CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 62-488

Approval Letter

Our reference: 62-488

NOV 0 8 1985

Carter-Glogau Laboratories, Inc.
Attention: Eliane K. Quinn, M.S.
5160 West Bethany Home Road
Glendale, Arizona 85301

Gentlemen:

Please refer to your Antibiotic Form 6 application for Neomycin and Polymyxin B Sulfates and Hydrocortisone Otic Suspension, U.S.P.

We acknowledge receipt of your submissions dated December 4, 1984, and March 19, August 28, and November 4, 1985.

We have completed our review of the application and it is approved.

An expiration date of twenty-four (24) months should be used on each batch of the drug to be marketed and packaged as described in the application.

Place drug samples from the first three production batches into your stability program and test each batch at three (3) month intervals during the first year of aging, at six (6) month intervals during the second year, annually thereafter. As the data become available they should be furnished to this office at six (6) month intervals throughout the authorized shelf life of the subject drug.

For Initial Campaigns: We request that you submit, in duplicate, any proposed advertising or promotional copy which you intend to use in your immediate advertising or promotional campaigns. Please submit all proposed materials in draft or mock-up form, not final printed. Submit both copies together with a copy of the proposed or final printed labeling to the Division of Drug Advertising and Labeling (HFN-240). Also, please do not use form FD-2253 for this submission.

For Subsequent Campaigns: We call your attention to regulation 21 CFR 314.81(b)(3) which requires that all material for any subsequent advertising or promotional campaigns at the time of their initial use be submitted to our Division of Drug Advertising and Labeling (HFN-240) with a completed Form FD-2253. A copy of Form FD-2253 is enclosed for your convenience.

Please be reminded that since you are manufacturing the subject drug for the first time, 21 CFR 314.81 requires certain records and reports be submitted following the date of approval.

The Form 6 should be kept up to date by submitting supplements whenever changes are contemplated in the manufacturing and/or laboratory procedures, controls, equipment and instrumentation, key scientific and production personnel, packaging, labeling, source of antibiotics, etc.

Sincerely yours,

/S/ for 11-6-85

Marvin Seife, M.D.
Director
Division of Generic Drugs
Office of Drug Standards
Center for Drugs and Biologics

Enclosure

11/5/85

NOTICE OF APPROVAL
NEW DRUG APPLICATION OR SUPPLEMENT

NDA NUMBER: 62-488

DATE APPROVAL LETTER ISSUED:

TO: Press Relations Staff (HFI-40)

FROM: ☒ Bureau of Drugs ☐ Bureau of Veterinary Medicine

ATTENTION

Forward original of this form for publication only after approval letter has been issued and the date of approval has been entered above.

TYPE OF APPLICATION: ☒ ORIGINAL NDA ☐ SUPPLEMENT TO NDA ☐ ABBREVIATED ORIGINAL NDA ☐ SUPPLEMENT TO ANDA

CATEGORY: ☒ HUMAN ☐ VETERINARY

TRADE NAME *(or other designated name)* AND ESTABLISHED OR NONPROPRIETARY NAME *(if any)* OF DRUG: Neomycin and Polymyxin B Sulfates and Hydrocortisone

DOSAGE FORM: Otic Suspension

HOW DISPENSED: ☒ Rx ☐ OTC

ACTIVE INGREDIENT(S) *(as declared on label. List by established or nonproprietary name(s) and include amount(s), if amount is declared on label.)*

	per ml
neomycin sulfate	10,000 units
polymyxin B sulfate	eq. to 3.5 mg base
hydrocortisone	10 mg

NAME OF APPLICANT *(Include City and State)*

Carter-Glogau Laboratories, Inc.
5160 West Bethany Home Road
Glendale, Arizona 85301

PRINCIPAL INDICATION OR PHARMACOLOGICAL CATEGORY: Antibiotic / Anti-inflammatory

COMPLETE FOR VETERINARY ONLY

ANIMAL SPECIES FOR WHICH APPROVED:

COMPLETE FOR SUPPLEMENT ONLY

CHANGE APPROVED TO PROVIDE FOR:

FORM PREPARED BY

/S/

DATE: 11/5/85

FORM APPROVED BY

NAME: /S/

DATE: 11-6-85

FORM FD 1642 (2/75) PREVIOUS EDITION MAY BE USED UNTIL SUPPLY IS EXHAUSTED.

NOTICE OF APPROVAL
NEW DRUG APPLICATION OR SUPPLEMENT

NDA NUMBER: 62-488

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/S/
DATE 11/5/85

FORM APPROVED BY
/S/
DATE 11-6-85

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CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 62-488

FINAL PRINTED LABELING

Sterile with Sterile Dropper 10 ml.

NDC 0381-0736-10

NEOMY
SULFATE
OTI

Each ml. contain
Sulfate (equivale
mg. (1%). Thime
Propylene Glycol

USUAL DOSE: F
for indications, d
(59° - 78° F).

CAUTION: Feder

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Sterile with Sterile

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Propylene Glycol.

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USUAL DOSE: Fo
for indications, do:
(59° - 78° F).

CAUTION: Federa

CART

NEOMYCIN AND POLYMYXIN B SULFATES AND HYDROCORTISONE OTIC SUSPENSION, USP

DESCRIPTION: Each ml. contains: Polymyxin B Sulfate 10,000 units, Neomycin Sulfate (equivalent to 3.5 mg. Neomycin base), Hydrocortisone 10 mg. (1%). The vehicle contains the inactive ingredients Cetyl Alcohol, Propylene Glycol, Polysorbate 80 and Thimerosal 0.01% (as preservative) ~~in Water for Injection~~.

CLINICAL PHARMACOLOGY: Hydrocortisone, the naturally occurring adrenal corticosteroid, affords antiallergic, antipruritic and anti-inflammatory activity.

Polymyxin B is one of a group of closely related substances produced by various strains of *Bacillus polymyxa*. Its activity is sharply restricted to gram-negative bacteria, including many strains of *Pseudomonas aeruginosa*.

Neomycin, isolated from *Streptomyces fradiae*, has antibacterial activity *in vitro* against a wide range of gram-negative and gram-positive organisms, with effectiveness against many strains of *Proteus*.

INDICATIONS AND USAGE: For the treatment of superficial bacterial infections of the external auditory canal caused by organisms susceptible to the action of the antibiotics, and for the treatment of infections of mastoidectomy and fenestration cavities caused by organisms susceptible to the antibiotics.

CONTRAINDICATIONS: This product is contraindicated in those individuals who have shown hypersensitivity to any of its components, and in herpes simplex, vaccinia and varicella.

WARNINGS: As with other antibiotic preparations, prolonged treatment may result in overgrowth of nonsusceptible organisms and fungi.

If the infection is not improved after one week, cultures and susceptibility tests should be repeated to verify the identity of the organism and to determine whether therapy should be changed.

When using Neomycin-containing products to control secondary infection in the chronic dermatoses, such as chronic otitis externa, it should be borne in mind that the skin in these conditions is more liable than is normal skin to become sensitized to many substances, including Neomycin. The manifestation of sensitization to Neomycin is usually a low grade reddening with swelling, dry scaling and itching; it may be manifest simply as a failure to heal. During long-term use of Neomycin-containing products, periodic examination for such signs is advisable and the patient should be told to discontinue the product if they are observed. These symptoms regress quickly on withdrawing the medication. Neomycin-containing applications should be avoided for that patient thereafter.

PRECAUTIONS: If sensitization or irritation occurs, medication should be discontinued promptly.

This drug should be used with care when the integrity of the tympanic membrane is in question because of the possibility of ototoxicity caused by Neomycin.

Patients who prefer to warm the medication before using should be cautioned against heating the solution above body temperature, in order to avoid loss of potency.

Treatment should not be continued for longer than ten days.

Allergic cross-reactions may occur which could prevent the use of any or all of the following antibiotics for the treatment of future infections: Kanamycin, Paromomycin, Streptomycin, and possibly Gentamicin.

ADVERSE REACTIONS: Neomycin is a not uncommon cutaneous sensitizer. There are articles in the current literature that indicate an increase in the prevalence of persons sensitive to Neomycin.

Stinging and burning have been reported when this drug has gained access to the middle ear.

DOSAGE AND ADMINISTRATION: The external auditory canal should be thoroughly cleansed and dried with a sterile cotton applicator.

For adults, 4 drops of the suspension should be instilled into the affected ear 3 or 4 times daily. For infants and children, 3 drops are suggested because of the smaller capacity of the ear canal.

The patient should lie with the affected ear upward and then the drops should be instilled. This position should be maintained for 5 minutes to facilitate penetration of the drops into the ear canal. Repeat, if necessary, for the opposite ear.

If preferred, a cotton wick may be inserted into the canal and then the cotton may be saturated with the solution. This wick should be kept moist by adding further solution every four hours. The wick should be replaced a least once every 24 hours.

The patient should be instructed to avoid contaminating the dropper with material from the ear, fingers, or other source. This caution is necessary if the sterility of the drops is to be preserved

SHAKE WELL PRIOR TO USE.

HOW SUPPLIED: Bottle of 10 ml. with sterile dropper.

Store at 15° - 26° C (59° - 78° F).

CAUTION: Federal law prohibits dispensing without prescription.

Literature Revised: October 1985

Product No.: 0736-10

Mfd. by
Carter-Glogau Laboratories, Inc.
Glendale, Arizona 85301

Sterile with Sterile Dropper 10 ml.

NDC 0381-0736-10

Glendale, Arizona 85301 U.S.A

Sterile with Sterile Dropper

NEOMYCIN AND F
HYDROCORTISON

Each ml contains Polymyxin B
3.5 mg. Neomycin base), Hydroc
with Cetyl Alcohol, Propylene G
FOR OTIC USE O

USUAL DOSE: Four (4) drops in
precautions, etc. STORE AT 15°
CAUTION: Federal law prohibit

CARTE
Glendale, Arizona 85301 U.S.A

Sterile with Sterile Dropper NDC 0381-0736-10 10 ml.

NEOMYCIN AND POLYMYXIN B SULFATES AND HYDROCORTISONE OTIC SUSPENSION, USP

Each ml contains: Polymyxin B Sulfate 10,000 Units, Neomycin Sulfate (equivalent to 3.5 mg. Neomycin base), Hydrocortisone 10 mg. (1%), Thimerosal (as preservative) 0.01% with Cetyl Alcohol, Propylene Glycol, Polysorbate 80 in Water for Injection.

FOR OTIC USE ONLY. SHAKE WELL PRIOR TO USE.

USUAL DOSE: Four (4) drops in affected ear. See package insert for indications, dosage, precautions, etc. STORE AT 15° - 26° C (59° - 78° F).

CAUTION: Federal law prohibits dispensing without prescription. 1085/0736-10

CARTER GLOGAU LABORATORIES INC
Glendale, Arizona 85301 U.S.A

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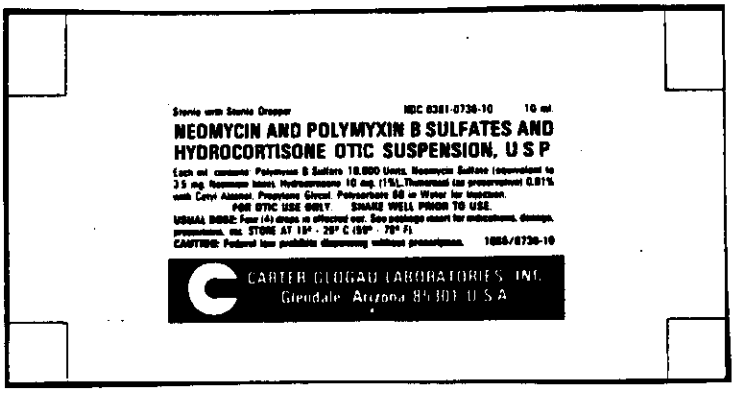
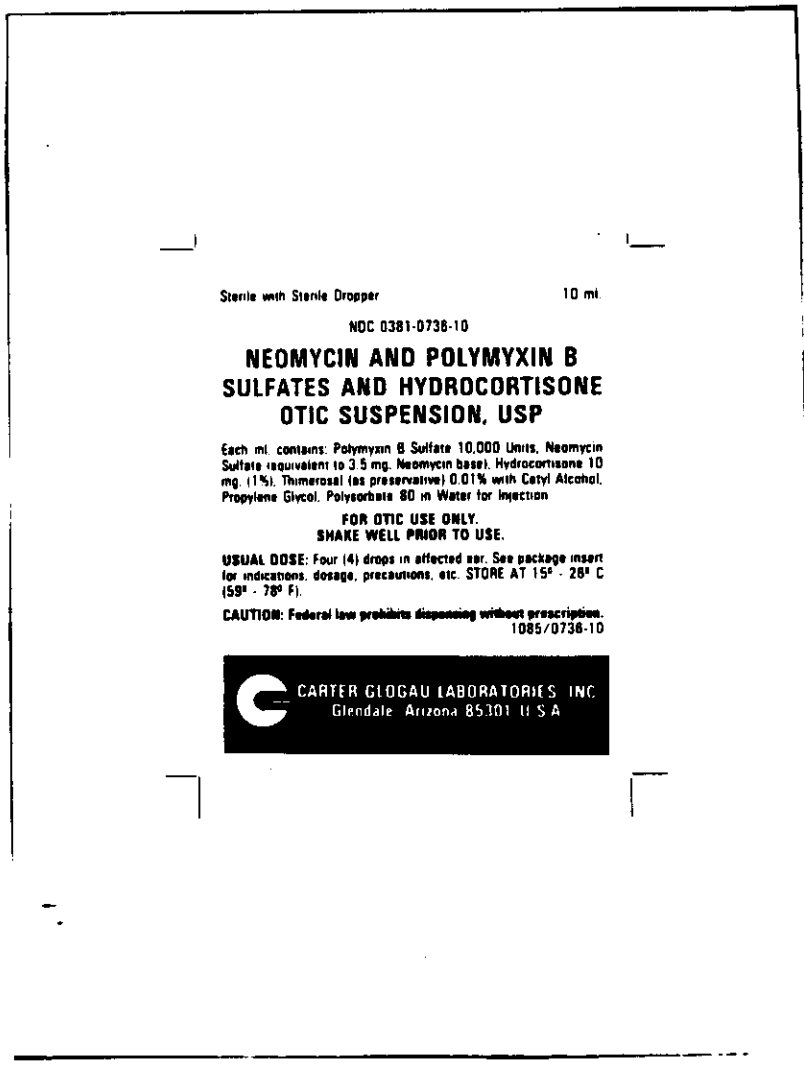
CARTER GLOGAU LABORATORIES INC
Glendale, Arizona 85301 U.S.A

CARTER-GLOGAU LABORATORIES, INC.
5160 WEST BETHANY HOME ROAD•GLENDALE, ARIZONA 85301•TELEPHONE (602) 939-7565•TELEX 66-8304

VIAL LABEL



CARTON LABEL



CARTER-GLOGAU LABORATORIES, INC.
5160 WEST BETHANY HOME ROAD•GLENDALE, ARIZONA 85301•TELEPHONE (602) 939-7565•TELEX 66-8304

PACKAGE INSERT

NEOMYCIN AND POLYMYXIN B SULFATES AND HYDROCORTISONE OTIC SUSPENSION, USP

DESCRIPTION: Each ml. contains: Polymyxin B Sulfate 10,000 units, Neomycin Sulfate (equivalent to 3.5 mg. Neomycin base), Hydrocortisone 10 mg. (1%). The vehicle contains the inactive ingredients Cetyl Alcohol, Propylene Glycol, Polysorbate 80 and Thimerosal 0.01% (as preservative) in Water for Injection.

CLINICAL PHARMACOLOGY: Hydrocortisone, the naturally occurring adrenal corticosteroid, affords antiallergic, antipruritic and anti-inflammatory activity.

Polymyxin B is one of a group of closely related substances produced by various strains of *Bacillus polymyxa*. Its activity is sharply restricted to gram-negative bacteria, including many strains of *Pseudomonas aeruginosa*.

Neomycin, isolated from *Streptomyces fradiae*, has antibacterial activity *in vitro* against a wide range of gram-negative and gram-positive organisms, with effectiveness against many strains of *Proteus*.

INDICATIONS AND USAGE: For the treatment of superficial bacterial infections of the external auditory canal caused by organisms susceptible to the action of the antibiotics, and for the treatment of infections of mastoidectomy and fenestration cavities caused by organisms susceptible to the antibiotics.

CONTRAINDICATIONS: This product is contraindicated in those individuals who have shown hypersensitivity to any of its components, and in herpes simplex, vaccinia and varicella.

WARNINGS: As with other antibiotic preparations, prolonged treatment may result in overgrowth of nonsusceptible organisms and fungi.

If the infection is not improved after one week, cultures and susceptibility tests should be repeated to verify the identity of the organism and to determine whether therapy should be changed.

When using Neomycin-containing products to control secondary infection in the chronic dermatoses, such as chronic otitis externa, it should be borne in mind that the skin in these conditions is more liable than is normal skin to become sensitized to many substances, including Neomycin. The manifestation of sensitization to Neomycin is usually a low grade reddening with swelling, dry scaling and itching; it may be manifest simply as a failure to heal. During long-term use of Neomycin-containing products, periodic examination for such signs is advisable and the patient should be told to discontinue the product if they are observed. These symptoms regress quickly on withdrawing the medication. Neomycin-containing applications should be avoided for that patient thereafter.

PRECAUTIONS: If sensitization or irritation occurs, medication should be discontinued promptly.

This drug should be used with care when the integrity of the tympanic membrane is in question because of the possibility of ototoxicity caused by Neomycin.

Patients who prefer to warm the medication before using should be cautioned against heating the solution above body temperature, in order to avoid loss of potency.

Treatment should not be continued for longer than ten days.

Allergic cross-reactions may occur which could prevent the use of any or all of the following antibiotics for the treatment of future infections: Kanamycin, Paromomycin, Streptomycin, and possibly Gentamicin.

ADVERSE REACTIONS: Neomycin is a not uncommon cutaneous sensitizer. There are articles in the current literature that indicate an increase in the prevalence of persons sensitive to Neomycin.

Stinging and burning have been reported when this drug has gained access to the middle ear.

DOSAGE AND ADMINISTRATION: The external auditory canal should be thoroughly cleansed and dried with a sterile cotton applicator.

For adults, 4 drops of the suspension should be instilled into the affected ear 3 or 4 times daily. For infants and children, 3 drops are suggested because of the smaller capacity of the ear canal.

The patient should lie with the affected ear upward and then the drops should be instilled. This position should be maintained for 5 minutes to facilitate penetration of the drops into the ear canal. Repeat, if necessary, for the opposite ear.

If preferred, a cotton wick may be inserted into the canal and then the cotton may be saturated with the solution. This wick should be kept moist by adding further solution every four hours. The wick should be replaced at least once every 24 hours.

The patient should be instructed to avoid contaminating the dropper with material from the ear, fingers, or other source. This caution is necessary if the sterility of the drops is to be preserved.

SHAKE WELL PRIOR TO USE.

HOW SUPPLIED: Bottle of 10 ml. with sterile dropper.

Store at 15° - 26° C (59° - 78° F).

CAUTION: Federal law prohibits dispensing without prescription.

Literature Revised: October 1985

Product No.: 0736-10

Mfd. by
Carter-Glogau Laboratories, Inc.
Glendale, Arizona 85301

Sterile with Sterile Dropper 10 ml.

NDC 0381-0736-10

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FOR OTIC USE ONLY.
SHAKE WELL PRIOR TO USE.

USUAL DOSE: Four (4) drops in affected ear. See package insert for indications, dosage, precautions, etc. STORE AT 15° - 26° C (59° - 78° F).

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SHAKE WELL PRIOR TO USE.

HOW SUPPLIED: Bottle of 10 ml. with sterile dropper.

Store at 15° - 26° C (59° - 78° F).

CAUTION: Federal law prohibits dispensing without prescription.

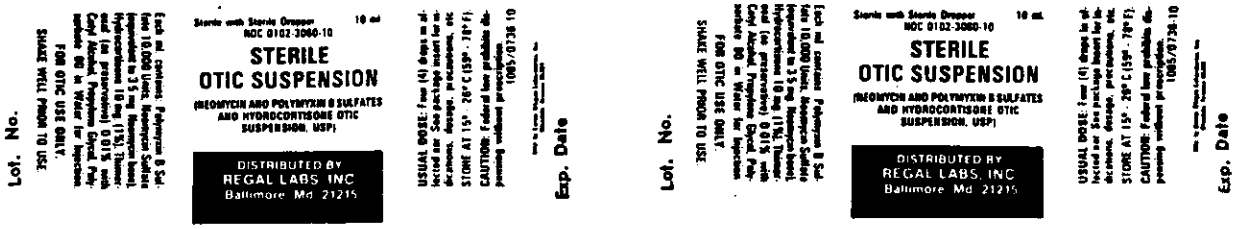
Literature Revised: October 1985

Product No.: 0736-10

Mfd. by
Carter-Glogau Laboratories, Inc.
Glendale, Arizona 85301

CARTER-GLOGAU LABORATORIES, INC.

5160 WEST BETHANY HOME ROAD•GLENDALE, ARIZONA 85301•TELEPHONE (602) 939-7565•TELEX 66-8304



NEOMYCIN AND POLYMYXIN B SULFATES AND HYDROCORTISONE OTIC SUSPENSION, USP

DESCRIPTION: Each ml. contains: Polymyxin B Sulfate 10,000 units, Neomycin Sulfate (equivalent to 3.5 mg. Neomycin base), Hydrocortisone 10 mg. (1%). The vehicle contains the inactive ingredients Cetyl Alcohol, Propylene Glycol, Polysorbate 80 and Thimerosal 0.01% (as preservative) in Water for Injection.

CLINICAL PHARMACOLOGY: Hydrocortisone, the naturally occurring adrenal corticosteroid, affords antiallergic, antipruritic and anti-inflammatory activity.

Polymyxin B is one of a group of closely related substances produced by various strains of *Bacillus polymyxa*. Its activity is sharply restricted to gram-negative bacteria, including many strains of *Pseudomonas aeruginosa*.

Neomycin, isolated from *Streptomyces fradiae*, has antibacterial activity *in vitro* against a wide range of gram-negative and gram-positive organisms, with effectiveness against many strains of *Proteus*.

INDICATIONS AND USAGE: For the treatment of superficial bacterial infections of the external auditory canal caused by organisms susceptible to the action of the antibiotics, and for the treatment of infections of mastoidectomy and fenestration cavities caused by organisms susceptible to the antibiotics.

CONTRAINDICATIONS: This product is contraindicated in those individuals who have shown hypersensitivity to any of its components, and in herpes simplex, vaccinia and varicella.

WARNINGS: As with other antibiotic preparations, prolonged treatment may result in overgrowth of nonsusceptible organisms and fungi.

If the infection is not improved after one week, cultures and susceptibility tests should be repeated to verify the identity of the organism and to determine whether therapy should be changed.

When using Neomycin-containing products to control secondary infection in the chronic dermatoses, such as chronic otitis externa, it should be borne in mind that the skin in these conditions is more liable than is normal skin to become sensitized to many substances, including Neomycin. The manifestation of sensitization to Neomycin is usually a low grade reddening with swelling, dry scaling and itching; it may be manifest simply as a failure to heal. During long-term use of Neomycin-containing products, periodic examination for such signs is advisable and the patient should be told to discontinue the product if they are observed. These symptoms regress quickly on withdrawing the medication. Neomycin-containing applications should be avoided for that patient thereafter.

PRECAUTIONS: If sensitization or irritation occurs, medication should be discontinued promptly.

This drug should be used with care when the integrity of the tympanic membrane is in question because of the possibility of ototoxicity caused by Neomycin.

Patients who prefer to warm the medication before using should be cautioned against heating the solution above body temperature, in order to avoid loss of potency.

Treatment should not be continued for longer than ten days.

Allergic cross-reactions may occur which could prevent the use of any or all of the following antibiotics for the treatment of future infections: Kanamycin, Paromomycin, Streptomycin, and possibly Gentamicin.

ADVERSE REACTIONS: Neomycin is a not uncommon cutaneous sensitizer. There are articles in the current literature that indicate an increase in the prevalence of persons sensitive to Neomycin.

Stinging and burning have been reported when this drug has gained access to the middle ear.

DOSAGE AND ADMINISTRATION: The external auditory canal should be thoroughly cleansed and dried with a sterile cotton applicator.

For adults, 4 drops of the suspension should be instilled into the affected ear 3 or 4 times daily. For infants and children, 3 drops are suggested because of the smaller capacity of the ear canal.

The patient should lie with the affected ear upward and then the drops should be instilled. This position should be maintained for 5 minutes to facilitate penetration of the drops into the ear canal. Repeat, if necessary, for the opposite ear.

If preferred, a cotton wick may be inserted into the canal and then the cotton may be saturated with the solution. This wick should be kept moist by adding further solution every four hours. The wick should be replaced at least once every 24 hours.

The patient should be instructed to avoid contaminating the dropper with material from the ear, fingers, or other source. This caution is necessary if the sterility of the drops is to be preserved.

SHAKE WELL PRIOR TO USE.

HOW SUPPLIED: Bottle of 10 ml. with sterile dropper. Store at 15° - 26° C (59° - 78° F).

CAUTION: Federal law prohibits dispensing without prescription.

Literature Revised: October 1985

Product No.: 0736-10

Mfd by
Carter-Glogau Laboratories, Inc.
Glendale, Arizona 85301

CARTER-GLOGAU LABORATORIES, INC.

5160 WEST BETHANY HOME ROAD•GLENDALE, ARIZONA 85301•TELEPHONE (602) 939-7565•TELEX 66-8304

Sterile with Sterile Dropper NDC 0381-0736-10 10 ml

NEOMYCIN AND POLYMYXIN B SULFATES AND HYDROCORTISONE OTIC SUSPENSION, U S P

Each ml. contains: Polymyxin B Sulfate 10,000 Units, Neomycin Sulfate (equivalent to 3.5 mg. Neomycin base), Hydrocortisone 10 mg. (1%), Thimerosal (as preservative) 0.01% with Cetyl Alcohol, Propylene Glycol, Polysorbate 80 in Water for Injection.

FOR OTIC USE ONLY. SHAKE WELL PRIOR TO USE.

USUAL DOSE: Four (4) drops in affected ear. See package insert for indications, dosage, precautions, etc. STORE AT 15° - 28° C (59° - 78° F).

CAUTION: Federal law prohibits dispensing without prescription. 1085/0736-10

CARTER GLOGAU LABORATORIES INC
Glendale Arizona 85301 U S A

Lot. No.

Exp. Date

Sterile with Sterile Dropper 10 ml.

NDC 0381-0736-10

NEOMYCIN AND POLYMYXIN B SULFATES AND HYDROCORTISONE OTIC SUSPENSION, USP

Each ml. contains: Polymyxin B Sulfate 10,000 Units, Neomycin Sulfate (equivalent to 3.5 mg. Neomycin base), Hydrocortisone 10 mg. (1%), Thimerosal (as preservative) 0.01% with Cetyl Alcohol, Propylene Glycol, Polysorbate 80 in Water for Injection.

FOR OTIC USE ONLY.
SHAKE WELL PRIOR TO USE.

USUAL DOSE: Four (4) drops in affected ear. See package insert for indications, dosage, precautions, etc. STORE AT 15° - 28° C (59° - 78° F).

CAUTION: Federal law prohibits dispensing without prescription. 1085/0736-10

CARTER-GLOGAU LABORATORIES, INC
Glendale Arizona 85301 U S A

Lot. No.

Exp. Date

NEOMYCIN AND POLYMYXIN B SULFATES AND HYDROCORTISONE OTIC SUSPENSION, USP

DESCRIPTION: Each ml. contains: Polymyxin B Sulfate 10,000 units, Neomycin Sulfate (equivalent to 3.5 mg. Neomycin base), Hydrocortisone 10 mg. (1%). The vehicle contains the inactive ingredients Cetyl Alcohol, Propylene Glycol, Polysorbate 80 and Thimerosal 0.01% (as preservative) in Water for Injection.

CLINICAL PHARMACOLOGY: Hydrocortisone, the naturally occurring adrenal corticosteroid, affords antiallergic, antipruritic and anti-inflammatory activity.

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WARNINGS: As with other antibiotic preparations, prolonged treatment may result in overgrowth of nonsusceptible organisms and fungi.

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When using Neomycin-containing products to control secondary infection in the chronic dermatoses, such as chronic otitis externa, it should be borne in mind that the skin in these conditions is more liable than is normal skin to become sensitized to many substances, including Neomycin. The manifestation of sensitization to Neomycin is usually a low grade reddening with swelling, dry scaling and itching; it may be manifest simply as a failure to heal. During long-term use of Neomycin-containing products, periodic examination for such signs is advisable and the patient should be told to discontinue the product if they are observed. These symptoms regress quickly on withdrawing the medication. Neomycin-containing applications should be avoided for that patient thereafter.

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ADVERSE REACTIONS: Neomycin is a not uncommon cutaneous sensitizer. There are articles in the current literature that indicate an increase in the prevalence of persons sensitive to Neomycin.

Stinging and burning have been reported when this drug has gained access to the middle ear.

DOSAGE AND ADMINISTRATION: The external auditory canal should be thoroughly cleansed and dried with a sterile cotton applicator.

For adults, 4 drops of the suspension should be instilled into the affected ear 3 or 4 times daily. For infants and children, 3 drops are suggested because of the smaller capacity of the ear canal.

The patient should lie with the affected ear upward and then the drops should be instilled. This position should be maintained for 5 minutes to facilitate penetration of the drops into the ear canal. Repeat, if necessary, for the opposite ear.

If preferred, a cotton wick may be inserted into the canal and then the cotton may be saturated with the solution. This wick should be kept moist by adding further solution every four hours. The wick should be replaced at least once every 24 hours.

The patient should be instructed to avoid contaminating the dropper with material from the ear, fingers, or other source. This caution is necessary if the sterility of the drops is to be preserved.

SHAKE WELL PRIOR TO USE.

HOW SUPPLIED: Bottle of 10 ml. with sterile dropper. Store at 15° - 28° C (59° - 78° F).

CAUTION: Federal law prohibits dispensing without prescription.

Literature Revised: October 1985

Product No.: 0736-10

Mfd. by
Carter-Glogau Laboratories, Inc.
Glendale, Arizona 85301

CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 62-488

CHEMISTRY REVIEW(S)

Manufacturing and Controls Review
Antibiotic Form 6 #62-488

Sterile Otic Suspension (Neomycin, Polymyxin B, Hydrocortisone)
Carter-Glogau Laboratories

Material Reviewed: Exhibit Sample testing results dated October 16, 1985
A-007 dated August 28, 1985

1. Exhibit Sample testing results - satisfactory. See HFN-178 memo dated October 16, 1985.

2. Stability Data - satisfactory.
The applicant has submitted room temperature and accelerated stability data from five batches of drug product (83L074, 83L075, 84J061, 84J062, and 84L037) stored in the 10 ml market container for periods up to 1 year.

Assays are satisfactory.

Expiration Dating Period - 24 months.

Recommendation - the application can be approved.

/S/
John M. Singer

"Trade name" needs to be revised — notify by telephone.
JDH 10/31/85

Manufacturing and Controls Review
Antibiotic Form 6 #62-488

Carter-Glogau Laboratories
Neomycin and Polymyxin B Sulfates and Hydrocortisone Otic Suspension, U.S.P.

Material Reviewed: Amendment dated November 4, 1985

A[illegible] to
"[illegible] P."

1. Final Printed Labeling - satisfactory.
   Package Insert - satisfactory.
   Container Label - satisfactory.
   Carton Label - satisfactory.

Recommendation - the application can be approved.

/S/

John M. Singer

OK JDB 10/1/85

Manufacturing and Controls Review
#62-488

Sterile Otic Suspension (polymyxin B-neomycin-hydrocortisone)
Carter-Glogau Laboratories, Inc.

Material reviewed: Amendment dated October 15, 1984

Applicant's submission dated October 15, 1984, responds to our letter dated October 4, 1984.

1. Exhibit Sample testing results - unsatisfactory.

2. Stability data - satisfactory.

Recommendation - the application remains not approvable due to #1. Letter to be sent to applicant.

/S/

John M. Singer

Manufacturing and Controls Review

Antibiotic Form 6 #62-488

Date of Application: October 20, 1983
Date of Receipt: October 21, 1983

Applicant: Carter-Glogau Laboratories, Inc.
5160 West Bethany Home Road
Glendale, Arizona 85301

Product: Sterile Otic Suspension (Polymyxin B Sulfate-Neomycin Sulfate-Hydrocortisone)

Product is eligible for marketing when it meets the specifications prescribed by 21 CFR 444.442g.

Page(s) 4

Contain Trade Secret,

Commercial/Confidential

Information and are not

releasable.

3. Samples were not submitted with the application. Please submit samples as required by 21 CFR 444.442g.

4. The package insert should be revised as follows:

   A. Change "Action" to "Clinical Pharmacology".

   B. Change "Indications" to "Indications and Usage".

   C. Add the National Drug Code to the "How Supplied" section.

5. The application did not contain the method used to sterilize the container/closure system.

6. The application did not contain the method used to sterilize the Nitrogen.

/S/

John M. Singer

Manufacturing and Controls Review
#62-488

Applicant has responded to our not approvable letter dated November 3, 1983.

1. Serial numbering system - satisfactory.

2. Stability Data - not available yet - unsatisfactory.

3. Samples - not submitted - unsatisfactory.

4. Labeling - satisfactory.

5. Sterilization - satisfactory.

6. Nitrogen sterilization - satisfactory.

The application is not approvable at this time due to lack of adequate stability data and exhibit samples.

John M. Singer

Manufacturing and Controls Review
#62-488

Sterile Otic Suspension (polymyxin B-neomycin-hydrocortisone)
Carter-Glogau Laboratories, Inc.

Material reviewed: Amendment dated October 15, 1984

Applicant's submission dated October 15, 1984, responds to our letter dated October 4, 1984.

1. Exhibit Sample testing results - unsatisfactory.

2. Stability data - satisfactory.

Recommendation - the application remains not approvable due to #1. Letter to be sent to applicant.

/S/

John M. Singer

Manufacturing and Controls Review
#62-488

Sterile Otic Suspension (polymyxin B-neomycin-hydrocortisone)
Carter-Glogau Laboratories, Inc.

Material Reviewed: Amendment A-003 dated July 20, 1984
Exhibit Sample testing results dated September 28, 1984

1. Stability data - the applicant submitted data for 2 more batches (83L074, 83L075) stored at room temperature and at accelerated conditions for three months in the market container. Although the three month results are satisfactory, the applicant did not provide testing results at 1 and 2 months.

2. Exhibit sample testing results - unsatisfactory. Applicant submitted "production batches" of only and iters. The laboratory feels that the small batch sizes do not meet the requirement to submit exhibit samples from production (size) batches of the product. I concur with their evaluation.

Recommendation - the application remains not approvable. Letter to be bent to firm which lists the deficiencies.

/S/

John M. Singer

CHEMISTRY REVIEW NOTES
SEPTEMBER 21, 1984

RE: Form 62-488
Poly B, Neo, HC Sterile Otic Susp.
Submitted by Carter-Glogau Labs.

Five exhibit samples comprising one bulk neomycin sulfate, one bulk polymyxin B, and three dosage forms were received in support of this application. Bulk neomycin sulfate is supplied by the); polymyxin B

The HPLC procedure refers to Snyder and Kirkland's Introduction to Chromatography, 2nd Ed. p. 287 which in turn refers to a paper by Tymes. However, the method differs somewhat from the one referenced, mainly in the use of a

w.

These exhibit samples meet the specifications of paragraph 444.442g of the CFR.

Number of Analysis = 9
Estimated time = 16 hrs.

Michel Margosis
Research Chemist

Reviewed by:
Thomas Alexander
Section Chief, CS

MM:stk
2415A

Table 1

M#	Lot#	Product	pH(a)		LOD	
			FDA	Mfr.	FDA	Mfr.
8771	22099	neo	--	6.45	5.89	5.6
8772	214-72	poly B	--	6.06	3.69	6.1
8773	83K001	susp.	4.62	4.53	---	---
8774	83L074	susp.	4.74	4.61		
8775	83L075	susp.	4.75	4.60		

(a) lim. 3.0 - 5.5

Manufacturing and Controls Review
#62-488

Applicant has responded to our not approvable letter dated November 3, 1983.

1. Serial numbering system - satisfactory.

2. Stability Data - not available yet - unsatisfactory.

3. Samples - not submitted - unsatisfactory.

4. Labeling - satisfactory.

5. Sterilization - satisfactory.

6. Nitrogen sterilization - satisfactory.

The application is not approvable at this time due to lack of adequate stability data and exhibit samples.

/S/
John M. Singer

Manufacturing and Controls Review

Antibiotic Form 6 #62-488

Date of Application: October 20, 1983
Date of Receipt: October 21, 1983

Applicant: Carter-Glogau Laboratories, Inc.
5160 West Bethany Home Road
Glendale, Arizona 85301

Product: Sterile Otic Suspension (Polymyxin B Sulfate-Neomycin Sulfate-Hydrocortisone)

Product is eligible for marketing when it meets the specifications prescribed by 21 CFR 444.442g.

1/2 Components/Composition:

STERILE OTIC SUSPENSION
(Polymyxin B-Neomycin-Hydrocortisone)

is composed of the following ingredients:

Ingredient	per ml	per batch
Polymyxin B Sulfate	10,000 U	
Neomycin Base (	3.5 mg	
Hydrocortisone		
Thimerosal		
Cetyl Alcohol		
Propylene Glycol		
Polysorbate		
Water for Injection		

3 Manufacturing Process:

Page(s) 2

Contain Trade Secret,

Commercial/Confidential

Information and are not

releasable.

Mfg Process

QC

6 Labeling:

The package insert should be revised as follows:

A. Change "Action" to "Clinical Pharmacology".

B. Change "Indications" to "Indications and Usage".

C. Add the National Drug Code to the "How Supplied" section.

Other labeling - satisfactory

7 The drug is limited in its labeling and by this application to use under the professional supervision of a practitioner licensed by law to administer it.

8 Labeling/Advertising:

Applicant will comply with requirements.

9 Bioavailability: not applicable. 21 CFR 320.22(b)(2) exempts this product since it is intended for local therapeutic effect.

Conclusions: - the application is not approvable at this time due to the following deficiencies:

1. The application describes the serial number system used for raw materials, but, it does not show how these numbers are used in subsequent plant operations.

2. The application did not include stability data. At a minimum, we require data from three batches of product stored in their market container under accelerated aging conditions (37°C/75% R.H.) and at room temperature for 90 days.

3. Samples were not submitted with the application. Please submit samples as required by 21 CFR 444.442g.

4. The package insert should be revised as follows:

   A. Change "Action" to "Clinical Pharmacology".

   B. Change "Indications" to "Indications and Usage".

   C. Add the National Drug Code to the "How Supplied" section.

5. The application did not contain the method used to sterilize the container/closure system.

6. The application did not contain the method used to sterilize the Nitrogen.

/S/

John M. Singer

CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 62-488

MICROBIOLOGY REVIEW(S)

MICROBIOLOGICAL ASSAY REVIEW NOTES
APRIL 17, 1985

RE: Form 6, #62-488
Polymyxin B, Neomycin,
Hydrocortisone Otic Suspension
Submitted by Carter-Glogau
Laboratories, Inc.

This application was reviewed by Antimicrobial Drugs Branch in September, 1984. At that time three lots of exhibit samples were tested, but none of them were of production size. There was also a lack of stability data presented in the application. Carter-Glogau has now sent samples from three production size ( ) batches. Certificates of analysis and quality control specification reports were also received for each batch. Carter-Glogau states that samples from all three of these new batches will be put into their stability program and results will be reported when available. No new stability data are submitted at this time.

We assayed the exhibit samples for neomycin and polymyxin potencies according to 21 CFR 444.442g. Our results follow:

M9104 (lot 84J061)

Neomycin - 3.5mg/ml	Polymyxin - 10,000u/ml
Bottle	Bottle
Average = 3.88mg/ml (110.9% of label)	Average = 11,130u/ml (111.3% of label)
Mfg =	Mfg =

pH = 4.2

M9105 (lot 84J062)

Neomycin - 3.5mg/ml	Polymyxin - 10,000u/ml
Bottle	Bottle
Average = 4.03mg/ml (115.1% of label)	Average = 11,030u/ml (110.3% of label)
Mfg =	Mfg =

pH = 4.3

M9106 (lot 84L037)

Neomycin - 3.5mg/ml	Polymyxin - 10,000u/ml
Bottle	Bottle
Average = 4.02mg/ml (114.9% of label)	Average = 11,010u/ml (110.1% of label)
Mfg =	Mfg =

pH = 4.3

All three lots meet the potency requirements of 90-130% of label for each antibiotic. Our results are also close to those reported by the manufacturer. [illegible]ories assayed all three batches for Carter-Glogau. The product is formulated to contain a [illegible] excess of neomycin and a [illegible] excess of polymyxin.

# of tests = 18
Time spent = 22 hours

Peter A. Dionne
Peter A. Dionne
Microbiologist/ADB

Reviewed by Evelyn E. Lewis
Evelyn E. Lewis
Microbiologsit/ADB

PAD:stk
2634A

MICROBIOLOGICAL ASSAY REVIEW NOTES
MAY 31, 1984

RE: Form 6, #62-488
Sterile Otic Suspension (Polymyxin B, Neomycin, Hydrocortisone)
Submitted by Carter-Glogau Laboratories, Inc.

Carter Glogau's application for the subject otic suspension fully describes "SOP's" for manufacturing, filling procedures, packaging, container controls, and sterile techniques. Microbiological assay procedures are not included, although the application does contain abbreviated copies of the USP monographs for the used in bulk antibiotics (not the finished dosage Form), and copies of the monographs for both the hydrocortisone and the preservative used.

The applicant proposes to use its own laboratory as well as the services of three contract laboratories to determine compliance of the otic suspension with 21 CFR 444.442g. The contract facilities are:

3 months storage at both room temperature and accelerated aging conditions for one exhibit batch. Data from the two additional exhibit batches will be submitted after completion of the 3 month storage time. The stability protocol specifies are accelerated storage temperature of 37°C, but the stability data show the storage temperature to be 40°C. The stability data from the accelerated studies also raise questions as to the stability of the product.

The neomycin shows a drop in potency from initial assay to after 3 months storage, which equals a change, while the polymyxin assay shows a drop from to or a change. The 3 month potencies are at or approaching the minimum requirements. Carter-Glogau proposes a two year initial expiry date with a projected 4 year shelf life dependent on future stability studies.

Samples of otic suspension received were tested according to 21 CRR 444.442g. The results are as follows:

		Neomycin - 3.5mg/ml (Limits = 90-130%)	Polymyxin - 10,000u/ml (Limits = 90-130%)
M7773 (Lot# 83K001)*	B^1		
	B^2		
	B^3		
	B^4		
	Avg. 4 =	3.95mg/ml (112.9% of label)	10,190u/ml (101.9% of label)
	Mfg. =		
M7774 (Lot# 83L074)			
	Avg. 4 =	3.84mg/ml (109.7% of label)	10,290u/ml (102.9% of label)
	Mfg. =		
M7775 (Lot# 83L075)			
	Avg. 4 =	4.27mg/ml (122% of label)	10,510u/ml (105.1% of label)
	Mfg. =		

* Stability batch

The neomycin bulk was tested according to 21 CFR 444.42, and the results follow:

M8771 - Limits = anhydrous
(Lot# 22099)

Avg. 4 = 735mcg/mg
% Moisture =
Anhydrous =

**Mfg = anhydrous

The polymyxin bulk was tested according to 21 CFR 448.30. Results are:

M8772 - Limits =) nhydrous
(Lot# R21472)

Avg. 4 = 8079mcg/mg
% Moisture =
Anhydrous =

**Mfg = , anhydrous

** Applicants tests results.

Sample potencies are within the required limits and are satisfactory. Our test results for the finished dosage form tend to be lower than those obtained by the applicant, but the two results do not differ enough to be of great concern. The applicant formulates with a excess for polymyxin and a excess for neomycin. The polymyxin assay results are some what on the low side, but the results generally are reflective of the formulated percentages.

# of tests = 32
# of hours = 40hrs.

/S/
Evelyn E. Lewis
Microbiologist/ADB

Reviewed by /S/
Peter A. Dionne
Microbiologist/ADB

EEL:stk
2268A

CHEMISTRY REVIEW NOTES
SEPTEMBER 21, 1984

RE: Form 62-488
Poly B, Neo, HC Sterile Otic Susp.
Submitted by Carter-Glogau Labs.

Number of Analysis = 9
Estimated time = 16 hrs.

/S/

Michel Margosis
Research Chemist

Reviewed by: /S/

Thomas Alexander
Section Chief, CS

MM:stk
2415A

Table 1

M#	Lot#	Product	pH(a) FDA	pH(a) Mfr.	LOD FDA	LOD Mfr.
8771	22099	neo	—	6.45	5.89	5.6
8772	214-72	poly B	—	6.06	3.69	6.1
8773	83K001	susp.	4.62	4.53	---	---
8774	83L074	susp.	4.74	4.61		
8775	83L075	susp.	4.75	4.60		

(a) lim. 3.0 - 5.5

MICROBIOLOGICAL ASSAY REVIEW NOTES
APRIL 17, 1985

RE: Form 6, #62-488
Polymyxin B, Neomycin,
Hydrocortisone Otic Suspension
Submitted by Carter-Glogau
Laboratories, Inc.

This application was reviewed by Antimicrobial Drugs Branch in September, 1984. At that time three lots of exhibit samples were tested, but none of them were of production size. There was also a lack of stability data presented in the application. Carter-Glogau has now sent samples from three production size (iter) batches. Certificates of analysis and quality control specification reports were also received for each batch. Carter-Glogau states that samples from all three of these new batches will be put into their stability program and results will be reported when available. No new stability data are submitted at this time.

We assayed the exhibit samples for neomycin and polymyxin potencies according to 21 CFR 444.442g. Our results follow:

M9104 (lot 84J061)

Neomycin - 3.5mg/ml	Polymyxin - 10,000u/ml
Bottle	Bottle
Average = 3.88mg/ml (110.9% of label)	Average = 11,130u/ml (111.3% of label)
Mfg =	Mfg =

pH = 4.2

M9105 (lot 84J062)

Neomycin - 3.5mg/ml	Polymyxin - 10,000u/ml
Bottle	Bottle
Average = 4.03mg/ml (115.1% of label)	Average = 11,030u/ml (110.3% of label)
Mfg =	Mfg =)%)

pH = 4.3

M9106 (lot 84L037)

Neomycin - 3.5mg/ml	Polymyxin - 10,000u/ml
Bottle	Bottle
Average = 4.02mg/ml (114.9% of label)	Average = 11,010u/ml (110.1% of label)
Mfg =	Mfg =

pH = 4.3

All three lots meet the potency requirements of 90-130% of label for each antibiotic. Our results are also close to those reported by the manufacturer. s assayed all three batches for Carter-Glogau. The product is formulated to contain a excess of neomycin and a excess of polymyxin.

# of tests = 18
Time spent = 22 hours

Peter A. Dionne
Microbiologist/ADB

Reviewed by

Evelyn E. Lewis
Microbiologsit/ADB

PAD:stk
2634A

MICROBIOLOGICAL ASSAY REVIEW NOTES
MAY 31, 1984

RE: Form 6, #62-488
Sterile Otic Suspension (Polymyxin B, Neomycin, Hydrocortisone)
Submitted by Carter-Glogau Laboratories, Inc.

Carter Glogau's application for the subject otic suspension fully describes "SOP's" for manufacturing, filling procedures, packaging, container controls, and sterile techniques. Microbiological assay procedures are not included, although the application does contain abbreviated copies of the USP monographs for the used in bulk antibiotics (not the finished dosage Form), and copies of the monographs for both the hydrocortisone and the preservative used.

The applicant proposes to use its own laboratory as well as the services of three contract laboratories to determine compliance of the otic suspension with 21 CFR 444.442g. The contract facilities are:

The potency assays for the exhibit samples were done by Detailed descriptions of the personnel and facilities of each laboratory are included in the submission.

The applicant submits a detailed stability protocol, and has included data for 3 months storage at both room temperature and accelerated aging conditions for one exhibit batch. Data from the two additional exhibit batches will be submitted after completion of the 3 month storage time. The stability protocol specifies are accelerated storage temperature of 37°C, but the stability data show the storage temperature to be 40°C. The stability data from the accelerated studies also raise questions as to the stability of the product.

The neomycin shows a drop in potency from initial assay to after 3 months storage, which equals a change, while the polymyxin assay shows a drop from to or a change. The 3 month potencies are at or approaching the minimum requirements. Carter-Glogau proposes a two year initial expiry date with a projected 4 year shelf life dependent on future stability studies.

Samples of otic suspension received were tested according to 21 CRR 444.442g. The results are as follows:

	Neomycin - 3.5mg/ml (Limits = 90-130%)	Polymyxin - 10,000u/ml (Limits = 90-130%)
M7773 (Lot# 83K001)*		B^1 B^2 B^3 B^4
	Avg. 4 = 3.95mg/ml (112.9% of label)	Avg. 4 = 10,190u/ml (101.9% of label)
	Mfg. =	Mfg. =
M7774 (Lot# 83L074)		
	Avg. 4 = 3.84mg/ml (109.7% of label)	Avg. 4 = 10,290u/ml (102.9% of label)
	Mfg. =	Mfg. =
M7775 (Lot# 83L075)		
	Avg. 4 = 4.27mg/ml (122% of label)	Avg. 4 = 10,510u/ml (105.1% of label)
	Mfg. =	Mfg. =

* Stability batch

The neomycin bulk was tested according to 21 CFR 444.42, and the results follow:

M8771 - Limits = NLT anhydrous
(Lot# 22099)

Avg. 4 = 735mcg/mg
% Moisture = 5.87
Anhydrous = 781mcg/mg

**Mfg = anhydrous

The polymyxin bulk was tested according to 21 CFR 448.30. Results are:

M8772 - Limits = NLT , anhydrous
(Lot# R21472)

Avg. 4 = 8079mcg/mg
% Moisture =
Anhydrous =

**Mfg = anhydrous

** Applicants tests results.

Sample potencies are within the required limits and are satisfactory. Our test results for the finished dosage form tend to be lower than those obtained by the applicant, but the two results do not differ enough to be of great concern. The applicant formulates with a xcess for polymyxin and a excess for neomycin. The polymyxin assay results are some what on the low side, but the results generally are reflective of the formulated percentages.

# of tests = 32
# of hours = 40hrs.

/S/
Evelyn E. Lewis
Microbiologist/ADB

Reviewed by /S/
Peter A. Dionne
Microbiologist/ADB

EEL:stk
2268A

CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 62-488

ADMINISTRATIVE DOCUMENTS

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

ANTIBIOTIC APPLICATION

Form approved:
OMB No. 57-R0126

TANT: No batches of Antibiotic Drugs may be certified or released unless this form, Antibiotic Application, Form FD 1675, has been filed with the Food and Drug Administration *(21 CFR, Parts 430 through 460).*

APPLICABLE PROCEDURES	Check one
n 5 request under 431.17 to provide for certification of a antibiotic or antibiotic-containing product.	
n 6 data to accompany or precede every initial request under) for certification of an antibiotic drug covered by existing ulations, Section	
n 5 amendment, Regulation Section _____, If known.	
n 6, Regulation Section CFR 444.442g	X

FOOD AND DRUG ADMINISTRATION USE ONLY

DATE APPROVED

ACCOUNT NO.

SIGNED

(For the Commissioner of Food and Drugs
Food and Drug Administration
Department of Health, Education, and Welfare

ME OF APPLICANT *(Last, First, MI)*
CARTER-GLOGAU LABORATORIES, INC

DATE OF APPLICATION
October 20, 1983

DRESS *(Number, Street, City, State, ZIP Code)* 5160 W. BETHANY HOME ROAD
GLENDALE, AZ 85301

ME OF DRUG
Sterile Otic Suspension (Polymyxin B-Neomycin-Hydrocortisone)

mmissioner
od and Drug Administration
partment of Health, Education, and Welfare
ockville, Maryland 20852

tention: Certifiable Drug Review, Staff (HFD-535)

cordance with regulations promulgated under Section 507 of the eral Food, Drug, and Cosmetic Act, as amended, we hereby submit this plication with respect to an antibiotic product.

Attached hereto, in triplicate (except for the information required ndet Item 9 (a) through (f) which is submitted in single copy) and onstituting a part of this application are the following:

1. A full list of the articles used as components of the drug. This list hould include all substances used in the fermentation, anythesis, extrac- ion, purification or other method of preparation of any antibiotic and in he preparation of the finished dosage form, regardless of whether they undergo any change or are removed in the process. Each substance should e identified by its established name, if any, or complete chemical name, using structural formulas when necessary for specific identification. If any proprietary preparation is used as a component, the proprietary name should be followed by a complete quantitative statement of composition. Reasonable alternatives for any listed substance may be specified.

2. A full statement of the composition of the drug. The statement shall set forth the name and amount of each ingredient, whether active or not, contained in a stated quantity of the drug in the form in which it is to be distributed, as for example, amount per tablet or per milliliter, and a batch formula representative of that to be employed for the manufacture of the finished dosage form. All components should be included in the batch formula regardless of whether they appear in the finished product. Any calculated excess of an ingredient over the label declaration should be designated as such and percent excess shown. Reasonable variations may be specified.

3. A complete description of the methods and processes used in manufacturing, packing and labeling of the drug to preserve its identity, strength, quality, and purity in conformity with good manufacturing practices including:

(a) Name and location of each plant conducting the operations.

(b) Whether or not each lot of raw materials is given a serial number to identify it, and the use made of such numbers in subsequent plant operations.

(c) Precautions to assure proper identity, strength, quality, and purity of the raw materials, whether active or not, including the specifications for acceptance and methods of testing for each lot of raw material used in the fermentation, synthesis, extraction, and purification of the drug and for each ingredient used in the manufacture of the drug that is to be dispensed.

(d) If it is a drug produced by fermentation:

(i) Source and type of microorganism used to produce the drug.

(ii) Composition of media used to produce the drug.

(iii) Type of precursor used, if any, to guide or enhance production of the antibiotic during fermentation.

(iv) Name and composition of preservative, if any, used in the broth.

(v) A complete description of the extraction and purification processes including the names and compositions of the solvents, precipitants, ion exchange resins, demulsifiers, and all other agents used.

(vi) If the drug is produced by a catalytic hydrogeneration process, *(such as tetracycline from chlortetracycline)*, a complete description of the process, including the name of the catalyst used, how it is removed, and how the drug is extracted and purified.

(e) If it is a drug that is synthesized by chemical processes, a detailed description of each chemical reaction with graphic formulas used to produce the drug, including the names and amounts of all substances used in the process.

(NOTE: If the applicant is not the manufacturer of the antibiotic used in making the drug, in lieu of the information required in 3(a) through 3(e), he should include the name and address of the manufacturer.)

(f) Method of preparation of the master formula records and individual batch records and manner in which these records are used.

(g) Number of individuals checking weight or volume of each individual ingredient entering into each batch of the drug.

(h) Whether or not the total weight or volume of each batch is determined at any stage of the manufacturing process subsequent to making up the batch according to the formula card, and at what stage and by whom this is done.

(i) At what point in the process the drug is mixed homogeneously and a description of the equipment used for this purpose and its total capacity in terms of pounds, kilograms, gallons, or liters of the drug and the maximum quantity of the drug that is mixed in such equipment.

(j) A description, where applicable, of all equipment used in the fermentation, snythesis, extraction, purification, filtration, sterilizing, grinding, blending, mixing, tableting, encapsulating, filling, packaging, and labeling of the drug.

(k) If it is a sterile drug, a description of the methods used to insure the sterility of each batch and the controls used for maintaining its sterility, including a detailed description of the sterile areas where the drug is produced and packaged.

(l) Additional procedures employed which are designed to exclude contaminants *(e.g., other drug substances, extraneous materials, etc.)* and otherwise assure proper control of the product.

(m) Adequate information with respect to the characteristics of and the test methods employed for the container, closure, or other component parts of the drug container to insure their suitability for the intended use.

(n) Controls used in the packaging and labeling of each batch to insure the standards of identity, strength, quality and purity of the drug.

(o) Precautions to check the total number of finished packages produced from a batch of the drug with the theoretical yield.

(p) Precautions to insure that each lot of the drug is packaged with the proper label and labeling, including provisions for labelling, storage, and inventory control.

(q) Copies of all printed forms used by the applicant in the manufacture, packaging, and labeling of a batch.

(r) The name of each person responsible for each of the above operations and information concerning his scientific training and experience.

4. A complete description of the tests and methods of assay and other controls used during the manufacture of the batch and after it is packaged.

(a) Details of analytical procedures for all active ingredients. The analytical procedures should be capable of determining the active components and of assuring the identity of such components.

(b) Standards used for acceptance of each lot of the finished drug.

(c) A detailed description of the collection of the samples to be tested by the applicant and by the Food and Drug Administration.

(d) Copies of all printed forms used by the applicant in the laboratory control of raw ingredients and the finished batch.

(e) A complete description of the laboratory facilities used in such controls, including:

(i) The location of the laboratory in relation to the plant where the drug is manufactured,

(ii) A description of the laboratory equipment available for performing tests and assays, and

(iii) The names of the persons who will be responsible for conducting the required laboratory tests and information concerning their scientific training and experience.

(f) If the applicant uses the services of a consulting laboratory, the name and address of such laboratory and a statement from such laboratory that includes the information required under 4(a), (b), and (e).

(g) An explanation of the exact significance of any batch numbers used in the manufacturing, processing, packaging, and labeling of the drug, including such control numbers that may appear on the label of the finished article. State whether these numbers enable determination of the complete manufacturing history of the product. Describe any methods used to permit determination of the distribution of any batch if its recall is required.

(h) A complete description of, and data derived from, stability studies of the potency and physical characteristics, including information showing the suitability of the analytical methods used. Describe any additional stability studies underway or contemplated. Stability data should be submitted for any new antibiotic, for the finished dosage form of the drug in the container including a multiple-dose container in which it is to be marketed, and if it is to be put into solution at the time of dispensing, for the solution prepared as directed.

(i) The expiration date needed to preserve the identity, strength, quality, and purity of the drug until it is used.

5. The following samples shall be submitted with the application or as soon thereafter as they become available:

(a) If it is a new antibiotic: 10 grams of the applicant's reference standard if an official standard has not been designated, plus 5 grams from each of three separate batches. Include for any reference standard a complete description of its preparation and the results of all laboratory tests on it. If the test methods differed from those described in the application, full details of the methods employed in obtaining the reported results shall be submitted.

(b) If it is a dosage form: 6 immediate containers (or 30 tablets or capsules) from each of three separate batches, except that if it is a sterile drug 30 containers shall be submitted from each of three batches.

(c) Include for samples submitted pursuant to items 5(a) or 5(b) detailed results of all laboratory tests made to determine the identity, strength, quality and purity of the batch represented by the sample.

(d) Additional samples shall be submitted on request.

(e) The requirements of items 5(a) or 5(b) may be waived in whole or in part on request of the applicant, or otherwise, when any such samples are not necessary.

6. Each copy of the application shall contain a copy of each label and all other labeling to be used for the drug.

(a) Each label, or other labeling, should be clearly identified as to its position on, or the manner in which it accompanies, the market package.

(b) The labeling on or within the retail package should include adequate directions for use by the layman under all the conditions for which the drug is intended for lay use, or is to be prescribed, recommended, or suggested in any labeling or advertising sponsored by or on behalf of the applicant and directed to laymen.

(c) If the drug is limited in its labeling to use under the professional supervision of a practitioner licensed by law to administer it, its labeling should bear information for use under which such practitioners can use the drug for the purpose for which it is intended, including all the purposes for which it is to be advertised or represented, in accord with 201.100 or 201.105.

(d) If no established name exists for a new antibiotic, the application shall propose a nonproprietary name for use as the established name for the substance.

(e) Typewritten or other draft labeling copy may be submitted for preliminary consideration of an application. An application will not be approved prior to the submission of the final printed label and labeling of the drug. No application may be approved if the labeling is false or misleading in any particular. *(If the article is a prescription drug, copies of proposed advertising may be submitted optionally for comment or approval).*

. State whether the drug is *(or is not)* limited in its labeling and by application to use under the professional supervision of a practitioner ised by law to administer it.

. It is understood that the labeling, and advertising for the antibiotic will prescribe, recommend, or suggest its use only under the ditions stated in the labeling which is part of this application; and if the le is a prescription drug, it is understood that any labeling which lishes or purports to furnish information for use or which prescribes, mmends, or suggests a dosage for use of the drug will also contain tantially the same information for its use, including indications, cts, dosages, routes, methods, and frequency and duration of adminis- on, any relevent hazards, contraindications, side effects, and pre- ns, contained in the labeling which is part of this application. It is stood that all representations in this application apply to the drug ed until an amendment providing for a change is approved by the and Drug Administration.

9. Full reports of investigations that have been made to show whether not the drug is safe for use and efficacious in use.

If this is a Form 5 application submit one copy of (a) through (f) below

(a) An application may be found unsatisfactory unless it contains full reports of adequate tests by all methods reasonably applicable to show whether or not the drug is safe and effective for use as suggested in the proposed labeling and includes all the following:

(i) Detailed reports of the preclinical investigations, including studies made on laboratory animals, in which the methods used and the results obtained are clearly set forth. Such information should include identification of the person who conducted each investigation, a statement of where the investigations were conducted, and where the underlying data are available for inspection. The animal studies may not be considered adequate unless they give proper attention to the conditions of use recommended in the proposed labeling for the drug such as, for example, whether the drug is for short - or long - term administration or whether it is to be used in infants, children, pregnant women, or prememopausal women.

(ii) Reports of all clinical tests sponsored by the applicant or received or otherwise obtained by the applicant should be attached. These reports should include adequate information concerning each subject treated with the drug or employed as a control, including age, sex, conditions treated, dosage, frequency of administration of the drug, results of all relevant clinical observations and laboratory examinations made, full information concerning any other treatment given previously or concurrently, and a full statement of adverse effects and useful results observed, together with an opinion as to whether such effects or results are attributable to the drug under investigation and a statement of where the underlying data are available for inspection. Ordinarily, the reports of clinical studies will not be regarded as adequate unless they include reports from more than one independent, competent investigator who maintain adequate case histories of an adequate number of subjects, designed to record observations and permit evaluation of any and all discernible effects attributable to the drug in each individual treated and comparable records on any individuals employed as controls. Except when the disease for which the drug is being tested occurs with such infrequency in the United States as to make testing impractical, some of the investigations should be performed by competent investigators within the United States.

(iii) All information pertinent to an evaluation of the safety and efficacy of the drug received or otherwise obtained by the applicant from any source, including information derived from other investigations or commercial marketing (for example, outside the United States), or reports in the scientific literature, involving the drug that is the subject of the application or pertinent information about any relevantly related drug. An adequate summary may be acceptable in lieu of a reprint of a published article which only supports other data submitted. Include any evaluation of the safety or efficacy of the drug that has been made by the applicant's medical department, expert committee, or consultants.

(iv) If the drug is a combination of previously ..... marketed drugs an adequate summary of pre-existing information from preclinical and clinical investigation and experience with its components, including all reports received or otherwise obtained by the applicant suggesting side effects, contraindications, and ineffectiveness in use of such components. Such summary should include an adequate bibliography of publications about the components and may incorporate by reference information concerning such components previously submitted by the applicant to the Food and Drug Administration.

(b) An application may be found unsatisfactory unless it includes substantial evidence consisting of adequate and well-controlled investigations, including clinical investigations, by experts qualified by scientific training and experience to evaluate the efficacy of the drug involved, on the basis of which it could fairly and responsibly be concluded by such experts that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the proposed labeling.

(c) The complete composition and/or method of manufacture of the drug used in each submitted report of investigation should be shown to the extent necessary to establish its identity, strength, quality, and purity if it differs from the description in item 1, 2, 3 or 4 of the application in any way that would bias an evaluation of the report.

(d) An application shall include a complete list of the names and post office addresses of all investigators who received the drug.

(e) The information required by 9(a) through 9(d) may be incorporated in whole or in part by specific reference to information submitted under the provision of §312.1.

(f) Explain any omission of reports from any investigator to whom the investigational drug has been made available. The unexplained omission of any reports of investigations made with the drug by the applicant, or submitted to him by an investigator, or the unexplained omission of any pertinent reports of investigations or clinical experience received or otherwise obtained by the applicant from published literature or other sources, that would bias an evaluation of the safety of the drug or its efficacy in use constitutes grounds for finding the application unsatisfactory.

(c) If this is a Form 6 application, in lieu of the information required in 9(a) through 9(f) it should include data adequate to demonstrate that the drug is comparable to the drug for which certification has previously been provided.

0. If this is an amendment, full information on each proposed change rning any statement made in the approved application. After an ation is approved, an amendment may propose changes. An ndment should be submitted for any change beyond the variations provided for in the application. Any statements made in the approved application concerning which no change is proposed. Any mailing or promotional piece used after the drug is placed on the market is labeling requiring an amendment. An amendment should be submitted for proposed changes in labeling. If a change is made in the components, composition, manufacturing methods, facilities or controls, or in the labeling or advertising from the representations in an approved application and the drug is marketed before an amendment is approved for such change, certification of the drug may be suspended.

Very truly yours, CARTER-GLOGAU LABORATORIES, INC

(Applicant)

Per Samuel M. Fainberg, Ph. D.

Director, Technical and Regulatory Affairs

(Indicate Authority)

is application must be signed by the applicant or by an thorized attorney, agent, or official. If the applicant or such thorized representative does not reside or have a place of business thin the United States, the application must also furnish the name d post office address of and must be countersigned by an thorized attorney, agent, or official residing or maintaining a ce of business within the United States. The data specified under several numbered headings should be on separate sheets or sets sheets, suitably identified. The sample of the drug, if sent under separate cover, should be addressed to the attention of the National Center for Antibiotic Analysis and identified on the outside of the shipping package with the name of the applicant and the name of the drug as shown on the application. All applications and correspondence should be submitted in triplicate except for the information required under item 9(a) through (f) which should be submitted as a single copy attached to the original copy of the application.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Memorandum

Date October 16, 1985

From Chief, Antimicrobial Drugs Branch (HFN-178)

Subject Form 62-488; Polymyxin B Sulfate/Neomycin Sulfate/ Hydrocortisone Otic Suspension; Carter-Glogau Laboratories, Inc.

To John M. Singer (HFN-235)

ADB's review of this application on September 28, 1984 concluded that it was "incomplete due to its lack of stability data nor does it meet the requirement to submit exhibit samples from production (size) batches of the product". This submission in support of the application only removes the latter deficiency. The three exhibit samples of production sized batches meet the CFR requirements for neomycin and polymyxin. The attached Microbiological Assay Review Notes contain the analytical data and also show their fairly good agreement with the applicant's data.

The application is still incomplete since there are no stability data submitted.

/S/

Joseph H. Graham, Ph.D.

2847A

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Memorandum

Date September 28, 1984

From Chief
Antimicrobial Drugs Branch (HFN-178)

Subject Form 62-488; Polymyxin B-Neomycin-Hydrocortisone Sterile Otic Suspension; Carter-Glogau Labs., Inc.

To John M. Singer (HFN-235)

This application lists the components of the drug and indicates specifications and test procedures for them. The sources of the active components are indicated. The master formula card indicates that the product is to be

Three exhibit batches, one sample each of bulk polymyxin and neomycin and certificates of analysis were received in ADB with this application. The assay data on these samples were obtained by The data sheets indicate that none of the exhibit batches (.) was of the production batch size as shown on the master formula card. ADB assayed the antibiotic components by the official microbiological procedures; we did not perform the assay for the hydrocortisone content however the attached Chemistry Review Notes do comment on it. The applicant's data are all higher than ADB's but both sets of polymyxin results are lower than what might have been anticipated from its excess in the formulation.

A suitable stability testing protocol is included in the application that calls for ambient and 40°C studies on production batches of the product. Data are reported on only one batch, 83K001 (M7773) which is hardly a production batch being only in size. After three months storage at room temperature, the neomycin content had dropped from an initial level of . This latter value compares well with our value of obtained approximately 7 months post manufacture. Storage for three months at 40°C resulted in a drop to for the neomycin and a drop from to for the polymyxin. These data suggest that if the theoretical formulation this batch is being met, the production losses are considerable

and that 24 month expiry dating for this product is dubious. The small size of this batch may have contributed to the poor performance of this product. Additional studies are said to be in progress on other batches of this product.

At this point we judge this application to be incomplete due to its lack of adequate stability data nor does it meet the requirement to submit exhibit samples from production (size) batches of the product.

Additional stability data on production batches should be requested and reviewed before further consideration of this application is made.

/S/
Joseph H. Graham, Ph.D.

Attachments

JHG:stk
2422A

DEPARTMENT OF HEALTH & . .MAN SERVICES

Memorandum

TO :Manufacturing Review Branch (HFN-322)
Division of Drug Quality Compliance

DATE: August 6, 1984

FROM :Division of Generic Drugs (HFN-235),
Requester's Name John M. Singe

T: 443-4340

SUBJECT: ESTABLISHMENT EVALUATION REQUEST

NDA, ANDA, AND SUPPLEMENT NUMBER: 62-488 and 62-520

DRUG TRADE MARK (if any) Sterile Otic Suspension/Kanamycin Sulfate

DRUG NONPROPRIETARY NAME: Polymyxin B Neomycin Hydrocortisone

DOSAGE FORM AND STRENGTH(S): Otic Suspension/Injection 1 gm/3 ml

DRUG CLASSIFICATION:
(Priority) _____ A or B _____ IC _____ Other _____

PROFILE CLASS CODE:
LIO and SVO

APPLICANT'S NAME: Barnes-Hind Laboratories, Inc.
ADDRESS: 5160 West Bethany Home Road Glendale, Arizona 85301

FACILITY TO BE INSPECTED (Name, Full Address, DMF# (if any), and Responsibility):

Barnes-Hind Laboratories, Inc
5160 West Bethany Home Road
Glendale, Arizona 85301

This firm appears on July 9, 1984 Alert List, and is the subject of May 18, 1984 memorandum from Thomas S. Bozzo.

Comments: ( ) See Attached.
( ) Actual on-site inspection requested.

Reason:

****

FOR HFN-322 USE ONLY:

Request Rec'd: _____ Inspection Requested: _____
(if applicable)

Firm(s) are in Compliance With CMPs: _____
Basis for Decision: _____
Recommending CSO: _____

cc: HFN-235
HFN-235/JD
HFN-322

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Memorandum

Date April 12, 1984

From Chemist, HFN-535

Subject Form 6 #62-488 - Sterile Otic Suspension (Polymyxin B, Neomycin, Hydrocortisone)

To Director, Anti-Microbial Drug Branch, HFN-416

Carter-Glogau Laboratories, Inc. has submitted a Form 6 application for Sterile Otic Suspension. Please perform the required compendial tests.

The following are being forwarded with this memo:

1. Triplicate copy of the application.
2. Samples with Certificates of Analysis for three batches.

If there are any questions, I may be reached at 443-4340.

John M. Singer

OK to file
4/1/85

April 1, 1985

Chemist, HFN-235

Form 6 #62-488

Director, Anti-Microbial Drug Branch, HFN-178

Carter-Glogau Laboratories has submitted a Form 6 application for Sterile Otic Suspension. Please perform the required compendial tests.

The following are being forwarded with this memo:

1. Triplicate copy of the application.

2. Samples with Certificates of Analysis for three production batches. Previous samples were submitted from experimental batches.

3. HFN-178 evaluation dated September 28, 1984, of samples from experimental batches.

If there are any questions, I may be reached at 443-4340.

John M. Singer

DEPARTMENT OF HEALTH & HUMAN SERVICES

(12)

Memorandum

TO :Manufacturing Review Branch (HFN-322) DATE: November 3, 1983
Division of Drug Quality Compliance

FROM :Division of Generic Drugs (HFN-535)
Requester's Name John M. Singer /S/ PHONE: 443-4340

SUBJECT: ESTABLISHMENT EVALUATION REQUEST

NDA, ANDA, AND SUPPLEMENT NUMBER: 62-488

DRUG TRADE MARK (if any) Sterile Otic Suspension

DRUG NONPROPRIETARY NAME: Polymyxin B, Neomycin, Hydrocortisone

DOSAGE FORM AND STRENGTH(S): Suspension

DRUG CLASSIFICATION: PROFILE CLASS CODE:
(Priority) _____ A or B_____ 1C_____Other_____ LIQ

APPLICANT'S NAME: Carter-Glogau Laboratories, Inc.
ADDRESS: Glendale, Arizona 85301

5/83 OK
2/82 ok
OR 3/20/83

FACILITIES TO BE EVALUATED: (Name, Full Address, DMF# (if any), and Responsibility)

01

Update for (liq)

Comments: ( ) See Attached.
( ) Actual on-site inspection requested.

Reason: These firms provide laboratory services to Carter-Glogau

****

FOR HFN-322 USE ONLY:

Request Rec'd: 11/4

Inspection Requested: Update Reg on Basis (if applicable) (LIQ)

Firm(s) are in Compliance With GMPs: Approved 11/21/83
Basis for Decision: Above ES
Reviewing CSC Concurrance: /S/

cc: /S/

FORM FDA 3274 (1/83)

DEPARTMENT OF HEALTH & HUMAN SERVICES

Memorandum

TO :Manufacturing Review Branch (HFN-322) DATE: November 3, 1983
Division of Drug Quality Compliance

FROM :Division of Generic Drugs (HFN-535)
Requester's Name John M. Singer PHONE: 443-4340

SUBJECT: ESTABLISHMENT EVALUATION REQUEST

NDA, ANDA, AND SUPPLEMENT NUMBER: 62-488

DRUG TRADE MARK (if any) Sterile Otic Suspension

DRUG NONPROPRIETARY NAME: Polymyxin B, Neomycin, Hydrocortisone

DOSAGE FORM AND STRENGTH(S): Suspension

DRUG CLASSIFICATION: PROFILE CLASS CODE:
(Priority) _____ A or B_____ 1C_____Other_____ LIO

APPLICANT'S NAME: Carter-Glogau Laboratories, Inc.
ADDRESS: Glendale, Arizona 85301

FACILITIES TO BE EVALUATED: (Name, Full Address, DMF# (if any), and Responsibility)

31

Comments: ( ) See Attached.
( ) Actual on-site inspection requested.

Reason: These firms provide laboratory services to Carter-Glogau

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FOR HFN-322 USE ONLY:

Request Rec'd:_____ Inspection Requested:_____
(if applicable)

Firm(s) are in Compliance With GMPs:_____
Basis for Decision:_____
Reviewing CSO: _____ Concurrance: _____

cc:

FORM FDA 3274 (1/83)

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Memorandum

Date October 16, 1985

From Chief, Antimicrobial Drugs Branch (HFN-178)

Subject Form 62-488; Polymyxin B Sulfate/Neomycin Sulfate/ Hydrocortisone Otic Suspension; Carter-Glogau Laboratories, Inc.

To John M. Singer (HFN-235)

ADB's review of this application on September 28, 1984 concluded that it was "incomplete due to its lack of stability data nor does it meet the requirement to submit exhibit samples from production (size) batches of the product". This submission in support of the application only removes the latter deficiency. The three exhibit samples of production sized (batches meet the CFR requirements for neomycin and polymyxin. The attached Microbiological Assay Review Notes contain the analytical data and also show their fairly good agreement with the applicant's data.

The application is still incomplete since there are no stability data submitted.

/S/

Joseph H. Graham, Ph.D.

√F)

2847A

Manufacturing and Controls Review
Antibiotic Form 6 #62-488

Carter-Glogau Laboratories
Neomycin and Polymyxin B Sulfates and Hydrocortisone Otic Suspension, U.S.P.

Material Reviewed: Amendment dated November 4, 1985

Applicant proposes to change the trade name from "Sterile Otic Suspension" to "Neomycin and Polymyxin B Sulfates and Hydrocortisone Otic Suspension, U.S.P."

1. Final Printed Labeling - satisfactory.
   Package Insert - satisfactory.
   Container Label - satisfactory.
   Carton Label - satisfactory.

Recommendation - the application can be approved.

/S/

John M. Singer

JMS 10/1/85

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Memorandum

Date September 28, 1984

From Chief
Antimicrobial Drugs Branch (HFN-178)

Subject Form 62-488; Polymyxin B-Neomycin-Hydrocortisone Sterile Otic Suspension; Carter-Glogau Labs., Inc.

To John M. Singer (HFN-235)

This application lists the components of the drug and indicates specifications and test procedures for them. The sources of the active components are indicated. The master formula card indicates that the product is to be

Three exhibit batches, one sample each of bulk polymyxin and neomycin and certificates of analysis were received in ADB with this application. The assay data on these samples were obtained by The data sheets indicate that none of the exhibit batches (was of the production batch size as shown on the master formula card. ADB assayed the antibiotic components by the official microbiological procedures; we did not perform the ssay for the hydrocortisone content however the attached Chemistry Review Notes do comment on it. The applicant's data are all higher than ADB's but both sets of polymyxin results are lower than what might have been anticipated from its xcess in the formulation.

A suitable stability testing protocol is included in the application that calls for ambient and 40°C studies on production batches of the product. Data are reported on only one batch, 83K001 (M7773) which is hardly a production batch being only ters in size. After three months storage at room temperature, the neomycin content had dropped from an initial level of This latter value compares well with our value of obtained approximately 7 months post manufacture. Storage for three months at 40°C resulted in a drop to or the neomycin and a drop from to for the polymyxin. These data suggest that if the theoretical formulation this batch is being met, the production losses are considerable

and that 24 month expiry dating for this product is dubious. The small size of this batch may have contributed to the poor performance of this product. Additional studies are said to be in progress on other batches of this product.

At this point we judge this application to be incomplete due to its lack of adequate stability data nor does it meet the requirement to submit exhibit samples from production (size) batches of the product.

Additional stability data on production batches should be requested and reviewed before further consideration of this application is made.

/S/

Joseph H. Graham, Ph.D.

Attachments

c

JHG:stk
2422A

TRANSMITTAL OF PERIODIC REPORTS FOR DRUGS FOR HUMAN USE
(21 CFR 310.300, 310.302, and 431.60)

DATE SUBMITTED: 2-6-86

Form Approved
OMB No. 0910-0017
Expiration Date: after June 30, 1984

NOTE: This report is required by law *(21 USC 355; 21 CFR 310.300)*. Failure to report can result in withdrawal of approval of the New Drug Application.

1. NDA OR ANDA NUMBER: N 6 2 4 8 8

2. REPORT NO. *(FDA Complete)*: R-

APPLICANT NOTE
Reference NDA and R numbers *(entered on Acknowledgment Copy)* in any subsequent correspondence regarding report.

3. CFR SECTION NUMBER *(Antibiotic only)*

INSTRUCTIONS

Submit a separate form *(parts 1 through 4-carbons intact)* for each NDA or Antibiotic Application for which the periodic report contains required reporting information. Attach two copies of report to the form.

Where the same item of information applies to more than one NDA or Antibiotic Application for preparations containing a common active ingredient, that information may be submitted as part of the report for only one such application provided all application numbers to which that part of the report applies are listed in Item 7 and provided a separate form, with duplicate copies of all other required information, is submitted for each number.

Forward form and attachments to Department of Health and Human Services, Food and Drug Administration *(HFN-106)*, 5600 Fishers Lane, Rockville, Maryland 20857.

4. APPLICANT: CARTER-GLOGAU LABORATORIES, INC.

5. DRUG NAME: NEOMYCIN AND POLYMYXIN B SULFATES AND HYDROCORTISONE OTIC SUSPENSION, USP

6. TYPE OF REPORT *(Check one (10))*
☒ QUARTERLY ☐ SEMIANNUAL ☐ ANNUAL ☐ OTHER

7. OTHER NDA/ANTIBIOTIC APPLICATION NUMBERS *(List all numbers if any part of report applies to more than one number.)*

8. PERIOD COVERED BY REPORT

FROM (11-14)		TO (15-18)	
YEAR	MONTH	YEAR	MONTH
85	11	86	2

9. REPORT INFORMATION REQUIRED *(See §§ 310.300(a) or 431.60(a) for description)*
(Enter an "X" in Column A if you have nothing to report. Enter identification of type of information attached in Column C.)
(ALWAYS INCLUDE INFORMATION REQUIRED UNDER "f" AND "g".)

NONE A	TYPE OF INFORMATION B	IDENTIFICATION *(Volume No.(s)/Tab(s)/Page(s) of Report)* C
(19) X	a. CLINICAL DATA	
(20) X	b. ADVERSE REACTION(S)	
(21) X	c. ANIMAL DATA	
(22)	d. CHEMICAL OR PHYSICAL DRUG PROPERTIES	ATTACHED
(23) X	e. MANUFACTURING OR CONTROL CHANGES (§§ 314.8 (a) (5))	
	f. CURRENT PACKAGE LABELING *(Whether or not previously submitted)*	ATTACHED
	g. QUANTITY DISTRIBUTED	1300 X 10 mL No foreign sales

TYPED NAME AND TITLE OF RESPONSIBLE OFFICIAL OR AGENT

Gerald F. Brunzie, Ph.D.
Vice President
Regulatory Affairs

SIGNATURE: Gerald F. Brunzie

APPLICANTS RETURN ADDRESS *(Type within the window envelope tic marks)*

CARTER-GLOGAU LABORATORIES, INC.
5160 W. Bethany Home Road
Glendale, AZ 85301

FDA USE ONLY

10. DATE OF RECEIPT: 24 25 26 27 28 29

11. REPORT FILED IN NDA NO.: 30 N 31 32 33 34 35

12. DIV. CODE (78)

13. TYPE CARD (80): B

14. FDA ACKNOWLEDGMENT

RECEIVED MAR 7 1986

FORM FDA 2252 (8/83) PREVIOUS EDITION MAY BE USED.

- (Fold line)

- (Fold Line)

DEPARTMENT OF HEALTH & HUMAN SERVICES

Memorandum

TO :Manufacturing Review Branch (HFN-322) DATE: November 3, 1983
Division of Drug Quality Compliance

FROM :Division of Generic Drugs (HFN-535)
Requester's Name John M. Singer PHONE: 443-4340

SUBJECT: ESTABLISHMENT EVALUATION REQUEST

NDA, ANDA, AND SUPPLEMENT NUMBER: 62-488

DRUG TRADE MARK (if any) Sterile Otic Suspension

DRUG NONPROPRIETARY NAME: Polymyxin B, Neomycin, Hydrocortisone

DOSAGE FORM AND STRENGTH(S): Suspension

DRUG CLASSIFICATION: PROFILE CLASS CODE:
(Priority) _____ A or B _____ 1C _____ Other _____ LIO

APPLICANT'S NAME: Carter-Glogau Laboratories, Inc.
ADDRESS: Glendale, Arizona 85301

FACILITIES TO BE EVALUATED: (Name, Full Address, DMF# (if any), and Responsibility)

Comments: ( ) See Attached.
( ) Actual on-site inspection requested.

Reason: These firms provide laboratory services to Carter-Glogau

****

FOR HFN-322 USE ONLY:

Request Rec'd: _____ Inspection Requested: _____
(if applicable)

Firm(s) are in Compliance With GMPs: _____
Basis for Decision: _____
Reviewing CSO: _____ Concurrance: _____

DEPARTMENT OF HEALTH & HUMAN SERVICES

127

Memorandum

TO :Manufacturing Review Branch (HFN-322)
Division of Drug Quality Compliance

DATE: November 3, 1983

FROM :Division of Generic Drugs (HFN-535)
Requester's Name John M. Singer

PHONE: 443-4340

SUBJECT: ESTABLISHMENT EVALUATION REQUEST

NDA, ANDA, AND SUPPLEMENT NUMBER: 62-488

DRUG TRADE MARK (if any) Sterile Otic Suspension

DRUG NONPROPRIETARY NAME: Polymyxin B, Neomycin, Hydrocortisone

DOSAGE FORM AND STRENGTH(S): Suspension

DRUG CLASSIFICATION:
(Priority) _____ A or B _____ 1C _____ Other _____ PROFILE CLASS CODE: LIQ

APPLICANT'S NAME: Carter-Glogau Laboratories, Inc.
ADDRESS: Glendale, Arizona 85301

5/83 OK

FACILITIES TO BE EVALUATED: (Name, Full Address, DMF# (if any), and Responsibility)

2/82 ok

OK 3/20/83

Update for (liq)

Comments: ( ) See Attached.
( ) Actual on-site inspection requested.

Reason: These firms provide laboratory services to Carter-Glogau

****

FOR HFN-322 USE ONLY:

Request Rec'd: 11/1

Inspection Requested: Update Reg or Basis (if applicable) (LIQ)

Firm(s) are in Compliance With GMPs: Approved 11/21/83
Basis for Decision: Above ES
Reviewing CSO: Linda Hartley Concurrance: Linda 11/22/83

Gold 4/1/85

April 1, 1985

Chemist, HFN-235

Form 6 #62-488

Director, Anti-Microbial Drug Branch, HFN-173

Carter-Glogau Laboratories has submitted a Form 6 application for Sterile Otic Suspension. Please perform the required compendial tests.

The following are being forwarded with this memo:

1. Triplicate copy of the application.

2. Samples with Certificates of Analysis for three production batches. Previous samples were submitted from experimental batches.

3. HFN-178 evaluation dated September 28, 1984, of samples from experimental batches.

If there are any questions, I may be reached at 443-4340.

John M. Singer

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Memorandum

Date April 12, 1984

From Chemist, HFN-535

Subject Form 6 #62-488 - Sterile Otic Suspension (Polymyxin B, Neomycin, Hydrocortisone)

To Director, Anti-Microbial Drug Branch, HFN-416

Carter-Glogau Laboratories, Inc. has submitted a Form 6 application for Sterile Otic Suspension. Please perform the required compendial tests.

The following are being forwarded with this memo:

1. Triplicate copy of the application.
2. Samples with Certificates of Analysis for three batches.

If there are any questions, I may be reached at 443-4340.

John M. Singer

DEPARTMENT OF HEALTH & HUMAN SERVICES

Memorandum

TO :Manufacturing Review Branch (HFN-322) DATE: August 6, 1984
Division of Drug Quality Compliance

FROM :Division of Generic Drugs (HFN-235)
Requester's Name John M. Singer *John M. Singer* PHONE: 443-4340

SUBJECT: ESTABLISHMENT EVALUATION REQUEST

NDA, ANDA, AND SUPPLEMENT NUMBER: 62-488 and 62-520

DRUG TRADE MARK (if any) Sterile Otic Suspension/Kanamycin Sulfate

DRUG NONPROPRIETARY NAME: Polymyxin B Neomycin Hydrocortisone

DOSAGE FORM AND STRENGTH(S): Otic Suspension/Injection 1 gm/3 ml

DRUG CLASSIFICATION: (Priority) ____ A or B ____ 1C ____ Other ____ PROFILE CLASS CODE: LIQ and SVP

APPLICANT'S NAME: Carter-Glogau Laboratories Inc.
ADDRESS: 5160 West Bethany Home Road, Glendale, Arizona 85301

FACILITIES TO BE EVALUATED (Name, Full Address, DMF# (if any), and Responsibility)

Carter-Glogau Laboratories, Inc
5160 West Bethany Home Road
Glendale, Arizona 85301

This firm appears on July 9, 1984 Alert List, and is the subject of May 18, 1984 memorandum from Thomas S. Bozzo.

Comments: ( ) See Attached.
( ) Actual on-site inspection requested.

Reason:

***

FOR HFN-322 USE ONLY:

Request Rec'd: ____ Inspection Requested: (if applicable)

Firm(s) are in Compliance With GMPs: *unacceptable*
Basis for Decision: [illegible]
Reviewing CSO: [illegible] Concurrence: [illegible]

cc: HFN-235
HFN-235/OD
HFN-322

FORM FDA 3274 (1/83)

CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 62-488

CORRESPONDENCE

gms 12/3/85 A-009 JS

CARTER-GLOGAU LABORATORIES, INC.
5160 WEST BETHANY HOME ROAD•GLENDALE, ARIZONA 85301•TELEPHONE (602) 939-7565•TELEX 66-8304

November 22, 1985

John M. Singer
Antibiotic Drug Review Branch (HFD-235)
Division of Generic Drugs
Center for Drugs and Biologics
Food and Drug Administration
5600 Fishers Lane
Rockville, Md 20857

SUBJECT: NEOMYCIN AND POLYMYXIN B SULFATES AND HYDROCORTISONE OTIC SUSPENSION
NDA 62-488

Dear Mr. Singer:

Reference is made to our Antibiotic Form 6 New Drug Application for Neomycin and Polymyxin B Sulfate and Hydrocortisone Otic Suspension, U.S.P.

Reference is also made to our communication of November 4, 1985.

As promised, twelve samples of final printed labels and inserts are enclosed.

Sincerely,

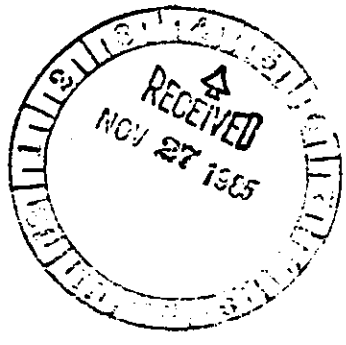
CARTER-GLOGAU LABORATORIES, INC.

Gerald F. Brunzie

Gerald F. Brunzie, Ph.D.
Vice President
Regulatory Affairs

cq

enc



gms 11/5/85 A-000
A-008

CARTER-GLOGAU LABORATORIES, INC.
5160 WEST BETHANY HOME ROAD•GLENDALE, ARIZONA 85301•TELEPHONE (602) 939-7565•TELEX 66-8304

JS

November 4, 1985

John M. Singer
Antibiotic Drug Review Branch (HFD-235)
Division of Generic Drugs
Office of Drug Standards
Center for Drugs and Biologics
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

SUBJECT: NEOMYCIN AND POLYMYXIN B SULFATES AND HYDROCORTISONE OTIC SUSPENSION, USP, Ref. 62-488

Dear Mr. Singer:

Reference is made to our Form 6 Antibiotic New Drug Application for Neomycin and Polymyxin B Sulfates and Hydrocortisone Otic Suspension filed October 20, 1983.

We also refer to our telephone conversations of October 31, 1985, and November 1, 1985, whereby we mutually agreed that the name "Neomycin and Polymyxin B Sulfates and Hydrocortisone Otic Suspension, USP" was a suitable name for the product, and further, that approval of this application would be granted upon our submitting print-ready copies of the labels and package insert bearing the revised name of the product.

Enclosed please find print-ready copies of the vial label, carton label, and package insert. These are identical in size, format, and content to final printed copies, since they are reproduced from the originals which will be used for printing.

Final printing of all labeling will be performed upon your approval of the application and final printed copies will be forwarded to your office as soon as they are available.

We trust that we have now fulfilled all the criteria necessary for approval of this application, as discussed during our telephone conversations, and would greatly appreciate receiving this approval promptly.

Sincerely,

CARTER-GLOGAU LABORATORIES, INC.

Eliane K. Quinn

Eliane K. Quinn, M.S.
Manager, NDA Submissions

Encl.Encl.

gms 9/19/85

A-007

CARTER-GLOGAU LABORATORIES, INC.
5160 WEST BETHANY HOME ROAD•GLENDALE, ARIZONA 85301•TELEPHONE (602) 939-7565•TELEX 66-8304

JS

FOOD AND DRUG ADMINISTRATION USE ONLY	
DATE APPROVED	ACCOUNT NO.
SIGNED	
(For the Commissioner of Food and Drugs *Food and Drug Administration* *Department of Health, Education, and Welfare*	

August 28, 1985

John M. Singer
Antibiotic Drug Review Branch (HFD-235)
Division of Generic Drugs
Office of Drug Standards
Center for Drugs and Biologics
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

SUBJECT; STERILE OTIC SUSPENSION, NEOMYCIN, POLYMYXIN-B, HYDROCORTISONE
NDA: 62-488

Dear Mr. Singer:

Reference is made to our Antibiotic Form 6 Application for Sterile Otic Suspension (Neomycin, Polymyxin B, Hydrocortisone) filed October 20, 1983.

We also refer to your letter dated November 2, 1984, our correspondence of December 4, 1984, and March 19, 1985, and our phone conversation of November 9, 1984.

As agreed during these communications, we are forwarding you, enclosed, additional stability data (Tables I through X), as follows:

1. Batch 83L074: liter production size batch.
   Accelerated-aging conditions (37C-40C): 0, 1, 2, and 3 months.
   Room Temperature (25C±2C): 0, 3, 6, 9, and 12 months.

2. Batch 83L075: liter production size batch.
   Accelerated-aging conditions (37C-40C): 0, 1, 2, and 3 months.
   Room Temperature (25C±2C): 0, 3,6, 9, and 12 months.

3. Batch 84J061: liter production size batch.
   Accelerated-aging conditions (37C-40C): 0, 1, 2, and 3 months.
   Room Temperature (25C±2C): 0, 1, 2, and 3 months.

4. Batch 84J062: liter production size batch.
   Accelerated-aging conditions (37C-40C): 0, 1, 2, and 3 months.
   Room Temperature (25C±2C): 0, 1, 2, and 3 months.

5. Batch 84L037: liter production size batch.
   Accelerated-aging conditions (37C-40C): 0, 1, 2, and 3 months.
   Room Temperature(25C±2C): 0, 1, 2, and 3 months.

Also enclosed are USP Preservative Effectiveness Test results for batches 84J061, 84J062, and 84L037 showing that the batches meet the USP specifications for this test.

Based on the submission of these additional stability data, derived from five (5) production size batches (liters, and liters), and demonstrating the excellent stability of the product, even when challenged under accelerated-aging storage conditions, we strongly believe that we have more than fulfilled the requirements which you specified to us with regard to this product, and request your prompt approval of this application with an initial 24-month expiration date.

Sincerely,

CARTER-GLOGAU LABORATORIES, INC.

Eliane K. Quinn, M.S.
Manager, NDA Submissions

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enc

CARTER-GLOGAU LABORATORIES, INC.
5160 WEST BETHANY HOME ROAD•GLENDALE, ARIZONA 85301•TELEPHONE (602) 939-7565•TELEX 66-8304

March 19, 1985

John M. Singer
Antibiotic Drug Review Branch (HFD-235)
Division of Generic Drugs
Office of Drug Standards
Center for Drugs and Biologics
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

SUBJECT: STERILE OTIC SUSPENSION, NEOMYCIN, POLYMYXIN-B, HYDROCORTISONE
NDA 62-488

Dear Mr. Singer:

Reference is made to our New Antibiotic Form 6 Application for Sterile Otic Suspension, Neomycin, Polymyxin B, Hydrocortisone submitted October 20, 1983.

We also refer to our letter dated December 4, 1984.

Enclosed please find final container samples, 30 each, from 3 new filter batches of the product, 84J061, 84J062, and 84L037.

As previously agreed we have put samples from all 3 batches on our stability program. Results will be reported as soon as available.

We look forward to your prompt review of these new exhibit samples.

Sincerely,

CARTER-GLOGAU LABORATORIES, INC.

Eliane K. Quinn, M.S.
Regulatory Affairs Officer

ht

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019022

RECEIVED
MAR 27 1985

CARTER-GLOGAU LABORATORIES, INC.
5160 WEST BETHANY HOME ROAD•GLENDALE, ARIZONA 85301•TELEPHONE (602) 939-7565•TELEX 66-8304

December 4, 1984

John M. Singer
Antibiotic Drug Review Branch (HFD-235)
Division of Generic Drugs
Office of Drug Standards
Center for Drugs and Biologics
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

SUBJECT: STERILE OTIC SUSPENSION, NEOMYCIN, POLYMYXIN-B, HYDROCORTISONE
NDA 62-488

Dear Mr. Singer:

With regard to our Antibiotic Form-6 Application for Sterile Otic Suspension, Neomycin, Polymyxin-B, Hydrocortisone, reference is made to our telephone conversation of November 9, 1984.

This is to confirm batch size and stability schedule criteria for Antiobiotic Form-6 Applications on which we mutually agreed during our conversation, as they relate to this particular application.

1. Batch size determination:

   Exhibit and stability samples will be derived from three (3) initial production batches of a size or more that of projected full production scale.

2. Stability schedule for determination of a 24 month expiration date:

   Samples from three (3) initial production batches will be stored under accelerated aging (37°C) and room temperature (25°C) conditions, and tested at 1, 2, and 3 months. Data will be reported. On the basis of these data falling within acceptable specification limits, as defined in the application, an initial 24-month expiration date will be granted, as we understand is the policy of the Antibiotic Drug Review Branch.

3. We understand that there are no other deficiencies in this application, and that approval will be granted promptly following submission of exhibit samples, and stability data from three (3) new batches of the product, conforming to the parameters stated in (1), and (2) above.

Exhibit samples will be submitted approximately 3 months prior to stability data. We also understand that this will allow sufficient time for review of samples so that approval is not delayed following submission of stability data.

We trust that the above stated criteria are representative of the requirements of the Antibiotic Drug Review Branch as you defined them by telephone.

New exhibit samples will be forwarded to you shortly.

Sincerely,

CARTER-GLOGAU LABORATORIES, INC.

Eliane K. Quinn, M.S.
Regulatory Affairs Officer

ht

Our reference: 62-488

Carter-Glogau Laboratories, Inc.
Attention: Eliane K. Quinn, M.S.
5160 West Bethany Home Road
Glendale, Arizona 85301

November 2, 1984

Gentlemen:

Please refer to your Antibiotic Form 6 application for Sterile Otic Suspension (polymyxin B-neomycin-hydrocortisone), and to your submission dated October 15, 1984, which responds to our letter dated October 4, 1984.

We have completed our review of the submission and find that the application remains not approvable at this time. Our review and our laboratory's review found the exhibit samples to be unsatisfactory. Specifically, the unusually small size of the "production" batches from which the exhibit samples were obtained.

Please submit new exhibit samples from three lots of product produced under manufacturing conditions as listed under 21 CFR 444.442g. In addition, room temperature and accelerated stability studies should be repeated using drug product from the new lots. Assays should be performed at 0, 1, 2, and 3 months.

Sincerely yours,

John M. Singer
Antibiotic Drug Review Branch (HFN-235)
Division of Generic Drugs

95

CARTER-GLOGAU LABORATORIES, INC.
5160 WEST BETHANY HOME ROAD•GLENDALE, ARIZONA 85301•TELEPHONE (602) 939-7565•TELEX 66-8304

October 15, 1984

FOOD AND DRUG ADMINISTRATION USE ONLY	
DATE APPROVED	ACCOUNT NO.
SIGNED	
(For the Commissioner of Food and Drugs *Food and Drug Administration* *Department of Health, Education, and Welfare*	

John M. Singer
Antibiotic Drug Review Branch (HFN-235)
Division of Generic Drugs
Office of Drug Standards
Center for Drugs and Biologics
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

SUBJECT: STERILE OTIC SUSPENSION (Polymyxin B, Neomycin, Hydrocortisone)
REF. 62-488

Dear Mr. Singer:

Reference is made to our Form 6 Application submitted October 20, 1983 for Sterile Otic Suspension (Polymyxin B, Neomycin, Hydrocortisone).

We also refer to your letters dated November 3, 1983, January 5, 1984, and October 4, 1984, and to our communications of December 9, 1983, April 2, 1984, and July 20, 1984.

1. The exhibit samples submitted were produced under manufacturing conditions. The initial batches made, although of smaller sizes, are produced under conditions which duplicate those which will be used when larger batches are manufactured after the application is approved.

   We are enclosing for your review a copy of the actual batch card used in the manufacture of batch 83L074. Please note that the procedure is the same as that on pages 19-23 of the Application submitted October 20, 1983.

2. The stability data submitted were generated in response to requirements stated in your letters of November 3, 1983, and January 5, 1984.

   In both of these communications you requested accelerated and room temperature data on 3 batches at 3-months, and we modified our standard stability protocol as a result of these requests.

   We have reported stability data on 3 batches which clearly demonstrate the stability of the product, and we have also satisfied all the other requirements which you specified.

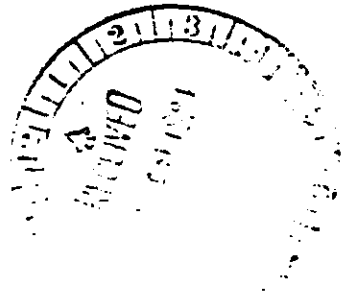
   We would therefore greatly appreciate your prompt approval of this application.

Sincerely,

CARTER-GLOGAU LABORATORIES, INC.

Eliane K. Quinn, M.S.
Regulatory Affairs Officer

Enc.



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q. s.

CARTER-GLOGAU LABORATORIES, INC.
5160 WEST BETHANY HOME ROAD•GLENDALE, ARIZONA 85301•TELEPHONE (602) 939-7585•TELEX 66-8304

FOOD AND DRUG ADMINISTRATION USE ONLY	
DATE APPROVED	ACCOUNT NO.
SIGNED	
(For the Commissioner of Food and Drugs *Food and Drug Administration* *Department of Health, Education, and Welfare*	

July 20, 1984

John M. Singer
Antibiotic Drug Review Branch (HFN-535)
Division of Generic Drugs
Office of Drug Standards
Center for Drugs and Biologics
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

SUBJECT: STERILE OTIC SUSPENSION (Polymyxin B, Neomycin, Hydrocortisone)
REF. 62-488

Dear Mr.Singer:

Reference is made to our Form 6 Application for Sterile Otic suspension, Polymyxin B, Neomycin, Hydrocortisone submitted on October 20, 1983.

Reference is also made to your letter dated January 5, 1984, and to our response dated April 2, 1984.

Enclosed please find stability data for 2 additional batches of the product, 83L074 and 83L075, which show that the product remains stable after 3-month storage at accelerated (40°C) and room temperature conditions.

Based on the recommendation of the Antibiotic Drug Review Branch, sufficient stability data have been submitted to obtain a conditional 2 year expiration date for this product. We therefore request your prompt approval of this application with initial 2-year expiration dating.

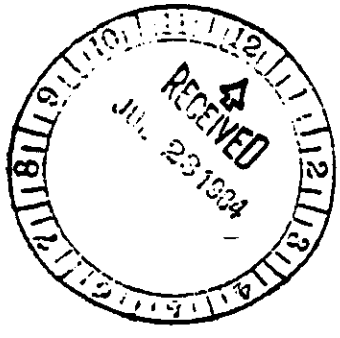
Sincerely,

CARTER-GLOGAU LABORATORIES, INC.

Eliane K. Quinn, M.S.
Regulatory Affairs Officer

ht

enc



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gyms 4117187

CARTER-GLOGAU LABORATORIES, INC.
5160 WEST BETHANY HOME ROAD•GLENDALE, ARIZONA 85301•TELEPHONE (602) 939-7565•TELEX 66-8304

April 2, 1984

FOOD AND DRUG ADMINISTRATION USE ONLY	
DATE APPROVED	ACCOUNT NO.
SIGNED	
(For the Commissioner of Food and Drugs *Food and Drug Administration* *Department of Health, Education, and Welfare*	

John M. Singer
Antibiotic Drug Review Branch (HFN-535)
Division of Generic Drugs
Office of Drug Standards
National Center for Drugs
and Biologics
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

SUBJECT: STERILE OTIC SUSPENSION (Polymyxin B, Neomycin, Hydrocortisone)
REF. 62-488

Dear Mr. Singer:

Reference is made to our Form 6 Application for Sterile Otic Suspension, Polymyxin B, Neomycin, Hydrocortisone submitted on October 20, 1983.

Reference is also made to your letter dated January 5, 1984, and to the telephone conversation our Regulatory Affairs Officer, Ms. E. Quinn had with you on February 22, 1984.

As agreed over the telephone, we are forwarding you, enclosed, the following:

1. 26 samples from each of the first three batches of the product, 83K001, 83L074, and 83L075.

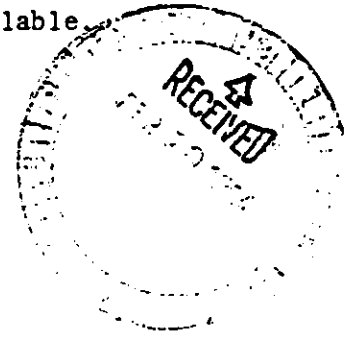
2. 3 grams of Neomycin Sulfate, R 22099.

3. 3 grams of Polymyxin B Sulfate, R 21472.

4. Certificates of Analysis for all samples submitted.

Also enclosed are results of testing batch 83K001 stored under accelerated (40°C), and room temperature conditions for 3 months.

Samples from batches 83L074 and 83L075 are being stored under accelerated (40°C) and room temperature conditions, and will also be assayed after 3 months at 40°C, and after 3, 6, 9, 12, 18, 24, 36, and 48 months at room temperature. Results will be reported when they become available.



On the basis of the stability data submitted and our commitment to report accelerated and room temperature data on two additional batches of the product, we request your prompt approval of this application with initial 24-month expiration dating.

Sincerely,

CARTER-GLOGAU LABORATORIES, INC.

Samuel M. Fainberg, Ph.D.
Director
Technical and Regulatory Affairs

ht

enc

Our reference: 62-488

Carter-Glogau Laboratories, Inc.
Attn: Samuel M. Fainberg, Ph.D.
5150 West Bethany Home Road
Glendale, Arizona 85301

January 5, 1984

Gentlemen:

Please refer to your Antibiotic Form 6 application for Sterile Otic Suspension (Polymyxin B, Neomycin, Hydrocortisone), and to your amendment dated December 9, 1983.

We have completed our review of the amendment and have the following comments at this time:

1. Concerning the submission of stability data, the Antibiotic Drug Review Branch recommends the submission of data from three batches of product stored at room temperature and at 37-40°C (75% Relative Humidity) for three months in its market container in order to obtain a conditional 2-year expiration date. Data from less than three batches is insufficient for us to fully evaluate the stability characteristics of the drug product.

2. In regard to your response concerning exhibit samples, you are correct in stating that the batch certification program has ended; but, this has not affected the requirement for exhibit samples as listed under 21 CFR 444.442 g and Form FDA 1675 (Section 5).

Please submit stability data and exhibit samples as requested in our letter dated November 3, 1983.

Sincerely yours,

John M. Singer
Antibiotic Drug Review Branch (HFN-535)
Division of Generic Drugs

CARTER-GLOGAU LABORATORIES, INC.
5160 WEST BETHANY HOME ROAD•GLENDALE, ARIZONA 85301•TELEPHONE (602) 939-7565•TELEX 66-8304

December 9, 1983

John M. Singer
Antibiotic Drug Review Branch (HFN-535)
Division of Generic Drugs
National Center for Drugs
and Biologics
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

SUBJECT: STERILE OTIC SUSPENSION (Polymyxin B, Neomycin, Hydrocortisone)
NDA 62-488

Dear Mr. Singer:

Reference is made to our Form 6 Application submitted pursuant to 21 CFR 444.442g for Sterile Otic Suspension (Polymyxin B, Neomycin, Hydrocortisone).

We also refer to your letter of November 3, 1983 concerning this application.

The following is submitted in response:

1. With reference to our numbering system, when raw materials are received a Receiving Report is filled out. These reports, pre-numbered sequentially, contain all the information pertinent to the particular lot, including description, manufacturer, date of delivery, and purchase order number. Once the receiving report has been prepared, a pressure-sensitive label bearing the same receiving number as the receiving report is applied to the raw material immediate container.

   In subsequent plant operations the lot of raw material is always identified by name and receiving number.

   To illustrate this, we are enclosing:

   a. The receiving report for Polymyxin- B sulfate used in the manufacture of our Sterile Otic Suspension. Please note the receiving number, R 21472, in the upper right-hand corner.

   b. A copy of the Raw Material Specification sheet showing the lot was released by Quality Control.

013625

   c. A copy of the Batch Formula Card for batch 83K001. Please note that Polymyxin B Sulfate is identified with receiving number R 21472.

   d. A copy of the formula weighing sheet for batch 83K001. Please note again that Polymyxin-B Sulfate, as weighed in the compounding of the batch, is identified by its receiving number, R 21472.
   Thus any component of any batch can be traced to its origin.

2. Stability data for this product will be reported as soon as they become available.

   Samples from the first three batches of the product will be stored in their market container under conditions specified in the labeling, i.e., at room temperature, 15°C-26°C, and tested after 3, 6, 9, 12, 18, 24, 36, and 48 months.

   Samples from the first batch of the product have been stored under accelerated-aging conditions (37°C) and will be tested after 30, 60, and 90 days.

   It has been the Generic Division's policy in the past to accept accelerated-aging data from only one batch, and to grant a 24-month expiration dating period on the basis of satisfactory data at the 90-day station. We are unaware of any changes in this policy that requires three batches to be tested in this manner.

3. Sample requirements under 21 CFR 444.442g are for batch certification. According to the final rule published in the Federal Register, Vol. 47, No. 173, Tuesday, September 7, 1982, all classes of antibiotic drugs are now exempt from batch certification, and samples need not be submitted. See copy of this Federal Register notice enclosed.

   Concerning the submission of samples of the finished dosage form as listed in Form 6, 5 (b), we have been requested not to send samples to Rockville, but to wait for instructions on where to submit samples (see enclosed communication from David Rosen). Samples will be forwarded following receipt of your instructions as to where to send them.

4. Our package insert has been revised as follows:

   a. "Action" has been replaced with "Clinical Pharmacology."

   b. "Indications" has been changed to "Indications and Usage."

   c. With regard to the National Drug Code (NDC) number, please note that it is listed (without the packager code portion) in the "How Supplied" section as our Product Number.This facilitates identification of the product and dosage form.

   Since most of our distributors routinely use our insert, the identification of this number as Carter-Glogau's NDC number would conflict with our customer's NDC numbers, e.g., as listed on their labels. Please note that the complete NDC number appears on our immediate-container label.

5.

6.

We look forward to your prompt approval of this application as amended.

Sincerely,

CARTER-GLOGAU LABORATORIES, INC.

Samuel M. ~~Fainberg, Ph.D.~~
Director
Technical and Regulatory Affairs

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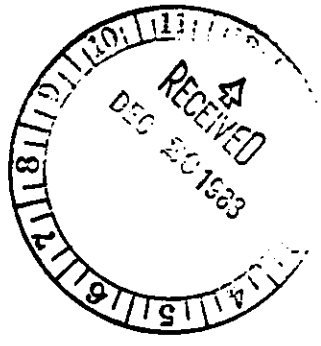

Our reference: 62-488

Carter-Glogau Laboratories, Inc.
Attention: Samuel M. Fainberg, Ph.D.
5160 West Bethany Home Road
Glendale, Arizona 85301

November 3, 1983

Gentlemen:

Please refer to your Antibiotic Form 5 application dated October 20, 1983, for Sterile Otic Suspension (Polymyxin B, Neomycin, Hydrocortisone).

We have completed our review of this application and it is not approvable at this time due to the following deficiencies:

1. The application describes the serial number system used for raw materials, but, it does not show how these numbers are used in subsequent plant operations.

2. The application did not include stability data. At a minimum, we require data from three batches of product stored in their market container under accelerated aging conditions (37°C/75% R.H.) and at room temperature for 90 days.

3. Samples were not submitted with the application. Please submit samples as required by 21 CFR 444.442g.

4. The package insert should be revised as follows:

   A. Change "Action" to "Clinical Pharmacology".

   B. Change "Indications" to "Indications and Usage".

   C. Add the National Drug Code to the "How Supplied" section.

5. The application did not contain the method used to sterilize the container/closure system.

6. The application did not contain the method used to sterilize the Nitrogen.

Please provide a prompt written response.

Sincerely yours,

John M. Singer
Antibiotic Drug Review Branch (HFN-535)
Division of Generic Drugs

HFN-535/JMSinger:w248p R/D JMSinger 11/1/83, HFN-530 (Dr. Seife)

CARTER-GLOGAU LABORATORIES, INC.
5160 WEST BETHANY HOME ROAD•GLENDALE, ARIZONA 85301•TELEPHONE (602) 939-7565•TELEX 66-8304

October 20, 1983

Marvin Seife, M.D.
Director
Generic Drugs Division
Office of Drug Standards
National Center for Drugs
and Biologics
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

SUBJECT: STERILE OTIC SUSPENSION (Polymyxin B, Neomycin, Hydrocortisone) (21 CFR 444.442g)

Dear Dr. Seife:

Enclosed is our Form 6 application for Sterile Otic Suspension, containing neomycin sulfate, polymixin B sulfate and hydrocortisone.

Please note that the potencies of the active ingredients in the drug product are in conformance with those specified in 21 CFR 444.442g, and that a suitable and harmless vehicle is utilized.

As provided for in 21 CFR 443.1 (c) (2), amended as stated in the Federal Register Notice of September 7, 1982, p. 39159, antibiotic Form 6 applications are now regarded as abbreviated new drug applications.

We request exemption from batch certification requirements as provided for in 21 CFR 443.1, as amended.

Sincerely,

CARTER-GLOGAU ~~LABORATORIES~~, INC.

Samuel M. ~~Fairberg~~, Ph.D.
Director
Technical and Regulatory Affairs

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enc.

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OCT 21 1983

RECEIVED
OCT 21 1983

Our reference: 62-488

NOV 04 1985

Carter-Glogau Laboratories, Inc.
Attention: Eliane K. Quinn, M.S.
5160 West Bethany Home Road
Glendale, Arizona 85301

Gentlemen:

Please refer to your Antibiotic Form 6 application for Neomycin and Polymyxin B Sulfates and Hydrocortisone Otic Suspension, U.S.P.

We acknowledge receipt of your submissions dated December 4, 1984, and March 19, August 28, and November 4, 1985.

We have completed our review of the application and it is approved.

An expiration date of twenty-four (24) months should be used on each batch of the drug to be marketed and packaged as described in the application.

Place drug samples from the first three production batches into your stability program and test each batch at three (3) month intervals during the first year of aging, at six (6) month intervals during the second year, annually thereafter. As the data become available they should be furnished to this office at six (6) month intervals throughout the authorized shelf life of the subject drug.

For Initial Campaigns: We request that you submit, in duplicate, any proposed advertising or promotional copy which you intend to use in your immediate advertising or promotional campaigns. Please submit all proposed materials in draft or mock-up form, not final printed. Submit both copies together with a copy of the proposed or final printed labeling to the Division of Drug Advertising and Labeling (HFN-240). Also, please do not use Form FD-2253 for this submission.

For Subsequent Campaigns: We call your attention to regulation 21 CFR 314.81(b)(3) which requires that all material for any subsequent advertising or promotional campaigns at the time of their initial use be submitted to our Division of Drug Advertising and Labeling (HFN-240) with a completed Form FD-2253. A copy of Form FD-2253 is enclosed for your convenience.

Please be reminded that since you are manufacturing the subject drug for the first time, 21 CFR 314.81 requires certain records and reports be submitted following the date of approval.

The Form 6 should be kept up to date by submitting supplements whenever changes are contemplated in the manufacturing and/or laboratory procedures, controls, equipment and instrumentation, key scientific and production personnel, packaging, labeling, source of antibiotics, etc.

Sincerely yours,

/S/ for 11-6-85

Marvin Seife, M.D.
Director
Division of Generic Drugs
Office of Drug Standards
Center for Drugs and Biologics

Enclosure

LOS-DO (HFR-9200)

ltr 11/5/85

JMS 12/3/85 A-507 JS

CARTER-GLOGAU LABORATORIES, INC.
5160 WEST BETHANY HOME ROAD•GLENDALE, ARIZONA 85301•TELEPHONE (602) 939-7565•TELEX 66-8304

November 22, 1985

John M. Singer
Antibiotic Drug Review Branch (HFD-235)
Division of Generic Drugs
Center for Drugs and Biologics
Food and Drug Administration
5600 Fishers Lane
Rockville, Md 20857

SUBJECT: NEOMYCIN AND POLYMYXIN B SULFATES AND HYDROCORTISONE OTIC SUSPENSION
NDA 62-488

Dear Mr. Singer:

Reference is made to our Antibiotic Form 6 New Drug Application for Neomycin and Polymyxin B Sulfate and Hydrocortisone Otic Suspension, U.S.P.

Reference is also made to our communication of November 4, 1985.

As promised, twelve samples of final printed labels and inserts are enclosed.

Sincerely,

CARTER-GLOGAU LABORATORIES, INC.

Gerald F. Brunzie

Gerald F. Brunzie, Ph.D.
Vice President
Regulatory Affairs

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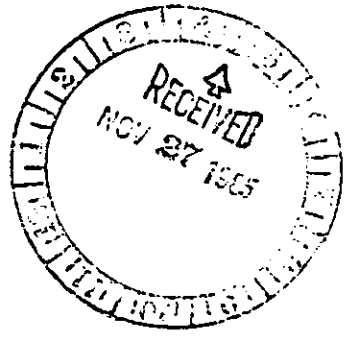

CARTER-GLOGAU LABORATORIES, INC.
5160 WEST BETHANY HOME ROAD•GLENDALE, ARIZONA 85301•TELEPHONE (602) 939-7565•TELEX 66-8304

November 22, 1985

John M. Singer
Antibiotic Drug Review Branch (HFD-235)
Division of Generic Drugs
Center for Drugs and Biologics
Food and Drug Administration
5600 Fishers Lane
Rockville, Md 20857

SUBJECT: NEOMYCIN AND POLYMYXIN B SULFATES AND HYDROCORTISONE OTIC SUSPENSION
NDA 62-488

Dear Mr. Singer:

Reference is made to our Antibiotic Form 6 New Drug Application for Neomycin and Polymyxin B Sulfate and Hydrocortisone Otic Suspension, U.S.P.

Reference is also made to our communication of November 4, 1985.

As promised, twelve samples of final printed labels and inserts are enclosed.

Sincerely,

CARTER-GLOGAU LABORATORIES, INC.

Gerald F. Brunzie

Gerald F. Brunzie, Ph.D.
Vice President
Regulatory Affairs

cq

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ymx 11/5/85

A-008

CARTER-GLOGAU LABORATORIES, INC.
5160 WEST BETHANY HOME ROAD•GLENDALE, ARIZONA 85301•TELEPHONE (602) 939-7565•TELEX 66-8304

JS

November 4, 1985

John M. Singer
Antibiotic Drug Review Branch (HFD-235)
Division of Generic Drugs
Office of Drug Standards
Center for Drugs and Biologics
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

SUBJECT: NEOMYCIN AND POLYMYXIN B SULFATES AND HYDROCORTISONE OTIC SUSPENSION, USP, Ref. 62-488

Dear Mr. Singer:

Reference is made to our Form 6 Antibiotic New Drug Application for Neomycin and Polymyxin B Sulfates and Hydrocortisone Otic Suspension filed October 20, 1983.

We also refer to our telephone conversations of October 31, 1985, and November 1, 1985, whereby we mutually agreed that the name "Neomycin and Polymyxin B Sulfates and Hydrocortisone Otic Suspension, USP" was a suitable name for the product, and further, that approval of this application would be granted upon our submitting print-ready copies of the labels and package insert bearing the revised name of the product.

Enclosed please find print-ready copies of the vial label, carton label, and package insert. These are identical in size, format, and content to final printed copies, since they are reproduced from the originals which will be used for printing.

Final printing of all labeling will be performed upon your approval of the application and final printed copies will be forwarded to your office as soon as they are available.

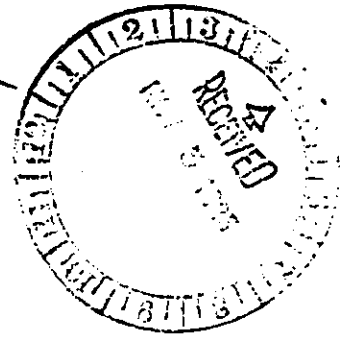
We trust that we have now fulfilled all the criteria necessary for approval of this application, as discussed during our telephone conversations, and would greatly appreciate receiving this approval promptly.

Sincerely,

CARTER-GLOGAU LABORATORIES, INC.

Eliane K. Quinn, M.S.
Manager, NDA-Submissions

Encl.Encl.



N-001

CARTER-GLOGAU LABORATORIES, INC.
5160 WEST BETHANY HOME ROAD•GLENDALE, ARIZONA 85301•TELEPHONE (602) 939-7565•TELEX 66-8304

JS

FOOD AND DRUG ADMINISTRATION USE ONLY	
DATE APPROVED	ACCOUNT NO.
SIGNED	
(For the Commissioner of Food and Drugs *Food and Drug Administration* *Department of Health, Education, and Welfare*	

August 28, 1985

John M. Singer
Antibiotic Drug Review Branch (HFD-235)
Division of Generic Drugs
Office of Drug Standards
Center for Drugs and Biologics
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

SUBJECT; STERILE OTIC SUSPENSION, NEOMYCIN, POLYMYXIN-B, HYDROCORTISONE
NDA: 62-488

Dear Mr. Singer:

Reference is made to our Antibiotic Form 6 Application for Sterile Otic Suspension (Neomycin, Polymyxin B, Hydrocortisone) filed October 20, 1983.

We also refer to your letter dated November 2, 1984, our correspondence of December 4, 1984, and March 19, 1985, and our phone conversation of November 9, 1984.

As agreed during these communications, we are forwarding you, enclosed, additional stability data (Tables I through X), as follows:

1. Batch 83L074: liter production size batch.
   Accelerated-aging conditions (37C-40C): 0, 1, 2, and 3 months.
   Room Temperature (25C±2C): 0, 3, 6, 9, and 12 months.

2. Batch 83L075: liter production size batch.
   Accelerated-aging conditions (37C-40C): 0, 1, 2, and 3 months.
   Room Temperature (25C±2C): 0, 3,6, 9, and 12 months.

3. Batch 84J061: liter production size batch.
   Accelerated-aging conditions (37C-40C): 0, 1, 2, and 3 months.
   Room Temperature (25C±2C): 0, 1, 2, and 3 months.

4. Batch 84J062: liter production size batch.
   Accelerated-aging conditions (37C-40C): 0, 1, 2, and 3 months.
   Room Temperature (25C±2C): 0, 1, 2, and 3 months.

5. Batch 84L037: liter production size batch.
   Accelerated-aging conditions (37C-40C): 0, 1, 2, and 3 months.
   Room Temperature(25C±2C): 0, 1, 2, and 3 months.

Also enclosed are USP Preservative Effectiveness Test results for batches 84J061, 84J062, and 84L037 showing that the batches meet the USP specifications for this test.

Based on the submission of these additional stability data, derived from five (5) production size batches (2 X liters, and 3 X liters), and demonstrating the excellent stability of the product, even when challenged under accelerated-aging storage conditions, we strongly believe that we have more than fulfilled the requirements which you specified to us with regard to this product, and request your prompt approval of this application with an initial 24-month expiration date.

Sincerely,

CARTER-GLOGAU LABORATORIES, INC.

Eliane K. Quinn, M.S.
Manager, NDA Submissions

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CARTER-GLOGAU LABORATORIES, INC.
5160 WEST BETHANY HOME ROAD•GLENDALE, ARIZONA 85301•TELEPHONE (602) 939-7565•TELEX 66-8304

December 4, 1984

John M. Singer
Antibiotic Drug Review Branch (HFD-235)
Division of Generic Drugs
Office of Drug Standards
Center for Drugs and Biologics
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

SUBJECT: STERILE OTIC SUSPENSION, NEOMYCIN, POLYMYXIN-B, HYDROCORTISONE
NDA 62-488

Dear Mr. Singer:

With regard to our Antibiotic Form-6 Application for Sterile Otic Suspension, Neomycin, Polymyxin-B, Hydrocortisone, reference is made to our telephone conversation of November 9, 1984.

This is to confirm batch size and stability schedule criteria for Antiobiotic Form-6 Applications on which we mutually agreed during our conversation, as they relate to this particular application.

1. Batch size determination:

   Exhibit and stability samples will be derived from three (3) initial production batches of a size or more that of projected full production scale.

2. Stability schedule for determination of a 24 month expiration date:

   Samples from three (3) initial production batches will be stored under accelerated aging (37°C) and room temperature (25°C) conditions, and tested at 1, 2, and 3 months. Data will be reported. On the basis of these data falling within acceptable specification limits, as defined in the application, an initial 24-month expiration date will be granted, as we understand is the policy of the Antibiotic Drug Review Branch.

3. We understand that there are no other deficiencies in this application, and that approval will be granted promptly following submission of exhibit samples, and stability data from three (3) new batches of the product, conforming to the parameters stated in (1), and (2) above.

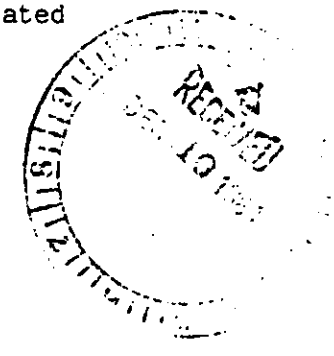

Exhibit samples will be submitted approximately 3 months prior to stability data. We also understand that this will allow sufficient time for review of samples so that approval is not delayed following submission of stability data.

We trust that the above stated criteria are representative of the requirements of the Antibiotic Drug Review Branch as you defined them by telephone.

New exhibit samples will be forwarded to you shortly.

Sincerely,

CARTER-GLOGAU LABORATORIES, INC.

Eliane K. Quinn, M.S.
Regulatory Affairs Officer

ht

Our reference: 62-488

Carter-Glogau Laboratories, Inc.
Attention: Eliane K. Quinn, M.S.
5160 West Bethany Home Road
Glendale, Arizona 85301

November 2, 1984

Gentlemen:

Please refer to your Antibiotic Form 6 application for Sterile Otic Suspension (polymyxin B-neomycin-hydrocortisone), and to your submission dated October 15, 1984, which responds to our letter dated October 4, 1984.

We have completed our review of the submission and find that the application remains not approvable at this time. Our review and our laboratory's review found the exhibit samples to be unsatisfactory. Specifically, the unusually small size of the "production" batches from which the exhibit samples were obtained.

Please submit new exhibit samples from three lots of product produced under manufacturing conditions as listed under 21 CFR 444.442g. In addition, room temperature and accelerated stability studies should be repeated using drug product from the new lots. Assays should be performed at 0, 1, 2, and 3 months.

Sincerely yours,

John M. Singer
Antibiotic Drug Review Branch (HFN-235)
Division of Generic Drugs

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CARTER-GLOGAU LABORATORIES, INC.
5160 WEST BETHANY HOME ROAD•GLENDALE, ARIZONA 85301•TELEPHONE (602) 939-7565•TELEX 66-8304

October 15, 1984

John M. Singer
Antibiotic Drug Review Branch (HFN-235)
Division of Generic Drugs
Office of Drug Standards
Center for Drugs and Biologics
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

FOOD AND DRUG ADMINISTRATION USE ONLY	
DATE APPROVED	ACCOUNT NO.
SIGNED	
(For the Commissioner of Food and Drugs *Food and Drug Administration* *Department of Health, Education, and Welfare*	

SUBJECT: STERILE OTIC SUSPENSION (Polymyxin B, Neomycin, Hydrocortisone)
REF. 62-488

Dear Mr. Singer:

Reference is made to our Form 6 Application submitted October 20, 1983 for Sterile Otic Suspension (Polymyxin B, Neomycin, Hydrocortisone).

We also refer to your letters dated November 3, 1983, January 5, 1984, and October 4, 1984, and to our communications of December 9, 1983, April 2, 1984, and July 20, 1984.

1. The exhibit samples submitted were produced under manufacturing conditions. The initial batches made, although of smaller sizes, are produced under conditions which duplicate those which will be used when larger batches are manufactured after the application is approved.

   We are enclosing for your review a copy of the actual batch card used in the manufacture of batch 83L074. Please note that the procedure is the same as that on pages 19-23 of the Application submitted October 20, 1983.

2. The stability data submitted were generated in response to requirements stated in your letters of November 3, 1983, and January 5, 1984.

   In both of these communications you requested accelerated and room temperature data on 3 batches at 3-months, and we modified our standard stability protocol as a result of these requests.

   We have reported stability data on 3 batches which clearly demonstrate the stability of the product, and we have also satisfied all the other requirements which you specified.

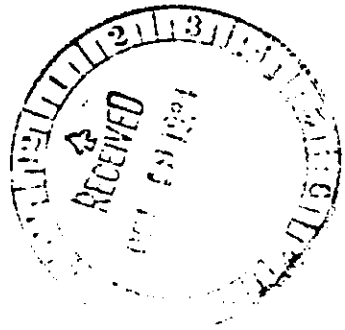
   We would therefore greatly appreciate your prompt approval of this application.

Sincerely,

CARTER-GLOGAU LABORATORIES, INC.

Eliane K. Quinn, M.S.
Regulatory Affairs Officer

Enc.



017515

Our reference: [illegible]

[illegible], Inc
[illegible]
[illegible]

Gentlemen:

Please refer to your Antibiotic Form 6 application for Sterile Otic Suspension (polymyxin B-neomycin-hydrocortisone) and to your submission dated July 20, 1984, which responded to our letter dated January 5, 1984.

We have completed our review of the submission and of the exhibit sample testing results and have the following comments at this time:

1. Your submissions dated April 2 and July 20, 1984, describe batches 83K001, 83L074, and 83L075 in this way: "Manufacturing Procedure: Production Batch". However, the batch records list the batch sizes as only [illegible] and [illegible] liters. Exhibit samples are required to be produced under manufacturing conditions, not laboratory conditions. Please respond.

2. The Stability Protocol requires accelerated testing to be performed at 1, 2 and 3 months. However, the testing results submitted in the application did not include testing at 1 and 2 months.

Sincerely yours,

[illegible]

CARTER-GLOGAU LABORATORIES, INC.
5160 WEST BETHANY HOME ROAD•GLENDALE, ARIZONA 85301•TELEPHONE (602) 939-7565•TELEX 66-8304

February 6, 1986

Marvin Seife, M.D.
Director, Generic Drugs Division
HFN-235 Room 16-B-09
Center for Drugs and Biologics
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

SUBJECT: NEOMYCIN AND POLYMYXIN B SULFATES AND HYDROCORTISONE OTIC SUSPENSION, USP; NDA 62-488

Dear Dr. Seife:

In accordance with the reporting requirements as set forth in 21 CFR 310.300, we are submitting the three month report for our approved NDA 62-488 for our product NEOMYCIN AND POLYMYXIN B SULFATES AND HYDROCORTISONE OTIC SUSPENSION, USP, approved 11-6-85.

Enclosed is labeling for new customers for this period:

Sincerely,

CARTER-GLOGAU LABORATORIES, INC.

Gerald F. Brunzie

Gerald F. Brunzie, Ph.D.
Vice President
Regulatory Affairs

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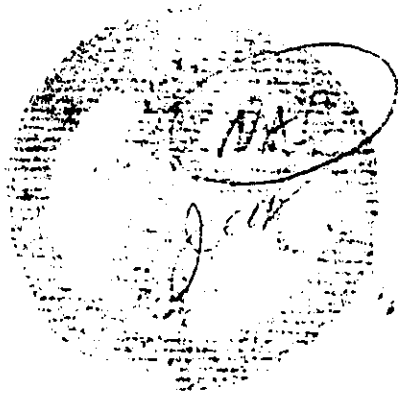

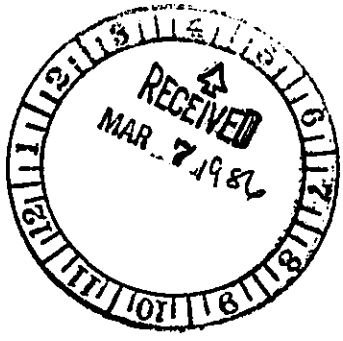

CARTER-GLOGAU LABORATORIES, INC.
5160 WEST BETHANY HOME ROAD•GLENDALE, ARIZONA 85301•TELEPHONE (602) 939-7565•TELEX 66-8304

October 20, 1983

Marvin Seife, M.D.
Director
Generic Drugs Division
Office of Drug Standards
National Center for Drugs
and Biologics
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

SUBJECT: STERILE OTIC SUSPENSION (Polymyxin B, Neomycin, Hydrocortisone) (21 CFR 444.442g)

Dear Dr. Seife:

Enclosed is our Form 6 application for Sterile Otic Suspension, containing neomycin sulfate, polymixin B sulfate and hydrocortisone.

Please note that the potencies of the active ingredients in the drug product are in conformance with those specified in 21 CFR 444.442g, and that a suitable and harmless vehicle is utilized.

As provided for in 21 CFR 443.1 (c) (2), amended as stated in the Federal Register Notice of September 7, 1982, p. 39159, antibiotic Form 6 applications are now regarded as abbreviated new drug applications.

We request exemption from batch certification requirements as provided for in 21 CFR 443.1, as amended.

Sincerely,

CARTER-GLOGAU LABORATORIES, INC.

Samuel M. ~~Fainberg~~, Ph.D.
Director
Technical and Regulatory Affairs

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enc.

01/29/04

RECEIVED
OCT 21 1983

OCT 21 1983

CENTER FOR DRUGS

Our reference: 62-488

Carter-Glogau Laboratories, Inc.
Attention: Samuel M. Fainberg, Ph.D.
5160 West Bethany Home Road
Glendale, Arizona 85301

November 3, 1983

Gentlemen:

Please refer to your Antibiotic Form 5 application dated October 20, 1983, for Sterile Otic Suspension (Polymyxin B, Neomycin, Hydrocortisone).

We have completed our review of this application and it is not approvable at this time due to the following deficiencies:

1. The application describes the serial number system used for raw materials, but, it does not show how these numbers are used in subsequent plant operations.

2. The application did not include stability data. At a minimum, we require data from three batches of product stored in their market container under accelerated aging conditions (37°C/75% R.H.) and at room temperature for 90 days.

3. Samples were not submitted with the application. Please submit samples as required by 21 CFR 444.442g.

4. The package insert should be revised as follows:

   A. Change "Action" to "Clinical Pharmacology".

   B. Change "Indications" to "Indications and Usage".

   C. Add the National Drug Code to the "How Supplied" section.

5. The application did not contain the method used to sterilize the container/closure system.

6. The application did not contain the method used to sterilize the Nitrogen.

Please provide a prompt written response.

Sincerely yours,

John M. Singer
Antibiotic Drug Review Branch (HFN-535)
Division of Generic Drugs

HFN-535/JMSinger:mw 11/1/83 w2487e R/D JMSinger 11/1/83, HFN-530 (Dr. Seife)

CARTER-GLOGAU LABORATORIES, INC.
5160 WEST BETHANY HOME ROAD•GLENDALE, ARIZONA 85301•TELEPHONE (602) 939-7565•TELEX 66-8304

December 9, 1983

John M. Singer
Antibiotic Drug Review Branch (HFN-535)
Division of Generic Drugs
National Center for Drugs
and Biologics
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

SUBJECT: STERILE OTIC SUSPENSION (Polymyxin B, Neomycin, Hydrocortisone)
NDA 62-488

Dear Mr. Singer:

Reference is made to our Form 6 Application submitted pursuant to 21 CFR 444.442g for Sterile Otic Suspension (Polymyxin B, Neomycin, Hydrocortisone).

We also refer to your letter of November 3, 1983 concerning this application.

The following is submitted in response:

1. With reference to our numbering system, when raw materials are received a Receiving Report is filled out. These reports, pre-numbered sequentially, contain all the information pertinent to the particular lot, including description, manufacturer, date of delivery, and purchase order number. Once the receiving report has been prepared, a pressure-sensitive label bearing the same receiving number as the receiving report is applied to the raw material immediate container.

   In subsequent plant operations the lot of raw material is always identified by name and receiving number.

   To illustrate this, we are enclosing:

   a. The receiving report for Polymyxin- B sulfate used in the manufacture of our Sterile Otic Suspension. Please note the receiving number, R 21472, in the upper right-hand corner.

   b. A copy of the Raw Material Specification sheet showing the lot was released by Quality Control.

   c. A copy of the Batch Formula Card for batch 83K001. Please note that Polymyxin B Sulfate is identified with receiving number R 21472.

   d. A copy of the formula weighing sheet for batch 83K001. Please note again that Polymyxin-B Sulfate, as weighed in the compounding of the batch, is identified by its receiving number, R 21472.
   Thus any component of any batch can be traced to its origin.

2. Stability data for this product will be reported as soon as they become available.

   Samples from the first three batches of the product will be stored in their market container under conditions specified in the labeling, i.e., at room temperature, 15°C-26°C, and tested after 3, 6, 9, 12, 18, 24, 36, and 48 months.

   Samples from the first batch of the product have been stored under accelerated-aging conditions (37°C) and will be tested after 30, 60, and 90 days.

   It has been the Generic Division's policy in the past to accept accelerated-aging data from only one batch, and to grant a 24-month expiration dating period on the basis of satisfactory data at the 90-day station. We are unaware of any changes in this policy that requires three batches to be tested in this manner.

3. Sample requirements under 21 CFR 444.442g are for batch certification. According to the final rule published in the Federal Register, Vol. 47, No. 173, Tuesday, September 7, 1982, all classes of antibiotic drugs are now exempt from batch certification, and samples need not be submitted. See copy of this Federal Register notice enclosed.

   Concerning the submission of samples of the finished dosage form as listed in Form 6, 5 (b), we have been requested not to send samples to Rockville, but to wait for instructions on where to submit samples (see enclosed communication from David Rosen). Samples will be forwarded following receipt of your instructions as to where to send them.

4. Our package insert has been revised as follows:

   a. "Action" has been replaced with "Clinical Pharmacology."

   b. "Indications" has been changed to "Indications and Usage."

   c. With regard to the National Drug Code (NDC) number, please note that it is listed (without the packager code portion) in the "How Supplied" section as our Product Number.This facilitates identification of the product and dosage form.

   Since most of our distributors routinely use our insert, the identification of this number as Carter-Glogau's NDC number would conflict with our customer's NDC numbers, e.g., as listed on their labels. Please note that the complete NDC number appears on our immediate-container label.

5. The product container, a 10-ml amber molded glass bottle, is sterilized by _ Copies of C/G Standard Operating Procedure 10.4.8, "Sterilization _ ," and Validation 17.13.5 "Validation of Sterilization," are enclosed.

The container closure is a lined aluminum ap. It is sterilized by for ours at a minimum temperature of Copies of C/G Standard Operating Procedure 10.4.7. "Sterilization and Validation Protocol 17.13.18 "Validation of Sterilization Process For Lined Caps," are enclosed.

6. The is sterilized by filtration through a sterilization filter, at the point of use. Copies of C/G Standard Operating Procedure 10.6.14.3 " Jse and Testing," and of Validation Report V0021 " olding Tank and Associated Piping," are enclosed.

We look forward to your prompt approval of this application as amended.

Sincerely,

CARTER-GLOGAU LABORATORIES, INC.

Samuel M. Fainberg, Ph.D.
Director
Technical and Regulatory Affairs

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CARTER-GLOGAU LABORATORIES, INC.
5160 WEST BETHANY HOME ROAD•GLENDALE, ARIZONA 85301•TELEPHONE (602) 939-7565•TELEX 66-8304

December 9, 1983

John M. Singer
Antibiotic Drug Review Branch (HFN-535)
Division of Generic Drugs
National Center for Drugs
and Biologics
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

SUBJECT: STERILE OTIC SUSPENSION (Polymyxin B, Neomycin, Hydrocortisone)
NDA 62-488

Dear Mr. Singer:

Reference is made to our Form 6 Application submitted pursuant to 21 CFR 444.442g for Sterile Otic Suspension (Polymyxin B, Neomycin, Hydrocortisone).

We also refer to your letter of November 3, 1983 concerning this application.

The following is submitted in response:

1. With reference to our numbering system, when raw materials are received a Receiving Report is filled out. These reports, pre-numbered sequentially, contain all the information pertinent to the particular lot, including description, manufacturer, date of delivery, and purchase order number. Once the receiving report has been prepared, a pressure-sensitive label bearing the same receiving number as the receiving report is applied to the raw material immediate container.

   In subsequent plant operations the lot of raw material is always identified by name and receiving number.

   To illustrate this, we are enclosing:

   a. The receiving report for Polymyxin- B sulfate used in the manufacture of our Sterile Otic Suspension. Please note the receiving number, R 21472, in the upper right-hand corner.

   b. A copy of the Raw Material Specification sheet showing the lot was released by Quality Control.

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   c. A copy of the Batch Formula Card for batch 83K001. Please note that Polymyxin B Sulfate is identified with receiving number R 21472.

   d. A copy of the formula weighing sheet for batch 83K001. Please note again that Polymyxin-B Sulfate, as weighed in the compounding of the batch, is identified by its receiving number, R 21472.
   Thus any component of any batch can be traced to its origin.

2. Stability data for this product will be reported as soon as they become available.

   Samples from the first three batches of the product will be stored in their market container under conditions specified in the labeling, i.e., at room temperature, 15°C-26°C, and tested after 3, 6, 9, 12, 18, 24, 36, and 48 months.

   Samples from the first batch of the product have been stored under accelerated-aging conditions (37°C) and will be tested after 30, 60, and 90 days.

   It has been the Generic Division's policy in the past to accept accelerated-aging data from only one batch, and to grant a 24-month expiration dating period on the basis of satisfactory data at the 90-day station. We are unaware of any changes in this policy that requires three batches to be tested in this manner.

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   a. "Action" has been replaced with "Clinical Pharmacology."

   b. "Indications" has been changed to "Indications and Usage."

   c. With regard to the National Drug Code (NDC) number, please note that it is listed (without the packager code portion) in the "How Supplied" section as our Product Number.This facilitates identification of the product and dosage form.

   Since most of our distributors routinely use our insert, the identification of this number as Carter-Glogau's NDC number would conflict with our customer's NDC numbers, e.g., as listed on their labels. Please note that the complete NDC number appears on our immediate-container label.

5.

6.

We look forward to your prompt approval of this application as amended.

Sincerely,

CARTER-GLOGAU LABORATORIES, INC.

Samuel M. ~~Fainberg, Ph.D.~~
Director
Technical and Regulatory Affairs

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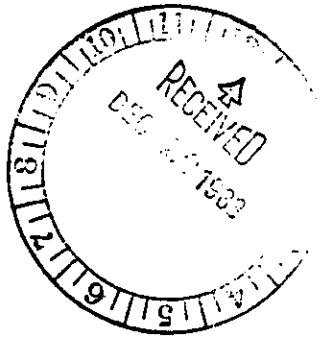


Our reference: 62-488

Carter-Glogau Laboratories, Inc.
Attn: Samuel M. Fainberg, Ph.D.
5160 West Bethany Home Road
Glendale, Arizona 85301

January 5, 1984

Gentlemen:

Please refer to your Antibiotic Form 6 application for Sterile Otic Suspension (Polymyxin B, Neomycin, Hydrocortisone), and to your amendment dated December 9, 1983.

We have completed our review of the amendment and have the following comments at this time:

1. Concerning the submission of stability data, the Antibiotic Drug Review Branch recommends the submission of data from three batches of product stored at room temperature and at 37-40°C (75% Relative Humidity) for three months in its market container in order to obtain a conditional 2-year expiration date. Data from less than three batches is insufficient for us to fully evaluate the stability characteristics of the drug product.

2. In regard to your response concerning exhibit samples, you are correct in stating that the batch certification program has ended; but, this has not affected the requirement for exhibit samples as listed under 21 CFR 444.442 g and Form FDA 1675 (Section 5).

Please submit stability data and exhibit samples as requested in our letter dated November 3, 1983.

Sincerely yours,

John M. Singer
Antibiotic Drug Review Branch (HFN-535)
Division of Generic Drugs

JAMS 4/17/84

CARTER-GLOGAU LABORATORIES, INC.
5160 WEST BETHANY HOME ROAD•GLENDALE, ARIZONA 85301•TELEPHONE (602) 939-7565•TELEX 66-8304

April 2, 1984

FOOD AND DRUG ADMINISTRATION USE ONLY	
DATE APPROVED	ACCOUNT NO.
SIGNED	
(For the Commissioner of Food and Drugs *Food and Drug Administration* *Department of Health, Education, and Welfare*	

John M. Singer
Antibiotic Drug Review Branch (HFN-535)
Division of Generic Drugs
Office of Drug Standards
National Center for Drugs
and Biologics
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

SUBJECT: STERILE OTIC SUSPENSION (Polymyxin B, Neomycin, Hydrocortisone)
REF. 62-488

Dear Mr. Singer:

Reference is made to our Form 6 Application for Sterile Otic Suspension, Polymyxin B, Neomycin, Hydrocortisone submitted on October 20, 1983.

Reference is also made to your letter dated January 5, 1984, and to the telephone conversation our Regulatory Affairs Officer, Ms. E. Quinn had with you on February 22, 1984.

As agreed over the telephone, we are forwarding you, enclosed, the following:

1. 26 samples from each of the first three batches of the product, 83K001, 83L074, and 83L075.

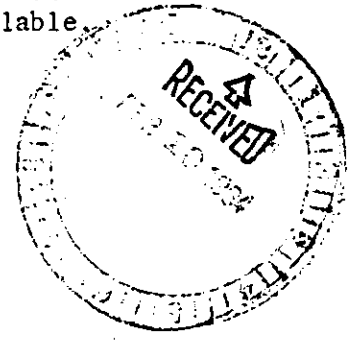
2. 3 grams of Neomycin Sulfate, R 22099.

3. 3 grams of Polymyxin B Sulfate, R 21472.

4. Certificates of Analysis for all samples submitted.

Also enclosed are results of testing batch 83K001 stored under accelerated (40°C), and room temperature conditions for 3 months.

Samples from batches 83L074 and 83L075 are being stored under accelerated (40°C) and room temperature conditions, and will also be assayed after 3 months at 40°C, and after 3, 6, 9, 12, 18, 24, 36, and 48 months at room temperature. Results will be reported when they become available.



On the basis of the stability data submitted and our commitment to report accelerated and room temperature data on two additional batches of the product, we request your prompt approval of this application with initial 24-month expiration dating.

Sincerely,

CARTER-GLOGAU LABORATORIES, INC.

Samuel M. Fainberg, Ph.D.
Director
Technical and Regulatory Affairs

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CARTER-GLOGAU LABORATORIES, INC.
5160 WEST BETHANY HOME ROAD•GLENDALE, ARIZONA 85301•TELEPHONE (602) 939-7565•TELEX 66-8304

FOOD AND DRUG ADMINISTRATION USE ONLY	
DATE APPROVED	ACCOUNT NO.
SIGNED	

(For the Commissioner of Food and Drugs
Food and Drug Administration
Department of Health, Education, and Welfare

July 20, 1984

John M. Singer
Antibiotic Drug Review Branch (HFN-535)
Division of Generic Drugs
Office of Drug Standards
Center for Drugs and Biologics
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

SUBJECT: STERILE OTIC SUSPENSION (Polymyxin B, Neomycin, Hydrocortisone)
REF. 62-488

Dear Mr.Singer:

Reference is made to our Form 6 Application for Sterile Otic suspension, Polymyxin B, Neomycin, Hydrocortisone submitted on October 20, 1983.

Reference is also made to your letter dated January 5, 1984, and to our response dated April 2, 1984.

Enclosed please find stability data for 2 additional batches of the product, 83L074 and 83L075, which show that the product remains stable after 3-month storage at accelerated (40°C) and room temperature conditions.

Based on the recommendation of the Antibiotic Drug Review Branch, sufficient stability data have been submitted to obtain a conditional 2 year expiration date for this product. We therefore request your prompt approval of this application with initial 2-year expiration dating.

Sincerely,

CARTER-GLOGAU LABORATORIES, INC.

Eliane K. Quinn, M.S.
Regulatory Affairs Officer

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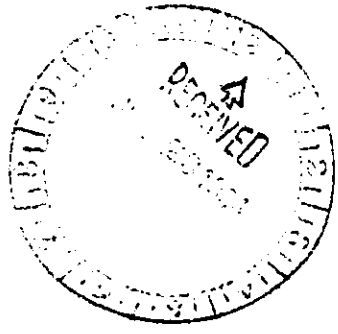

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