CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 50-788

ADMINISTRATIVE DOCUMENTS
CORRESPONDENCE

NDA/EFFICACY SUPPLEMENT ACTION PACKAGE CHECKLIST

NDA 50-788	Efficacy Supplement Type N/A	Supplement Number N/A
Drug: Mupirocin Ointment 2%	Applicant: Clay-Park Labs, Inc.	
RPM: Maureen Dillon-Parker	HFD-520	Phone # 301-827-2125
Application Type: ( ) 505(b)(1) (X) 505(b)(2)	Reference Listed Drug (NDA #, Drug name): NDA50-591, Bactroban Ointment	

❖ Application Classifications:	
• Review priority	(X) Standard ( ) Priority
• Chem class (NDAs only)	3
• Other (e.g., orphan, OTC)	Not Applicable
❖ User Fee Goal Dates	December 7, 2002
❖ Special programs (indicate all that apply)	(X) None Subpart H ( ) 21 CFR 314.510 (accelerated approval) ( ) 21 CFR 314.520 (restricted distribution) ( ) Fast Track ( ) Rolling Review
❖ User Fee Information	
• User Fee	( ) Paid
• User Fee waiver	( ) Small business ( ) Public health ( ) Barrier-to-Innovation ( ) Other
• User Fee exception	( ) Orphan designation (X) No-fee 505(b)(2) ( ) Other
❖ Application Integrity Policy (AIP)	
• Applicant is on the AIP	( ) Yes (X) No
• This application is on the AIP	( ) Yes (X) No
• Exception for review (Center Director's memo)	Not applicable
• OC clearance for approval	Not applicable
❖ Debarment certification: verified that qualifying language (e.g., willingly, knowingly) was not used in certification and certifications from foreign applicants are co-signed by U.S. agent.	(X) Verified
❖ Patent **Old 507 – Patent certification not necessary**	
• Information: Verify that patent information was submitted	( ) Verified [Not applicable]
• Patent certification [505(b)(2) applications]: Verify type of certifications submitted	21 CFR 314.50(i)(1)(*i*)(A) ( ) I ( ) II ( ) III ( ) IV 21 CFR 314.50(i)(1) ( ) (ii) ( ) (iii)
• For paragraph IV certification, verify that the applicant notified the patent holder(s) of their certification that the patent(s) is invalid, unenforceable, or will not be infringed (certification of notification and documentation of receipt of notice).	( ) Verified [Not applicable]
❖ Exclusivity Summary (approvals only)	Enclosed

❖ Administrative Reviews (Project Manager, ADRA) *(indicate date of each review)*	None
[redacted]	[redacted]
❖ Actions	[redacted]
• Proposed action	(X) AP ( ) TA ( ) AE ( ) NA
• Previous actions (specify type and date for each action taken)	This is the first action
• Status of advertising (approvals only)	(X) Materials requested in AP letter ( ) Reviewed for Subpart H
❖ Public communications	[redacted]
• Press Office notified of action (approval only)	(X) Yes ( ) Not applicable
• Indicate what types (if any) of information dissemination are anticipated	(X) None ( ) Press Release ( ) Talk Paper ( ) Dear Health Care Professional Letter
❖ Labeling (package insert, patient package insert (if applicable), MedGuide (if applicable)	[redacted]
• Division's proposed labeling (only if generated after latest applicant submission of labeling)	Enclosed
• Most recent applicant-proposed labeling	Enclosed
• Original applicant-proposed labeling	Enclosed
• Labeling reviews (including DDMAC, Office of Drug Safety trade name review, nomenclature reviews) and minutes of labeling meetings *(indicate dates of reviews and meetings)*	No tradename requested by applicant; No safety meeting held – not an NME
• Other relevant labeling (e.g., most recent 3 in class, class labeling)	Enclosed (Bactroban Ointment 2%)
❖ Labels (immediate container & carton labels)	[redacted]
• Division proposed (only if generated after latest applicant submission)	None
• Applicant proposed	Enclosed
• Reviews	See Chemistry Review
❖ Post-marketing commitments	[redacted]
• Agency request for post-marketing commitments	None
• Documentation of discussions and/or agreements relating to post-marketing commitments	None
❖ Outgoing correspondence (i.e., letters, E-mails, faxes)	Enclosed
❖ Memoranda and Telecons	None
❖ Minutes of Meetings	[redacted]
• EOP2 meeting (indicate date)	Not held
• Pre-NDA meeting (indicate date)	September 5, 2001 – Enclosed
• Pre-Approval Safety Conference (indicate date; approvals only)	Not an NME – not held
• Other	Not applicable
❖ Advisory Committee Meeting	[redacted]
• Date of Meeting	No meeting held
• 48-hour alert	Not applicable
❖ Federal Register Notices, DESI documents, NAS, NRC (if any are applicable)	Not applicable

Clinical and Summary Information	
❖ Summary Reviews (e.g., Office Director, Division Director, Medical Team Leader) *(indicate date for each review)*	None
❖ Clinical review(s) *(indicate date for each review)*	10/24/02; 11/7/02 (2)
❖ Microbiology (efficacy) review(s) *(indicate date for each review)*	11/20/02 (2)
❖ Safety Update review(s) *(indicate date or location if incorporated in another review)*	See MO review of 10-24-02
❖ Pediatric Page(separate page for each indication addressing status of all age groups)	Enclosed
❖ Statistical review(s) *(indicate date for each review)*	9-18-02 (1)
❖ Biopharmaceutical review(s) *(indicate date for each review)*	11/21/02 (1)
❖ Controlled Substance Staff review(s) and recommendation for scheduling *(indicate date for each review)*	Not applicable
❖ Clinical Inspection Review Summary (DSI)	
• Clinical studies	No inspections requested
• Bioequivalence studies	No inspections requested
CMC Information	
❖ CMC review(s) *(indicate date for each review)*	11/27/02, 12/04/02 (2)
❖ Environmental Assessment	
• Categorical Exclusion *(indicate review date)*	See Chemistry Review page 46
• Review & FONSI *(indicate date of review)*	See Chemistry Review
• Review & Environmental Impact Statement *(indicate date of each review)*	See Chemistry Review
❖ Micro (validation of sterilization & product sterility) review(s) *(indicate date for each review)*	Not applicable
❖ Facilities inspection (provide EER report)	Date completed: 14-Nov-02 (X) Acceptable ( ) Withhold recommendation
❖ Methods validation	(X) Completed ( ) Requested ( ) Not yet requested
Nonclinical Pharm/Tox Information	
❖ Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)*	4/24/02 (1); IND 60,189 (1/14/02)
❖ Nonclinical inspection review summary	Not applicable
❖ Statistical review(s) of carcinogenicity studies *(indicate date for each review)*	Not applicable
❖ CAC/ECAC report	Not applicable

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

Form Approved: OMB No. 0910-0297
Expiration Date: February 29, 2004.

USER FEE COVER SHEET

See Instructions on Reverse Side Before Completing This Form

A completed form must be signed and accompany each new drug or biologic product application and each new supplement. See exceptions on the reverse side. If payment is sent by U.S. mail or courier, please include a copy of this completed form with payment. Payment instructions and fee rates can be found on CDER's website: http://www.fda.gov/cder/pdufa/default.htm

1. APPLICANT'S NAME AND ADDRESS

Clay-Park Labs, Inc.
1700 Bathgate Avenue
Bronx, NY 10457

2. TELEPHONE NUMBER *(Include Area Code)*

(718) 960-9976

3. PRODUCT NAME

Mupirocin Ointment, 2%

4. BLA SUBMISSION TRACKING NUMBER (STN) / NDA NUMBER

—

5. DOES THIS APPLICATION REQUIRE CLINICAL DATA FOR APPROVAL?

☒ YES ☐ NO

IF YOUR RESPONSE IS "NO" AND THIS IS FOR A SUPPLEMENT, STOP HERE AND SIGN THIS FORM.

IF RESPONSE IS 'YES', CHECK THE APPROPRIATE RESPONSE BELOW:

☒ THE REQUIRED CLINICAL DATA ARE CONTAINED IN THE APPLICATION.

☐ THE REQUIRED CLINICAL DATA ARE SUBMITTED BY REFERENCE TO:

N/A
(APPLICATION NO. CONTAINING THE DATA).

6. USER FEE I.D. NUMBER

N/A

7. IS THIS APPLICATION COVERED BY ANY OF THE FOLLOWING USER FEE EXCLUSIONS? IF SO, CHECK THE APPLICABLE EXCLUSION.

☐ A LARGE VOLUME PARENTERAL DRUG PRODUCT APPROVED UNDER SECTION 505 OF THE FEDERAL FOOD, DRUG, AND COSMETIC ACT BEFORE 9/1/92
(Self Explanatory)

☒ A 505(b)(2) APPLICATION THAT DOES NOT REQUIRE A FEE
(See item 7, reverse side before checking box.)

☐ THE APPLICATION QUALIFIES FOR THE ORPHAN EXCEPTION UNDER SECTION 736(a)(1)(E) of the Federal Food, Drug, and Cosmetic Act
(See item 7, reverse side before checking box.)

☐ THE APPLICATION IS A PEDIATRIC SUPPLEMENT THAT QUALIFIES FOR THE EXCEPTION UNDER SECTION 736(a)(1)(F) of the Federal Food, Drug, and Cosmetic Act
(See item 7, reverse side before checking box.)

☐ THE APPLICATION IS SUBMITTED BY A STATE OR FEDERAL GOVERNMENT ENTITY FOR A DRUG THAT IS NOT DISTRIBUTED COMMERCIALLY
(Self Explanatory)

8. HAS A WAIVER OF AN APPLICATION FEE BEEN GRANTED FOR THIS APPLICATION? ☐ YES ☐ NO
(See item 8, reverse side if answered YES)

SIGNATURE OF AUTHORIZED COMPANY REPRESENTATIVE	TITLE	DATE
	Director of Regulatory Affairs	1/28/02

FORM FDA 3397 (4/01)

INSTRUCTIONS FOR COMPLETING USER FEE COVER SHEET FORM FDA 3397

Form FDA 3397 is to be completed for and submitted with each new drug or biologic product original application or supplemental application submitted to the Agency on or after April 30, 2001, unless specifically exempted below. Form 3397 should be placed in the first volume of the application with the application form.

NOTE: Form FDA 3397 need not be submitted for:

CDER

505(j) applications
Supplements to 505(j) applications

CBER

Any supplement that does not require clinical data for approval
Applications (including supplements) for:

- Products for further manufacturing only
- Whole Blood or Blood Component for Transfusion
- Bovine Blood Product for Topical Application Licensed before September 1, 1992
- A crude Allergenic Extract Product
- An *In-Vitro* diagnostic biological product licensed under section 351 of the PHS Act

ITEM NO.: **INSTRUCTIONS**

1-2. **Self-explanatory**

3. **PRODUCT NAME** - Include generic name and trade name, as applicable.

4. **BLA STN / NDA NUMBER**

FOR BIOLOGIC PRODUCTS - Indicate the 6-digit Biologics License Application STN if known.

FOR DRUG PRODUCTS - Indicate the NDA number, including a leading zero. NDA numbers can be obtained by calling the Center for Drug Evaluation and Research, Central Document Room, at (301) 827-4210.

EXAMPLE: For NDA 99999, the number would be: N099999.

5. **CLINICAL DATA** - The definition of 'clinical data' for the assessment of user fees is found in FDA's Guidance for Indusry: Submitting Separate Marketing Applications and Clinical Data for Purposes of Assessing User Fees. FDA's guidance on the definition of clinical data can be found on CDER's web site: http://www.fda.gov/cder/pdufa/default.htm

6. **USER FEE I.D. NUMBER - PLEASE INCLUDE THIS NUMBER ON THE APPLICATION PAYMENT CHECK.** If the application is exempted from a fee, a User Fee I.D. Number is not required. To obtain the appropriate User Fee I.D. Number, read and complete the following:

FOR DRUG PRODUCTS - A unique identification number will be assigned to each submission. This individual identification number may be obtained by calling the Center for Drug Evaluation and Research, Central Document Room, at (301) 827-4210. Questions regarding the CDER User Fee I.D. Number should be directed to CDER's User Fee Staff at (301) 594-2041.

FOR BIOLOGIC PRODUCTS - The User Fee I.D. Number is the applicant's four digit U.S. License Number, followed by a sequential number for each fee paying submission from the applicant; starting with number 1. If the firm is unlicensed, a number may be obtained by calling CBER's Regulatory Information Management Staff (RIMS) at (301) 827-3503. Questions regarding the CBER User Fee I.D. number should also be directed to RIMS.

EXAMPLE: For U.S. License Number 0222, the fifth submission would be given the User Fee I.D. Number: 0222-5.

7. **EXCLUSIONS:**

Section 505(b)(2) applications, as defined by the Federal Food, Drug, and Cosmetic (FD&C) Act, are excluded from application fees if: they are NOT for a new molecular entity which is an active ingredient (including any salt or ester of an active ingredient); and NOT a new indication for a use.

The application is for an orphan product. Under section 736(a)(1)(E) of the FD&C Act, a human drug application is not subject to an application fee if the proposed product is for a rare disease or condition designated under section 526 of the FD&C Act (orphan drug designation) AND the application does not include an indication that is not so designated. A supplement is not subject to an application fee if it proposes to include a new indication for a rare disease or condition, and the drug has been designated pursuant to section 526 for a rare disease or condition with regard to the indication proposed in the supplement.

The submission is a supplement for a new pediatric indication. Under section 736(a)(1)(F) of the FD&C Act, a supplement to a "human drug application" proposing to include a new indication for use in pediatric populations is not subject to a fee.

8. **WAIVER** - Complete this section only if a waiver of user fees, including the small business waiver, has been granted for this application. A copy of the official FDA notification that the waiver has been granted must be provided with the submission.

CLAY-PARK LABS, INC.

AGIS GROUP

1700 BATHGATE AVE. BRONX, NY 10457 (718)901-2800

DEBARMENT CERTIFICATION

Clay-Park Labs, Inc. hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with the 505(b)(2) NDA application for Mupirocin Ointment, 2%.

01/17/02

Candis Edwards
Director of Regulatory Affairs
Clay-Park Labs, Inc.

SECTION 13: PATENT INFORMATION

13.2 STATEMENT CONCERNING PATENT INFORMATION FOR MUPIROCIN OINTMENT, 2%

APPEARS THIS WAY
ON ORIGINAL

13.2 STATEMENT CONCERNING PATENT INFORMATION FOR MUPIROCIN OINTMENT, 2%

In accordance with the transitional section 125(d)(2) of the Food and Drug Administration Modernization Act of 1997 ("FDAMA"), which provides that the provisions of section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act ("FDC Act") requiring the filing and publication of certain patent information "shall not apply to any application for marketing in which the drug that is the subject of the application contains an antibiotic drug and the antibiotic drug was the subject of any application for marketing received by the Secretary for Health and Human Services under section 507 of" the FDC Act prior to FDAMA's enactment, the undersigned applicant has not included any patent information with the enclosed new drug application for Mupirocin Ointment, 2%.

CPL notes that the active ingredient at issue in this new drug application was the subject of a marketing application received by FDA on or before November 20, 1997 (NDA 50591, approved December 31, 1987). Thus, CPL's NDA is a new application received by FDA after November 21, 1997 for a drug that contains an "old" antibiotic, as defined by FDA. As a result, CPL's NDA need not include patent information as set forth in proposed 21 CFR § 314.109(a)(1) and (b) (65 Fed. Reg. 3623 (2000) and FDA's Guidance for Industry and Reviewers, Repeal of Section 507 of the Federal Food, Drug, and Cosmetic Act (May 1998).

CLAY-PARK LABS, INC.

AGIS GROUP

1700 BATHGATE AVE. BRONX, NY 10457 (718)901-2800

MEMO TO THE FILE: Mupirocin Ointment, 2%

SUBJECT: Reason Why Patent Certification Statement Will Not Be Required for NDA

A Patent Certification Statement is required for a 505(b)(2) NDA pursuant to Section 505(b)(2)(A) of the Federal Food, Drug and Cosmetic Act ("FDCA"). That Section says that a (b)(2) NDA "shall also include – (A) a certification,...with respect to each patent which claims the drug...."

Congress changed that statutory requirement in 1997, pursuant to Section 125(d)(2) of the Food and Drug Administration Act of 1997 ("FDAMA"). Specifically, Section 125(d)(2) states,

> (2) EXCEPTION. – *The following subsections* of section 505 (21 U.S.C 355) *shall not apply* to any application for marketing in which the drug that is the subject of the application contains *an antibiotic drug* and the antibiotic drug was the subject of any application for marketing received by the Secretary of Health and Human services under section 507 of such Act (21 U.S.C. 357) before the date of the enactment of this Act:
>
> (A) ....
>
> (B) Subsections *(b)(2)(A)*, (b)(2)(b), (b)(3), and (c)(3)....

See Exhibit 1 (emphasis added). In other words, a 505(b)(2) NDA for a pre-November 20, 1997 antibiotic is not required to submit a Patent Certification Statement.

Clay-Park Labs, Inc.'s 505(b)(2) NDA seeks approval for an antibiotic that was originally approved by FDA in 1987. In particular, GlaxoSmithKline holds NDA 50591 for a mupirocin ointment, 2% drug product that received FDA approval on December 31, 1987. Because of this pre-November 20, 1997 approval, mupirocin is considered to be an "old" antibiotic. Any subsequent NDAs for a mupirocin drug product, therefore, are not subject to the Patent Certification Statement requirements of the FDCA. In summary, *FDAMA Section 125(d)(2) applies and overrides the FDCA requirement.* [1] (Exhibit 2)

[1] FDA explained the conjunction of these FDCA and FDAMA Sections in more detail in a 1998 Guidance document. In so doing, FDA stated that, in order to implement FDAMA Section 125, "several of the Agency's administrative processes for reviewing and approving antibiotic drug applications must be changed". See FDA's Guidance for Industry and Reviewers, Repeal of Section 507 of the Federal Food, Drug, and Cosmetic Act (May 1998), at subsection II.3.c (page 2) and subsection III.C. (pages 3-5).

"(4) A drug manufactured in a pilot or other small facility may be used to demonstrate the safety and effectiveness of the drug and to obtain approval for the drug prior to manufacture of the drug in a larger facility, unless the Secretary makes a determination that a full scale production facility is necessary to ensure the safety or effectiveness of the drug.".

SEC. 125. INSULIN AND ANTIBIOTICS.

(a) CERTIFICATION OF DRUGS CONTAINING INSULIN.—

(1) AMENDMENT.—Section 506 (21 U.S.C. 356), as in effect before the date of the enactment of this Act, is repealed.

(2) CONFORMING AMENDMENTS.—

(A) Section 301(j) (21 U.S.C. 331(j)) is amended by striking "506, 507,".

(B) Subsection (k) of section 502 (21 U.S.C. 352) is repealed.

(C) Sections 301(i)(1), 510(j)(1)(A), and 510(j)(1)(D) (21 U.S.C. 331(i)(1), 360(j)(1)(A), 360(j)(1)(D)) are each amended by striking ", 506, 507,".

(D) Section 801(d)(1) (21 U.S.C. 381(d)(1)) is amended by inserting after

"503(b)" the following: "or composed wholly or partly of insulin".

(E) Section 8126(h)(2) of title 38, United States Code, is amended by inserting "or" at the end of subparagraph (B), by striking "; or" at the end of subparagraph (C) and inserting a period, and by striking subparagraph (D).

(b) CERTIFICATION OF ANTIBIOTICS.—

(1) AMENDMENT.—Section 507 (21 U.S.C. 357) is repealed.

(2) CONFORMING AMENDMENTS.—

(A) Section 201(aa) (21 U.S.C. 321(aa)) is amended by striking out "or 507", section 201(dd) (21 U.S.C. 321(dd)) is amended by striking "507,", and section 201(ff)(3)(A) (21 U.S.C. 321(ff)(3)(A)) is amended by striking ", certified as an antibiotic under section 507,".

(B) Section 301(e) (21 U.S.C. 331(e)) is amended by striking "507(d) or (g),".

(C) Section 306(d)(4)(B)(ii) (21 U.S.C. 335a(d)(4)(B)(ii)) is amended by striking "or 507".

(D) Section 502 (21 U.S.C. 352) is amended by striking subsection (l).

(E) Section 520(l) (21 U.S.C. 360j(l)) is amended by striking paragraph (4) and by striking "or Antibiotic Drugs" in the subsection heading.

(F) Section 525(a) (21 U.S.C. 360aa(a)) is amended by inserting "or" at the end of paragraph (1), by striking paragraph (2), and by redesignating paragraph (3) as paragraph (2).

(G) Section 525(a) (21 U.S.C. 360aa(a)) is amended by striking ", certification of such drug for such disease or condition under section 507,".

(H) Section 526(a)(1) (21 U.S.C. 360bb) is amended by striking "the submission of an application for certification of the drug under section 507,", by inserting "or" at the end of subparagraph (A), by striking subparagraph (B), and by redesignating subparagraph (C) as subparagraph (B).

(I) Section 526(b) (21 U.S.C. 360bb(b)) is amended—

(i) in paragraph (1), by striking ", a certificate was issued for the drug under section 507,"; and

(ii) in paragraph (2) by striking ", a certificate has not been issued for the drug under section 507," and by striking ", approval of an application for certification under section 507,".

(J) Section 527(a) (21 U.S.C. 360cc(a)) is amended by inserting "or" at the end of paragraph (1), by striking paragraph (2), by redesignating paragraph (3) as paragraph (2), and by striking ", issue another certification under section 507,".

(K) Section 527(b) (21 U.S.C. 360cc(b)) is amended by striking ", if a certification is issued under section 507 for such a drug,", ", of the issuance of the certification under section 507,", ", issue another certification under section 507,", ", of such certification,", ", of the certification,", and ", issuance of other certications,".

(L) Section 704(a)(1) (21 U.S.C. 374(a)(1)) is amended by striking ", section 507 (d) or (g),".

(M) Section 735(1) (21 U.S.C. 379g(1)(C)) is amended by inserting "or" at the end of subparagraph (B), by striking sub-

paragraph (C), and by redesignating subparagraph (D) as subparagraph (C).

(N) Subparagraphs (A)(ii) and (B) of sections 5(b)(1) of the Orphan Drug Act (21 U.S.C. 360ee(b)(1)(A), 360ee(b)(1)(B)) are each amended by striking "or 507".

(O) Section 45C(b)(2)(A)(ii)(II) of the Internal Revenue Code of 1986 is amended by striking "or 507".

(P) Section 156(f)(4)(B) of title 35, United States Code, is amended by striking "507," each place it occurs.

(c) EXPORTATION.—Section 802 (21 U.S.C. 382) is amended by adding at the end the following:

"(i) Insulin and antibiotic drugs may be exported without regard to the requirements in this section if the insulin and antibiotic drugs meet the requirements of section 801(e)(1).".

(d) TRANSITION.—

(1) IN GENERAL.—An application that was approved by the Secretary of Health and Human Services before the date of the enactment of this Act for the marketing of an antibiotic drug under section 507 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 357), as in effect on the day before the

date of the enactment of this Act, shall, on and after such date of enactment, be considered to be an application that was submitted and filed under section 505(b) of such Act (21 U.S.C. 355(b)) and approved for safety and effectiveness under section 505(c) of such Act (21 U.S.C. 355(c)), except that if such application for marketing was in the form of an abbreviated application, the application shall be considered to have been filed and approved under section 505(j) of such Act (21 U.S.C. 355(j)).

(2) EXCEPTION.—The following subsections of section 505 (21 U.S.C 355) shall not apply to any application for marketing in which the drug that is the subject of the application contains an antibiotic drug and the antibiotic drug was the subject of any application for marketing received by the Secretary of Health and Human Services under section 507 of such Act (21 U.S.C. 357) before the date of the enactment of this Act:

(A)(i) Subsections (c)(2), (d)(6), (e)(4), (j)(2)(A)(vii), (j)(2)(A)(viii), (j)(2)(B), (j)(4)(B), and (j)(4)(D); and

(ii) The third and fourth sentences of subsection (b)(1) (regarding the filing and publication of patent information); and

(B) Subsections (b)(2)(A), (b)(2)(B), (b)(3), and (c)(3) if the investigations relied upon by the applicant for approval of the application were not conducted by or for the applicant and for which the applicant has not obtained a right of reference or use from the person by or for whom the investigations were conducted.

(3) PUBLICATION.—For purposes of this section, the Secretary is authorized to make available to the public the established name of each antibiotic drug that was the subject of any application for marketing received by the Secretary for Health and Human Services under section 507 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 357) before the date of enactment of this Act.

(e) DEFINITION.—Section 201 (21 U.S.C. 321), as amended by section 121(a)(1), is further amended by adding at the end the following:

"(jj) The term 'antibiotic drug' means any drug (except drugs for use in animals other than humans) composed wholly or partly of any kind of penicillin, streptomycin, chlortetracycline, chloramphenicol, bacitracin, or any other drug intended for human use containing any quantity of any chemical substance which is produced by

a micro-organism and which has the capacity to inhibit or destroy micro-organisms in dilute solution (including a chemically synthesized equivalent of any such substance) or any derivative thereof.".

SEC. 126. ELIMINATION OF CERTAIN LABELING REQUIREMENTS.

(a) PRESCRIPTION DRUGS.—Section 503(b)(4) (21 U.S.C. 353(b)(4)) is amended to read as follows:

"(4)(A) A drug that is subject to paragraph (1) shall be deemed to be misbranded if at any time prior to dispensing the label of the drug fails to bear, at a minimum, the symbol 'Rx only'.

"(B) A drug to which paragraph (1) does not apply shall be deemed to be misbranded if at any time prior to dispensing the label of the drug bears the symbol described in subparagraph (A).".

(b) MISBRANDED DRUG.—Section 502(d) (21 U.S.C. 352(d)) is repealed.

(c) CONFORMING AMENDMENTS.—

(1) Section 503(b)(1) (21 U.S.C. 353(b)(1)) is amended—

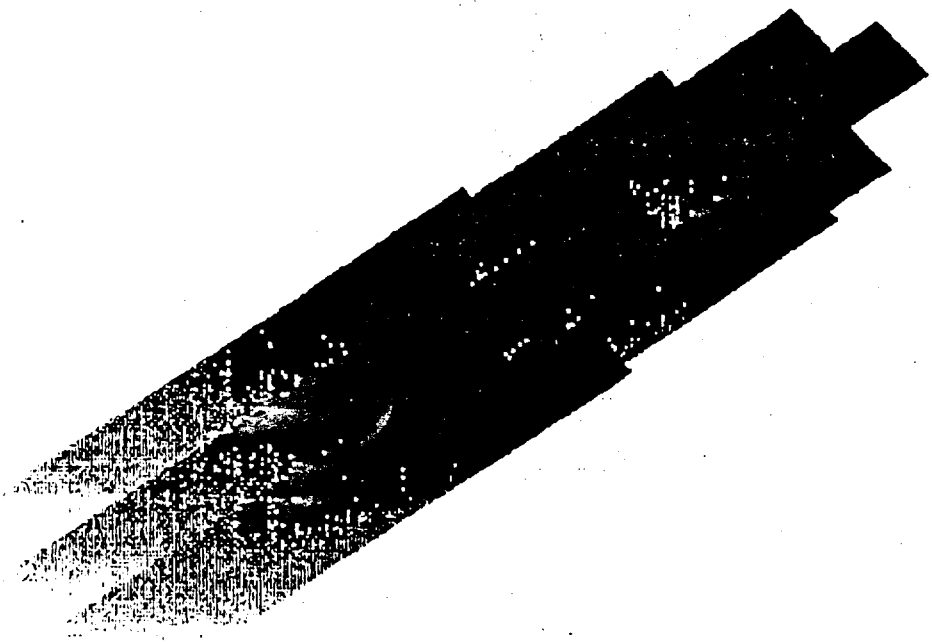
(A) by striking subparagraph (A); and

(B) by redesignating subparagraphs (B) and (C) as subparagraphs (A) and (B), respectively.

EXHIBIT 2

Guidance for Industry and Reviewers

Repeal of Section 507 of the Federal Food, Drug, and Cosmetic Act



U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Procedural 1

Revised, May 1998

Guidance for Industry and Reviewers

Repeal of Section 507 of the Federal Food, Drug, and Cosmetic Act

Additional copies are available from:
Office of Training and Communications
Division of Communications Management
The Drug Information Branch, HFD-210
5600 Fishers Lane
Rockville, MD 20857

(Tel) 301-827-4573
(Internet) http://www.fda.gov/cder/guidance/index.htm

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

Procedural 1

Revised, May 1998

Table of Contents

GUIDANCE FOR INDUSTRY AND REVIEWERS[1]

Repeal of Section 507 of the Federal Food, Drug, and Cosmetic Act

I. INTRODUCTION

Section 125 of Title I of the Food and Drug Administration Modernization Act of 1997 (the Modernization Act), signed into law by President Clinton on November 21, 1997, repealed section 507 of the Federal Food, Drug, and Cosmetic Act (the Act). As a result of the repeal of section 507, which took effect immediately, several of the Agency's administrative processes for reviewing and approving antibiotic drug applications must be changed. This document is intended to clarify, on an interim basis, the administrative processes that will be followed in implementing section 125 of the Modernization Act. In the current revision, the Agency clarifies the procedures applicable to bulk drug substances for products previously regulated under section 507.

II. SUMMARY OF SECTION 125 OF THE FDAMA

Prior to the enactment of the Modernization Act, the Agency approved antibiotic drug marketing applications under section 507 of the Act. In addition, section 507 required the Agency to publish regulations (antibiotic monographs) that set forth standards of identity, strength, quality, and purity for each marketed antibiotic drug.

As a result of the repeal of section 507, the Agency's legal obligation to publish antibiotic monographs has been eliminated from the Act. Moreover, all antibiotic drug applications will now be filed, reviewed, and approved under section 505 of the Act, as are all other new drugs.

Section 125 of the Modernization Act specifically provides that:

1. All full applications approved under section 507 on or before November 20, 1997, are now deemed to have been submitted and filed under section 505(b) and approved for safety and effectiveness under section 505(c).

2. All abbreviated applications approved under section 507 on or before November 20, 1997, are now deemed to have been filed and approved under section 505(j). (The status of antibiotic bulk drug applications that were submitted or approved under former section

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[1]This guidance has been prepared by the Antibiotic Working Group of the Center for Drug Evaluation and Research (CDER) at the Food and Drug Administration. This guidance document represents the Agency's current thinking on the implementation of the repeal of section 507 of the Federal Food, Drug, and Cosmetic Act. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. An alternative approach may be used if such approach satisfies the requirements of the applicable statute, regulations, or both.

507 is discussed in section III.F., below.)

3. All applications for drugs that contain an antibiotic that was the subject of any marketing application ***received by the Secretary*** on or before November 20, 1997, (hereafter referred to as an "old" antibiotic) are exempt from the patent listing, patent certification, and exclusivity provisions in section 505. (See section III.C, below.) The effects of this exemption provision include the following:

   a. Antibiotic drug marketing applications that were pending in FDA on or before November 20, 1997, need not be updated with the patent information required under section 505(b)(1) and would not be eligible to claim exclusivity under sections 505(c) or 505(j).

   b. Already approved antibiotic drug marketing applications need not be updated with patent information and cannot seek exclusivity under sections 505(c) or 505(j).

   c. New applications (those received on or after November 21, 1997) under section 505(b) or 505(j) for drugs that contain "old" antibiotics need not include patent information and are not eligible for exclusivity under sections 505(c) or 505(j).

   d. An application received on or after November 21, 1997, that does not contain an "old" antibiotic would be required to file patent information and could seek exclusivity, as appropriate, under sections 505(c) or 505(j).

   e. An abbreviated application under section 505(j) or an application under section 505(b)(2) that refers to a drug that does not contain an "old" antibiotic would be required to include appropriate patent certifications and may be subject to the exclusivity provisions in sections 505(c) or (j), as appropriate.

4. Finally, section 125 preserves for all products containing an antibiotic drug the special export status that has been allowed over the years for antibiotic drugs.

III. POLICIES

A. Definitions

For purposes of section 125 of the Modernization Act, the "date of the enactment of this Act" is November 21, 1997. *Before the date of the enactment of this Act* means on or before November 20, 1997.

B. Application Numbering Conventions

Because of the exemptions that apply to *old* antibiotics, we will continue to maintain our numbering system for new drug applications to allow us to distinguish between applications that contain *old* antibiotics and all other applications. Beginning November 21, 1997, we will apply our NDA numbering system as follows:

1. All applications (except bulk drug applications) assigned a series 50,000 or series 60,000 NDA number on or before November 20, 1997, will keep that number. As discussed above, the exemption provisions in section 125 that exempt applications for drugs that contain "old" antibiotic drugs from the patent listing, patent certification, and exclusivity provisions in section 505 of the Act apply to these applications. For bulk drug applications assigned series 60,000 numbers on or before November 20, 1997, see section III.F, below.

2. Series 50,000 numbers will be assigned to all marketing applications submitted under 505(b) on or after November 21, 1997, to which the section 125 exemptions apply.

3. Series 60,000 numbers will be assigned to all marketing applications submitted under 505(j) on or after November 21, 1997, to which the section 125 exemptions apply.

4. Series 20,000 numbers will be assigned to all marketing applications submitted under 505(b) on or after November 21, 1997, to which the section 125 exemptions do not apply.

5. Series 70,000 or 40,000 numbers will be assigned to all marketing applications submitted under 505(j) on or after November 21, 1997, to which the section 125 exemptions do not apply.

Example. The marketing application (NDA) for azithromycin was submitted to FDA (i.e., the Secretary) before November 21, 1997. If, on or after November 21, 1997, another NDA is submitted for a new dosage form or a new indication for azithromycin, this newly submitted NDA would be assigned a series 50,000 number because the drug (i.e., azithromycin) that is the subject of the new NDA was originally received by the Secretary (see section C.2., below) prior to November 21, 1997.

C. Applications Subject to Section 125 Exemptions

Section 125 of the Modernization Act exempts from the patent listing, patent certification, and sections 505(c) and (j) marketing exclusivity provisions, marketing applications for drugs that contain *old* antibiotics. (See section 125(d)(2) of the Modernization Act for a list of the specific provisions in section 505 of the Act that do not apply to applications that contain *old* antibiotics.) For purposes of implementing this provision, consider these

points in deciding whether an application is subject to the exemption.

1. The drug that is the subject of the application must contain (in whole or as part of a combination) an *antibiotic drug*. As was the case prior to the repeal of section 507, an *antibiotic drug* is:

   any drug (except drugs for use in animals other than humans) composed wholly or partly of any kind of penicillin, streptomycin, chlortetracycline, chloramphenicol, bacitracin, or any other drug intended for use by man containing any quantity of any chemical substance which is produced by a micro-organism and which has the capacity to inhibit or destroy micro-organisms in dilute solution (including the chemically synthesized equivalent of any such substance) or any derivative thereof. (See new section 201(jj) of the Act.)

2. The antibiotic drug that is contained in the application must have been the subject of a marketing application that was *received by the Secretary* on or before November 20, 1997. For purposes of section 125 of the Modernization Act, this would include any antibiotic application (including an old Form 5 or Form 6 application) that was:

   a. Received by FDA (as evidenced by an Agency date stamp) on or before November 20, 1997.

   b. Filed or approved on or before November 20, 1997.

   c. Received on or before November 20, 1997, and is presently under review.

   d. The subject of an action letter on or before November 20, 1997 (e.g., AE, NA, or WD), and is now *back with the company*.

   e. Received on or before November 20, 1997, filed, reviewed, approved, and then withdrawn from the market (either for safety or other reasons).

   f. Received on or before November 20, 1997, and then withdrawn prior to filing and has not been further submitted.

   g. Received on or before November 20, 1997, and subsequently refused filing and has not been further submitted.

   h. Received on or before November 20, 1997, and was unacceptable for filing under PDUPA for failure to submit the appropriate user fee and has not been further submitted.

   For purposes of section 125 of the Modernization Act *received by the Secretary* does ***not*** mean (1) canceled applications (i.e., administrative errors) or (2)

applications for which only a *presubmission* was received without a full submission ever having been received subsequently by the Agency. (See also 21 CFR 314.101(d).)

3. Other factors, such as the extent to which derivatives of the active moiety of an *old* antibiotic are also considered to be *old* antibiotics, are beyond the scope of this administrative guidance and may be addressed as part of an Agency rulemaking proceeding.[2]

D. Action Letters

Beginning November 21, 1997, the action letter templates for 507 drugs will no longer be used. Section 507 no longer provides a statutory basis for approval of a drug product. All action letters must use the 505(b) or 505(j) templates, even for drugs that originally were submitted under section 507, but are the subject of Agency action on or after November 21, 1997.

For action letters on marketing applications to which the section 125 exemptions apply, the following sentence should be added after the initial reference to section 505: "We note that this application is subject to the exemption provisions contained in section 125(d)(2) of Title I of the FDA Modernization Act of 1997."

E. Monographs

On and after November 21, 1997, FDA will no longer publish or maintain antibiotic monographs in the Code of Federal Regulations (CFR). Products approved under section 505 do not require such monographs. The Agency recently published a direct final rule to remove the antibiotic monographs from the CFR (63 FR 26066, May 12, 1998).

F. Bulk Drug Applications (Pending and Approved)

Prior to the repeal, the Agency consistently read section 507 to require that bulk antibiotic drug substances must be either batch certified or exempted from batch certification through the approval of an antibiotic drug application. Applications for bulk antibiotic drugs were previously assigned 60,000 application numbers. The Agency, however, has not required the filing or approval of such an application under section 505 for bulk drug substances used in the manufacture of non-antibiotic new drug products. Rather, in accordance with 21 CFR 314.420, information about drug substances, drug substance intermediates, and materials used in their preparation or in the preparation of new drug

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[2] Section 125 of the Modernization Act also authorizes the Secretary to publish the established name of each antibiotic drug that is subject to the section 125 exemption (i.e., each "old" antibiotic drug). The Agency has not yet decided how it will implement this authority.

products may be filed and maintained as Type II Drug Master Files (DMFs). Alternatively, drug substance information may be filed as part of the marketing application for the finished dosage form of the drug.

In light of the repeal of section 507 and the Agency's longstanding regulatory approach to handling bulk drug substances under section 505, the Agency intends to administratively convert all antibiotic bulk drug substance applications ("bulk applications") into DMFs.

Action — After August 31, 1998, all unapproved bulk applications that were pending in CDER as of November 21, 1997, will be administratively converted into DMFs. Likewise, after August 31, 1998, FDA will begin administratively converting all approved bulk applications into DMFs. Any bulk application received by CDER after November 21, 1997, will be returned to the applicant. The agency has not approved any bulk applications since the repeal of section 507 went into effect on November 21, 1997.

Following issuance of this revised guidance, the Agency will provide written notice to each sponsor of a bulk application of the Agency's intention to convert the application into a DMF. Following the conversion of each application, the Agency will notify the sponsor of the newly assigned DMF reference number.

The Agency does not intend at this time to require sponsors of converted bulk applications to submit new letters of authorization for each of the dosage form manufacturers who may reference the DMF. Similarly, the Agency does not expect to require dosage form manufacturers to amend their marketing applications to reference the newly assigned DMF number. However, following conversion of a bulk application, any new letters of authorization or other correspondence relating to the bulk substance will be expected to reference the new DMF number, in accordance with 21 CFR 314.420(b).

Sponsors of bulk applications need not take any action for their applications to be converted. The Agency expects most, if not all, bulk applications will be handled under this process. However, if a sponsor does not wish to maintain a DMF for a particular bulk drug substance, the information in the bulk application may be merged into one or more dosage form applications, or the Agency may cancel and retire the application in accordance with Agency record keeping practices. The Agency also would consider requests for more expeditious conversion of bulk applications to DMFs from sponsors who would like their applications converted before August 31, 1998. Sponsors interested in one of these alternatives should contact Jerry Phillips, Director, Division of Labeling and Program Support, CDER, at 301-827-5846, before August 31, 1998.

ATTACHMENT D

APPEARS THIS WAY
ON ORIGINAL

CLAY-PARK LABS, INC.

AGIS GROUP

1700 BATHGATE AVE. BRONX, NY 10457 (718)901-2800

PATENT CERTIFICATION STATEMENT

Although a Patent Certification Statement is not statutorily required for Clay-park labs, Inc.'s NDA for Mupirocin Ointment, 2%, Clay-Park Labs, Inc. submits the following statement as referenced in 21 C.F.R. § 314.50(i):

> In accordance with the Federal Food, Drug and Cosmetic Act, a Patent Certification Statement is hereby provided for Clay-Park Labs, Inc.'s 505(b)(2) NDA for Mupirocin Ointment, 2%. Clay-Park Labs, Inc. hereby certifies that, in its opinion and to the best of its knowledge, there are no patents that claim the drug on which investigations that are relied in this application were conducted or that claim a use of such drug.

Candis Edwards
Director of Regulatory Affairs
Clay-Park Labs, Inc.

11/21/02
Date

EXCLUSIVITY SUMMARY for NDA # 50-788 SUPPL #

Trade Name none **Generic Name** Mupirocin Ointment, 2%
Applicant Name ClayPark Laboratories **HFD-** 520
Approval Date December 4, 2002

PART I: IS AN EXCLUSIVITY DETERMINATION NEEDED?

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

   a) Is it an original NDA? YES/ X / NO /___/

   b) Is it an effectiveness supplement? YES /___/ NO / X /

   If yes, what type(SE1, SE2, etc.)?

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

   YES / X / NO /___/

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

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

d) Did the applicant request exclusivity?

YES /___/ NO /_X_/

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

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

YES /___/ NO /_X_/

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule previously been approved by FDA for the same use? (Rx to OTC) Switches should be answered No - Please indicate as such).

YES /_X_/ NO /___/

If yes, NDA #50-591 Drug Name Bactroban (mupirocin ointment) 2%

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

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

YES /___/ NO /___/

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9 (even if a study was required for the upgrade).

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

1. Single active ingredient product.

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

YES /___/ NO /___/

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

NDA #

NDA #

NDA #

2. Combination product.

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

YES /___/ NO /___/

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

NDA #

NDA #

NDA #

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9. IF "YES," GO TO PART III.

PART III: <u>THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS</u>

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

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES /___/ NO /___/

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis

for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

For the purposes of this section, studies comparing two products with the same ingredient(s) are considered to be bioavailability studies.

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

YES /___/ NO /___/

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval **AND GO DIRECTLY TO SIGNATURE BLOCK ON Page 9:**

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

YES /___/ NO /___/

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

YES /___/ NO /___/

If yes, explain:

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

YES /___/ NO /___/

If yes, explain:

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

Investigation #1, Study #

Investigation #2, Study #

Investigation #3, Study #

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

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

Investigation #1 YES /___/ NO /___/

Investigation #2 YES /___/ NO /___/

Investigation #3 YES /___/ NO /___/

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

NDA # _____ Study #
NDA # _____ Study #
NDA # _____ Study #

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

Investigation #1 YES /___/ NO /___/

Investigation #2 YES /___/ NO /___/

Investigation #3 YES /___/ NO /___/

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

NDA # _____ Study #

NDA # _____ Study #

NDA # _____ Study #

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

Investigation #__, Study #

Investigation #__, Study #

Investigation #__, Study #

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

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

Investigation #1	
IND # _____ YES /___/	NO /___/ Explain:
Investigation #2	
IND # _____ YES /___/	NO /___/ Explain:

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

Investigation #1	
YES /___/ Explain _____	NO /___/ Explain _____
_____	_____
_____	_____
Investigation #2	
YES /___/ Explain _____	NO /___/ Explain _____
_____	_____
_____	_____

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

YES /___/ NO /___/

If yes, explain: _____

_____

_____

_____
Signature of Preparer Date
Title:

Signature of Office or Division Director Date

cc:
Archival NDA
HFD-520/Division File
HFD-520/RPM
HFD-093/Mary Ann Holovac
HFD-104/PEDS/T.Crescenzi

Form OGD-011347
Revised 8/7/95; edited 8/8/95; revised 8/25/98, edited 3/6/00

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

/s/

Janice Soreth
12/16/02 03:58:39 PM

Maureen Dillon-Parker
12/16/02 11:41:44 AM

APPEARS THIS WAY
ON ORIGINAL

SECTION 14: PATENT AND EXCLUSIVITY CERTIFICATIONS

14.2 STATEMENT CONCERNING PATENT INFORMATION AND EXCLUSIVITY FOR MUPIROCIN OINTMENT, 2%

APPEARS THIS WAY
ON ORIGINAL

14.2 STATEMENT CONCERNING PATENT INFORMATION AND EXCLUSIVITY FOR MUPIROCIN OINTMENT, 2%

FDA first approved mupirocin ointment for marketing as an antibiotic drug on December 31, 1987 under Section 507 of the Federal Food, Drug, and Cosmetic Act. Therefore, by operation of Section 125(d)(2)(B) of the Food and Drug Administration Modernization Act of 1997, no patent certification or method of use statement is required or permitted in this application. Similarly, no market exclusivity statement is required or permitted in this application. (*See also*, FDA's proposed regulation, 21 CFR § 314.109(a)(2), (a)(7) and (b), 65 Fed. Reg. 3623 (Jan. 24, 2000), although its final promulgation is not required for enforceability of the statute.)

APPEARS THIS WAY
ON ORIGINAL

CLAY-PARK LABS, INC.

AGIS GROUP

1700 BATHGATE AVE. BRONX, NY 10457 (718)901-2800

December 2, 2002

Maureen Dillon-Parker – Project Manager
Food and Drug Administration
Center For Drug Evaluation and Research
Division of Anti-Infective Drug Products
HFD-520
Attention: Division of Document Control
9201 Corporate Boulevard
Rockville, MD 20850-3202

Submitted by Fax
Hard Copy Letter to Follow

Re: Correspondence to NDA #50-788
Mupirocin Ointment, 2%

Dear Ms. Dillon-Parker:

In reference to the Agency's correspondence dated November 27, 2002 (see **Attachment A**) on our New Drug Application for Mupirocin Ointment, 2%, NDA 50-788, Clay-Park Labs, Inc. hereby submits our response for the Clinical, Chemistry and Labeling reviewers' comments and recommendation as follows:

CLINICAL

Comment #1:

The proposed revision of line 145 from ——— , to n=233 and from ——— to n=242 in the **CLINICAL STUDIES** section is acceptable.

Response #1:

Clay-Park Labs, Inc. agrees and has incorporated this information into its revised proposed draft labeling for Mupirocin Ointment, 2%. See **Attachment B, line 126-127.**

concern that these mupirocin resistance rates will be increasing with time. Thus, the Division recommends that the existing sentence remain.

Response:

The statement proposed by the agency, "Methicillin resistance and mupirocin resistance commonly occur together in *Staphylococcus aureus* and coagulase negative staphylococci" was added back to the **Microbiology** section of the revised proposed draft labeling submitted on November 21, 2002. See **Attachment B, line 36-37.**

Additionally, in **line 35**, Clay-Park Labs, Inc. spelled out "*S.* " *in* " *S. Aureus*" to "*Staphylococcus*". Also, we added a hyphen in the Clay-Park Labs, Inc. name in **line 139**. See **Attachment B, lines 35 and 139**.

The final labeling for Mupirocin Ointment, 2% is presented in **Attachment C**.

Should you have any further questions, please contact the undersigned as follows:

Telephone: (718) 960-9976 **Fax: (718) 960-0111**

Sincerely,

Candis Edwards
Director, Regulatory Affairs

CLAY-PARK LABS, INC.

AGIS GROUP

1700 BATHGATE AVE. BRONX, NY 10457 (718)901-2800

November 21, 2002

Maureen Dillon-Parker – Project Manager
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Anti-Infective Drug Products
HFD-520
Attention: Division of Document Control
9201 Corporate Boulevard
Rockville, MD 2080-3202

Re: Correspondence to NDA # 50-788, Mupirocin Ointment, 2%

Dear Ms. Dillon-Parker:

In response to the Agency's correspondence dated November 15, 2002, and its telephone contact on November 20, 2002, Clay-Park Labs, Inc. is hereby submitting the requested information for Mupirocin Ointment, 2%, NDA # 50-788, with respect to revised proposed draft labeling (with rationale), and additional patent certification statement (with rationale). In particular, we are submitting the following:

The revised proposed draft labeling for Mupirocin Ointment, 2% (**see Attachment A**), in response to your fax correspondence dated November 15, 2002 (**see Attachment B**). CPL has concerns about several of the FDA's revisions to the proposed labeling for Mupirocin Ointment, 2%. Nevertheless, because of our interest in obtaining expeditious approval of the NDA, we are requesting that FDA accept two small corrections and reconsider its recommendation for only one item (Item (1) below) that CPL believes is critical to a fair and proper scientific understanding of the data supporting the safe and effective use of Mupirocin Ointment, 2%.

Specifically, we have implemented all of the changes requested by the Agency with the exception of the following three items:

(1) SECTION: CLINICAL PHARMACOLOGY

Line 48-49: Deletion of the statement: "

Comment #2:

The proposed revision of line 156 ' —— ' to 413 in the **Pediatrics** section is acceptable.

Response #2:

Clay-Park Labs, Inc. agrees and has incorporated this information into its revised proposed draft labeling for Mupirocin Ointment, 2%. See **Attachment B, line 131.**

CHEMISTRY

Comment #1:

Bactroban Ointment has the specifications of absence of *Pseudomonas species* and *Staphylococcus aureus*. Please commit to include or revise the microbiological test to indicate the absence of pathogens to assure the same or similar microbiological quality.

Response #1:

Clay-Park Labs, Inc. commits to include the microbial limit test for *Pseudomonas species* and *Staphylococcus aureus* in Mupirocin Ointment, 2%.

Comment #2:

The statement in the first paragraph of section 3.6.2 of the submission states the formulation is to consist of a '" ——— . Is this a typographical error since the drug product is lipophilic? Please clarify.

Response #2:

The statement in the first paragraph of section 3.6.2 of the submission stating that the formulation is to consist of a ' ——— ' is a typographical error. The statement should state "lipophilic".

MICROBIOLOGY

Recommendation:

The statement proposed by the agency, "Methicillin resistance and mupirocin resistance commonly occur together in *Staphylococcus aureus* and coagulase negative staphylococci" is supportable by published literature. It is possible that we could modify the statement to reflect the rates of resistance as described in the reference but there is

Rational for deletion of this statement:

a. The statement conflicts with one in the previous paragraph indicating that "Due to this unique mode of action, mupirocin does not demonstrate cross-resistance with other classes of antimicrobial agents." (lines 40-41)

b. The statement is not supported by data submitted in Clay-Park Labs, Inc.'s NDA, nor do we believe that the literature references provided by Clay-Park Labs, Inc. support such a statement.

c. Based on FDA's comments during the pre-NDA meeting (held on September 5, 2001), it was Clay-Park Labs, Inc.'s understanding that no reference should be made to [redacted] because specific data on that issue was not provided for Clay-Park Labs, Inc.'s product. CPL complied with the Agency's request by removing all references to [redacted] in the proposed labeling, making no claims related to the effectiveness of its Mupirocin Ointment, 2% product against [redacted] isolates. Because of the absence of information related to [redacted] in the labeling, it would seem to be inconsistent and inappropriate to include the FDA's suggested statement.

(2) SECTION: CLINICAL STUDIES

Line 145: Change from [redacted], to (n=233) and from [redacted] to (n=242)

Rational for changes in the number of evaluable populations:

The numbers in parentheses now refer to the number of evaluable patients that used either Mupirocin Ointment, 2% (n=233) or Bactroban® Ointment (Mupirocin Ointment, 2%) (n=242), whereas previously they referred only to the number of successes in each treatment group. This modification made the way of reporting subject numbers consistent between the first (adults and pediatric patients) and second paragraph (pediatric patients only), as corrected by the FDA.

(3) SECTION: Pediatrics

Line 156: Change [redacted] to 413

Rationale for Changes in the number of pediatrics patients in the evaluable population:

There were only 413 pediatric patients in the evaluable population. This is now consistent with the numbers of evaluable pediatric patients reported for each of the two treatment groups (199+214=413). There were more than 413 pediatric patients in the clinical study (Modified Intent-to-Treat population [redacted], therefore addition of the word evaluable denotes that it refers only to the evaluable (Per-Protocol) population.

- A memo to file for Mupirocin Ointment, 2% in response to our telephone conversation on November 20, 2002 regarding the reason why a patent certification statement will not be required for NDA # 50-788 **(see Attachment C)**

- Patent Certification Statement as you have requested from our telephone conversation on November 20, 2002 **(see Attachment D)**

Should you have any further questions, please contact the undersigned as follows:

Telephone: (718) 960-9976 **Fax: (718) 960-0111**

Sincerely,

Candis Edwards
Director, Regulatory Affairs

APPEARS THIS WAY
ON ORIGINAL

ATTACHMENT A

Number of Pages Redacted 29

❖❖❖

Draft Labeling
(not releasable

2.3.1.2.4 ANNOTATED SIDE BY SIDE LABELING COMPARISON

Similarities and Differences for CPL's Mupirocin Ointment, 2% Tube and Outer Folding Carton Labeling, and GSK's Bactroban® Ointment Tube and Outer Folding Carton Labeling

1. Differences

a. The inactive ingredient qualitative composition statement for CPL's Mupirocin Ointment, 2% is different from Bactroban® Ointment.
b. CPL does not use comparator product's logo.
c. CPL does not use comparator product's trade name.
d. CPL does not use comparator product's NDC numbers.
e. CPL is listed as the manufacturer for its Mupirocin Ointment, 2%.
f. CPL does not use the comparator product's bar code on their outer folding carton
g. The Net Wt. is stated as " 22 grams (Net Wt.)" on the comparator product's tube and outer folding carton, whereas on Clay-Park Labs, Inc.'s tube and outer folding carton, it is stated as "Net Wt. 22 grams".

2. Similarities

a. Same strength
b. Same active ingredient
c. Same dosage information statement
d. Same storage requirements

TUBE MASTER 3/4 X 4

SHOULDER — TUBE LENGTH 4 — OPEN END

B.M. 1/16

NDC 45802-473-37

MUPIROCIN OINTMENT, 2%

Rx only

Net Wt. 15 grams

Store at controlled room temperature 20° to 25°C (68° to 77°F).
Each gram contains 20 mg mupirocin in a soft white ointment base consisting of castor oil, cetyl alcohol, hard fat (Softisan® 378) and propylene glycol monostearate.
Dosage: For dermatologic use only. Apply a small amount of ointment to the affected area three times daily. Patients not showing a clinical response within 3 to 5 days should be re-evaluated. See accompanying prescribing information.
Mfg. By: CLAY-PARK LABS, INC.
Bronx, NY 10457

TM47315CPL-2X N1201

Pharmacode 000

[redacted]

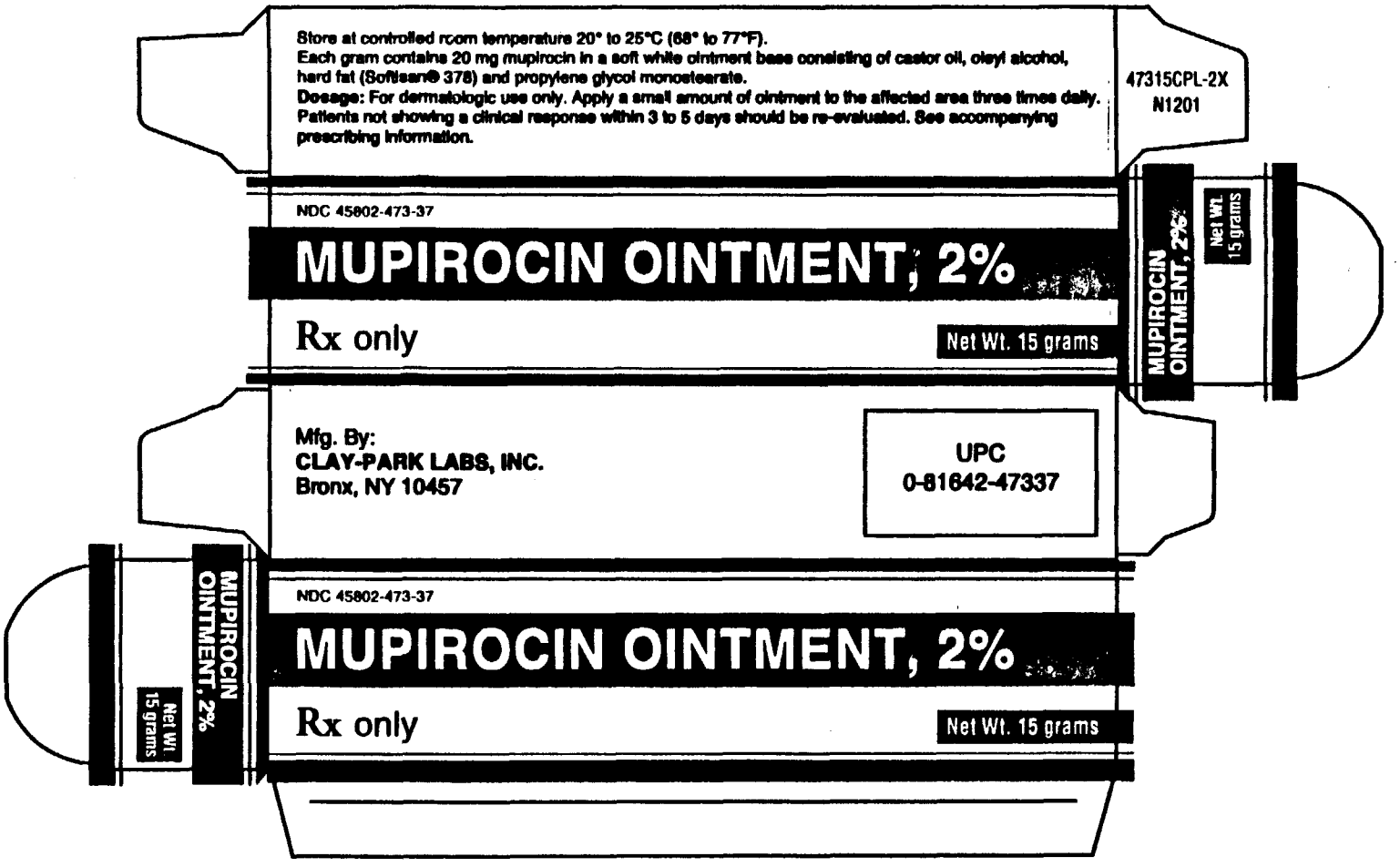
3

Statement of Identity			Disclaimer			Size (Tube, Label, Box)		
Net Wt.			UPC			Tamper		
Compare to...			Dist By.					

Clay Park Labs, Inc. Graphics Dept. (Ph 718 960-9967)

DIE# 8016	COLORS: 540, Black	PRODUCT NO: 473
PHARMACODE# 000		MAC ARTIST: Angel

**Please see the Pantone® Color Guide to verify colors.



11

Statement of Identity			Disclaimer			Size (Tube, Label, Box)		
Net Wt.			UPC			Tamper		
Compare to...			Dist By.					

Clay Park Labs,Inc. Graphics Dept. (Ph 718 960-9967)

DIE# 8016 PHARMACODE# 000	COLORS: 540, Black	PRODUCT NO: 473 MAC ARTIST: Angel

**Please see the Pantone® Color Guide to verify colors.

TUBE MASTER 7/8 X 4 1/2

SHOULDER | TUBE LENGTH 4 1/2 | OPEN END

B.M. I/16

NDC 45802-473-22

MUPIROCIN OINTMENT, 2%

Rx only

Net Wt 22 grams

Store at controlled room temperature 20° to 25°C (68° to 77°F).
Each gram contains 20 mg mupirocin in a soft white ointment base consisting of castor oil, oleyl alcohol, hard fat (Softisan® 378) and propylene glycol monostearate.
Dosage: For dermatologic use only. Apply a small amount of ointment to the affected area three times daily. Patients not showing a clinical response within 3 to 5 days should be re-evaluated. See accompanying prescribing information.
Mfg. By: CLAY-PARK LABS, INC.
Bronx, NY 10457 TM47322CPL-2X N1201

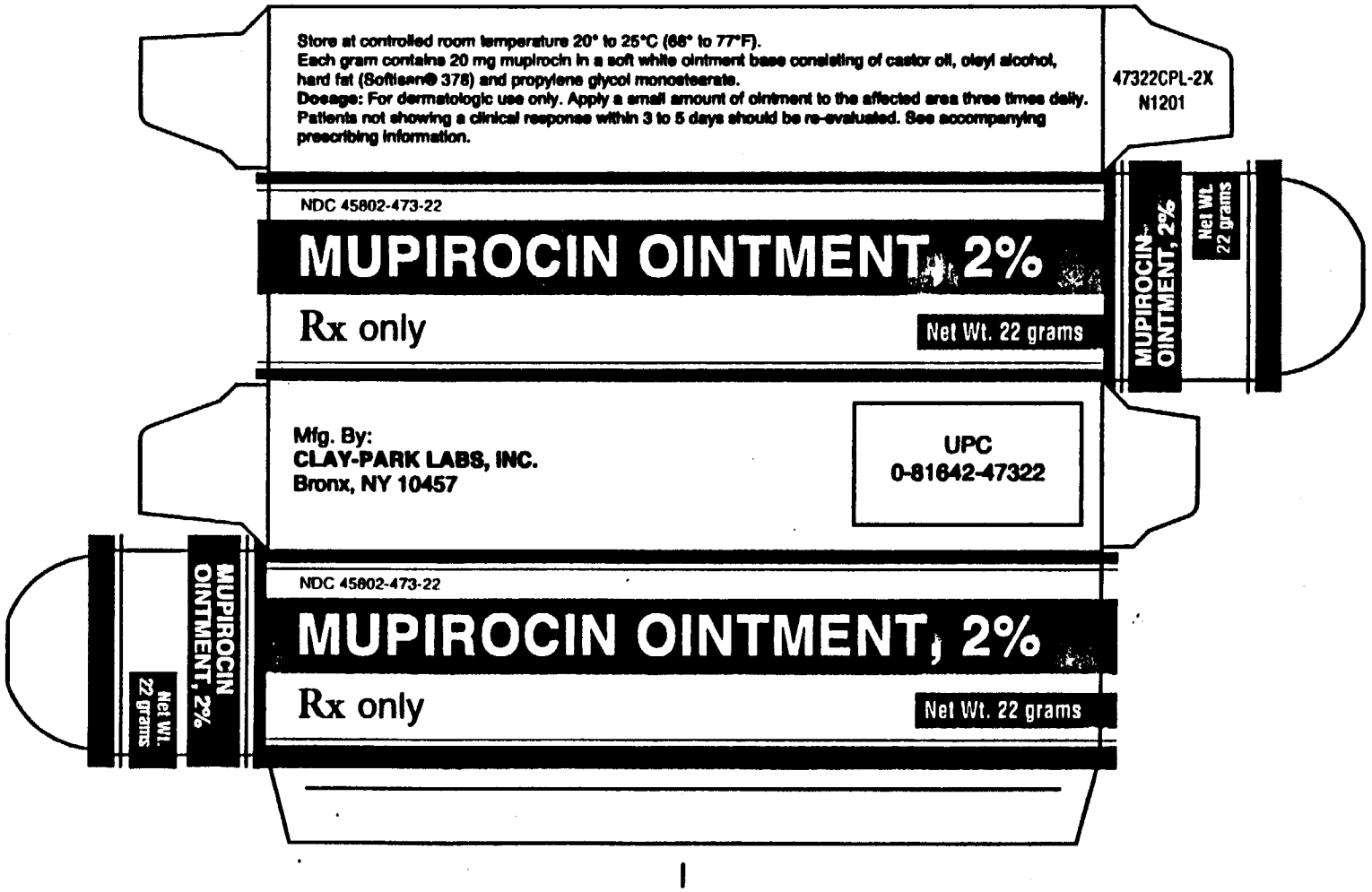
Pharmacode

Statement of Identity			Disclaimer			Size (Tube, Label, Box)		
Net Wt.			UPC			Tamper		
Compare to...			Dist By.					

Clay Park Labs,Inc. Graphics Dept. (Ph 718 960-9967)

DIE# 8016 PHARMACODE# 000	COLORS: 540, Black	PRODUCT NO: 473 MAC ARTIST: Angel

**Please see the Pantone® Color Guide to verify colors.



8

Statement of Identity			Disclaimer			Size (Tube, Label, Box)		
Net Wt.			UPC			Tamper		
Compare to...			Dist By.					

Clay Park Labs,Inc. Graphics Dept. (Ph 718 960-9967)		
DIE# 8016 PHARMACODE# 000	COLORS: 540, Black	PRODUCT NO: 473 MAC ARTIST: Angel

**Please see the Pantone® Color Guide to verify colors.

TUBE MASTER 7/8 X 5 1/8

NDC 45802-473-11

MUPIROCIN OINTMENT, 2%

Rx only

Net Wt. 30 grams

Store at controlled room temperature 20° to 25°C (68° to 77°F).
Each gram contains 20 mg mupirocin in a soft white ointment base consisting of castor oil, cetyl alcohol, hard fat (Softisan® 378) and propylene glycol monostearate.
Dosage: For dermatologic use only. Apply a small amount of ointment to the affected area three times daily. Patients not showing a clinical response within 3 to 5 days should be re-evaluated.
See accompanying prescribing information.
Mfg. By: CLAY-PARK LABS, INC.
Bronx, NY 10457

TM47330CPL-2X N1201

PHARMACODE 000

[redacted]

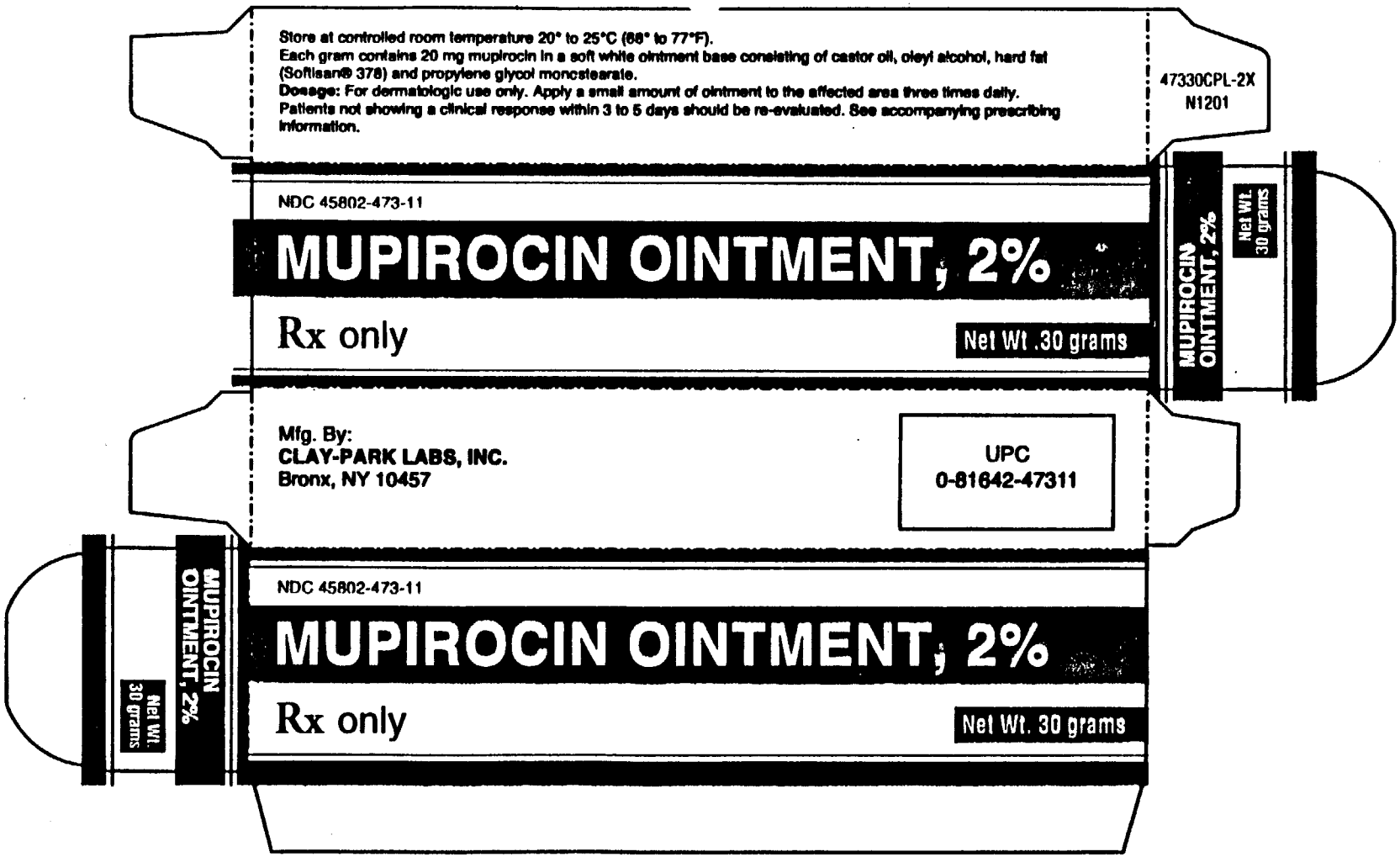
10

Statement of Identity			Disclaimer			Size (Tube, Label, Box)		
Net Wt.			UPC			Tamper		
Compare to...			Dist By.					

Clay Park Labs,Inc. Graphics Dept. (Ph 718 960-9967)

DIE# 8016 PHARMACODE# 000	COLORS: 540, Black	PRODUCT NO: 473 MAC ARTIST: Angel

**Please see the Pantone® Color Guide to verify colors.



4

Statement of Identity			Disclaimer			Size (Tube, Label, Box)		
Net Wt.			UPC			Tamper		
Compare to...			Dist By.					

Clay Park Labs,Inc. Graphics Dept. (Ph 718 960-9967)

DIE# 1521Q1A PHARMACODE# 000	COLORS: 541, Black	PRODUCT NO: 112 MAC ARTIST: Angel

**Please see the Pantone® Color Guide to verify colors.

Number of Pages Redacted 2

Confidential,
Commercial Information

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation IV

FACSIMILE TRANSMITTAL SHEET

DATE: November 27, 2002

To: Candis Edwards Director Regulatory Affairs	**From:** Maureen Dillon-Parker Project Manager
Company: Clay-Park Labs, Inc.	FDA - Division of Division of Anti-Infective Drug Products
Fax number: 718-960-0111	**Fax number:** 301-827-2325
Phone number: 718-960-9976	**Phone number:** 301-827-2125

Subject: Chemistry Comments on NDA 50-788 submission and Clinical and Microbiology Comments on the 11/21/02 submission.

Total no. of pages including cover: 5

Comments: Please review the attached comments.

Document to be mailed: ☐ YES ☑ NO

NDA 50-788 – Mupirocin Ointment 2%
Clay-Park Labs, Inc.

CLINICAL

1. The proposed revision of line 145 from [redacted] to n=233 and from [redacted] to n=242 in the **CLINICAL STUDIES** section is acceptable.

2 The proposed revision of line 156 from [redacted] to 413 in the **Pediatrics** section is acceptable.

CHEMISTRY

1. Bactroban Ointment has the specifications of absence of *Pseudomonas species* and *Staphylococcus aureus*. Please commit to include or revise the microbiological test to indicate the absence of pathogens to assure the same or similar microbiological quality.

2. The statement in the first paragraph of section 3.6.2 of the submission states the formulation is to consist of a ' [redacted] . Is this a typographical error since the drug product is lipophilic? Please clarify.

MICROBIOLOGY

Reviewer Remarks:

Clay-Park labs submitted, on November 21, 2002, a facsimile requesting that we consider deleting a sentence found in the microbiology section of the proposed package insert. The facsimile document contains a request to delete the following sentence from line 48-49 of the proposed package insert:

[redacted]

The applicant, in support of the deletion of this statement, submits the following rationale. Their comments are highlighted in italics followed by the reviewer's comments.

1. *The statement conflicts with one in the previous paragraph indicating that "Due to the unique mode of action, mupirocin does not demonstrate cross-resistance with other classes of antimicrobials." (lines 40-41)*

   Reviewer's comments: The statements are not in conflict. The definition of cross-resistance at the genetic level is a mechanism of resistance that affects the efficacy of different classes of drugs simultaneously. For example, resistance to the macrolide, lincosamide and streptogramin B class of antimicrobials is mediated by the erythromycin resistance methylase (erm). This resistance mechanism mediates its action by methylation of the adenine of 23S ribosomal RNA resulting in cross-resistance to the three antibiotic drug classes. Thus, the *erm* gene mediates resistance to three classes of antibiotics.

The fact that an organism carries resistance to multiple and unrelated antibiotics does not characterize it as cross-resistant to antibiotics. It characterizes the microorganism as resistant to multiple antibiotics.
The statement that we provide in the mupirocin product label does not suggest that resistance to mupirocin results in cross-resistance to Methicillin or visa versa. What we do say is that both resistance mechanisms appear to be found together frequently in staphylococcal species. This frequency range is discussed below in comment 3.

2 *This statement is not supported by the data submitted in Clay-Park Labs, Inc.'s NDA, nor do we believe that the literature reference provided by Clay-Park Labs, Inc support such a statement.*

Reviewers comments: The published literature, including the referenced footnote at the end of this facsimile, supports inclusion of the statement.

3. *Based on FDA's comments during the pre-NDA meeting (held on September 5, 2001), it was Clay-Park Labs, Inc. understanding that no reference should be made to ——— because specific data on that issue was not provided for Clay-Park Labs, Inc's product. CPL complied with the Agency's request by removing all references to —— in the proposed labeling, making no claims related to effectiveness of its Mupirocin Ointment 2% product against ——— Because of the absence of information related to —— in the labeling, it would seem to be inconsistent and inappropriate to include the FDA's suggested statement."*

Reviewers comments: According to the agencies minutes of the Pre-NDA meeting, the applicant of ——— Clay-Park Labs, was advised that "with regards to the Microbiology section of the labeling, data will need to be provided in order to support the statements regarding —— in the labeling. CPL stated that they would remove the statement in the labeling unless there was data to support its inclusion. In general, the FDA stated that unless CPL can demonstrate that '—— is a pathogen in the indication impetigo, then—— cannot be included in the labeling."

It is clear from the previous material from the Agency's minutes and additional details provided within that document, that we had concern regarding the inclusion of [redacted] in the product label for several reasons. One reason is that published scientific literature is now available that suggests that [redacted] have begun to emerge that are also resistant to mupirocin. Prior to 1995, the published evidence was minimal in that few publications addressed mupirocin resistance in [redacted]. Since then, more than 50 papers have been published that address the emergence of resistance in [redacted] and coagulase-negative staphylococci. For example, the [redacted] Antimicrobial Surveillance Program assessed the mupirocin resistance rates in 2,779 staphylococcal isolates obtained from four regions of the world (Table 1).[i] There are several conclusions that can be drawn from this table.

- The first is that the rate of mupirocin resistance is more closely associated with oxicillin (methicillin) resistant staphylococcal strains than oxacillin susceptible strains. Mupirocin resistance in staphylococci is approximately 14.5% in [redacted] strains and 1.5% in MSSA strains in the United States. That is, mupirocin resistance is 10-fold higher in [redacted] strains than in MSSA strains. In coagulase-negative staphylococci, the same trend is noted; mupirocin resistance is higher in MRCoNS (43.1%) than in MSCoNS (6.0%). The rate of mupirocin resistance is 7.2 fold greater in methicillin resistant coagulase-negative staphylococci that in susceptible strains. This evidence clearly supports the notion that there is more mupirocin resistance in and MRCoNS than in sensitive strains. This is an expected result since Bactroban is approved for prophylaxis of [redacted] nasal carriage in health care professionals. It is likely this use that has driven the emergence of mupirocin resistance in methicillin resistant staphylococci.
- The second observation that can be made from Table 1 is that the coagulase-negative staphylococci (CoNS) are more likely to be mupirocin resistant than are *S. aureus*.

Conclusion:

We believe that the sentence, as proposed by the FDA, is supported by the scientific evidence that the prevalence of mupirocin resistance is greater in methicillin resistant strains than in methicillin susceptible strains. These observations do not imply that there is cross-resistance between mupirocin and methicillin.

Table 1
Distribution of mupirocin-resistant (MIC, ≥16 μg/mL) strains and resistance rates among 2,776 staphylococcal isolates in the SENTRY Antimicrobial Surveillance Program (2000)

Region	*S. aureus*		CoNS[a]	
	Oxacillin[S] (1,345)	Oxacillin[R] (814)	Oxacillin[S] (130)	Oxacillin[R] (487)
Europe	1.9	17.8	6.7	14.0
Latin America	0.0	4.6	5.9	33.7
North America	1.5	14.1	6.0	43.1
Total	1.3	13.8	6.2	32.4

[a] CoNS = coagulase-negative staphylococci.
Oxacillin[S] = oxacillin-susceptible (MIC, ≤2 μg/mL [*S. aureus*] or ≤0.25 μg/mL [CoNS])
Oxacillin[R] = oxacillin-resistant (MIC, ≥4 μg/mL [*S. aureus*] or ≥0.5 μg/mL [CoNS]) per NCCLS [2002].

RECOMMENDATION:

The statement proposed by the agency, "Methicillin resistance and mupirocin resistance commonly occur together in *Staphylococcus aureus* and coagulase negative staphylococci" is supportable by the published literature. It is possible that we could modify the statement to reflect the rates of resistance as described in the reference but there is concern that these mupirocin resistance rates will be increasing with time. Thus, the Division recommends that the existing sentence remain.

**APPEARS THIS WAY
ON ORIGINAL**

[i] Deshpande, LM, AM Fix, and MA Pfaller (2002) Emerging elevated mupirocin resistance rates among staphylococcal isolates in the SENTRY Antimicrobial Surveillance Program (2000): correlations of results from disk diffusion, Etest and reference dilution. Diagnostic Microbiology & Infectious Disease. 42:283-290.

Number of Pages Redacted 5

❖❖❖

Draft Labeling
(not releasable

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation IV

FACSIMILE TRANSMITTAL SHEET

DATE: March 21, 2002

To: Candis Edwards Director Regulatory Affairs	**From:** Maureen Dillon-Parker Project Manager
Company: Clay-Park Labs, Inc.	FDA - Division of Division of Anti-Infective Drug Products
Fax number: 718-960-0111	**Fax number:** 301-827-2325
Phone number: 718-960-9976	**Phone number:** 301-827-2125

Subject: Case Report Forms – request from the Clinical Reviewer Attached

Total no. of pages including cover: 3

Comments: Please provide the Case Report Forms for the patients in the attached listing per the Clinical Reviewer.

Document to be mailed: ☐ YES ☑ NO

Number of Pages Redacted 2

Confidential,
Commercial Information

MEMORANDUM OF MEETING MINUTES

MEETING DATE: September 5, 2001

TIME: 10:00 a.m.

LOCATION: 9201 Corporate Blvd, Room S-300

APPLICATION: ~~~~

TYPE OF MEETING: Pre-NDA

MEETING CHAIR: Janice M. Soreth, M.D.

MEETING RECORDER: Maureen P. Dillon-Parker

FDA ATTENDEES, TITLES, AND OFFICE/DIVISION

Name of FDA Attendee	Title	Division Name & HFD#
1. Maureen P. Dillon-Parker	Project Manager	Anti-Infectives, HFD-520
2. Janice M. Soreth, M.D.	Acting Division Director	Anti-Infectives, HFD-520
3. Mamodikoe Makhene, M.D.	Clinical Team Leader	Anti-Infectives, HFD-520
4. David C. Bostwick	Clinical Reviewer	Anti-Infectives, HFD-520
5. Erica Brittain, Ph.D.	Statistical Reviewer	Biometrics, HFD-725
6. Harold V. Silver	Microbiology Reviewer	Anti-Infectives, HFD-520
7. Albert T. Sheldon, Ph.D.	Microbiology Team Leader	Anti-Infectives, HFD-520
8. David B. Katague, Ph.D.	Chemistry Team Leader	Division of New Drug Chemistry III
9. Milton J. Sloan, Ph.D.	Chemistry Reviewer	Division of New Drug Chemistry III
10. Daphne Lin, Ph.D.	Statistical Team Leader	Biometrics, HFD-725
11. Terry Peters, D.V.M.	Veterinary Medical Officer	Anti-Infectives, HFD-520

EXTERNAL CONSTITUENT ATTENDEES AND TITLES:

External Attendee	Title	Sponsor/Firm Name
1. Candis Edwards	Director of Regulatory Affairs	Clay-Park Labs, Inc.
2. Mridul Shah	Senior Reg. Affairs Associate	Clay-Park Labs, Inc.
3. Joseph Kaspi, Ph.D	Vice President R & D	AGIS Group
4. Shin-Wei Sung	Director of Chemistry	Clay-Park Labs, Inc.
5. Michael Dalith, Ph.D	Sen. VP International Clin. Aff.	Clay-Park Labs, Inc.
6. W. Todd Kays, Ph.D.	Director of Clinical Research	Clay-Park Labs, Inc.
7. Steven Goldner, Ph.D	Manager of Microbiology	Clay-Park Labs, Inc.
8. Amira Zeevi, Ph.D.	Pharmaceutical R & D Director	AGIS Group
9. Ilana Lavon	Pharm R & D Project Manager	AGIS Group

3. *Does the agency accept the proposed documentation as adequate to support the use of the inactive ingredient, propylene glycol monostearate, pure, in the formulation for Mupirocin Ointment, 2%?*

- The FDA finds the proposal adequate.

4. *Does the agency agree that the proposed specifications for the finished product, and stability testing is adequate?*

- The FDA requested that justification for the impurity levels be provided. FDA stated that their levels are much higher than those seen in the approved Bactroban product.
- FDA requested that the shelf life data for the mupirocin in the drug substance be provided.

5. *Does the agency agree that the proposed modified USP analytical method for the assay of mupirocin is appropriate to support the NDA submission?*

- FDA finds the proposal acceptable. A methods validation package must be submitted.

6. *Does the agency agree that the proposed stability test data and projections are adequate to support the 36 month stability of its Mupirocin Ointment, 2% product?*

- FDA stated that the expiration date will be determined at the time of approval. The expiry date is determined based on the data in house at the time of approval plus 6 months.

7. *Will the agency accept the proposed data submitted in accordance with FDA's bracketing policy to support approval of a 22 g tube packaging size?*

- FDA stated that this plan is acceptable. A comparative protocol should be submitted for review. CPL stated that the NDA will contain 90 days of accelerated data.

8. *Does the Agency agree that the information presented in CPL's package insert meets the statutory and regulatory requirements for prescription drug labeling for the purposes of filing an NDA for Mupirocin Ointment, 2%?*

- FDA stated that the following comments are preliminary:
  -The Precautions section should contain a statement that the product is not intended for nasal use, since a nasal formulation does exist.
  -The exclusion of warnings concerning polyethylene glycol is acceptable.
  -The labeling will need an Adverse Reactions section based on data from the CPL clinical study.
  -The How Supplied section appears acceptable.
  -The Clinical Trials section will need to be rewritten. Data from the original Bactroban trial will need to be removed. Further, the topical drug product labels do not usually contain statements of equivalence.

ADDITIONAL DISCUSSION POINTS:

- The Clinical Reviewer requested Sections 1, 4, 6, 7, 9, and 10 in paper, however, stated that electronic submission of the CRF's is adequate. The Microbiology Reviewer requested Volume 1.1 and all of Section 7 in paper.
- The statistical reviewer commented that she had completed her reviews of their September and December 2000 submission. CPL stated that they need the December 2000 comments. FDA agreed to provide these.
- FDA stated that when preparing the electronic document, they should pay particular attention to the links and make sure that they are accurate.
- CPL stated that the Orange Book requires that equivalence be demonstrated for their product to carry a BE (bioequivalence) rating. This rating would allow for the substitution of this product with the approved Bactroban product.
- FDA stated that CPL must show that their product works both *in vivo* and *in vitro*. Both the clinical outcome and the overall microbiological outcome are reviewed. FDA stated that just because a product carries an equivalency rating this does not mean they would get all the statements (———) which are in the label of the original Bactroban product. CPL stated that unless they can support the inclusion of ——— with data, they will remove it from the labeling.

DECISIONS (AGREEMENTS) REACHED:

CPL to provide:

1. the chemical structure for the impurities in the drug substance;
2. justification that the overage is due to manufacturing loss of product and not due to degradation;
3. the shelf life data for the mupirocin in the drug substance;
4. a methods validation package;
5. a comparative protocol for bracketing;
6. revised labeling;
7. justification/data to support ———
8. any resistance data collected during their studies;
9. literature references/articles on the inactive ingredients;
10. if available, any susceptibility zone diameter data collected;
11. reasons why patients did not reach end of therapy.

UNRESOLVED ISSUES OR ISSUES REQUIRING FURTHER DISCUSSION:
FDA to provide:

1. CPL with the statistical reviewer comments on their submission from December 2000;

2. biopharmaceutical comments on the submitted protocol.

Minutes Preparer: _____
Maureen P. Dillon-Parker
Project Manager

Chair Concurrence: _____
Janice M. Soreth, M.D.
Division Director

APPEARS THIS WAY
ON ORIGINAL

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

/s/

Maureen Dillon-Parker
12/18/01 09:50:51 AM

Janice Soreth
12/20/01 06:27:43 PM