

During our filing review of your application, we identified the following potential review issues:

Clinical:

1. Insufficient information has been provided to assess the effect of the product on cardiac repolarization.

Pharmacology/Toxicology:

2. We remind you that three issues were identified from a pharmacology/toxicology perspective and relayed to you during the preNDA meeting on November 4, 2008. (Please refer to the preNDA meeting minutes, additional comments for Question 2). The following three issues were not addressed in your NDA submission:
    a. No nonclinical cardiovascular safety pharmacology studies were submitted. EKG evaluation was not performed in the toxicology studies in dogs.
    b. No toxicokinetic (TK) data for oral diet toxicology studies in rats or dogs were submitted. No TK data for reproductive/developmental toxicology studies were submitted. It would be difficult to determine the adequacy of toxicology studies without the support of TK data.
    c. No juvenile animal toxicology studies were submitted.

3. Section 13 "Nonclinical Toxicology" was omitted from the submitted label in your NDA submission.

CMC:

4. The definition of the drug substance needs to be established.

5. The specification for the drug substance (both drug substance raw material and the active ingredient in the drug product) is inadequate to assure identity, strength, and purity.

6. Information for the container/closure system of the drug product is inadequate.

7. The dosage form nomenclature, (b) (4) is unacceptable.

We are providing the above comments to give you preliminary notice of potential review issues. Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review. Issues may be added, deleted, expanded upon, or modified as we review the application.

We also request that you submit the following information:

Clinical:

1. Provide information to assess the effect of the product on cardiac repolarization

2. Provide a pediatric assessment per 21 CFR 314.55.

3. Provide a completed Form FDA 3454 and/or Form FDA 3455 attesting to the financial interests and arrangements as described in 21 CFR 54.4 (a)(1) and (a)(3), respectively.

Pharmacology/Toxicology:

4. For the three issues conveyed to you during your preNDA meeting, provide either additional data or a rationale to justify the reason why additional data are not needed to support the safety of your drug product. If you believe that you have addressed these issues in your NDA submission, you should specify the location of the appropriate data or rationale in your NDA submission.

5. Submit a revised label that contains appropriate nonclinical toxicology information in Section 13 of the label for your drug product.

CMC:

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

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

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

9. 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.

Regulatory:

10. Provide a correctly worded Debarment Certification as indicated in Federal Food, Drug, and Cosmetic Act section 306(k)(1). That is, "[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application."

Please respond only to the above requests for additional information. While we anticipate that any response submitted in a timely manner will be reviewed during this review cycle, such review decisions will be made on a case-by-case basis at the time of receipt of the submission.

Upon review of the draft labeling submitted in Physician Labeling Rule (PLR) format, we have identified the following formatting issues in the proposed label:

Highlights Section:

1. The Initial U.S. Approval statement should be placed immediately beneath the established name of the product.

2. The section "Use in Specific Populations" is listed in the Full Prescribing Information section, but is not listed in the Highlights section. This section with its sub-sections should be included in the Highlights section for consistency per 21 CFR 201.57(a)(13).

3. The revision dated should appear in bold type.

Contents (Table of Contents) Section:

4. The heading "FULL PRESCRIBING INFORMATION: CONTENTS" should appear in all upper case letters and bold type.

5. The table of contents subsection headings should be in regular text, not all upper case text.

Full Prescribing Information (FPI) Section:

6. The heading "FULL PRESCRIBING INFORMATION" should appear in bold type.

7. Section 12 "CLINICAL PHARMACOLOGY" is not included in the label. Please provide an updated label with this section per 21 CFR 201.57 (c)(13).

8. Section 13 "NONCLINICAL TOXICOLOGY" is not included in the label. Please provide an updated label with this section per 21 CFR 201.57 (c)(14).

9. In Section 17 "PATIENT COUNSELING INFORMATION", subheadings and identifying numbers should be in bold type to prominently distinguish the subheadings from other labeling information.

10. According to 21 CFR 201.1, manufacturing information should be located at the end of the label, after the Patient Counseling Information section. The manufacturing information should be included for this product according to regulations.

Address the identified labeling deficiencies/issues and re-submit labeling by May 1, 2009.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We note that you have not addressed how you plan to fulfill this requirement. Within 30 days of the date of this letter, please submit (1) a full waiver request, (2) a partial waiver request and a pediatric development plan for the pediatric age groups not covered by the partial waiver request,

or (3) a pediatric drug development plan covering the full pediatric age range. All waiver requests must include supporting information and documentation. A pediatric drug development plan must address the indication proposed in this application.

If you request a full waiver, we will notify you if the full waiver is denied and a pediatric drug development plan is required.

Pediatric studies conducted under the terms of section 505B of the Federal Food, Drug, and Cosmetic Act (the Act) may also qualify for pediatric exclusivity under the terms of section 505A of the Act. If you wish to qualify for pediatric exclusivity please consult the Division of Dermatology and Dental Products. Please note that satisfaction of the requirements in section 505B of the Act alone may not qualify you for pediatric exclusivity under 505A of the Act.

If you have any questions, call Catherine Carr, Regulatory Project Manager, at (301) 796-2311.

Sincerely,

{See appended electronic signature page}

Susan J. Walker, M.D., F.A.A.D.
Director
Division of Dermatology and Dental Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

Susan Walker
4/6/2009 03:39:27 PM

MEMORANDUM OF TELECON

DATE: March 17, 2009

APPLICATION NUMBER: NDA 22-408/Spinosad (b) (4)

BETWEEN:

Name: Reed Tarwater, Ph.D./Director, Pharmaceutical Consulting Services/Anson Group
Bill Culpepper III/Director, ParaPRO Pharmaceuticals
Bill Kozarek/Senior CMC Scientist, Anson/ParaPRO Pharmaceuticals

Representing: ParaPRO Pharmaceuticals

AND

Name: Shulin Ding, Ph.D./Pharmaceutical Assessment Lead/ONDQA
Moo-Jhong Rhee, Ph.D./Branch Chief/ONDQA
Stanka Kukich, M.D./Deputy Director/DDDP, HFD-540
Catherine Carr, MSc./Regulatory Project Manager/DDDP, HFD-540
Barbara Gould, MBA HCM/Chief, Project Management/DDDP, HFD-540

SUBJECT: Clarification of CMC Potential Filing Issues

The applicant requested a teleconference with the Agency to gain clarification regarding the potential filing issues communicated to them via fax on March 5, 2009. The purpose of the teleconference was to allow the applicant the opportunity to ask questions regarding the information in the fax and to discuss issues surrounding the Drug Master File (DMF) held by Dow AgroSciences.

Prior to initiating the teleconference, the Agency requested that representatives from Dow AgroSciences be dismissed from the call in order for the Agency to convey confidential information to the applicant regarding the drug product.

The Agency provided the following clarification/explanation for the applicant regarding the issue conveyed in the potential filing issues letter sent on March 5, 2009:

- The drug substance is not adequately defined. Specifically, concentrations of components A and D are not provided, and the ratio between A and D is not defined.

- The concentrations on individual components (A, D, and other minor components) can not be found in the NDA for drug product.

- In the pre-NDA meeting, the Agency advised the applicant concerning the importance of the individual concentrations on components A and D, and the ratio in the control of drug substance/drug product.

- Minor factors should be categorized as related substances and should not be included as a part of assay or strength. This is because the definition of spinosad consists of only components A and D.

- Minor factors, as related substances, should comply with ICH Q3B for drug product, and with ICH Q3A for drug substance

- The CMC reviewer has reviewed the updated version of spinosad DMF.

The applicant stated that they believed the concentrations of individual components of A, D and minor components are provided in the NDA for the drug product, and agreed to provide page numbers to the CMC reviewer by March 18, 2009.

At the conclusion of the teleconference, the Agency agreed to provide clarification via email on the points discussed during the call. The teleconference ended cordially.

Telconference Memo Prepared by:
Catherine Carr, Regulatory Health Project Manager
Division of Dermatology and Dental Products

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/s/

Catherine Carr
3/17/2009 04:15:09 PM
CSO

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 22-408

ParaPro Pharmaceuticals, LLC
Attention: O. Reed Tarwater, Ph. D., RAC
Senior Regulatory Consultant
11460 N. Meridian Street, Suite150
Carmel, IN 46032

Dear Dr. Tarwater:

Please refer to your new drug application (NDA) dated January 21, 2009, received January 22, 2009, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act, for TRADENAME (spinosad) (b) (4)

In our filing review, we have identified the following potential filing issues:

Your application does not contain information to establish the identity of the drug substance. Consequently, adequate specifications for the drug substance and drug product can not be established to assure the identity, strength, purity, and quality of the product (refer to the Agency's Pre-NDA meeting minutes, dated November 19, 2008). Thus, this application is incomplete in its present form.

We are providing the above comments to give you preliminary notice of potential filing issues. We remind you that the filing date for this application is March 20, 2009.

If you have any questions, call Catherine Carr, Regulatory Project Manager, at (301) 796-2311.

Sincerely,

{See appended electronic signature page}

Susan J. Walker, M.D., F.A.A.D.
Director
Division of Dermatology and Dental Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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

/s/

Stanka Kukich
3/5/2009 02:42:15 PM
Signing for Dr. Susan Walker, Division Director

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 22-408

NDA ACKNOWLEDGMENT

ParaPro Pharmaceuticals, LLC
c/o Anson Group
Attention: O. Reed Tarwater, Ph.D., RAC
Director
11460 N. Meridian Street, Suite 150
Carmel, IN 46032

Dear Dr. Tarwater:

We have received your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for the following:

Name of Drug Product: Spinosad (b) (4)

Date of Application: January 21, 2009

Date of Receipt: January 22, 2009

Our Reference Number: NDA 22-408

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on March 20, 2009 in accordance with 21 CFR 314.101(a).

If you have not already done so, promptly submit the content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at http://www.fda.gov/oc/datacouncil/spl.html. Failure to submit the content of labeling in SPL format may result in a refusal-to-file action under 21 CFR 314.101(d)(3). The content of labeling must conform to the content and format requirements of revised 21 CFR 201.56-57.

Please note that you are responsible for complying with the applicable provisions of sections 402(i) and 402(j) of the Public Health Service Act (PHS Act) (42 USC §§ 282(i) and (j)), which was amended by Title VIII of the Food and Drug Administration Amendments Act of 2007 (FDAAA) (Public Law No. 110-85, 121 Stat. 904). Title VIII of FDAAA amended the PHS Act by adding new section 402(j) (42 USC § 282(j)), which expanded the current database known as ClinicalTrials.gov to include mandatory registration and reporting of results for applicable clinical trials of human drugs (including biological products) and devices. FDAAA requires that, at the time of submission of an application under section 505 of the FDCA, the application must be accompanied by a certification that all applicable requirements of 42 USC § 282(j) have been

met. Where available, the certification must include the appropriate National Clinical Trial (NCT) control numbers. 42 USC 282(j)(5)(B). You did not include such certification when you submitted this application. You may use Form FDA 3674, *Certification of Compliance, under 42 U.S.C. § 282(j)(5)(B), with Requirements of ClinicalTrials.gov Data Bank*, to comply with the certification requirement. The form may be found at http://www.fda.gov/opacom/morechoices/fdaforms/default.html.

In completing Form FDA 3674, you should review 42 USC § 282(j) to determine whether the requirements of FDAAA apply to any clinical trials referenced in this application. Additional information regarding the certification form is available at: http://internet-dev.fda.gov/cder/regulatory/FDAAA_certification.htm. Additional information regarding Title VIII of FDAAA is available at: http://grants.nih.gov/grants/guide/notice-files/NOT-OD-08-014.html. Additional information on registering your clinical trials is available at the Protocol Registration System website http://prsinfo.clinicaltrials.gov/.

The NDA number provided above should be cited at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Dermatology and Dental Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

All regulatory documents submitted in paper should be three-hole punched on the left side of the page and bound. The left margin should be at least three-fourths of an inch to assure text is not obscured in the fastened area. Standard paper size (8-1/2 by 11 inches) should be used; however, it may occasionally be necessary to use individual pages larger than standard paper size. Non-standard, large pages should be folded and mounted to allow the page to be opened for review without disassembling the jacket and refolded without damage when the volume is shelved. Shipping unbound documents may result in the loss of portions of the submission or an unnecessary delay in processing which could have an adverse impact on the review of the submission. For additional information, please see http:www.fda.gov/cder/ddms/binders.htm.

If you have any questions, call me, at (301) 796-2311.

Sincerely,

{See appended electronic signature page}
Catherine Carr, MSc.
Regulatory Health Project Manager
Division of Dermatology and Dental Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

Catherine Carr

3/4/2009 12:12:21 PM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADM NISTRATION

REQUEST FOR CONSULTATION

TO *(Division/Office)*:
Mail: ODS

FROM: Catherine Carr, Regulatory Project Manager, Division of Dermatology and Dental Products, 301-796-2311

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
February 24, 2009		22-408	Original Labeling	January 21, 2009

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
Spinosad	Standard		June 1, 2009

NAME OF FIRM: ParaPRO Pharmaceuticals, LLC

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE/ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE--NDA MEETING
- ☐ END OF PHASE II MEETING
- ☐ RESUBMISSION
- ☐ SAFETY/EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☐ OTHER *(SPECIFY BELOW)*:

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
☐ TYPE A OR B NDA REVIEW ☐ END OF PHASE II MEETING ☐ CONTROLLED STUDIES ☐ PROTOCOL REVIEW ☐ OTHER (SPECIFY BELOW):	☐ CHEMISTRY REVIEW ☐ PHARMACOLOGY ☐ BIOPHARMACEUTICS ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE IV STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL-BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG EXPERIENCE

- ☐ PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS:

Please review the Package Insert and Carton/Container Labeling for NDA 22-408 Spinosad. The Mid-Cycle due date is June 21, 2009. The PDUFA date is November 21, 2009.

The labeling is attached and available in the EDR.

SIGNATURE OF REQUESTER	METHOD OF DELIVERY (Check one)
Catherine Carr, RPM	X MAIL ☐ HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

1.14.1.2 Annotated Labeling Text

The annotated labeling is attached. It is presented in a two-column table format, the left column contains the Sponsor's proposed labeling text, and the right column contains the annotations/comments for that particular row of the table.

25 Pages of Draft Labeling have been Removed as B4 (CCI/TS) Immediately Following This Page

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/s/

Catherine Carr
2/24/2009 09:23:17 AM

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION[1]		
NDA # 022408 BLA #	NDA Supplement # BLA STN #	If NDA, Efficacy Supplement Type:
Proprietary Name: Natroba Established/Proper Name: spinosad Dosage Form: Topical Suspension		Applicant: ParaPRO Pharmaceuticals, LLC Agent for Applicant (if applicable): Anson Group
RPM: Dawn Williams		Division: DDDP

NDAs:	505(b)(2) Original NDAs and 505(b)(2) NDA supplements:
NDA Application Type: ☒ 505(b)(1) ☐ 505(b)(2) Efficacy Supplement: ☐ 505(b)(1) ☐ 505(b)(2) (A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). Consult page 1 of the NDA Regulatory Filing Review for this application or Appendix A to this Action Package Checklist.)	Listed drug(s) referred to in 505(b)(2) application (include NDA/ANDA #(s) and drug name(s)): Provide a brief explanation of how this product is different from the listed drug. ☐ If no listed drug, check here and explain: **Prior to approval, review and confirm the information previously provided in Appendix B to the Regulatory Filing Review by re-checking the Orange Book for any new patents and pediatric exclusivity. If there are any changes in patents or exclusivity, notify the OND ADRA immediately and complete a new Appendix B of the Regulatory Filing Review.** ☐ No changes ☐ Updated Date of check: **If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.** **On the day of approval, check the Orange Book again for any new patents or pediatric exclusivity.**

❖ User Fee Goal Date Action Goal Date (if different)	January 26, 2011 January 18, 2011
❖ Actions	
• Proposed action	☒ AP ☐ TA ☐ AE ☐ NA ☐ CR
• Previous actions *(specify type and date for each action taken)*	☐ None CR- November 18, 2009
❖ Promotional Materials *(accelerated approvals only)* Note: If accelerated approval (21 CFR 314.510/601.41), promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see guidance http://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf). If not submitted, explain _____	☐ Received

[1] The **Application Information** section is (only) a checklist. The **Contents of Action Package** section (beginning on page 5) lists the documents to be included in the Action Package.

❖ Application Characteristics [2]	

Review priority: ☒ Standard ☐ Priority
Chemical classification (new NDAs only):

☐ Fast Track
☐ Rolling Review
☐ Orphan drug designation
☐ Rx-to-OTC full switch
☐ Rx-to-OTC partial switch
☐ Direct-to-OTC

NDAs: Subpart H
☐ Accelerated approval (21 CFR 314.510)
☐ Restricted distribution (21 CFR 314.520)
Subpart I
☐ Approval based on animal studies

BLAs: Subpart E
☐ Accelerated approval (21 CFR 601.41)
☐ Restricted distribution (21 CFR 601.42)
Subpart H
☐ Approval based on animal studies

☐ Submitted in response to a PMR
☐ Submitted in response to a PMC

Comments: _____

❖ Date reviewed by PeRC *(required for approvals only)* If PeRC review not necessary, explain: _____	September 22, 2010
❖ BLAs only: *RMS-BLA Product Information Sheet for TBP* has been completed and forwarded to OBPS/DRM *(approvals only)*	☐ Yes, date
❖ BLAs only: is the product subject to official FDA lot release per 21 CFR 610.2 *(approvals only)*	☐ Yes ☐ No
❖ Public communications *(approvals only)*	
• Office of Executive Programs (OEP) liaison has been notified of action	☒ Yes ☐ No
• Press Office notified of action (by OEP)	☒ Yes ☐ No
• Indicate what types (if any) of information dissemination are anticipated	☐ None ☒ HHS Press Release ☐ FDA Talk Paper ☐ CDER Q&As ☒ Other FDA Information Advisory

[2] All questions in all sections pertain to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA. For example, if the application is a pending BLA supplement, then a new *RMS-BLA Product Information Sheet for TBP* must be completed.

❖ Exclusivity	
• Is approval of this application blocked by any type of exclusivity?	☒ No ☐ Yes
• NDAs and BLAs: Is there existing orphan drug exclusivity for the "same" drug or biologic for the proposed indication(s)? *Refer to 21 CFR 316.3(b)(13) for the definition of "same drug" for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification.*	☒ No ☐ Yes If, yes, NDA/BLA # and date exclusivity expires:
• (b)(2) NDAs only: Is there remaining 5-year exclusivity that would bar effective approval of a 505(b)(2) application)? *(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)*	☐ No ☐ Yes If yes, NDA # and date exclusivity expires:
• (b)(2) NDAs only: Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? *(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)*	☐ No ☐ Yes If yes, NDA # and date exclusivity expires:
• (b)(2) NDAs only: Is there remaining 6-month pediatric exclusivity that would bar effective approval of a 505(b)(2) application? *(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)*	☐ No ☐ Yes If yes, NDA # and date exclusivity expires:
• NDAs only: Is this a single enantiomer that falls under the 10-year approval limitation of 505(u)? *(Note that, even if the 10-year approval limitation period has not expired, the application may be tentatively approved if it is otherwise ready for approval.)*	☒ No ☐ Yes If yes, NDA # and date 10-year limitation expires:
❖ Patent Information (NDAs only)	
• Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought. If the drug is an old antibiotic, skip the Patent Certification questions.	☒ Verified ☐ Not applicable because drug is an old antibiotic.
• Patent Certification [505(b)(2) applications]: Verify that a certification was submitted for each patent for the listed drug(s) in the Orange Book and identify the type of certification submitted for each patent.	21 CFR 314.50(i)(1)(*i*)(A) ☐ Verified 21 CFR 314.50(i)(1) ☐ (ii) ☐ (iii)
• [505(b)(2) applications] If the application includes a **paragraph III** certification, it cannot be approved until the date that the patent to which the certification pertains expires (but may be tentatively approved if it is otherwise ready for approval).	☐ No paragraph III certification Date patent will expire
• [505(b)(2) applications] For **each paragraph IV** certification, verify that the applicant notified the NDA holder and patent owner(s) of its certification that the patent(s) is invalid, unenforceable, or will not be infringed (review documentation of notification by applicant and documentation of receipt of notice by patent owner and NDA holder). *(If the application does not include any paragraph IV certifications, mark "N/A" and skip to the next section below (*Summary Reviews*)).*	☐ N/A (no paragraph IV certification) ☐ Verified

- [505(b)(2) applications] For **each paragraph IV** certification, based on the questions below, determine whether a 30-month stay of approval is in effect due to patent infringement litigation.

  Answer the following questions for **each** paragraph IV certification:

  (1) Have 45 days passed since the patent owner's receipt of the applicant's notice of certification? ☐ Yes ☐ No

  (Note: The date that the patent owner received the applicant's notice of certification can be determined by checking the application. The applicant is required to amend its 505(b)(2) application to include documentation of this date (e.g., copy of return receipt or letter from recipient acknowledging its receipt of the notice) (see 21 CFR 314.52(e))).

  *If "**Yes**," skip to question (4) below. If "**No**," continue with question (2).*

  (2) Has the patent owner (or NDA holder, if it is an exclusive patent licensee) submitted a written waiver of its right to file a legal action for patent infringement after receiving the applicant's notice of certification, as provided for by 21 CFR 314.107(f)(3)? ☐ Yes ☐ No

  *If "**Yes,**" there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip the rest of the patent questions.*

  *If "**No**," continue with question (3).*

  (3) Has the patent owner, its representative, or the exclusive patent licensee filed a lawsuit for patent infringement against the applicant? ☐ Yes ☐ No

  (Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2))).

  *If "**No**," the patent owner (or NDA holder, if it is an exclusive patent licensee) has until the expiration of the 45-day period described in question (1) to waive its right to bring a patent infringement action or to bring such an action. After the 45-day period expires, continue with question (4) below.*

  (4) Did the patent owner (or NDA holder, if it is an exclusive patent licensee) submit a written waiver of its right to file a legal action for patent infringement within the 45-day period described in question (1), as provided for by 21 CFR 314.107(f)(3)? ☐ Yes ☐ No

  *If "**Yes,**" there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (*Summary Reviews*).*

  *If "**No**," continue with question (5).*

(5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the (b)(2) applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification? (Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced within the 45-day period). *If "**No**," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (*Summary Reviews*).* *If "**Yes**," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the OND ADRA and attach a summary of the response.*	☐ Yes ☐ No
CONTENTS OF ACTION PACKAGE	
❖ Copy of this Action Package Checklist[3]	Yes
Officer/Employee List	
❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list *(approvals only)*	☒ Included
Documentation of consent/non-consent by officers/employees	☒ Included
Action Letters	
❖ Copies of all action letters *(including approval letter with final labeling)*	Action(s) and date(s) Approval, January 18, 2011 Complete Response, November 18, 2009
Labeling	
❖ Package Insert *(write submission/communication date at upper right of first page of PI)*	
• Most recent division-proposed labeling (only if generated after latest applicant submission of labeling)	January 10, 2011
• Most recent submitted by applicant labeling (only if subsequent division labeling does not show applicant version)	
• Original applicant-proposed labeling	July 26, 2009
• Other relevant labeling (e.g., most recent 3 in class, class labeling), if applicable	sNDA 022129/004 Ulesfia (benzyl alcohol) Lotion, 5%
❖ Medication Guide/Patient Package Insert/Instructions for Use *(write submission/communication date at upper right of first page of each piece)*	☐ Medication Guide ☒ Patient Package Insert ☒ Instructions for Use ☐ None

[3] Fill in blanks with dates of reviews, letters, etc.

• Most-recent division-proposed labeling (only if generated after latest applicant submission of labeling)	January 10, 2011
• Most recent submitted by applicant labeling (only if subsequent division labeling does not show applicant version)	
• Original applicant-proposed labeling	July 26, 2010
• Other relevant labeling (e.g., most recent 3 in class, class labeling), if applicable	NDA 022129 Ulesfia (benzyl alcohol) Lotion, 5%
❖ Labels (**full color** carton and immediate-container labels) *(write submission/communication date on upper right of first page of each submission)*	
• Most-recent division proposal for (only if generated after latest applicant submission)	November 1, 2010
• Most recent applicant-proposed labeling	
❖ Proprietary Name • Review(s) *(indicate date(s))* • Acceptability/non-acceptability letter(s) *(indicate date(s))*	October 22, 2010/ proprietary name review May 27, 2009/proprietary name review October 22, 2010/proprietary name conditionally acceptable letter July 12, 2010/proprietary name request withdrawn May 27, 2009/proprietary name conditionally acceptable letter
❖ Labeling reviews *(indicate dates of reviews and meetings)*	☒ RPM March 31, 2009 ☒ DMEPA November 6, 2010 and November 2, 2010 ☒ DRISK September 28, 2010 ☒ DDMAC September 7, 2010 ☐ CSS ☒ Other reviews SEALD Review 2-January 12, 2011 SEALD Review 1- December 17, 2010 PMHS Label Review 1- October 6, 2010 PMHS Label Review 2- October 6, 2010
Administrative / Regulatory Documents	
❖ Administrative Reviews *(e.g., RPM Filing Review[4]/Memo of Filing Meeting) (indicate date of each review)*	RPM Filing Review and Memo of Filing Meeting- March 31, 2009
❖ NDAs only: Exclusivity Summary *(signed by Division Director)*	☒ Included

[4] Filing reviews for scientific disciplines should be filed behind the respective discipline tab.

❖ Application Integrity Policy (AIP) Status and Related Documents http://www fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm	
• Applicant in on the AIP	☐ Yes ☒ No
• This application is on the AIP o If yes, Center Director's Exception for Review memo *(indicate date)* o If yes, OC clearance for approval *(indicate date of clearance communication)*	☐ Yes ☒ No ☐ Not an AP action
❖ Pediatric Page *(approvals only, must be reviewed by PERC before finalized)*	☒ Included
❖ Debarment certification (original applications only): verified that qualifying language was not used in certification and that certifications from foreign applicants are cosigned by U.S. agent *(include certification)*	☒ Verified, statement is acceptable
❖ Outgoing communications *(letters (except previous action letters), emails, faxes, telecons)*	November 5, 2009- Inspection Site letter October 29, 2009- Inspection Site letter October 19, 2009- Inspection Site letter October 14, 2009- Inspection Site letter September 21, 2009- Inspection Site letter September 3, 2009- ECAC Final Report September 3, 2009- Information Request September 2, 2009- Inspection Site letter August 26, 2009- DMF Deficiency letter June 26, 2009- Information Request June 19, 2009- Information Request (fax) April 6, 2009- Filing Communication March 5, 2009- Information Request March 4, 2009- Acknowledgement Letter
❖ Internal memoranda, telecons, etc.	Clarification of CMC Potential Filing Issues Telecon- March 17, 2009
❖ Minutes of Meetings	
• PeRC *(indicate date of mtg; approvals only)*	☐ Not applicable September 22, 2010
• Pre-Approval Safety Conference *(indicate date of mtg; approvals only)*	☒ Not applicable
• Regulatory Briefing *(indicate date of mtg)*	☒ No mtg
• Pre-NDA/BLA meeting *(indicate date of mtg)*	☐ No mtg November 4, 2008
• EOP2 meeting *(indicate date of mtg)*	☐ No mtg October 31, 2006
• Other (e.g., EOP2a, CMC pilot programs)	March 25, 2010- Post-Action (CR)

	Meeting Minutes June 27, 2007- SPA Meeting- Draft responses sent to sponsor. Meeting never took place after sponsor received these draft responses. May 17, 2007- Guidance Meeting- Draft responses sent to sponsor. After reviewing these responses, sponsor cancelled meeting. April 23, 2007- Guidance Meeting February 9, 2007- Guidance Meeting November 3, 2004- Guidance Meeting February 9, 2004- Pharm. Tox. Guidance Meeting (PIND stage) May 12, 2003- Pre-IND Meeting
❖ Advisory Committee Meeting(s)	☒ No AC meeting
• Date(s) of Meeting(s)	
• 48-hour alert or minutes, if available *(do not include transcript)*	
Decisional and Summary Memos	
❖ Office Director Decisional Memo *(indicate date for each review)*	☐ None January 18, 2011 November 18, 2009
Division Director Summary Review *(indicate date for each review)*	☐ None December 13, 2010 November 4, 2009
Cross-Discipline Team Leader Review *(indicate date for each review)*	☐ None December 9, 2010 November 5, 2009 (addendum) November 2, 2009
PMR/PMC Development Templates *(indicate total number)*	☐ None PREA PMR- PK Study in Subjects 6 Months to 4 Years of Age with Active Head Lice Infestation
Clinical Information[5]	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) *(indicate date for each review)*	See CDTL reviews
• Clinical review(s) *(indicate date for each review)*	December 9, 2010 October 30, 2009 March 20, 2009 (Filing Review)
• Social scientist review(s) (if OTC drug) *(indicate date for each review)*	☐ None
❖ Safety update review(s) *(indicate location/date if incorporated into another review)*	addressed on page 108 of October 30, 2009 Clinical Review
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, review/memo explaining why not	Page 16 of October 30, 2009 Clinical Review
❖ Clinical reviews from other clinical areas/divisions/Centers *(indicate date of each review)*	☐ None

[5] Filing reviews should be filed with the discipline reviews.

	QT-IRT Consult-June 23, 2009
❖ Controlled Substance Staff review(s) and Scheduling Recommendation *(indicate date of each review)*	☒ Not needed
❖ Risk Management • REMS Document and Supporting Statement *(indicate date(s) of submission(s))* • REMS Memo *(indicate date)* • Review(s) and recommendations (including those by OSE and CSS) *(indicate date of each review and indicate location/date if incorporated into another review)*	☒ None
❖ DSI Clinical Inspection Review Summary(ies) *(include copies of DSI letters to investigators)*	☐ None requested Clinical Inspection Summary-October 16, 2009 VAI Letter- Dr. Stough-October 29, 2009 VAI Letter- Dr. Moore-October 19, 2009 NAI Letter- Ms. Shepherd-October 14, 2009 NAI Letter-Dr. Haber-September 21, 2009 NAI Letter-Mr. Culpepper-September 2, 2009
Clinical Microbiology ☒ None	
❖ Clinical Microbiology Team Leader Review(s) *(indicate date for each review)*	☐ None
Clinical Microbiology Review(s) *(indicate date for each review)*	☐ None
Biostatistics ☐ None	
❖ Statistical Division Director Review(s) *(indicate date for each review)*	☒ None
Statistical Team Leader Review(s) *(indicate date for each review)*	☐ None January 7, 2011
Statistical Review(s) *(indicate date for each review)*	☐ None August 25, 2010 May 19, 2010 October 26, 2009 March 19, 2009 (Filing Review)
Clinical Pharmacology ☐ None	
❖ Clinical Pharmacology Division Director Review(s) *(indicate date for each review)*	☒ None
Clinical Pharmacology Team Leader Review(s) *(indicate date for each review)*	☒ None
Clinical Pharmacology review(s) *(indicate date for each review)*	☐ None October 6, 2010 October 6, 2009 October 6, 2009 (Filing Review)
❖ DSI Clinical Pharmacology Inspection Review Summary *(include copies of DSI letters)*	☒ None
Nonclinical ☐ None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) *(indicate date for each review)*	☐ None December 20, 2010 September 18, 2009
• Supervisory Review(s) *(indicate date for each review)*	☐ None September 4, 2009

• Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)*	☐ None September 30, 2010 September 3, 2009 March 11, 2009 (Filing Review)
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer *(indicate date for each review)*	☒ None
❖ Statistical review(s) of carcinogenicity studies *(indicate date for each review)*	☐ No carc December 3, 2009
❖ ECAC/CAC report/memo of meeting	☐ None August 20, 2009 Also included in P/T review, pages 48-51
❖ DSI Nonclinical Inspection Review Summary *(include copies of DSI letters)*	☒ None requested
Product Quality ☐ None	
❖ Product Quality Discipline Reviews	
• ONDQA/OBP Division Director Review(s) *(indicate date for each review)*	☐ None September 23, 2009
• Branch Chief/Team Leader Review(s) *(indicate date for each review)*	☒ None
• Product quality review(s) *(indicate date for each review)*	☐ None September 28, 2010 November 17, 2009 November 4, 2009 September 23, 2009 September 17, 2009 April 22, 2009 March 23, 2009 (Filing Review)
• ONDQA Biopharmaceutics review *(indicate date for each review)*	
• BLAs only: Facility information review(s) *(indicate dates)*	☐ None
❖ Microbiology Reviews • NDAs: Microbiology reviews (sterility & pyrogenicity) *(indicate date of each review)* • BLAs: Sterility assurance, product quality microbiology *(indicate date of each review)*	☒ Not needed
❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer *(indicate date of each review)*	☒ None
❖ Environmental Assessment (check one) (original and supplemental applications)	
☒ Categorical Exclusion *(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)*	Page 51 of September 23, 2009 CMC Primary Review
☐ Review & FONSI *(indicate date of review)*	
☐ Review & Environmental Impact Statement *(indicate date of each review)*	
❖ Facilities Review/Inspection	
• NDAs: Facilities inspections (include EER printout) *(date completed must be within 2 years of action date)*	Date completed: November 2, 2009 ☒ Acceptable ☐ Withhold recommendation
• BLAs: o TBP-EER o Compliance Status Check (approvals only, both original and all	Date completed: ☐ Acceptable ☐ Withhold recommendation Date completed:

supplemental applications except CBEs) *(date completed must be within 60 days prior to AP)*	☐ Requested ☐ Accepted ☐ Hold
❖ NDAs: Methods Validation	☐ Completed ☐ Requested ☐ Not yet requested ☒ Not needed

Appendix A to Action Package Checklist

An NDA or NDA supplemental application is likely to be a 505(b)(2) application if:

(1) It relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application.
(2) **Or** it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval.
(3) **Or** it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations(see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

(1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies).
(2) **And** no additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application.
(3) **And** all other “criteria” are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

(1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2).
(2) **Or** the applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement.
(3) **Or** the applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your ODE’s ADRA.

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

/s/

DAWN WILLIAMS
01/19/2011