CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

ANDA 078743

Name: Malathion Lotion USP 0.5%

Sponsor: Synerx Pharma, LLC

Approval Date: March 6, 2009

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 078743

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 078743

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville, MD 20857

ANDA 78-743

Synerx Pharma, LLC
Attention: Walter G. Jump, Pharm.D.
Vice-President
100 North State Street
Newtown, PA 18940

Dear Sir:

This is in reference to your abbreviated new drug application (ANDA) dated December 26, 2006, submitted pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act (the Act), for Malathion Lotion USP, 0.5%.

Reference is also made to your amendments dated July 11, and August 13, 2007, April 15, July 9, and August 15, 2008, January 16, and February 17, 2009.

We have completed the review of this ANDA and have concluded that adequate information has been presented to demonstrate that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly the ANDA is approved, effective on the date of this letter. The Division of Bioequivalence has determined your Malathion Lotion USP, 0.5% to be bioequivalent and, therefore, therapeutically equivalent to the reference listed drug, Ovide Lotion, 0.5%, of Taro Pharmaceuticals.

Under section 506A of the Act, certain changes in the conditions described in this ANDA require an approved supplemental application before the change may be made.

We note that if FDA requires a Risk Evaluation & Mitigation Strategy (REMS) for a listed drug, an ANDA citing that listed drug also will be required to have a REMS, See 505-1(i).

Postmarketing reporting requirements for this ANDA are set forth in 21 CFR 314.80-81 and 314.98. The Office of Generic Drugs should be advised of any change in the marketing status of this drug.

Promotional materials may be submitted to FDA for comment prior to publication or dissemination. Please note that these submissions are voluntary. If you desire comments on proposed launch promotional materials with respect to compliance with applicable regulatory requirements, we recommend you submit, in draft or mock-up form, two copies of both the promotional materials and package insert(s) directly to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications
5901-B Ammendale Road
Beltsville, MD 20705

We call your attention to 21 CFR 314.81(b)(3) which requires that all promotional materials be submitted to the Division of Drug Marketing, Advertising, and Communications with a completed Form FDA 2253 at the time of their initial use.

Within 14 days of the date of this letter, submit updated content of labeling [21 CFR 314.50(1)] in structured product labeling (SPL) format, as described at http://www.fda.gov/oc/datacouncil/spl.html, that is identical in content to the approved labeling. Upon receipt and verification, we will transmit that version to the National Library of Medicine for public dissemination. For administrative purposes, please designate this submission as "***Miscellaneous Correspondence – SPL for Approved ANDA 78-743***".

Sincerely yours,

{See appended electronic signature page}

Gary Buehler
Director
Office of Generic Drugs
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/

Gary Buehler

3/6/2009 12:17:13 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 078743

LABELING

NDC 68882-014-60

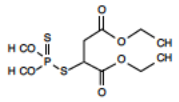
Malathion Lotion, USP 0.5%

Rx Only

For topical use only. Not for oral or ophthalmic use.

DESCRIPTION

Malathion Lotion contains 0 005 g o malathion per mL in a vehicle o isopropyl alcohol (78%), terpineol, dipentene, and pine needle oil he chemical name o malathion is ( ) - [(dimethoxyphosphinothioyl) - thio butanedioic acid diethyl ester Malathion has a molecular weight o 330 36, represented by $C_{0}H_{9}O_{6}PS_{2}$, and has the ollowing chemical structure



CLINICAL PHARMACOLOGY

Malathion is an organophosphate agent which acts as a pediculicide by inhibiting cholinesterase activity in vivo nadvertent transdermal absorption o malathion has occurred rom its agricultural use n such cases, acute toxicity was mani ested by excessive cholinergic activity, i e , increased sweating, salivary and gastric secretion, gastrointestinal and uterine motility, and bradycardia (see **OVERDOSAGE**) Because the potential or transdermal absorption o malathion rom Malathion Lotion is not known at this time, strict adherence to the dosing instructions regarding its use in children, method o application, duration o exposure, and requency o application is required

INDICATIONS AND USAGE

Malathion Lotion is indicated or patients in ected with *Pediculus humanus capitis* (head lice and their ova) o the scalp hair

CONTRAINDICATIONS

Malathion Lotion is contraindicated or neonates and in ants because their scalps are more permeable and may have increased absorption o malathion Malathion Lotion should also not be used on individuals known to be sensitive to malathion or any o the ingredients in the vehicle

WARNINGS

1 Malathion Lotion is **flammable** he lotion and wet hair should not be exposed to open flames or electric heat sources, including hair dryers and electric curlers Do not smoke while applying lotion or while hair is wet Allow hair to dry naturally and to remain uncovered a ter application o Malathion Lotion

2 Malathion Lotion should only be used on children under the direct supervision o an adult

3 Malathion Lotion comes into contact with the eyes, flush immediately with water Consult a physician i eye irritation persists

4 skin irritation occurs, discontinue use o product until irritation clears Reapply the Malathion Lotion, and i irritation reoccurs, consult a physician

5 Slight stinging sensations may occur with the use o Malathion Lotion

General: Keep out o reach o children Close eyes tightly during product application accidentally placed in the eye, flush immediately with water Use only on scalp hair

INFORMATION TO PATIENTS

1 Malathion Lotion is **flammable** he lotion and hair wet with lotion should not be exposed to open flames or electric heat sources, including hair dryers and electric curlers Do not smoke while applying lotion or while hair is wet he person applying Malathion Lotion should wash hands a ter application Allow hair to dry naturally and to remain uncovered a ter application o Malathion Lotion

2 Malathion Lotion should only be used on children under the direct supervision o an adult Children should be warned to stay away rom lighted cigarettes, open flames, and electric heat sources while the hair is wet

3 n case o accidental ingestion o Malathion Lotion by mouth, seek medical attention immediately

4 you are pregnant or nursing, you should contact your physician be ore using Malathion Lotion

5 Malathion Lotion comes into contact with the eyes, flush immediately with water Consult a physician i eye irritation persists or i visual changes occur

6 skin irritation occurs, wash scalp and hair immediately the irritation clears, Malathion Lotion may be reapplied irritation reoccurs, consult a physician

7 Slight stinging sensations may be produced when using Malathion Lotion

8 Apply Malathion Lotion on the scalp hair in an amount just su icient to thoroughly wet hair and scalp Pay particular attention to the back o the head and neck when applying Malathion Lotion Anyone applying Malathion Lotion should wash hands immediately a ter the application process is complete

9 Allow hair to dry naturally and to remain uncovered Shampoo hair a ter 8 to 12 hours, again paying attention to the back o the head and neck while shampooing

10 Rinse hair and use a fine-toothed(nit) comb to remove dead lice and eggs

11 lice are still present a ter 7-9 days, repeat with a second application o Malathion Lotion

12 urther treatment is generally not necessary Other amily members should be evaluated by a physician to determine i in ested, and i so, receive treatment

Laboratory Tests: here are no special laboratory tests needed in order to use this medication

Carcinogenesis, Mutagenesis, and Impairment o Fertility: Although carcinogenesis, mutagenesis, and impairment o ertility have not been studied with Malathion Lotion, malathion has been shown to be genotoxic in a number o *in vitro* and *in vivo* mutation and clastogenicity assays However, there was no evidence o a carcinogenic e ect ollowing long-termoral administration o malathion in 344 rats a ter 2 years eeding with up to 0 4% (~ 200 - 400 mg/kg/day) nor was it tumorigenic in Osborne - Mendel rats or B6C3 1 mice a ter similar eeding or 80 weeks with 0 8% (~ 400 - 600 mg/kg/day) or 1 6% (~ 1,000 - 2,000 mg/kg/day), respectively Based on body sur ace area, doses tested are approximately 4 to 40 old greater than those anticipated in humans (assuming 100% bioavailability)

Reproduction studies per ormed with malathion in rats at doses over 180 old greater than those anticipated in a 60 kg adult (based on body sur ace area and assuming 100% bioavailability) revealed no evidence o impaired ertility

Pregnancy: Pregnancy Category B here was no evidence o teratogenicity in studies in rats and rabbits at doses up to 900 mg/kg/day and 100 mg/kg/day malathion, respectively A study in rats ailed to show any gross etal abnormalities attributable to eeding malathion up to 2,500 ppm (~ 200 mg/kg/day) in the diet during a three-generation evaluation period

hese doses were approximately 40 to 180 times higher than the dose anticipated in a 60 kg adult (based on body sur ace area and assuming 100% bioavailability) Because animal reproduction studies are not always predictive o human responses, this drug should be used (or handled) during pregnancy only i clearly needed

Nursing Mothers: Malathion in an acetone vehicle has been reported to be absorbed through human skin to the extent o 8% o the applied dose However, percutaneous absorption rom the Malathion Lotion, 0 5% ormulation has not been studied, and it is not known whether malathion is excreted in human milk Because many drugs are excreted in human milk, caution should be exercised when Malathion Lotion is administered to (or handled by) a nursing mother

Pediatric Use: he sa ety and e ectiveness o Malathion Lotion in children less than 6 years o age has not been established via well-controlled trials

ADVERSE REACTIONS

Malathion has been shown to be irritating to the skin and scalp Accidental contact with the eyes can result in mild conjunctivitis t is not known i Malathion Lotion has the potential to cause contact allergic sensitization

OVERDOSAGE

Consideration should be given, as part o the treatment program, to the high concentration o isopropyl alcohol in the vehicle

Malathion, although a weaker cholinesterase inhibitor than some other organophosphates, may be expected to exhibit the same symptoms o cholinesterase depletion a ter accidental ingestion orally accidentally swallowed, vomiting should be induced promptly or the stomach lavaged with 5% sodium bicarbonate solution

Severe respiratory distress is the major and most serious symptom o organophosphate poisoning requiring artificial respiration, and atropine may be needed to counteract the symptoms o cholinesterase depletion

Repeat analyses o serum and RBC cholinesterase may assist in establishing the diagnosis and ormulating a long-range prognosis

DOSAGE AND ADMINISTRATION

1 Apply Malathion Lotion on **DRY** hair in amount just su icient to thoroughly wet the hair and scalp Pay particular attention to the back o the head and neck while applying Malathion Lotion Wash hands a ter applying to scalp

2 Allow hair to dry naturally—use no electric heat source, and allow hair to remain uncovered

3 A ter 8 to 12 hours, the hair should be shampooed

4 Rinse and use a fine-toothed(nit) comb to remove dead lice and eggs

5 lice are still present a ter 7-9 days, repeat with a second application o Malathion Lotion

urther treatment is generally not necessary Other amily members should be evaluated by a physician to determine i in ested, and i so, receive treatment

Clinical Studies: wo controlled clinical trials evaluated the pediculicidal activity o Malathion Lotion Patients applied the lotion to the hair and scalp in quantities, up to a maximum o 2 fl oz , su icient to thoroughly wet the hair and scalp he lotion was allowed to air dry and was shampooed with Prell shampoo 8 to 12 hours a ter application Patients in both the Malathion Lotion group and in the vehicle group were examined immediately a ter shampooing, 24 hours a ter, and 7 days a ter or the presence o live lice Results are shown in the ollowing table

Number o Patients Without Live Scalp Lice

Treatment	Immediately A ter	24 Hrs. A ter	7 Days A ter
Malathion Lotion	129/129	122/129	114/126
Malathion Vehicle	105/105	63/105	31/105

he presence or absence o ova at day 7 was not evaluated in these studies he presence or absence o live lice or ova at 14 days ollowing treatment was not evaluated in these studies

he residual amount o malathion on hair and scalp is unknown

HOW SUPPLIED

Malathion Lotion, USP 0 5%, is supplied in bottles o 2 fl oz (59 mL)
NDC 68882-014-60
Store at controlled room temperature 20° to 25°C (68° to 77°) [see USP

Flammable. Keep away rom heat and open flame.

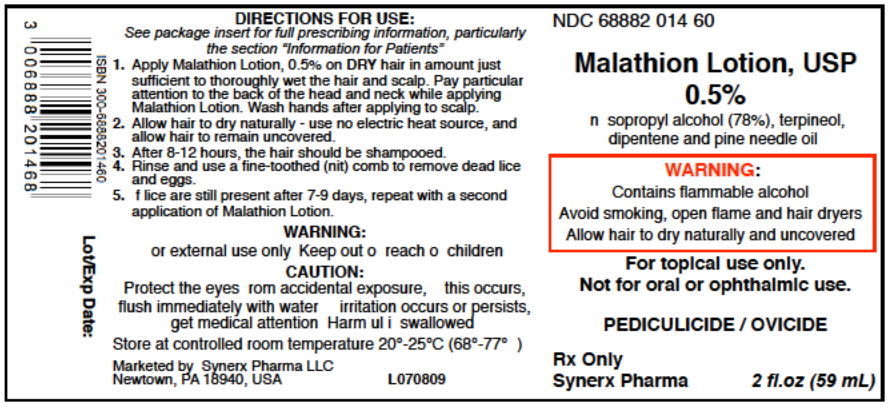
Manu actured or
Synerx Pharma LLC, Newtown, PA 18940
by DP Lakewood, nc Lakewood, NJ 08701

P070809
Aug 2007

Section 1.14.2.1 Final Printed Carton and Container Labels

In this section of the ANDA we are providing final printed container labels and carton labels in accordance with 21 CFR 314.94. We have incorporated the requested revisions by the FDA as indicated in their August 9, 2007 Telephone Fax deficiency.

Container Labeling



3 006882014 68

ISBN 300-68882014 60

Lot/Exp Date:

DIRECTIONS FOR USE:

See package insert for full prescribing information, particularly the section "Information for Patients"

1. Apply Malathion Lotion, 0.5% on DRY hair in amount just sufficient to thoroughly wet the hair and scalp. Pay particular attention to the back of the head and neck while applying Malathion Lotion. Wash hands after applying to scalp.
2. Allow hair to dry naturally - use no electric heat source, and allow hair to remain uncovered.
3. After 8-12 hours, the hair should be shampooed.
4. Rinse and use a fine-toothed (nit) comb to remove dead lice and eggs.
5. f lice are still present after 7-9 days, repeat with a second application of Malathion Lotion.

WARNING:

or external use only Keep out o reach o children

CAUTION:

Protect the eyes rom accidental exposure, this occurs, flush immediately with water irritation occurs or persists, get medical attention Harm ul i swallowed

Store at controlled room temperature 20°-25°C (68°-77°)

Marketed by Synerx Pharma LLC
Newtown, PA 18940, USA L070809

NDC 68882 014 60

Malathion Lotion, USP 0.5%

n sopropyl alcohol (78%), terpineol, dipentene and pine needle oil

WARNING:
Contains flammable alcohol
Avoid smoking, open flame and hair dryers
Allow hair to dry naturally and uncovered

For topical use only.
Not for oral or ophthalmic use.

PEDICULICIDE / OVICIDE

Rx Only
Synerx Pharma ***2 fl.oz (59 mL)***

Malathion Lotion, USP
0.5%

FPO Bar Code for Labeling
Component Code

C070809

DIRECTIONS FOR USE:

See package insert for full prescribing information, particularly the section "Information for Patients"

1. Apply Malathion Lotion, 0.5% on **DRY** hair in amount just sufficient to thoroughly wet the hair and scalp. Pay particular attention to the back of the head and neck while applying Malathion Lotion. Wash hands after applying to scalp.
2. Allow hair to dry naturally – use no electric heat source, and allow hair to remain uncovered.
3. After 8–12 hours, the hair should be shampooed.
4. Rinse and use a fine-toothed (nit) comb to remove dead lice and eggs.
5. If lice are still present after 7–9 days, repeat with a second application of Malathion Lotion.

NDC 68882–014–60

Malathion Lotion, USP
0.5%

In Isopropyl alcohol (78%), terpineol, dipentene and pine needle oil.

WARNING:
Contains flammable alcohol.
Avoid smoking, open flame and hair dryers.
Allow hair to dry naturally and uncovered.

For topical use only.
Not for oral or ophthalmic use.

PEDICULICIDE / OVICIDE

Rx Only

Synerx Pharma ***2 fl.oz (59 mL)***

ISBN 300-6888201460

3 006888 201468

Lot/Exp Date:

WARNING:
For external use only.
Keep out of reach of children.

CAUTION:
Protect the eyes from accidental exposure, If this occurs, flush immediately with water. If irritation occurs or persists, get medical attention. Harmful if swallowed.

Store at controlled room temperature 20°-25°C (68°-77°F).

Marketed by:
Synerx Pharma LLC
Newtown, PA 18940, USA

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 078743

LABELING REVIEWS

REVIEW OF PROFESSIONAL LABELING - #1
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: 78-743
Date of Submission: December 26, 2006
Applicant's Name: Synerx Pharma LLC.
Established Name: Malathion Lotion USP. 0.5%

Labeling Deficiencies:

1. **GENERAL COMMENT:** Please note that your drug product is the subject of a USP monograph. We encourage you to include USP in the established name of your drug product.
2. **CONTAINER:**
   a. When submitting in final print, please assure that the i**mportant labeling statements are prominent,** especially the established name, product strength, Directions for Use and Warning:Contains flammable alcohol… and Caution statements. To ensure the important labeling statements are prominent **you may decrease the prominence of your marketed by" and "Rx Only" statements, company name and net quantity.**
   b. Please assure that your container labels are of actual size, color and clarity when submitting in final print.
   c. Add the route of administration "For topical use only.
   d. If space permits add the statement "Not for oral or ophthalmic use"
3. **CARTON :**
   a. When submitting in final print, please assure that the i**mportant labeling statements are prominent,** especially the established name, product strength, Directions for Use and Warning:Contians flammable alcohol… and Caution statements. To ensure the important labeling statements are prominent **you may decrease the prominence of your logo "S", marketed by" and "Rx Only" statements, company name and net quantity.**
   b. See CONTAINER comments (c) and (d)
4. **INSERT**
   a. Carcinogenesis, Mutagenesis, and Impairment of Fertility: Revise the last paragraph of the **Carcinogenesis, Mutagenesis, and Impairment of Fertility** section to read as "Reproduction studies performed with malathion in rats at doses over 180 fold greater than those anticipated in a 60 kg adult (based on body surface area and assuming 100% bioavailability) revealed no evidence of impaired fertility."
   b. Pregnancy: Pregnancy Category B: Revise the third sentence in the **Pregnancy** section to read as "These doses were approximately 40 to 180 times higher than the dose anticipated in a 60 kg adult (based on body surface area and assuming 100% bioavailability)."
5. (b) (4)**:** Delete the (b) (4) you have provided since this has not been approved by the FDA and therefore can not be approved for your application.

Revise your labeling and labels, as instructed above, and submit final printed labeling electronically.

Prior to approval, it may be necessary to revise your labeling subsequent to approved changes for the reference listed drug. In order to keep ANDA labeling current, we suggest that you subscribe to the daily or weekly updates of new documents posted on the CDER web site at the following address - http://www.fda.gov/cder/cdernew/listserv.html

To facilitate review of your next submission, please provide a side-by-side comparison of your proposed labeling with that of your last submission with all differences annotated and explained.

NOTES/QUESTIONS TO THE CHEMIST: NONE

FOR THE RECORD:

1. MODEL LABELING

This review was based on the labeling for Ovide by Medicis; NDA 18-613/S011; approved April 04, 2003. This supplemental drug application provides for revised wording to the Carcinogenesis, Mutagenesis, and Impairment of Fertility section of the label. Please note that they firm was requested to make changes to the Carcinogenesis, Mutagenesis, and Impairment of Fertility and Pregnancy section of the label as follows:

> The last paragraph of the **Carcinogenesis, Mutagenesis, and Impairment of Fertility** section of the label should read: "Reproduction studies performed with malathion in rats at doses over 180 fold greater than those anticipated in a 60 kg adult (based on body surface area and assuming 100% bioavailability) revealed no evidence of impaired fertility."
>
> The third sentence in the **Pregnancy** section should read: "These doses were approximately 40 to 180 times higher than the dose anticipated in a 60 kg adult (based on body surface area and assuming 100% bioavailability)."

In addition, the firm was requested to submit the changes in their next annual report.

2. INACTIVE INGREDIENTS

There does not appear to be a discrepancy in inactives between the DESCRIPTION and the composition statement.

Ingredient	Reference Listed Drug (RLD), Ovide	Amount (Percent vol/vol)	Units	FDA IIG and PI Label Percents
Malathion, USP*	X	0.406	mL/100 mL	0.5% wt/vol label claim
(b) (4) Terpineol	X	(b) (4)	mL/100 mL	(b) (4)
(b) (4) Limonene	X		mL/100 mL	
Isopropyl Alcohol, USP	X		mL/100 mL	78 % vol/vol label claim
Pine Needle Oil	X		mL/100 mL	(b) (4)
Total		100	v/v	

3. PATENTS/EXCLUSIVITIES

Patent Data – NDA 18-613

Patent No.	Patent Expiration	Use Code	Description	How Filed	Labeling Impact
NONE	NONE	NONE	NONE	NONE	NONE

Exclusivity-Data – NDA 18-613

Code	Reference	Expiration	Labeling Impact
NONE	NONE	NONE	NONE

4. **STORAGE TEMPERATURE RECOMMENDATIONS COMPARISON**

- USP: Preserve in tight, glass containers.
- RLD: Stored at controlled room temperature 20° to 25°C (68° to 77°F).
- ANDA: Same as RLD.

5. **PACKAGE CONFIGURATION**

- RLD: Packaged in 2 oz glass bottles.
- ANDA: Malathion Lotion USP, 0.5% is packaged in a 2 fl oz (59 mL) (b) (4) amber glass bottle with sprinkler top and capped with a plastic, child-resistant closure.

6. **CONTAINER/CLOSURE** - The container closure system for this product consists of an amber glass bottle with a sprinkler top and a child resistant closure. The RLD is packaged in a clear glass bottle with a sprinkler top and a child resistant closure. During development we measured the sprinkler opening of the RLD and we utilized the same diameter opening for our product. As we have the same relative viscosity as the RLD this will provide that same functionality. We chose an amber bottle versus a clear bottle to decrease any potential light effect on the malathion or one of the natural ingredients used as excipients. As the RLD is packaged in a carton we performed light stability studies of our product within a carton and without a carton.

Component	Primary or Secondary Component	Manufacturer
Amber (b) (4) Round (b) (4) Glass Bottle	Primary	(b) (4)
(b) (4) White, Round, Ribbed, (b) (4) CRC cap	Primary	
Closure - Cap		
Closure - Seal		
White Printed Carton	Secondary	
Package Insert/ Patient Instructions	Secondary	
Bottle Label	Secondary	

7. **FINISHED DOSAGE FORM**

- RLD: Supplied in a 2 oz glass bottle as a 0.5% lotion.
- ANDA: A clear, colorless solution

8. **MANUFACTURING FACILITY OF FINISHED DOSAGE FORM**

DPT Laboratories
1200 Paco Way
Lakewood, NJ 08701

Date of Submission: December 26, 2006

Primary Reviewer: Beverly Weitzman **Date:**

Team Leader: John Grace **Date:**

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

/s/

Beverly Weitzman
8/9/2007 12:23:12 PM
LABELING REVIEWER

John Grace
8/9/2007 02:33:16 PM
LABELING REVIEWER

APPROVAL SUMMARY #1

REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: 78-743
Date of Submission: August 13, 2007
Applicant's Name: Synerx Pharma LLC.
Established Name: Malathion Lotion USP. 0.5%

APPROVAL SUMMARY (List the package size, strength(s), and date of submission for approval):
Do you have Final Printed Labels and Labeling? Yes

1. **CONTAINER** (2 fl. oz) **-** Satisfactory in Final Print as of **August 13, 2007** electronic submission.
\\Cdsesub1\nonectd\N78743\N_000\2007-08-13\pdf_labeling\Section 1.14.2.1.pdf
2. **CARTON** (2 fl. oz) – Satisfactory in Final Print as of **August 13, 2007** electronic submission.
\\Cdsesub1\nonectd\N78743\N_000\2007-08-13\pdf_labeling\Section 1.14.2.1.pdf
3. **PACKAGE INSERT** - Satisfactory in Final Print as of **August 13, 2007** electronic submission.
\\Cdsesub1\nonectd\N78743\N_000\2007-08-13\pdf_labeling\Section 1.14.2.3.pdf

BASIS OF APPROVAL:

- Was this approval based upon a petition? No
- What is the RLD on the 356(h) form: Ovide Lotion, 0.5%
- NDA Number: 18-613
- NDA Drug Name: Malathion Lotion USP. 0.5%
- NDA Firm: Medicis
- Date of Approval of NDA Insert: **NDA 18-613/S011: Approved April 04, 2003.**
- Has this been verified by the MIS system for the NDA? Yes
- Was this approval based upon an OGD labeling guidance? No
- Basis of Approval for the Container Labels: Side-by-side comparison
- Basis of Approval for the Carton Labels: Side-by-side comparison
- Revisions needed post-approval: No
- Patents/Exclusivities: Refer to chart below.
- Comment: None

Patent Data – NDA 18-613

Patent No.	Patent Expiration	Use Code	Description	How Filed	Labeling Impact
NONE	NONE	NONE	NONE	NONE	NONE

Exclusivity-Data – NDA 18-613

Code	Reference	Expiration	Labeling Impact
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(b) (4) Limonene	X		mL/100 mL	
Isopropyl Alcohol, USP	X		mL/100 mL	78 % vol/vol label claim
Pine Needle Oil	X		mL/100 mL	(b) (4)
Total		100	v/v	

3. PATENTS/EXCLUSIVITIES

Patent Data – NDA 18-613

Patent No.	Patent Expiration	Use Code	Description	How Filed	Labeling Impact
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Exclusivity-Data – NDA 18-613

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- RLD: Packaged in 2 oz glass bottles.
- ANDA: Malathion Lotion USP, 0.5% is packaged in a 2 fl oz (59 mL) (b) (4) amber glass bottle with sprinkler top and capped with a plastic, child-resistant closure.

6. **CONTAINER/CLOSURE** - The container closure system for this product consists of an amber glass bottle with a sprinkler top and a child resistant closure. The RLD is packaged in a clear glass bottle with a sprinkler top and a child resistant closure. During development we measured the sprinkler opening of the RLD and we utilized the same diameter opening for our product. As we have the same relative viscosity as the RLD this will provide that same functionality. We chose an amber bottle versus a clear bottle to decrease any potential light effect on the malathion or one of the natural ingredients used as excipients. As the RLD is packaged in a carton we performed light stability studies of our product within a carton and without a carton.

Component	Primary or Secondary Component	Manufacturer
Amber (b) (4) Round (b) (4) Glass Bottle	Primary	(b) (4)
(b) (4) White, Round, Ribbed, CRC cap	Primary	
Closure - Cap		
Closure - Seal		
White Printed Carton	Secondary	
Package Insert/ Patient Instructions	Secondary	
Bottle Label	Secondary	

7. **FINISHED DOSAGE FORM**

- RLD: Supplied in a 2 oz glass bottle as a 0.5% lotion.
- ANDA: A clear, colorless solution

8. **MANUFACTURING FACILITY OF FINISHED DOSAGE FORM**

DPT Laboratories
1200 Paco Way
Lakewood, NJ 08701

Date of Submission: August 13, 2007

Primary Reviewer: Beverly Weitzman **Date:**

Team Leader: John Grace **Date:**

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

/s/

Beverly Weitzman
9/25/2007 02:27:01 PM
LABELING REVIEWER

John Grace
9/25/2007 09:16:30 PM
LABELING REVIEWER

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 078743

CHEMISTRY REVIEW

ANDA 78-743

Malathion Lotion, USP, 0.5% (w/v)

Synerx Pharma LLC

Mahnaz Farahani, Ph.D.
Division of Chemistry I
Office of Generic Drugs

Chemistry Review # 1
and telephone amendment,
Addendum 1

Table of Contents

Chemistry Review Data Sheet

1. ANDA #78-743

2. REVIEW #: 1, addendum

3. REVIEW DATE: 2/19/09

4. REVIEWER: Mahnaz Farahani, Ph.D.

5. PREVIOUS DOCUMENTS: None

Previous Documents	Document Date

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original application	December 26, 2006
Acceptable for filing	December 28, 2006
Amendment to Filling for Acceptability for Filing	April 2, 2007
Telephone amendment	July 12, 2007
Amendment	April 15, 2008
Telephone amendment	July 9, 2008
Telephone Amendment	August 15, 2008
Telephone Amendment	February 18, 2009

7. NAME & ADDRESS OF APPLICANT:

Name:	Synerx Pharma LLC
Address:	100 North State Street Newtown, PA 19840

Chemistry Review Data Sheet

Representative: Walter Jump

Telephone: 215-860-4202

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: N/A
b) Non-Proprietary Name (USAN): Malathion Lotion, USP

9. LEGAL BASIS FOR SUBMISSION:

Reference listed drug: Ovide® (Malathion) Lotion
Holder of Approved Application: TARO Pharms North
Application Number: N018-613
Strength: 0.5% w/v

Patent Certification: Paragraph II (U.S. Parent 2,578,652 and 2,962,521 are expired.) The applicant certifies on page 6 that to the best of their knowledge the patents are expired.

Exclusivity: The applicant certifies that according to the information published in current list including supplements, Ovide® (Malathion) Lotion, 0.5% is not entitled to a period of exclusivity.

10. PHARMACOL. CATEGORY:

For patients infected with Pediculus humanus capitis (head lice and their ova) of the scalp hair.

11. DOSAGE FORM: Lotion; Topical

12. STRENGTH/POTENCY:0.5%

13. ROUTE OF ADMINISTRATION: Topical

14. Rx/OTC DISPENSED: _X__Rx ___OTC

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

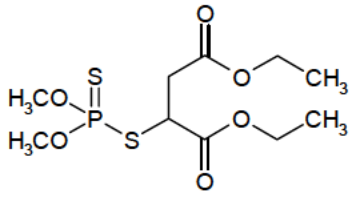
_____SPOTS product – Form Completed

___X___Not a SPOTS product

Chemistry Review Data Sheet

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

Chemical Name: (S-1,2-bis(ethoxycarbonyl)ethyl)-O,O-dimethyl-phosphorodithioate
$C_{10}H_{19}O_6PS_2$ Mol. Wt. 330.36 CAS 121-75-5



17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
DMF is part of ANDA	II	(b) (4)	(b) (4)	7			DMF is part of ANDA and no DMF # has been assigned.
(b) (4)	III			4			
	III			4			
	III			4			
	III			4			
	III			4			

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

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

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	N/A		
EES	Acceptable	6/3/08	S. Adams
Methods Validation	N/A		
Labeling	Acceptable	9/25/07	Beverly Weitzman
Bioequivalence	Acceptable	8/27/07	Linda Ulrich
EA	Satisfactory Waiver (Acceptable) 21 CFR 25.31		
Radiopharmaceutical	N/A		

19. ORDER OF REVIEW

The application submission(s) covered by this review was taken in the date order of receipt. __X__ Yes ____ No If no, explain reason(s) below:

Chemistry Assessment Section

The Chemistry Review for ANDA 78-743

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

This application is approvable.

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

N/A

II. Summary of Chemistry Assessments

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

The reference listed drug for this application is Ovide® (Malathion) Lotion, 0.5% by Taro Pharmaceuticals North.

Drug Substance:

The drug substance, Malathion, USP is a clear, colorless to slightly yellowish liquid having a characteristic odor. Congeals at about 2.9°. Slightly soluble in water. Miscible with alcohols, with esters, with ketones, with ethers, with aromatic and alkylated aromatic hydrocarbons and with vegetables oils.

Drug Product:

The drug product, Malathion Lotion USP., 0.5% is for topical application for patients infected with Pediculus humanus capitis (head lice and their ova) of the scalp hair. The drug product contains as excipients; (b) (4) Terpineol, (b) (4) Limonene, Isopropyl Alcohol, USP, and Pine Needle oil.

B. Description of how the drug product is intended to be used

The maximum daily dose (MDD) of Malathion Lotion, 0.5% (0.005 g/mL) is calculated as 295 mg using following equation:
0.005 g/mL x 59 mL (volume in 1 bottle) = 0.295 g

The drug substance: based on the ICH Guideline Q3A dated February 2003
IT is 0.10% for any single unknown impurities (unspecified).
QT is 0.15% for any specified identified or specified unidentified impurity.

The drug product: based on the ICH Guideline Q3B dated July 2006

IT is 0.20% for any single unknown impurities (unspecified).
QT is 0.20% for any specified identified or specified unidentified impurity.

C. Basis for Approvability or Not-Approval Recommendation

The application is approvable.

Following this page, 35 pages withheld in full (b)(4)

cc: ANDA 78743 Original
ANDA 78743 DUP
DIV FILE
Field Copy

Endorsements (Draft and Final with Dates):

HFD-645/MFarahani/Review Chemist /2/19/09
HFD-627/J.Fan/Team Leader/
HFD-617/R. Adigun/Project Manager/

F/T by

V:\Chemistry Division I\Team 3\FIRMSNZ\Synerx Pharma\LTRS&RVS\78743. Rev1, addendum.doc

TYPE OF LETTER: Approvable

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

/s/

TRANG Q TRAN
04/13/2012

This chemistry review was not archived prior to approval

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 078743

BIOEQUIVALENCE REVIEW

Review of a Request for Waiver of an *in vivo* Bioequivalence Study

ANDA 78-743

Drug Product:	**Malathion Lotion USP, 0.5%**
Sponsor:	**Synerx Pharma**
Reference Listed Drug:	**Ovide® (malathion) Lotion, 0.5%** **Taro Pharmaceuticals North, NDA 18-613**
Date of Submission:	**December 26, 2006**
Date of Review:	**August 13, 2007**
Reviewer:	**Linda C. Ulrich, M.D.** **Medical Officer** **Office of Generic Drugs**

Synerx Pharma requests a waiver of *in vivo* bioequivalence studies for its generic Malathion Lotion USP, 0.5%. This product is a solution, and the generic formulation is qualitatively and quantitatively the same as the reference listed drug.

Regulatory Background

A controlled correspondence (OGD# 01-591, (b) (4)) was submitted to the OGD on November 29, 2001 regarding the eligibility of malathion lotion for a waiver of *in-vivo* bioequivalence. Based upon USP definitions, the firm felt that the malathion lotion, 0.5% is more accurately defined as a solution dosage form. After further review by the OGD, it was determined that the malathion lotion, 0.5% is indeed a solution and may be eligible for a waiver of *in-vivo* bioequivalence .

Synerx Pharma requests a waiver of *in-vivo* bioequivalence based on 21 CFR 320.22(b)(3)(i-iii). This regulation states that a drug product's *in vivo* bioavailability or bioequivalence may be considered self-evident based on other data in the application if the drug product is…(i) a solution for application to the skin…(ii) contains an active ingredient in the same concentration and dosage form as the drug product that is the subject of an approved full new drug application; AND (iii) contains no inactive ingredient or other change in formulation from the drug product that is the subject of the approved full new drug application that may significantly affect absorption of the active drug ingredient or active moiety for products that are systemically absorbed, or that may significantly affect systemic or local availability for products intended to act locally.

21 CFR 314.94 (a)(9)(v) states that generally, a drug product intended for topical use…shall contain the same inactive ingredients as the reference listed drug identified by the applicant ….However, an abbreviated application may include different inactive ingredients provided that the applicant identifies and characterizes the differences and provides information demonstrating that the differences do not affect the safety or efficacy of the proposed drug product.

Topical solutions may receive a waiver of *in-vivo* bioequivalence if the products are qualitatively and quantitatively the same or do not contain any inactive ingredients that may affect safety and/or efficacy of the drug product.

Background

The reference listed drug is Ovide® (malathion) Lotion, 0.5%, by Taro Pharmaceuticals North, NDA 18-613, approved August 2, 1982. Ovide Lotion is indicated for the treatment of *Pediculus humanus capitis* (head lice and their ova) infestation of the scalp hair. The recommended dosing regimen is the following: Apply on dry hair in amount just sufficient to thoroughly wet the hair and scalp. Pay particular attention to the back of the head and neck. Wash hands after applying to scalp. Allow hair to dry naturally-use no electric heat source, and allow hair to remain uncovered. After 8-12 hours, the hair should be shampooed. Rinse and use a fine-toothed (nit) comb to remove dead lice and eggs. If lice are still present after 7-9 days, repeat with a second application.

Malathion is an organophosphate agent which acts as a pediculicide by inhibiting cholinesterase activity *in vivo*. Inadvertent transdermal absorption of malathion has occurred from its agricultural use. In such cases, acute toxicity was manifested by excessive cholinergic activity, i.e., increased sweating, salivary and gastric secretion, gastrointestinal and uterine motility, and bradycardia. Because the potential for transdermal absorption of malathion from malathion lotion is not known at this time, strict adherence to the dosing instructions regarding its use in children, method of application, duration of exposure, and frequency of application is required.

The typical adverse events observed with malathion lotion include irritation to the skin and scalp.

Discussion

Pediculus humanus capitis, or head lice and their ova, have infested humans for thousands of years. Infestation with lice is quite often inappropriately attributed to poor hygiene and low socio-economic status. Head lice grip onto hair by their claws and rapidly move from hair to hair. By injecting saliva into the infected scalp they are able to suck blood which provides their nutrition. Itching and irritation results from the louse feeding. Lice lay eggs (nits) on the hair shaft close to the scalp. Here the warmth of the scalp will incubate them. The nits are cemented on to the hair and are carried away from the scalp as the hair grows. They hatch at around 8 days. The empty egg case then turns white and becomes more visible. The louse reaches full maturity at around 10 days after hatching. If mating occurs, the female louse can lay 50-100 eggs at a rate of six per day.

Head lice usually cause itching and irritation in the scalp. This can take several weeks to develop after the initial infestation. Scratching can cause crusting and scaling on the scalp. Occasionally secondary bacterial infection of the scalp results in small sores on the scalp with tender glands in the neck. Dermatitis can also occur with a heavy infestation of lice. Fortunately head lice are not known to carry any diseases which can affect humans. It is important to identify the lice (or nits) to make a correct diagnosis. Lice are around 3 mm in length and can be seen moving from hair to hair. Unhatched eggs are within a few millimeters of the scalp and have a dark area within the shell while hatched eggs are transparent.

Ovide® (malathion) Lotion, 0.5% is indicated for *Pediculus humanus capitis* (head lice and their ova) infestation of the scalp hair. Two controlled clinical trials evaluated the pediculicidal activity of malathion lotion. Two treatment groups, malathion lotion and vehicle, applied lotion to the scalp, air dried, and shampooed with Prell® shampoo. Patients in both treatment groups were examined immediately after shampooing, and 24 hours and 7 days later for the presence of live lice. Results were as follows:

Number of Patients With Absence of Live Scalp Lice

Treatment	Immediately after	24 Hrs. After	7 Days After
Malathion Lotion	129/129	122/129	114/126
Malathion Vehicle	105/105	63/105	31/105

Comparative Composition

Ingredient	**Reference Listed Drug (RLD) Percent vol/vol**	**Test Percent vol/vol**	**% Difference between the Test and Reference**
Malathion (ACTIVE)	(b) (4)	0.406 (0.5% w/v)	(b) (4)
Terpineol		(b) (4)	
Dipentene (Limonene)			
Pine Needle Oil			
Isopropyl Alcohol			

*The RLD Formulation was referenced in a DFS Pharmacology /Toxicology Labeling Addendum review, November 2000.

Reviewer's Comment: *This reviewer spoke with Manaz Farahani, the chemistry reviewer for this product, about the apparent differences in the amount of ACTIVE ingredient between the test and reference products. The chemist stated that malathion is listed in the USP with quantitative specifications ranging from 0.485—0.55 % w/v; the generic should be acceptable, so long as the amount of malathion falls within this range.*

Excipient Function

Excipient	**Function**
Malathion	Active
Isopropyl Alcohol	(b) (4)
Terpineol	
Dipentene	
Pine Needle Oil	

Conclusions

The formulation of the proposed product and the RLD are quantitatively and qualitatively the same (within 5%) in terms of inactive ingredients; the (b) (4) difference in the amount of active ingredient is acceptable, per OGD's Chemistry Review Division.

Recommendation

A waiver of *in vivo* bioequivalence based on 21 CFR 320.22 (b)(3)(iii) is granted.

_____ Date:_____

Linda C. Ulrich, M.D.
Medical Reviewer
Office of Generic Drugs

Concur: _____ Date:_____

Dena R. Hixon, M.D.
Associate Director for Medical Affairs
Office of Generic Drugs

Concur: _____ Date:_____

Dale P. Conner, Pharm.D.
Director
Division of Bioequivalence
Office of Generic Drugs

COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 78-743 APPLICANT: Synerx Pharma

DRUG PRODUCT: Malathion Lotion USP, 0.5%

The Division of Bioequivalence has completed its review and has no further questions at this time.

Please note that the bioequivalency comments provided in this communication are preliminary. These comments are subject to revision after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling, or other scientific or regulatory issues. Please be advised that these reviews may result in the need for additional bioequivalency information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

Sincerely yours,

Dale P. Conner, Pharm.D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

CC: ANDA 78-743
DIVISION FILE
HFD-651/ Bio Drug File
HFD-600/ L. Ulrich
HFD-600/ D. Hixon

V:\FIRMSNZ\SYNERX\LTRS&REV\78743W.1206.mor.doc

BIOEQUIVALENCY - ACCEPTABLE - Bio Waiver Granted submission dates:
December 26, 2006

1. Bioequivalence Study Waiver Request (STU); August 13, 2007
   Strengths: (b) (4)
   Outcome: **AC**

Please note: This review should close the BCE and BST assignments.

Outcome Decisions:
AC - Acceptable
WC – Without charge
IC – Incomplete
UC - Unacceptable

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/s/

Linda Ulrich
8/27/2007 02:16:08 PM
MEDICAL OFFICER

Dena Hixon
8/27/2007 04:38:54 PM
MEDICAL OFFICER

Dale Conner
8/27/2007 04:46:32 PM
BIOPHARMACEUTICS

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 078743

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

78-743

1.2.1 Cover letter - Original Filing

SYNERX PHARMA

SYNERGY IN PHARMACEUTICALS

505(j)(2)(A)

3 April 2007

Mr. Gary Buehler
Director
Office of Generic Drugs (HFD-600)
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II
7500 Standish Place, Room 150
Rockville, Maryland 20855-2773

Re: Malathion Lotion, USP
0.5 % wt/vol
Original ANDA Filing

Dear Mr. Buehler:

Pursuant to 21 CFR 314.92, Synerx Pharma respectfully submits this application for Malathion Lotion, USP, 0.5% wt/vol. The filing provides documentation supporting the manufacturing, filling, packaging, testing and Quality Control (QC) release of commercial batches produced at our contract manufacturing site, DPT. A waiver of the bioequivalence testing required is included in our filing.

Consistent with 21 CFR 314.94, the filing includes the following:
Comparison between the proposed drug and the reference-listed drug
Labeling
Waiver of bioequivalency
Components and Composition Statements
Active and Inactive Components/Formula
Raw Material Controls
Description of the Manufacturing Facility
Information about outside firms/contract laboratories
Method of manufacture
In-process specifications
Packaging and Labeling procedures
Packaging Components
Drug substance information
Drug product specifications
Analytical methods

RECEIVED
DEC 2 8 2006
OGD / CDER

Marketed product stability of our product
Environmental Impact analysis statement
Appropriate letters of authorization

The filing also certifies that:

no patents or exclusivity time periods will be violated by Synerx Pharma LLC;
the development and submission of the filing was not provided by any person or persons currently debarred by the FDA;
all non clinical laboratory work was performed according to GLPs;
all manufacturing work was performed according to cGMP;

An archival copy of the ANDA, bound in blue, and a review copy, bound in red, and three separately bound copies of the analytical method validation documents are provided. Additionally, in accordance with FDA regulations, a true third copy of the ANDA was forwarded to our home district office.

The ANDA was formated according to the FDA guideline on provision of ANDAs in the common technical document format (CTD). As this format is new to Synerx, any guidance the Agency may provide on improving its structure and clarity would be appreciated. As Synerx Pharma is a small business we are not yet able to provide the application in electronic format. However as indicated in the FDA guidance on electronic labeling submissions, we have provided the draft labeling in electronic format on a compact disk (CD ROM) secured inside the front cover of the first archival volume.

I trust the application is complete and that we will receive a prompt review. We look forward to an approval from the Agency. If, however, comments or questions arise during the review of this application, please do not hesitate to call me directly at 215-860-4202 or FAX your comments to me at 215-895-9629. Timely responses will be provided.

Sincerely,

Walter G. Jump, Pharm.D.
Vice President
Synerx Pharma, LLC
100 North State Street
Newtown, PA 18940
T: 215-860-4202
F: 215-895-9629

CLINICAL REVIEW TEAM CHECKLIST FOR GENERIC ANDA
FOR APPLICATION COMPLETENESS

ANDA# __78-743_____ **FIRM NAME**_Synerx Pharma LLC_____

DRUG NAME __Malathion lotion, USP 0.5%_____

DOSAGE FORM _lotion_____

Requested by: _____Eda Howard_____ Date: _3/1/07_____
Chief, Regulatory Support Team, (HFD-615)

	Summary of Findings by Clinical Review Team
	Study meets statutory requirements
	Study does NOT meet statutory requirements
	Reason:
X	**Waiver meets statutory requirements**
	Waiver does NOT meet statutory requirements
	Reason:

RECOMMENDATION: X___COMPLETE ___INCOMPLETE

Reviewed by:

_____ Date: _____
Reviewer
Carol Y. Kim, Pharm.D.
Clinical Reviewer

_____ Date: _____
Dena R. Hixon, M.D.
Associate Director for Medical Affairs

Item Verified:	YES	NO	Required Amount	Amount Sent	Comments
Protocol		X			
Summary of Study		X			
Clinical Site (s)		X			
Study Investigator (s)		X			
List of subjects included in PP/ (M)ITT populations per treatments		X			
List of subjects excluded/ from PP/ (M)ITT per treatments		X			
Reasons for discontinuation from the study if discontinued		X			
Adverse Events		X			
Concomitant Medications		X			
Individual subject's scores/data per visit		X			
Pre-screening of Patients		X			
IRB Approval		X			
Consent Forms		X			
Randomization Schedule		X			
Protocol Deviations		X			
Case Report Forms		X			
PD Data Disk (or Elec Subm)		X			
Study Results		X			
Clinical Raw Data/ Medical Records		X			
Composition	X				Vol. 1.1; appears to be qualitatively and quantitatively the same as the

					RLD
BioStudy Lot Numbers		X			
Date of Manufacture		X			
Exp. Date of RLD		X			
Statistical Reports		X			
Defined BE endpoints		X			
Summary results provided by the firm indicate studies pass BE criteria		X			
Summary results provided by the firm indicate superiority of the active treatments over the vehicle/placebo		X			
Waiver requests	X				Per 21 CFR 320.22(b)(3)(i)

Additional Comments regarding the ANDA:

The sponsor states that their product is a solution for application to the skin.

The OGD has determined that malathion lotion, 0.5%, is eligible for waiver of *in vivo* BE provided that the generic product meets all the conditions of 21 CFR 320.22 (b) (3). See control document #01-591 for details.

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

/s/

Dena Hixon

3/6/2007 03:01:25 PM

1.2.2 Cover Letter of Acceptability to File Letter

SYNERX PHARMA

SYNERGY IN PHARMACEUTICALS

Me

Mr. Gary Buehler
Director
Office of Generic Drugs (HFD-600)
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II
7500 Standish Place, Room 150
Rockville, Maryland 20855-2773

Re: Malathion Lotion, USP
ANDA 78-743
Amendment to Filing for Acceptability for Filing

Dear Mr. Buehler:

Pursuant to 21 CFR 314.92, Synerx Pharma respectfully submits this amendment for Malathion Lotion, USP. The amendment addresses the comments provided by Dr. Ian Margand on Monday April 2nd concerning elements needed for an acceptable for filing letter to be issued.

According to Dr. Ian Margand the following elements need to be addressed:

- Revision of the FDA 356h Form to remove the generic name from the proprietary name field
- Add an Exclusivity Statement
- Add a Reprocessing Statement to the filing
- Add a statement to the Drug Product Certificate of Analysis (CofA) indicating the lot of material to which the CofA applies

In addition he requested that I provide an electronic version of the CTD Section 2.3. This amendment provides all the requested information and was sent via FAX to Dr. Ian Margand at 301-827-3847 and by hard copy to the Agency.

I trust this amendment makes the application complete and that we will receive a prompt review. We look forward to an approval from the Agency. If, however, comments or questions arise during the review of this application, please do not hesitate to call me directly at 215-860-4202 or FAX your comments to me at 215-895-9629. Timely responses will be provided.
Sincerely,

Walter G. Jump, Pharm.D.
Vice President
Synerx Pharma, LLC
100 North State Street
Newtown, PA 18940
T: 215-860-4202
F: 215-895-9629

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville, MD 20857

ANDA 78-743

Synerx Pharma, LLC
Attention: Walter G. Jump
100 North State Street
Newtown, PA 18940-2048

Dear Sir:

We acknowledge the receipt of your abbreviated new drug application submitted pursuant to Section 505(j) of the Federal Food, Drug and Cosmetic Act.

Reference is also made to the telephone conversation dated April 2, 2007 and your correspondence dated April 2, 2007.

NAME OF DRUG: Malathion Lotion USP, 0.5%

DATE OF APPLICATION: December 26, 2006

DATE (RECEIVED) ACCEPTABLE FOR FILING: December 28, 2006

We will correspond with you further after we have had the opportunity to review the application.

Please identify any communications concerning this application with the ANDA number shown above.

Should you have questions concerning this application, contact:

Rosalyn Adigun
Project Manager
301-827-5754

Sincerely yours,

{See appended electronic signature page}

Wm Peter Rickman
Director
Division of Labeling and Program Support
Office of Generic Drugs
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/

Martin Shimer
4/3/2007 11:08:31 AM
Signing for Wm Peter Rickman

ANDA CHECKLIST FOR CTD or eCTD FORMAT
FOR COMPLETENESS and ACCEPTABILITY of an APPLICATION FOR FILING

For More Information on Submission of an ANDA in Electronic Common Technical Document (eCTD) Format please go to: http://www fda.gov/cder/regulatory/ersr/ectd.htm
***For a Comprehensive Table of Contents Headings and Hierarchy please go to:**
http://www fda.gov/cder/regulatory/ersr/5640CTOC-v1.2.pdf
**** For more** CTD and eCTD informational links **see the final page of the ANDA Checklist**
*** **A model Quality Overall Summary for an immediate release tablet and an extended release capsule can be found on the OGD webpage** http://www.fda.gov/cder/ogd/ ***

ANDA #: 78-743 **FIRM NAME**: SYNERX PHARMA LLC.

PIV: NO **Electronic or Paper Submission:** CTD FORAMT PAPER

RELATED APPLICATION(S): NA

First Generic Product Received? NO

DRUG NAME: MALATHION

DOSAGE FORM: LOTION USP, 0.5%

Bio Assignments:		**Micro Review (No)**
☒ **BPH**	☒ **BCE**	
☐ **BST**	☐ **BDI**	

Random Queue: 3

Chem Team Leader: Fan, Jim PM: Rosalyn Adigun Labeling Reviewer: Beverly Wietzman

Letter Date: DECEMBER 26, 2006 **Received Date**: DECEMBER 28, 2006

Comments: EC- 1 YES **On Cards:** YES

Therapeutic Code: 4020140 PEDICULICIDES (TOPICAL)

Archival copy: CTD FORMAT PAPER **Sections** I

Review copy: YES E-Media Disposition: YES S ENT TO EDR

Not applicable to electronic sections

PART 3 Combination Product Category N Not a Part3 Combo Product

(Must be completed for ALL Original Applications) Refer to the Part 3 Combination Algorithm

Reviewing CSO/CST Iain Margand **Date 4/2/07**	**Recommendation:** ☒ **FILE** ☐ **REFUSE to RECEIVE**
Supervisory Concurrence/Date: _____	**Date:** _____

ADDITIONAL COMMENTS REGARDING THE ANDA:

4/2/07: Requested revision of 356h "Proprietary Name" section to remove information.
Requested an Exclusivity Statement.
Requested a Reprocessing Statement.
Requested confirmation that COA lot # for drug product is the same lot # as the exhibit batch.

Contact: Walter Jump 215-860-4202

MODULE 1
ADMINISTRATIVE

		ACCEPTABLE
1.1	**1.1.2** **Signed and Completed Application Form (356h) (original signature)** (Check Rx/OTC Status) RX YES	☒
1.2	**Cover Letter** Dated: DECEMBER 26, 2006	☒
*	**Table of Contents (paper submission only)** YES	☒
1.3.2	**Field Copy Certification (original signature)** YES **(N/A for E-Submissions)**	☒
1.3.3	**Debarment Certification-GDEA (Generic Drug Enforcement Act)/Other:** 1. Debarment Certification (original signature) YES 2. List of Convictions statement (original signature) YES	☒
1.3.4	**Financial Certifications** Bioavailability/Bioequivalence Financial Certification (Form FDA 3454) or Disclosure Statement (Form FDA 3455) NO	☐
1.3.5	**1.3.5.1** **Patent Information** Patents listed for the RLD in the Electronic Orange Book Approved Drug Products with Therapeutic Equivalence Evaluations N **1.3.5.2** **Patent Certification** 1. Patent number(s) N/A 2. Paragraph: (Check all certifications that apply) MOU ☐ PI ☐ PII ☒ PIII ☐ PIV ☐ No Relevant Patents ☐ 3. Expiration of Patent(s): NA a. Pediatric exclusivity submitted? b. Expiration of Pediatric Exclusivity? 4. Exclusivity Statement: YES No exclusivities (see amendment)	☒
1.4.1	**References** Letters of Authorization 1. DMF letters of authorization a. Type II DMF authorization letter(s) or synthesis for Active Pharmaceutical Ingredient No DMF for Drug Substance b. Type III DMF authorization letter(s) for container closure Y 2. US Agent Letter of Authorization (U.S. Agent [if needed, countersignature on 356h]) N/A	☒
1.12.11	**Basis for Submission** NDA# : 18-613 Ref Listed Drug: OVIDE Firm: TARO PHARMS NORTH ANDA suitability petition required? NA If Yes, then is change subject to PREA (change in dosage form, route or active ingredient) see section 1.9.1	☒

MODULE 1 (Continued)
ADMINISTRATIVE

ACCEPTABLE

1.12.12	**Comparison between Generic Drug and RLD-505(j)(2)(A)** 1. Conditions of use Same 2. Active ingredients Malathion 3. Inactive ingredients Same 4. Route of administration Topical 5. Dosage Form Lotion 6. Strength 0.5%	☒
1.12.14	**Environmental Impact Analysis Statement** YES	☒
1.12.15	**Request for Waiver** Request for Waiver of In-Vivo BA/BE Study(ies): Paper, YES	☒
1.14.1	**Draft Labeling (Mult Copies N/A for E-Submissions)** **1.14.1.1** 4 copies of draft (each strength and container) Y **1.14.1.2** 1 side by side labeling comparison of containers and carton with all differences annotated and explained Y **1.14.1.3** 1 package insert (content of labeling) submitted electronically Y ***Was a proprietary name request submitted? No (If yes, send email to Labeling Reviewer indicating such.)	☒
1.14.3	**Listed Drug Labeling** **1.14.3.1** 1 side by side labeling (package and patient insert) comparison with all differences annotated and explained Y **1.14.3.3** 1 RLD label and 1 RLD container label Y	☒

ACCEPTABLE

2.3	**Quality Overall Summary** **E-Submission: _____PDF (archive) ____ Word Processed e.g., MS Word** A model Quality Overall Summary for an immediate release table and an extended release capsule can be found on the OGD webpage http://www.fda.gov/cder/ogd/ **Question based Review (QbR) _____ YES X____ NO** **2.3.S** **Drug Substance (Active Pharmaceutical Ingredient)** **2.3.S.1** **General Information** **2.3.S.2** **Manufacture** **2.3.S.3** **Characterization** **2.3.S.4** **Control of Drug Substance** **2.3.S.5** **Reference Standards or Materials** **2.3.S.6** **Container Closure System** **2.3.S.7** **Stability** **2.3.P** **Drug Product** **2.3.P.1** **Description and Composition of the Drug Product** **2.3.P.2** **Pharmaceutical Development** **2.3.P.2.1** **Components of the Drug Product** **2.3.P.2.1.1** **Drug Substance** **2.3.P.2.1.2** **Excipients** **2.3.P.2.2** **Drug Product** **2.3.P.2.3** **Manufacturing Process Development** **2.3.P.2.4** **Container Closure System** **2.3.P.3** **Manufacture** **2.3.P.4** **Control of Excipients** **2.3.P.5** **Control of Drug Product** **2.3.P.6** **Reference Standards or Materials** **2.3.P.7** **Container Closure System** **2.3.P.8** **Stability**	☒

2.7	**Clinical Summary (Bioequivalence) N/A** **E-Submission: _____PDF (archive) ____ Word Processed e.g., MS Word** **2.7.1** **Summary of Biopharmaceutic Studies and Associated Analytical Methods** **2.7.1.1** **Background and Overview** **2.7.1.2** **Summary of Results of Individual Studies** **2.7.1.3** **Comparison and Analyses of Results Across Studies** 1. Summary Bioequivalence tables: Table 1. Summary of Comparative Bioavailability (BA) Studies Table 2. Statistical Summary of the Comparative BA Data Table 4. Summary of In Vitro Dissolution Studies **2.7.1.4** **Appendix**	☐

MODULE 3

3.2.S DRUG SUBSTANCE

ACCEPTABLE

3.2.S.1	**General Information** **3.2.S.1.1** **Nomenclature** **3.2.S.1.2** **Structure** **3.2.S.1.3** **General Properties**	☒
3.2.S.2	**Manufacturer** **3.2.S.2.1** **Manufacturer(s) (This section includes contract manufacturers and testing labs)** **Drug Substance (Active Pharmaceutical Ingredient)** 1. Addresses of bulk manufacturers Y 2. Manufacturing Responsibilities Y 3. Type II DMF number for API N/A 4. CFN or FEI numbers	☒
3.2.S.3	**Characterization**	☒

3.2.S.4	**Control of Drug Substance (Active Pharmaceutical Ingredient)** **3.2.S.4.1** **Specification** Testing specifications and data from drug substance manufacturer(s) Y **3.2.S.4.2** **Analytical Procedures** Y **3.2.S.4.3** **Validation of Analytical Procedures** **1.** Spectra and chromatograms for reference standards and test samples Y 2. Samples-Statement of Availability and Identification of: a. Drug Substance see sec. 3.2.P.6 b. Same lot number(s) **3.2.S.4.4** **Batch Analysis** 1. COA(s) specifications and test results from drug substance mfgr(s) Y 2. Applicant certificate of analysis Y **3.2.S.4.5** **Justification of Specification** Y	☒
3.2.S.5	**Reference Standards or Materials**	☒
3.2.S.6	**Container Closure Systems**	☒
3.2.S.7	**Stability**	☒

MODULE 3

3.2.P DRUG PRODUCT ACCEPTABLE

3.2.P.1	**Description and Composition of the Drug Product** 1) Unit composition Y 2) Inactive ingredients are appropriate per IIG see attached formulation from DFS. Drug Products use the same inactive ingredients.	☒
3.2.P.2	**Pharmaceutical Development** Pharmaceutical Development Report	☒
3.2.P.3	**Manufacture** **3.2.P.3.1** **Manufacture(s)** (Finished Dosage Manufacturer and Outside Contract Testing Laboratories) 1. Name and Full Address(es)of the Facility(ies) Yes 2. CGMP Certification: Yes 3. Function or Responsibility Yes 4. CFN or FEI numbers **3.2.P.3.2** **Batch Formula** Batch Formulation Y **3.2.P.3.3** **Description of Manufacturing Process and Process Controls** 1. Description of the Manufacturing Process Y 2. Master Production Batch Record(s) for largest intended production runs (no more than 10x pilot batch) with equipment specified (b) (4) 3. If sterile product: Aseptic fill / Terminal sterilization N/A 4. Reprocessing Statement Y see amendment **3.2.P.3.4** **Controls of Critical Steps and Intermediates** Y **3.2.P.3.5** **Process Validation and/or Evaluation** Y 1. Microbiological sterilization validation N/A 2. Filter validation (if aseptic fill) N/A	☒
3.2.P.4	**Controls of Excipients (Inactive Ingredients)** Source of inactive ingredients identified Y **3.2.P.4.1** **Specifications** 1. Testing specifications (including identification and characterization) Y 2. Suppliers' COA (specifications and test results) Y **3.2.P.4.2** **Analytical Procedures** Y **3.2.P.4.3** **Validation of Analytical Procedures** Y **3.2.P.4.4** **Justification of Specifications** Applicant COA Y	☒

MODULE 3

3.2.P DRUG PRODUCT

ACCEPTABLE

3.2.P.5	**Controls of Drug Product** **3.2.P.5.1** **Specification(s)** Y - USP **3.2.P.5.2** **Analytical Procedures** Y **3.2.P.5.3** **Validation of Analytical Procedures** Samples - Statement of Availability and Identification of: 1. Finished Dosage Form see sec. 3.2.P.6 2. Same lot numbers **3.2.P.5.4** **Batch Analysis** Certificate of Analysis for Finished Dosage Form Y see amendment for lot # verification **3.2.P.5.5** **Characterization of Impurities** Y **3.2.P.5.6** **Justification of Specifications** Y	☒
3.2.P.7	**Container Closure System** 1. Summary of Container/Closure System (if new resin, provide data) Y 2. Components Specification and Test Data Y 3. Packaging Configuration and Sizes 60 cc glass bottles 4. Container/Closure Testing Y 5. Source of supply and suppliers address Y	☒
3.2.P.8	**3.2.P.8.1** **Stability (Finished Dosage Form)** 1. Stability Protocol submitted Y 2. Expiration Dating Period (b) (4) months **3.2.P.8.2** **Post-approval Stability and Conclusion** Post Approval Stability Protocol and Commitments Y **3.2.P.8.3** **Stability Data** 1. 3 month accelerated stability data Y 2. Batch numbers on stability records the same as the test batch **lot# 604725**	☒

MODULE 3

3.2.R Regional Information

ACCEPTABLE

3.2.R (Drug Substance)	**3.2.R.1.S** **Executed Batch Records for drug substance (if available) N/A** **3.2.R.2.S** **Comparability Protocols N/A** **3.2.R.3.S** **Methods Validation Package** YES Methods Validation Package (3 copies) (Mult Copies N/A for E-Submissions) (Required for Non-USP drugs)	☒

MODULE 3

3.2.R Regional Information

ACCEPTABLE

3.2.R (Drug Product)	**3.2.R.1.P.1** **Executed Batch Records** Copy of Executed Batch Record with Equipment Specified, including Packaging Records (Packaging and Labeling Procedures), Batch Reconciliation and Label Reconciliation Lot # 604725 Theoretical Yield (b) (4) Actual Yield Packaged Yield **3.2.R.1.P.2** **Information on Components** N/A **3.2.R.2.P** **Comparability Protocols** N/A **3.2.R.3.P** **Methods Validation Package Y** Methods Validation Package (3 copies) (Mult Copies N/A for E-Submissions) (Required for Non-USP drugs)	☒

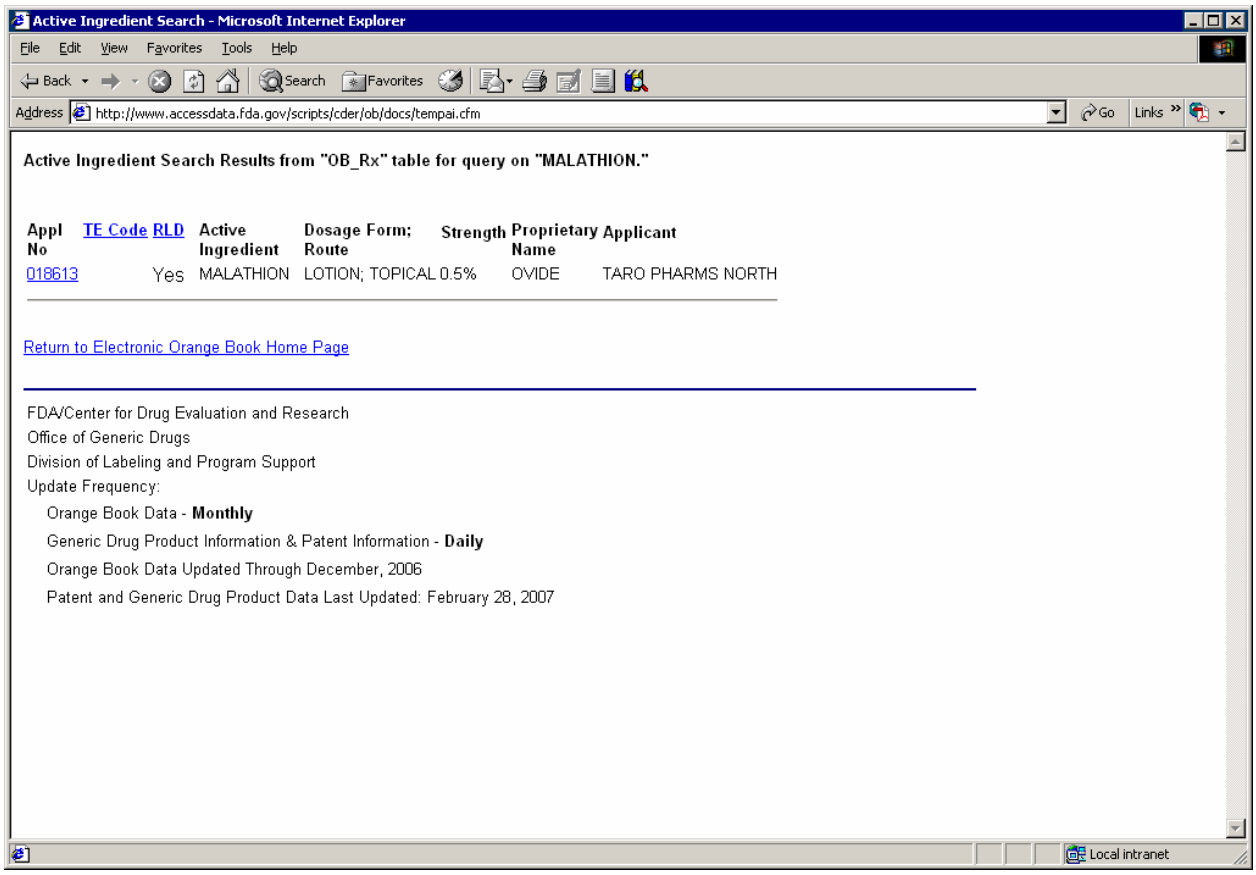
MODULE 5

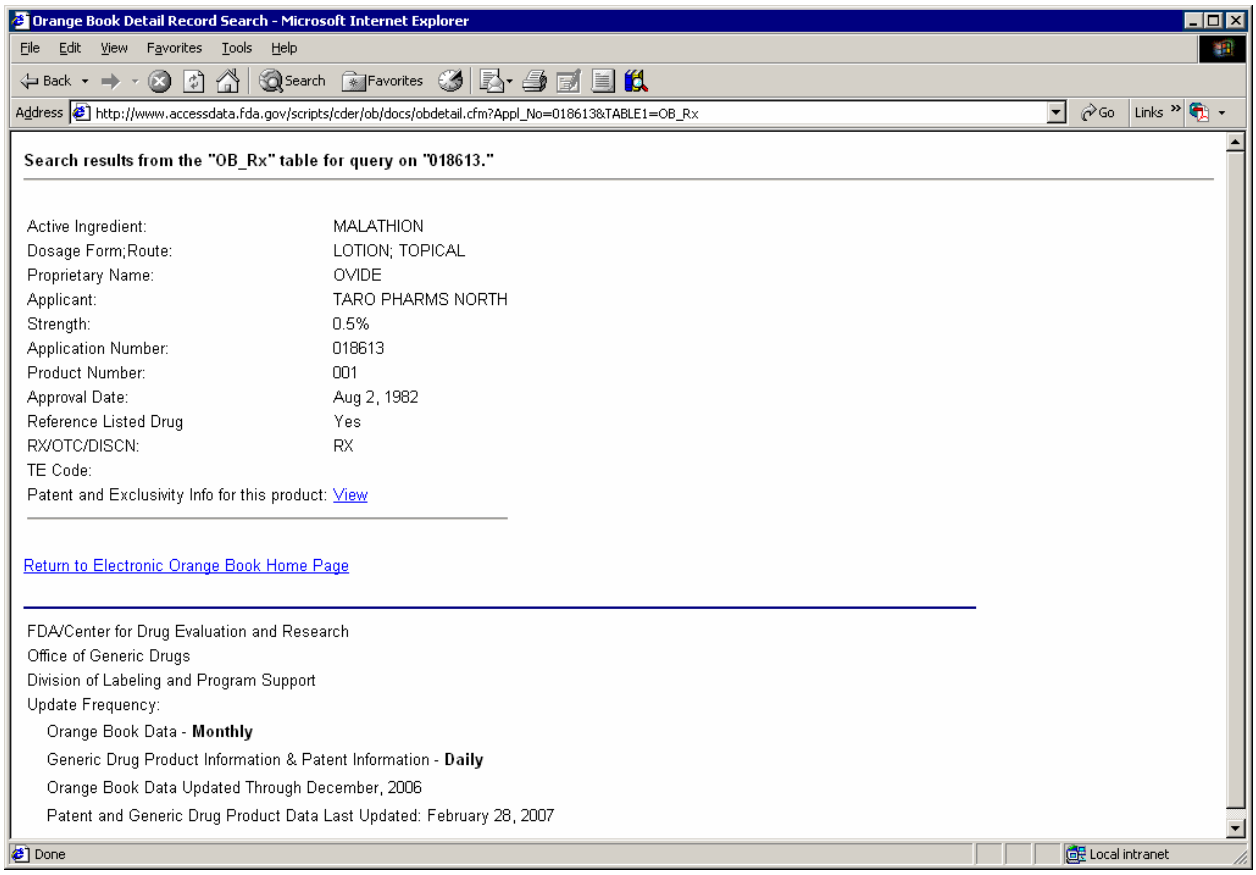
CLINICAL STUDY REPORTS N/A

ACCEPTABLE

5.2	**Tabular Listing of Clinical Studies**	☐
5.3.1 (complete study data)	**Bioavailability/Bioequivalence** **1. Formulation data same?** a. Comparison of all Strengths (check proportionality of multiple strengths) b. Parenterals, Ophthalmics, Otics and Topicals per 21 CFR 314.94 (a)(9)(iii)-(v) **2. Lot Numbers of Products used in BE Study(ies):** **3. Study Type:** (Continue with the appropriate study type box below)	☐
	5.3.1.2 **Comparative BA/BE Study Reports** 1. Study(ies) meets BE criteria (90% CI of 80-125, C max, AUC) 2. Summary Bioequivalence tables: Table 6. Demographic Profile of Subjects Completing the Comparative BA Study Table 7. Incidence of Adverse Events in Individual Studies Table 8. Reanalysis of Study Samples **5.3.1.3** **In Vitro-In-Vivo Correlation Study Reports** 1. Summary Bioequivalence tables: Table 4. Summary of In Vitro Dissolution Studies Table 5. Formulation Data **5.3.1.4** **Reports of Bioanalytical and Analytical Methods for Human Studies** 1. Summary Bioequivalence table: Table 3. Bioanalytical Method Validation **5.3.7** **Case Report Forms and Individual Patient Listing**	☐

5.4	**Literature References**	
	Possible Study Types:	
Study Type	**IN-VIVO PK STUDY(IES)** (i.e., fasting/fed/sprinkle) NA 1. Study(ies) meets BE criteria (90% CI of 80-125, C max, AUC) 2. EDR Email: Data Files Submitted: NA 3. In-Vitro Dissolution: NA	☐
Study Type	**IN-VIVO BE STUDY with CLINICAL ENDPOINTS** YES /BIO/STU 1. Properly defined BE endpoints (eval. by Clinical Team) 2. Summary results meet BE criteria: 90% CI of the proportional difference in success rate between test and reference must be within (-0.20, +0.20) for a binary/dichotomous endpoint. For a continuous endpoint, the test/reference ratio of the mean result must be within (0.80, 1.25). 3. Summary results indicate superiority of active treatments (test & reference) over vehicle/placebo ($p<0.05$) (eval. by Clinical Team) 4. EDR Email: Data Files Submitted YES SENT TO EDR	☐
Study Type	**IN-VITRO BE STUDY(IES)** (i.e., in vitro binding assays) NO 1. Study(ies) meets BE criteria (90% CI of 80-125) 2. EDR Email: Data Files Submitted: 3. In-Vitro Dissolution:	☐
Study Type	**NASALLY ADMINISTERED DRUG PRODUCTS** NO 1. Solutions (Q1/Q2 sameness): a. In-Vitro Studies (Dose/Spray Content Uniformity, Droplet/Drug Particle Size Distrib., Spray Pattern, Plume Geometry, Priming & Repriming, Tail Off Profile) 2. Suspensions (Q1/Q2 sameness): a. In-Vivo PK Study 1. Study(ies) meets BE Criteria (90% CI of 80-125, C max, AUC) 2. EDR Email: Data Files Submitted b. In-Vivo BE Study with Clinical End Points 1. Properly defined BE endpoints (eval. by Clinical Team) 2. Summary results meet BE criteria (90% CI within +/- 20% or 80-125) 3. Summary results indicate superiority of active treatments (test & reference) over vehicle/placebo ($p<0.05$) (eval. by Clinical Team) 4. EDR Email: Data Files Submitted c. In-Vitro Studies (Dose/Spray Content Uniformity, Droplet/Drug Particle Size Distrib., Spray Pattern, Plume Geometry, Priming & Repriming, Tail Off Profile)	☐
Study Type	**TOPICAL CORTICOSTEROIDS (VASOCONSTRICTOR STUDIES)** NO 1. Pilot Study (determination of ED50) 2. Pivotal Study (study meets BE criteria 90%CI of 80-125)	☐
Study Type	**TRANSDERMAL DELIVERY SYSTEMS** NO 1. In-Vivo PK Study 1. Study(ies) meet BE Criteria (90% CI of 80-125, C max, AUC) 2. In-Vitro Dissolution 3. EDR Email: Data Files Submitted 2. Adhesion Study 3. Skin Irritation/Sensitization Study	☐


Active Ingredient Search - Microsoft Internet Explorer
File Edit View Favorites Tools Help
Back Search Favorites
Address http://www.accessdata.fda.gov/scripts/cder/ob/docs/tempai.cfm
Go Links
Active Ingredient Search Results from "OB_Rx" table for query on "MALATHION."
Appl No
TE Code
RLD
Active Ingredient
Dosage Form; Route
Strength
Proprietary Name
Applicant
018613
Yes
MALATHION
LOTION; TOPICAL
0.5%
OVIDE
TARO PHARMS NORTH
Return to Electronic Orange Book Home Page
FDA/Center for Drug Evaluation and Research
Office of Generic Drugs
Division of Labeling and Program Support
Update Frequency:
Orange Book Data - Monthly
Generic Drug Product Information & Patent Information - Daily
Orange Book Data Updated Through December, 2006
Patent and Generic Drug Product Data Last Updated: February 28, 2007
Local intranet



Search results from the "OB_Rx" table for query on "018613."

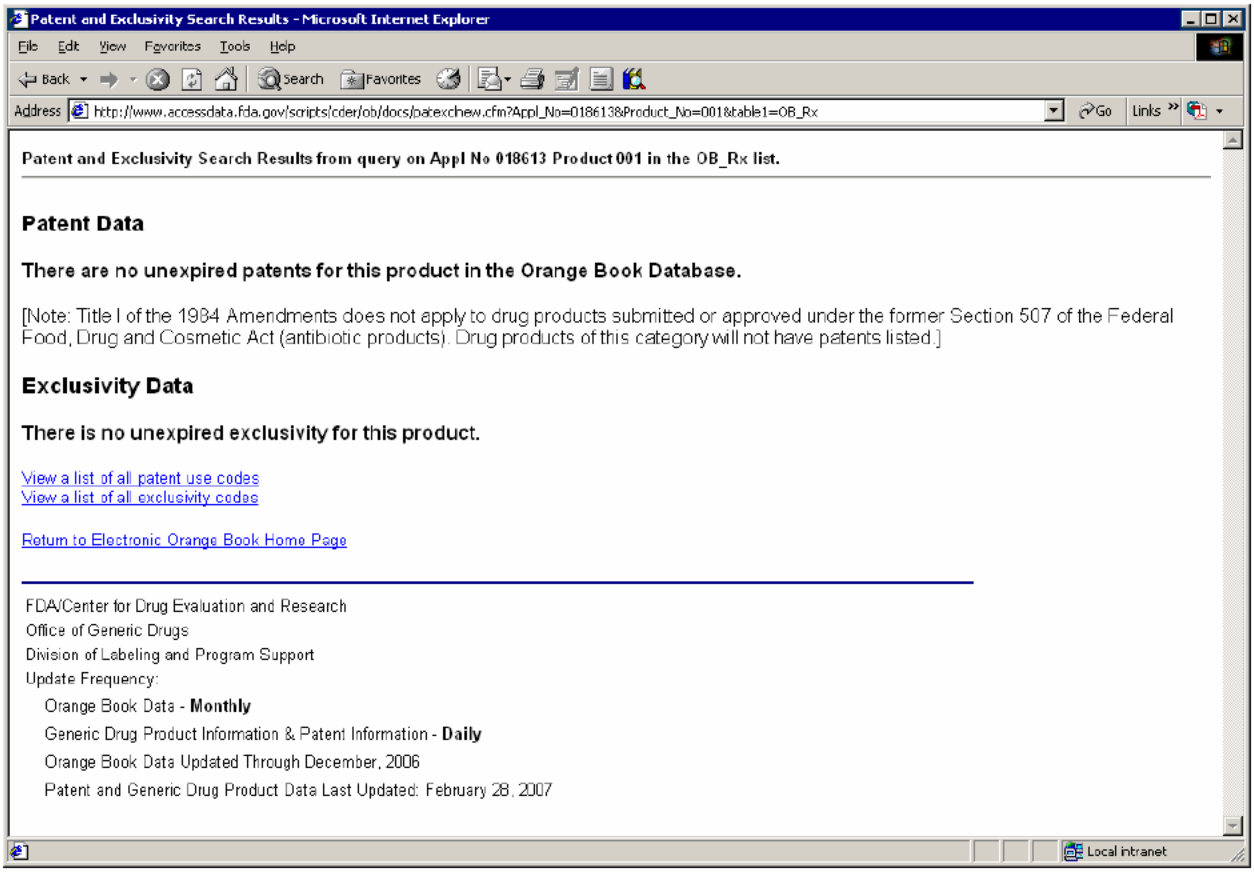
Active Ingredient:	MALATHION
Dosage Form;Route:	LOTION; TOPICAL
Proprietary Name:	OVIDE
Applicant:	TARO PHARMS NORTH
Strength:	0.5%
Application Number:	018613
Product Number:	001
Approval Date:	Aug 2, 1982
Reference Listed Drug	Yes
RX/OTC/DISCN:	RX
TE Code:	

Patent and Exclusivity Info for this product: View

Return to Electronic Orange Book Home Page

FDA/Center for Drug Evaluation and Research
Office of Generic Drugs
Division of Labeling and Program Support
Update Frequency:

- Orange Book Data - **Monthly**
- Generic Drug Product Information & Patent Information - **Daily**
- Orange Book Data Updated Through December, 2006
- Patent and Generic Drug Product Data Last Updated: February 28, 2007



Percent v/v

Ingredient	Sp Gr Specs	Ave Specific Gravity (g/mL)	Amount (Percent vol/vol)
Malathion, USP*		(b) (4)	0.406
(b) (4) Terpineol			(b) (4)
(b) (4) Limonene			
Isopropyl Alcohol, USP qs**			
Pine Needle Oil			
Total		(b) (4)	100

*Note: The RLD is labeled 0.5% wt/vol malathion which is equivalent to 0.406 % vol/vol (0.406 mL/ 100 mL = (0.5% g/100 ml)/1.23 g/mL)

**Note: IPA is used to qs volume to 100 mL

***Note: Theoretical Specific Gravity

Clinical Formulation:

Ingredients	% v/v
Malathion	(b) (4)
Terpineol	
Dipentene	
Pine Needle Oil	
Isopropyl Alcohol	78 (b) (4)

Ovide® Lotion 0.5% Is supplied in 2 fl oz (59 ml) bottles containing (b) (4) malathion.

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

/s/

Martin Shimer

4/3/2007 11:09:38 AM

RECORD OF TELEPHONE CONVERSATION
Office of Generic Drugs
Division of Chemistry 1
Team 3

FROM: Mahnaz Farahani

DATE: July 3, 2007

ANDA: 78-743

NAME/TITLE OF INDIVIDUAL(S) from FDA: Mahnaz Farahani, chemist
FIRM: Synerx Pharma LLC
PRODUCT NAME: Malathion Lotion, USP0.5%
TEL #: (215) 860-4202

NAME/TITLE OF INDIVIDUAL(S) from the firm: Walter Jump

Notes of Conversation:

Deficiency:

1. (b) (4)

2.

3.

SIGNATURE OF OGD REPRESENTATIVES:
Mahnaz Farahani, chemist

Location of Electronic Copy:

V:\Division I\Team3\T-CON\78743.TCON

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

/s/

Mahnaz Farahani

7/3/2007 03:03:10 PM

CHEMIST

N/AC

SYNERX PHARMA
SYNERGY IN PHARMACEUTICALS

RECEIVED
JUL 12 2007
OGD

Mr. Gary Buehler
Director
Office of Generic Drugs, HFD-600
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20857-2773

100 North State Street
Newtown, PA 18940
T 215.860.4202
F 215.895.9629
walterjump@synerxpharma.com
www.synerxpharma.com

TELEPHONE AMENDMENT
FDA TELEPHONE DEFICIENCY: 07/03/2007

RE: ANDA 78-743
Applicant: Synerx Pharma LLC
Drug Product: Malathion Lotion, USP
0.5% w/v

Dear Director Buehler,

In accordance with 21 CFR 314.96, Synerx Pharma is amending the above application in response to comments received from the Office of Generic Drugs on July 3, 2007, from Dr. Mahnaz Farahani. She indicated this is to be considered a telephone amendment if we responded within 10 days to our application.

This correspondence represents a full response to all the comments received. A complete and accurate copy of this amendment has been provided to our district field office in accordance with Agency guidelines.

For ease of Agency review we have repeated the Agency's comments in bold followed by our response in plain text. If any of our responses need clarification please call my office at the number listed on the side of this letter. I will endeavor to provide a quick response to facilitate your review.

Thank you for your timely review and we look forward to receiving FDA approval of this application.

Sincerely yours,

Walter G. Jump, Pharm.D.
Vice President

Telephone Fax

ANDA 78-743

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North I
7520 Standish Place
Rockville, MD 20855-2773
240 276-8984

TO: Synerx Pharma LLC

TEL: 215-860-4202

ATTN: Walter G. Jump

FAX: 215-895-9629

FROM: Beverly Weitzman

This facsimile is in reference to your abbreviated new drug application submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Malathion Lotion 0.5%
Pages (including cover): 4

Labeling Comments

REVIEW OF PROFESSIONAL LABELING - #1
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: 78-743

Date of Submission: December 26, 2006

Applicant's Name: Synerx Pharma LLC.

Established Name: Malathion Lotion USP. 0.5%

Labeling Deficiencies:

1. **GENERAL COMMENT:** Please note that your drug product is the subject of a USP monograph. We encourage you to include USP in the established name of your drug product.

2. **CONTAINER:**

   a. When submitting in final print, please assure that the i**mportant labeling statements are prominent,** especially the established name, product strength, Directions for Use and Warning:Contains flammable alcohol… and Caution statements. To ensure the important labeling statements are prominent **you may decrease the prominence of your marketed by" and "Rx Only" statements, company name and net quantity.**

   b. Please assure that your container labels are of actual size, color and clarity when submitting in final print.

   c. Add the route of administration "For topical use only.

   d. If space permits add the statement "Not for oral or ophthalmic use"

3. **CARTON :**

   a. When submitting in final print, please assure that the i**mportant labeling statements are prominent,** especially the established name, product strength, Directions for Use and Warning:Contians flammable alcohol… and Caution statements. To ensure the important labeling statements are prominent **you may decrease the prominence of your logo "S", marketed by" and "Rx Only" statements, company name and net quantity.**

   b. See CONTAINER comments (c) and (d)

4. **INSERT**

   a. Carcinogenesis, Mutagenesis, and Impairment of Fertility: Revise the last paragraph of the **Carcinogenesis, Mutagenesis, and Impairment of Fertility** section to read as "Reproduction studies performed with malathion in rats at doses over 180 fold greater than those anticipated in a 60 kg adult (based on body surface area and assuming 100% bioavailability) revealed no evidence of impaired fertility."

   b. Pregnancy: Pregnancy Category B: Revise the third sentence in the **Pregnancy** section to read as "These doses were approximately 40 to 180 times higher than the dose anticipated in a 60 kg adult (based on body surface area and assuming 100% bioavailability)."

5. (b) (4) Delete the (b) (4) you have provided since this has not been approved by the FDA and therefore can not be approved for your application.

Revise your labeling and labels, as instructed above, and submit final printed labeling electronically.

Prior to approval, it may be necessary to revise your labeling subsequent to approved changes for the reference listed drug. In order to keep ANDA labeling current, we suggest that you subscribe to the daily or weekly updates of new documents posted on the CDER web site at the following address -

http://www.fda.gov/cder/cdernew/listserv.html

To facilitate review of your next submission, please provide a side-by-side comparison of your proposed labeling with that of your last submission with all differences annotated and explained.

{See appended electronic signature page}

_____

Wm. Peter Rickman
Director
Division of Labeling and Program Support
Office of Generic Drugs
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/

John Grace
8/9/2007 02:27:37 PM
for Wm Peter Rickman

ORIGINAL

SYNERX PHARMA
SYNERGY IN PHARMACEUTICALS

Mr. Gary Buehler
Director
Office of Generic Drugs, HFD-600
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20857-2773

ORIG AMENDMENT

N/AF

100 North State Street
Newtown, PA 18940
T 215.860.4202
F 215.895.9629
walterjump@synerxpharma.com
www.synerxpharma.com

TELEPHONE LABELING AMENDMENT
FDA TELEPHONE FAX DEFICIENCY: 08/09/2007

RE: ANDA 78-743
Applicant: Synerx Pharma LLC
Drug Product: Malathion Lotion, USP
0.5% w/v

Dear Director Buehler,

In accordance with 21 CFR 314.96, Synerx Pharma is amending the above application in response to comments received from the Office of Generic Drugs on August 9, 2007, from Mr. Peter W. Rickman. As indicated in the fax this is to be considered a telephone labeling amendment to our application.

This correspondence represents a full response to all the comments received. A complete and accurate copy of this amendment has been provided to our district field office in accordance with Agency guidelines.

For ease of Agency review we have repeated the Agency's comments in bold followed by our response in plain text. If any of our responses need clarification please call my office at the number listed on the side of this letter. I will endeavor to provide a quick response to facilitate your review.

Thank you for your timely review and we look forward to receiving FDA approval of this application.

Sincerely yours,

Walter G. Jump, Pharm.D.
Vice President

RECEIVED
AUG 14 2007
OGD

SYNERX PHARMA
SYNERGY IN PHARMACEUTICALS

ORIG AMENDMENT
N/AC

Mr. Gary Buehler
Director
Office of Generic Drugs, HFD-600
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20857-2773

100 North State Street
Newtown, PA 18940
T 215.860.4202
F 215.895.9629
walterjump@synerxpharma.com
www.synerxpharma.com

AMENDMENT - Revised Response
FDA TELEPHONE DEFICIENCY: 07/03/2007
RE: ANDA 78-743
Applicant: Synerx Pharma LLC
Drug Product: Malathion Lotion, USP
0.5% w/v

Dear Director Buehler,

In accordance with 21 CFR 314.96, Synerx Pharma is amending the above application in response to comments received from the Office of Generic Drugs on July 3, 2007, from Dr. Mahnaz Farahani. Our original response was submitted within ten days. It contained a complete response to the FDA questions.

OGD has indicated that our response requires the assessment of Pharmacology and Toxicology Consultants outside of its office. As the response submitted in July of 2007 has not been reviewed and we do not have a clear indication of when it may be reviewed, we would like to revise our original response based on data we have subsequently generated.

We have repeated the Agency's original comments in bold followed by our revised response in plain text. By submission of this revised response we are withdrawing our request for a Pharmacologic/ Toxicologic review. We understand that if we want to raise the impurity level in the future, based on our previous submission, we will have to re-submit the data and wait for the Agency's prior approval.

Thank you for your timely review and we look forward to receiving FDA approval of this application.

Sincerely yours,

Walter G. Jump, Pharm.D.
Vice President

RECEIVED
APR 16 2008
OGD

SYNERX PHARMA
SYNERGY IN PHARMACEUTICALS

Mr. Gary Buehler
Director
Office of Generic Drugs, HFD-600
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20857-2773

N/AC

ORIG AMENDMENT

100 North State Street
Newtown, PA 18940
T 215.860.4202
F 215.895.9629
walterjump@synerxpharma.com
www.synerxpharma.com

AMENDMENT
FDA TELEPHONE DEFICIENCY: 07/02/2008
RE: ANDA 78-743
Applicant: Synerx Pharma LLC
Drug Product: Malathion Lotion, USP
0.5% w/v

Dear Director Buehler,

In accordance with 21 CFR 314.96, Synerx Pharma is amending the above application in response to comments received from the Office of Generic Drugs on July 2, 2008, from Dr. James Fan and Dr. Mahnaz Farahani. During this teleconference they indicated that our previous amendment was acceptable, however they had additional requests concerning our specifications. This is a complete response to their questions.

OGD has indicated that our ANDA requires a statement and appropriate specifications in response to the USP <467> General Chapter revision which went into effect on July 1, 2008. Synerx Pharma previously committed to and continues to commit to meeting the USP requirements for this monograph product.

We have provided the Agency's comments in bold followed by our revised response in plain text.

Thank you for your timely review and we look forward to receiving FDA approval of this application.

Sincerely yours,

7/9/2008

Walter G. Jump, Pharm.D.
Vice President

RECEIVED
JUL 11 2008
OGD

SYNERX PHARMA
SYNERGY IN PHARMACEUTICALS

ORIG AMENDMENT

Mr. Gary Buehler
Director
Office of Generic Drugs, HFD-600
Center for Drug Evaluation and Research
Food and Drug Administration
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7500 Standish Place, Room 150
Rockville, MD 20857-2773

100 North State Street
Newtown, PA 18940
T 215.860.4202
F 215.895.9629
walterjump@synerxpharma.com
www.synerxpharma.com

AMENDMENT
FDA TELEPHONE DEFICIENCY: 08/14/2008
RE: ANDA 78-743
Applicant: Synerx Pharma LLC
Drug Product: Malathion Lotion, USP
0.5% w/v

Dear Director Buehler,

In accordance with 21 CFR 314.96, Synerx Pharma is amending the above application in response to comments received from the Office of Generic Drugs on August 14, 2008, from Dr. Paul Schwartz and Dr. Mahnaz Farahani. During this teleconference they indicated that they had concerns about the elimination of the (b) (4) specification in the finished product specifications. This is a complete response to their questions.

We have provided the Agency's comments in bold followed by our revised response in plain text.

Thank you for your timely review and we look forward to receiving FDA approval of this application.

Sincerely yours,

8/15/04

Walter G. Jump, Pharm.D.
Vice President

RECEIVED
AUG 18 2008
OGD

SYNERX PHARMA
SYNERGY IN PHARMACEUTICALS

Mr. Gary Buehler
Director
Office of Generic Drugs, HFD-600
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20857-2773

100 North State Street
Newtown, PA 18940
T 215.860.4202
F 215.895.9629
walterjump@synerxpharma.com
www.synerxpharma.com

AMENDMENT
FDA TELEPHONE DEFICIENCY: 10/03/2008
RE: ANDA 78-743
Applicant: Synerx Pharma LLC
Drug Product: Malathion Lotion, USP
0.5% w/v

ORIG AMENDMENT

N/AC

Dear Director Buehler,

In accordance with 21 CFR 314.96, Synerx Pharma is amending the above application in response to comments received from the Office of Generic Drugs on October 3, 2008, from Dr. James Fan and Dr. Radhika Rajagopalan. During this teleconference they indicated that they had a few additional questions prior to determining a recommendation for approval of the application. This is a complete response to their questions.

We have provided the Agency's comments in bold followed by our revised response in plain text.

Thank you for your timely review and we look forward to receiving FDA approval of this application.

Sincerely yours,

1/16/2009

Walter G. Jump, Pharm.D.
Vice President

RECEIVED
JAN 21 2009
OGD

Record of Telephone Conversation

As a follow up to the meeting between Team 3 and Radhika, we called Synerx Pharma to discuss our response to the proposals made in their amendment dated January 16, 2009. *Agency: We have reviewed your telephone amendment and the two options you have proposed to address the impurities in your drug product. The first proposal to follow the USP monograph is Not Acceptable for this drug product (Malathion) as there are no impurity limits or test provided. We can accept the second proposal to set procedures for establishing the limits with modifications added by OGD. How much work have you done to identify the peak you are getting at RT of 1.7 minutes?* Firm: We missed this peak in earlier submissions because we assumed it was a solvent front. It was later on when we ran the placebo against the Malathion that we observed the peak in only the Malathion. It was then we realized it was from the drug product. We have since obtained chromatograms from the innovator product Ovide (performed in our contract labs) and overlaid it with the Chromatogram from our product and observed the same peak. We have not identified the peak however, using LC Mass Spectroscopy they (our contract analytical lab) have tried to reconstruct the molecule from the peaks but have not been successful. What we do know is that our contract lab have evaluated the peaks eluting from the column from our Malathion application and compared it to the peaks eluted in the innovator product (Ovide) and have concluded that it is the same molecule via MS. We have included those observations in our January amendment under the LCMS study (R R08123 4EN) *Agency: Have you performed any secondary or confirmatory tests(using Refractive methods/Fluorescence)* Firm: We did not perform a secondary test. We tried to follow up on our primary method to identify the compound.	**Date:** February 17, 2009 **ANDA Number:** 78-743 **Product Name:** Malathion Lotion USP, 0.5% (w/v) **Firm Name:** Synerx Pharma **Firm Representative:** Doug Hamilton (President) Walter Jump (Vice-President) J. Engel (Regulatory Counsel) J. Wood (Regulatory Counsel) **Phone Number:** (800) 261 3225 Code: (b) (4) **FDA Representative:** Radhika Rajagopalan Paul Schwartz James Fan Mahnaz Farahani

Agency: Do you have information on the levels of the compound in your product compared to the innovator product? Firm: Yes we do. We have provided information on the innovator product and our product on stability. The information provided is not extensive, however we have demonstrated that there are comparable amounts of degradants in the innovator product and our Malathion. *Agency: Did you reach out to any Mass Spec experts to assist in identifying the compound?* Firm: We had an expert assist with viewing our chromatograms, identifying the peaks and quantifying them. *Agency: Can you provide the Agency with the copies of the actual chromatograms rather than the tabulated results. Any tracings your contract labs have from the mass specs will be helpful so that the Agency can evaluate the results ourselves.* Firm: We are not sure what we will be able to provide as our contract labs provide their findings as reports which can be up to a thousand pages and cumbersome, but we can call them and see what they are able to provide us. As we are no MS experts, I think they report their findings to us as mass ions with peaks at certain times or peaks at certain mass weights. *Agency: That's fine, but sends us the information as provided not Synerx's interpretation. We would like to interpret the findings ourselves.* Firm: Ok we will follow up on this request *Agency: In your amendment, you provided the stability data in the "upright" position on page 7/8 with the following findings 12 months RT 1.7%, 18 months RT 7.8%, 24 months 9%. On page 8/8, You did not report any of the corresponding information at these same time points for the "inverted position"?* Firm: Subsequent to the submission being made, we now have some data on the inverted position. We put the product on stability in the "inverted" position at a month difference interval than the "upright" and because of this, the data we have on the inverted position is not as complete. Because the placebo batch was stored in the upright position, we were able to get the information on the episodic time points. *Agency: Do you have the information on stability at 12 months in the inverted position?* Firm: Yes we do, but I do not have it in front of me . *Agency: What does the data indicate? Can you provide the information?* Firm: There is no difference in the upright and inverted positions and we can submit the information.	**Signatures:**

Agency: Can you commit to placing 10% of your product in clear glass and placing it on stability?
Firm: We can entertain the idea; however our stability data so far in the upright position, indicates a similar profile between our product and the innovator.

Agency: Are you aware or the potential interaction between the amber glass used to for packaging and your product?
Firm: Not really. In our preliminary work, we came across combination Malathion products marketed in Europe in Amber glass.

Agency: Do you have information on any US Malathion products marketed in Amber glass or any issues about metal extractions?
Firm: No. The innovator is marketed in a Clear glass with a shaker top and packaged in a carton. The USP recommends the API be protected from light. The enhanced packaging ensures no photo degradation. Initially we were going to eliminate the need for carton but not anymore.

Agency: Based on our evaluation of the information in your amendment and out discussions we are requesting a Telephone amendment with the following issues addressed:

- Provide the inverted data at 12 months (make sure the product passes) showing all degradants before we can grant your application (b) (4) for total impurities and (b) (4) for unknown impurities
- (b) (4)
- Any extension of the expiration will be based on room temperature data from 3 batches. Agree to this in writing that only ambient data will be used to request any extension in the expiration.
- You are also to provide the raw data from the Mass Spectroscopy for the Agency's interpretation

Post approval you are also expected to:

- (b) (4)
-

Firm: The firm repeated the requests from the Agency and verbalized understanding.	

CC: 78-743

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

/s/

Rosalyn Adigun
2/26/2009 07:40:38 AM
CSO

James Fan
2/26/2009 08:43:38 AM
CHEMIST

Mahnaz Farahani
3/5/2009 10:38:33 AM
CHEMIST

Paul Schwartz
3/5/2009 01:03:58 PM
CHEMIST

Radhika Rajagopalan
3/9/2009 10:37:01 AM
CHEMIST
Acceptable

SYNERX PHARMA
SYNERGY IN PHARMACEUTICALS

Mr. Gary Buehler
Director
Office of Generic Drugs, HFD-600
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AMENDMENT
N/AC

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Newtown, PA 18940
T 215.860.4202
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AMENDMENT
FDA TELEPHONE DEFICIENCY: 2/17/2009
RE: ANDA 78-743
Applicant: Synerx Pharma LLC
Drug Product: Malathion Lotion, USP
0.5% w/v

Dear Director Buehler,

In accordance with 21 CFR 314.96, Synerx Pharma is amending the above application in response to comments received from the Office of Generic Drugs on February 19, 2009 from Mr. James Fan, Dr. Paul Schwartz, Dr. Farahani, and Dr. Radhika Rajagopalan. During this teleconference they indicated that they had a few additional Commitments prior to determining a recommendation for approval of the application. This is a complete response to their request.

We have provided the Agency's comments in bold followed by our revised response in plain text.

Thank you for your timely review and we look forward to receiving FDA approval of this application.

Sincerely yours,

Walter G. Jump, Pharm.D.
Vice President

OGD APPROVAL ROUTING SUMMARY

ANDA # 78-743 Applicant Synerx Pharma LLC
Drug Malathion Lotion USP, Strength(s) 0.5% (w/v)

APPROVAL ☒ **TENTATIVE APPROVAL** ☐ **SUPPLEMENTAL APPROVAL (NEW STRENGTH)** ☐ **OTHER** ☐

REVIEWER:	**DRAFT Package**	**FINAL Package**
1. **Martin Shimer**	Date 12AUG08	Date _____
Chief, Reg. Support Branch	Initials MHS	Initials _____

Contains GDEA certification: Yes ☒ No ☐ (required if sub after 6/1/92)
Determ. of Involvement? Yes ☐ No ☐
Pediatric Exclusivity System
RLD = _____ NDA# _____
Patent/Exclusivity Certification: Yes ☒ No ☐
Date Checked _____
If Para. IV Certification- did applicant
Nothing Submitted ☐
Notify patent holder/NDA holder Yes ☐ No ☐
Written request issued ☐
Was applicant sued w/in 45 days: Yes ☐ No ☐
Study Submitted ☐
Has case been settled: Yes ☐ No ☐
Date settled:
Is applicant eligible for 180 day
Generic Drugs Exclusivity for each strength: Yes ☐ No ☒
Date of latest Labeling Review/Approval Summary _____
Any filing status changes requiring addition Labeling Review Yes ☐ No ☒
Type of Letter:
Comments: ANDA submitted on 12/28/2006, BOS=Ovide NDA 18613, no relevant patent cert. ANDA ack for filing on 12/28/2006 (LO dated 4/3/2007). There are no remaining patents or exclusivities which protect the RLD. This ANDA is eligible for Full Approval.

2. Project Manager, Rosalyn Adigun Team 3 — Date August 11, 2008 — Date _____
Review Support Branch — Initials RA — Initials _____

Original Rec'd date December 26, 2006
Date Acceptable for Filing December 28, 2006
Patent Certification (type) II
Date Patent/Exclus.expires N/A
Citizens' Petition/Legal Case Yes ☐ No ☒
(If YES, attach email from PM to CP coord)
First Generic Yes ☐ No ☐
Priority Approval Yes ☐ No ☒
(If yes, prepare Draft Press Release, Email it to Cecelia Parise)

EER Status Pending ☐ Acceptable ☒ OAI ☐
Date of EER Status June 3, 2008
Date of Office Bio Review August 27, 2007
Date of Labeling Approv. Sum Sept. 25, 2007
Date of Sterility Assur. App. N/A
Methods Val. Samples Pending Yes ☐ No ☐
MV Commitment Rcd. from Firm Yes ☐ No ☐
Modified-release dosage form: Yes ☐ No ☐
Interim Dissol. Specs in AP Ltr: Yes ☐

Acceptable Bio reviews tabbed Yes ☒ No ☐
Bio Review Filed in DFS: Yes ☒ No ☐
Suitability Petition/Pediatric Waiver
Pediatric Waiver Request Accepted ☐ Rejected ☐ Pending ☐
Previously reviewed and tentatively approved ☐ Date _____
Previously reviewed and CGMP def. /NA Minor issued ☐ Date _____
Comments:

3. Labeling Endorsement
Reviewer: — Labeling Team Leader:
Date _____ — Date _____
Name/Initials _____ — Name/Initials _____
Comments:

4. David Read **(PP IVs Only)** Pre-MMA Language included ☐ — Date _____
OGD Regulatory Counsel, Post-MMA Language Included ☐ — Initials _____
Comments:

5. Div. Dir./Deputy Dir. — Date 9/19/08
Chemistry Div. I — Initials PS
Comments: cmc ok; 467 ok

6. Frank Holcombe **First Generics Only** Date 3/3/09
Assoc. Dir. For Chemistry Initials RR
Comments: (First generic drug review)
12 months expriation for DP is granted based on available data; anda holder to extend expiration based on successful demonstration of post approval ambient stability data, and will evaluate (b) (4) packaging of drug proudct. No (b) (4) is present in formulation. For Frank,

7. Vacant Date _____
Deputy Dir., DLPS Initials _____

8. Peter Rickman Date 3/5/09
Director, DLPS Initials wpr
Para.IV Patent Cert: Yes☐ No☒;Pending Legal Action: Yes ☐ No ☒; Petition: Yes☐ No☒
Comments:no patents or exclusivity issues; Labeling acceptable 9/25/07 per AP Summary; Bio acceptable 8/27/07 (waiver granted); EER acceptable 6/3/08; 1st generic

OR

8. Robert L. West Date _____
Deputy Director, OGD Initials _____
Para.IV Patent Cert: Yes☐ No☐; Pending Legal Action: Yes☐ No☐; Petition: Yes☐ No☐
Press Release Acceptable ☐
Comments:

9. Gary Buehler Date _____
Director, OGD Initials _____
Comments:
First Generic Approval ☐ PD or Clinical for BE ☐ Special Scientific or Reg.Issue ☐
Press Release Acceptable ☐

10. Project Manager, Rosalyn Adigun Team 3 Date March 6, 2009

Review Support Branch Initials RA
_____Date PETS checked for first generic drug (just prior to notification to firm)

Applicant notification:
12: 35 pm Time notified of approval by phone
12: 39 pm Time approval letter faxed

FDA Notification:
March 6, 2009 Date e-mail message sent to "CDER-OGDAPPROVALS" distribution list.
March 6, 2009 Date Approval letter copied to \\CDS014\DRUGAPP\ directory.

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

/s/

Rosalyn Adigun

3/6/2009 12:46:37 PM