CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 74-579

ADMINISTRATIVE DOCUMENTS

Application: **ANDA 74579/000**
Stamp: **02-DEC-1994** Regulatory Due:
Applicant: **CLAY-PARK LABS**
1700 BATHGATE AVE
BRONX, NY 10457

Priority: Org Code: **600**
Action Goal: District Goal: **02-FEB-1996**
Brand Name:
Established Name: **BETAMETHASONE DIPROPIONAT**
Generic Name:
Dosage Form: **CRM (CREAM)**
Strength: **0.05%**

FDA Contacts:			
J. BUCCINE	**(HFD-617)**	**301-827-5848**	**, Project Manager**
E. SCHAEFER	**(HFD-627)**	**301-827-5848**	**, Review Chemist**
P. SCHWARTZ	**(HFD-629)**	**301-827-5848**	**, Team Leader**

Overall Recommendation:

ACCEPTABLE on 28-OCT-1997 by M. EGAS (HFD-322) 301-594-0095
WITHHOLD on 12-AUG-1997 by J. SINGER (HFD-324) 301-594-1089
WITHHOLD on 10-APR-1997 by S. FERGUSON (HFD-324) 301-827-0062

Establishment:

Profile: **NEC** OAI Status: **NONE** Responsibilities:
Last Milestone: **OC RECOMMENDATI05-MAR-1997** **FINISHED DOSAGE OTHER TESTER**
Decision: **ACCEPTABLE**
Reason: **BASED ON PROFILE**

Establishment: **2450054**
CLAY PARK LABORATORIES INC
1700 BATHGATE AVE
BRONX, NY 10457

DMF No:
AADA No:

Profile: **OIN** OAI Status: **NONE** Responsibilities:
Last Milestone: **OC RECOMMENDATI28-OCT-1997** **FINISHED DOSAGE MANUFACTURER**
Decision: **ACCEPTABLE**
Reason: **DISTRICT RECOMMENDATION**

Establishment:

Profile: **CSN**
Last Milestone:
Decision:
Reason:

NCE MANUFACTURER

CDER Establishment Evaluation Report for November 21, 1997

Application: **ANDA 74579/000**
Stamp: **02-DEC-1994** Regulatory Due:
Applicant: **CLAY-PARK LABS**
1700 BATHGATE AVE
BRONX, NY 10457

Priority:
Org Code: **600**
Action Goal:
District Goal: **02-FEB-1996**
Brand Name:
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Establishment:

Profile: **NEC** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDAT 05-MAR-1997**
Decision: **ACCEPTABLE**
Reason: **BASED ON PROFILE**
Responsibilities: **FINISHED DOSAGE OTHER TESTER**

Establishment: **2450054**
CLAY PARK LABORATORIES INC
1700 BATHGATE AVE
BRONX, NY 10457
DMF No:
AADA No:

Profile: **OIN** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDAT 28-OCT-1997**
Decision: **ACCEPTABLE**
Reason: **DISTRICT RECOMMENDATION**
Responsibilities: **FINISHED DOSAGE MANUFACTURER**

Establishme

Profile: **CSN** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDAT 05-MAR-1997**
Decision: **ACCEPTABLE**
Reason: **BASED ON PROFILE**
Responsibilities: **DRUG SUBSTANCE MANUFACTURER**

ANDA APPROVAL SUMMARY

ANDA: 74-579 DRUG PRODUCT: Betamethasone Dipropionate

FIRM: Clay-Park DOSAGE FORM: Cream STRENGTH: 0.05%

CGMP STATEMENT/EIR UPDATE STATUS:

The facilities were found to be acceptable on 10/28/97.

BIO STUDY:

The applicant was informed on 2/12/96 that "The Division of Bioequivalence has completed its review and has no further questions at this time."

ANALYTICAL METHODS VALIDATION:

The drug substance and the drug product are covered by monographs in USP 23.

STABILITY - ARE CONTAINERS USED IN STUDY IDENTICAL TO THOSE IN CONTAINER SECTION?:

Yes.

LABELING:

Lillie Golson found the labeling to be satisfactory on 12/9/96.

STERILIZATION VALIDATION (IF APPLICABLE): N/A

SIZE OF BIO BATCH (FIRM'S SOURCE OF NDS OK?):

is adequate as of 1/16/97.

SIZE OF STABILITY BATCHES - (IF DIFFERENT FROM BIO BATCH, WERE THEY MANUFACTURED VIA THE SAME PROCESS?):

PROPOSED PRODUCTION BATCH - MANUFACTURING PROCESS THE SAME AS BIO/STABILITY?:

The proposed production batch sizes are he proposed instructions are the same as those which were used to make the exhibit batch.

CHEMIST: Eugene L. Schaefer, Ph.D. DATE: 11/7/97

TEAM LEADER: Paul Schwartz, Ph.D /S/ DATE: 11/7/97

/S/

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration

Memorandum

Date AUG 12 1997

From Consumer Safety Officer
Investigations & Preapproval Compliance Br/DMPQ (HFD-324)

Subject Recommendation to Withhold Approval
Betamethasone Dipropionate Cream, 0.05% (ANDA 74-579)

To Gordon R. Johnston
Office of Generic Drugs (HFD-601)

Applicant/Firm: Clay-Park Labs, Inc
1700 Bathgate Ave
Bronx, NY 10457
CFN #2450054

We have completed our review of the Establishment Inspection Report (EIR) for Clay-Park Labs located at 1700 Bathgate Ave, Bronx, NY 10457. The facility was inspected by the FDA New York District Office from May 20 to June 6, 1997.

We have also completed our review of the Clay-Park submission dated June 17, 1997, which responded to the Observations listed in the Form FDA 483.

The Division of Manufacturing and Product Quality (DMPQ) concurs with the District's recommendation to withhold approval of ANDA 74-579. Significant CGMP deficiencies noted during the inspection include but are not limited to the following:

A copy of the EIR is attached for your review.

If you have any questions please contact me at (301) 827-0066.

John M. Singer

John M. Singer

Attachment

F/e 74-579

RECORD OF TELEPHONE CONVERSATION/MEETING

I returned a call from Gaybrial Lieber of ClayPark who asked what can be done to move their applicatation forward. I checked record and noted we had sent a cGMP letter dated 5/20/97 which stated that when Claypark was informed by the District that they were acceptable cGMP wise that they could amend the application. At time letter was prepared we had been informed that Clay Park would not be ready for inspection until 12/97. Mr. Lieber said an inspection had occured from late May until early June. They were issued a 483 which they responded to.

{I checked EES and noted that a withhold recommendation had been made by district which has been recently upheld by OC}

I suggested Mr. Lieber contact district for status - though it appears a new inspection will be needed.

DATE
8/20/97

ANDA NUMBER
74-579

IND NUMBER

TELECON

INITIATED BY X **APPLICANT/SPONSOR** _ **FDA**

MADE X **BY TELE.** _ **IN PERSON**

PRODUCT NAME
Betamethasone

FIRM NAME
Clay Park

NAME AND TITLE OF PERSON WITH WHOM CONVERSATION WAS HELD
Gabriel Lieber

TELEPHONE NUMBER
718-960-0142

SIGNATURE
/S/

U.S. FOOD AND DRUG ADMINISTRATION

NORTHEAST REGION
NEW YORK DISTRICT

Memorandum

DATE : July 29, 1997

TO : CDER/Office of Compliance/Drug Manufacturing Product Quality (HFD-324)
Attn: John Singer

FROM : New York District
William Friedrich Compliance Officer (HFR-NE140)

SUBJECT: District withold recommendation
ANDA 74-579, Betamethasone Diproprionate 0.05% Cream
EIR 5/20...6/4/97

FIRM : Clay Park Labs, Inc.
Bronx NY

1. Contacts

New York District:
William Friedrich, Compliance officer
850 Third Ave
Brooklyn NY 11232
Telephone 718/340-7000 ext. 5532 Alternate: Larry Daurio, Lead Compliance Officer 718/340-7000 ext. 5708
Larry Farina, Preapproval Manager
LIRP
6800 Jericho Tpk. Suite 109E
Syosset NY 11791
516/921-2869

2. Summary

As per my July 28's conversation with Mr. Singer, I am submitting relevant portions of the firm's response of June 17, 1997 to the FDA483 issued at the close of the subject inspection. This is to provide you with as complete information as possible relative to the district's recommended withhold approval of the application as a result of the inspection. The firm manufactured one in July 1992, and filled portions in September and November 1992 that totalled about ½ the batch. The inspection took this finding and cited on the FDA483

The submitted portions of the firm's response include Exhibits I through VII. Exhibit VIII is a duplicate of the [redacted] and [redacted] room temperature data on September 1992 fills, already submitted as Exhibit II and with the EIR. The Exhibit II contains data from more recent testing vs the EIR charts: Both the [redacted] and [redacted] add 27 month and 42 month potency, 42 month preservative assay, and 54 month microbial limits (MLT). Exhibits IX through XII pertain to cleaning validations, and are not submitted because the issues do not have specific significance for preapproval of this product and the district finds that the submissions are adequate explanations and promises of correction.

/S/

William Friedrich
Compliance Officer
New York District

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
FOOD AND DRUG ADMINISTRATION

ESTABLISHMENT EVALUATION REQUEST

REQUEST TYPE *(Check One)* ☒ Original ☐ FollowUp ☐ FUR	DATE April 17, 1995 AMW	PHONE NO . 594-1841	EER ID # 8008
REQUESTORS NAME: Gene Schaefer/ AM Weikel	DIVISION: Office of Generic Drugs		MAIL CODE: HFD-629
APPLICATION AND SUPPLEMENT NUMBER: ANDA 74-579			
BRAND NAME:	ESTABLISHED NAME: Betamethasone Dipropionate Cream		
DOSAGE STRENGTH: 0.05%			STERILE ☐Yes ☒ No
PROFILE CLASS:: OIN	PRIORITY CLASSIFICATION *(See SMG CDER-4820.3)*		
APPLICANT'S NAME: Clay-Park Labs, Inc.			
APPLICANT'S ADDRESS: 1700 Bathgate Ave. Bronx, NY 10457			
COMMENTS :			

FACILITIES TO BE EVALUATED

(Name and Complete Address)	RESPONSIBILITY	DMF NUMBER/ PROFILE CODE	FKEY CIRTS ID	HFD-324 USE ONLY
1. Applicant	Manufacturing and testing facilities	oin	19684 CPLR 19185	UN 1/30 firm not ready
	Testing facilities: Antimicrobial Effectiveness			C 1/24/95
	Manufacturer of NDS			C 8/10/94
4.				
5.				

FOR HFD-324 USE ONLY:	CSO C	/S/	DATE RECEIVED APR 18 1995 DATE 4/10/97

FORM FDA 3274 (8/92) Distribution: Original and Yellow Copy: HFD-324.
cc: ANDA 74-579 HFD-629/Div File, HFD-617/DWilson, HFD-617/TAmes, HFD-629/JSimmons HFD-629/GJSmith
x:\wpfile\eerforms\74579

DATE: March 12, 1997

TO: Mark Lynch, Director, Investigations & Compliance

Evaluation Branch, CDER/HFD-324

INFO: Edward T. Warner, RFDD - Northeast Region, HFR-NE1
Paul D'Eramo, Office of the RFDD-Mid-Atl Rgn, HFR-MA1

George Boone, Director, NYK-RL, HFR-NE500
Jerome Woyshner, Dir-Dom Invest Br. NYK-DO, HFR-NE150
Larry Farina, NYK-DO, New Drug Approval Mgr. HFR-NE1500

FROM: Acting Director, New York District, HFR-NE100

SUBJECT: 10-Day Notification ANDA 74-579

PRODUCT: Betamethasone Dipropionate Cream 0.05%

APPLICANT & ESTABLISHMENT: Clay Park Labs, Inc.
1700 Bathgate Ave.
Bronx, NY 10457
CFN #2450054

ESTABLISHMENT TYPE: Manufacturer

DATE OF ASSIGNMENT: Originally issued 4/24/95

DATE ANDA AUDITED: 3/4/97

DISTRICT RECOMMENDATION: See comments

SAMPLES COLLECTED: None

COMMENTS: —

During the inspection in 6/96, the firm had planned on withdrawing this ANDA. However, the current inspection of this firm found that they will not be ready for this application until 12/97. A pre-approval inspection is planned for 12/97.

DIANA AMADOR
Acting DISTRICT DIRECTOR
New York District

LABELING REVIEW WORKSHEET

Approval Summary Date 11/1/96 Supersedes this Worksheet.

FIRM: Clay Park Labs, Inc USP ANDA: 74-579
DRUG: Betamethasone Dipropionate Cream, 0.05%

LABELING OF THE LISTED DRUG

FIRM: Schering (Diprosone) NDA: 17-536
APPROVAL DATE: 12/2/82 REV.DATE: 4/82

CONTAINER LABELS

APPROVED COPY ON FILE? Yes
USP CONTAINER/CLOSURE REQUIREMENTS: Preserve in collapsible tubes or in tight containers.

RECOMMENDED STORAGE STATEMENT:
ANDA: Store between 2° and 30° C (36° and 86° F)
NDA: same as ANDA

OTHER KEY ISSUES: none

INSERT LABELING

PATENT & EXCLUSIVITY ISSUES: none

BIO ISSUES: Pending

ALL INACTIVE INGREDIENTS CITED? Yes
OTHER KEY ISSUES: The lotion is an approved application ANDA

APPROVAL SUMMARY

CONTAINER LABELS: 15 g and 45 g submitted ~~April 20~~ October 11, 1995.

CARTON LABELING: 15 g and 45 g submitted ~~April 20,~~ October 11 1995

INSERT LABELING (SUBMISSION DATE): November 12, 1995 (R 11/95)

FORMULATION/SCORING SUMMARY: Cream.

COMMENTS OR FUTURE REVISIONS NEEDED: Minor changes needed: The product name should be relocated closer to the dosage form (See draft). Chemical name insert the beta symbol in two location after the 11 & 16. PRECAUTIONS - Bold the subsection headings "General" and "Pregnancy:...".

1° REVIEWER: Angela Payne /S/ 3/95

SUPERVISOR: /S/ DATE: 11/22/95

See Rev 9.1996 review

74579ap.1

Clay Park was called on 10/24/95 to request FPL of the insert labeling - the amendment is in a memo stating labeling is satisfactory for approval. except that there is draft labeling.

Mrs Billeta said she could have FPL insert labeling in 2 weeks.

NDA NUMBER
114-579

IND NUMBER
10/24/95

TELECON/MEETING

INITIATED BY
- ☐ APPLICANT/ SPONSOR
- ☐ FDA

MADE
- ☒ BY TELEPHONE
- ☐ IN PERSON

PRODUCT NAME
Betamethasone Dipropionate Cream

FIRM NAME
Clay Park

NAME AND TITLE OF PERSON WITH WHOM CONVERSATION WAS HELD
Tsion Billeta

TELEPHONE NO.
(718) 901-2800

NATURE OF DOCUMENT

/S/

10/24/95

DIVISION

ORIGINATOR

RECORD OF TELEPHONE CONVERSATION

The sponsor sent a FAX dated 12/12/96 (attached) requesting a telecon to discuss information requested in a prior telecon dated 12/6/96 (also attached). FDA participants included Dr. Paul Schwartz, Dr. Gene Schaefer, and Mr. Joseph Buccine. The following issues were discussed.

1. The sponsor has collected 24 months stability data. These data should be used to set pH limits. The data and revised limits will be submitted.

2. The sponsor commits to conduct PET at and below the lowest spec for preservative concentration (80%) post approval.

3. The sponsor agrees to set degradent specs as follows:

The sponsor will submit a telephone amendment and f/u with a hard copy to the ANDA.

ons\7457

DATE 12/17/96

ANDA NUMBER 74-579

TELECON

INITIATED BY
_ APPLICANT/ SPONSOR
X FDA

MADE
X BY TELE.
_ IN PERSON

PRODUCT NAME
Betamethasone Dipropionate Cream USP, 0.05% (base)

FIRM NAME
Clay-Park

NAME AND TITLE OF PERSON WITH WHOM CONVERSATION WAS HELD
Gene Anders
Tsion Bellete

TELEPHONE NUMBER
(718)960-9952

SIGNATURE
/S/
Joseph Buccine

I
30
arTz 12/17/96

Telephone Conversation Memorandum

ANDA: 74-579

DRUG: Betamethasone Dipropionate Cr.

FIRM: Clay-Park Labs

PERSONS INVOLVED: Tison Bellete

PHONE NUMBER:

DATE: December 6, 1996

Background:

GSchaefer requested I contact firm to relate two deficiencies noted during the review of a telephone amendment dated 11/21/96. The deficiencies detail a change from a previous specification for the pH range and a request to perform preservative effectiveness testing to demonstrate the preservative is effective at the lower limit of the preservative concentration.

I related the following information to TBellete:

New Deficiency: Page 6 of , and page 5 of which you provided on November 21, 1996, are <u>unsatisfactory</u> because their pH limits are "between ather than as in your amendment of October 29, 1996.

TBellete indicated this was an intentional change and I recommended that supporting data be supplied or referenced in their telephone amendment response.

New Deficiency: Pages 1974 to 1976 of the original ANDA support the effectiveness of the preservative at 100% of it's label concentration, but not at it's lower limit. Please make a small test batch containing p-chloro-m-cresol at some concentration <u>lower than</u> the lower limit of w/w), have APET performed on that test batch, and report the results.

TBellete indicated that this request would be discussed with quality control individuals and further clarification may be required. I recommended she contact Joe Buccine for further clarification if necessary.

Timothy W. Ames, R.Ph., M.P.H.
Project Manager, Div Chem II, Branch 7, OGD

/S/

:lecons\phone.135

RECORD OF TELEPHONE CONVERSATION/MEETING

At the request of Drs. Schwartz and Schaefer, I called Ms. Bellete and requested that the following information be submitted as a telephone amendment:

1. Preservative Effectiveness Test results supporting the stability limits for p-chloro-m-cresol.

2. Page 6 of and Page 5 of

3. Stability data to support the proposed limits for Betamethasone 17-Propionate, Betamethasone 21-Propionate, and Total Related Substances.

The response should be submitted by fax and followed with a hard copy submission to the ANDA.

Ms. Bellete agreed.

ons\7457

DATE 11/20/96

ANDA NUMBER 74-579

IND NUMBER

TELECON

INITIATED BY _ APPLICANT/ SPONSOR X FDA

MADE X BY TELE. _ IN PERSON

PRODUCT NAME
Betamethasone Dipropionate Cream USP, 0.05% (base)

FIRM NAME
Clay-Park

NAME AND TITLE OF PERSON WITH WHOM CONVERSATION WAS HELD
Tsion Bellete

TELEPHONE NUMBER
(718)960-9952

SIGNATURE
/S/
Joseph Buccine

SUPERSEDES APPROVAL SUMMARY DATED NOVEMBER 22, 1995

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

ANDA Number: 74-579 (phone amendment)
Date of Submission: November 1, 1996

Applicant's Name: Clay-Park Labs, Inc.

Established Name: Betamethasone Dipropionate Cream USP, 0.05%

APPROVAL SUMMARY (List the package size, strength(s), and date of submission for approval):

Do you have 12 Final Printed Labels and Labeling? Yes

Container Labels: 15 g and 45 g
Satisfactory as of October 11, 1995 submission

Carton Labeling: 15 g and 45 g
Satisfactory as of November 1, 1996 submission

Professional Package Insert Labeling:
Satisfactory as of November 12, 1995 submission (Rev 11/95)

BASIS OF APPROVAL:

Was this approval based upon a petition? No

What is the RLD on the 356(h) form: Diprosone Cream

NDA Number: 17-536

NDA Drug Name: Betamethasone Dipropionate

NDA Firm: Schering Corporation

Date of Approval of NDA Insert and supplement #: 12/2/82.
Has this been verified by the MIS system for the NDA?
Yes

Was this approval based upon an OGD labeling guidance? No

Basis of Approval for the Container Labels: NDA 17-536

Basis of Approval for the Carton Labeling: NDA 17-536

Post Approval Revisions:

In addition to those listed on approval worksheet of November 22, 1995:

Revise carton labeling and container label to read, "Usual Dosage".

FOR THE RECORD:

This review supersedes Approval Summary of November 22, 1995. Clay-Park telephoned our office October 31, 1996, with the discovery that the carton labeling was incorrect (0.5% rather than 0.05%). They amended the application with corrected labeling. The container labels and insert labeling were not effected.

Date of Review:
December 9, 1996

Date of Submission:
November 1, 1996

Primary Reviewer:

Date:
12/10/96

Secondary Reviewer: /S/

Date:
12/10/96

Team Leader: /S/

Date:
12/10/96

---

cc:

1.1

REVIEW OF PROFESSIONAL LABELING #1

ANDA

DRAFT Container labels, carton and insert labeling

DATE OF REVIEW: March 16, 1995

ANDA #: 74-579

NAME OF FIRM: Clay Park labs

NAME OF DRUG: Betamethasone Dipropionate Cream USP, 0.05% (base)

DATE OF SUBMISSION: December 1, 1994

COMMENTS:

Container: 15 g and 45 g

1. Relocate the "(potency expressed as betamethasone) to appear directly below the product name.

2. Please revise "ceteth-20" to read:

"Polyethylene Glycol 1000 cetyl Ether"

3. Delete "#" after NDC.

Carton: Not submitted 15 g and 45 g

We acknowledge your comment that the proposed labeling will be the same on the carton and tube. Please submit separate labels and labeling at the time of next submission.

Insert:

1. GENERAL COMMENTS

   a. As of this review, we have no record of an ANDA submission for Betamethasone Dipropionate Ointment that you reference in your combined insert labeling. Please delete all references to the ointment formulation from your insert labeling at this time. Please comment.

   b. Your insert is difficult to read. We encourage inserting paragraph breaks to separate paragraphs.

2. DESCRIPTION

   a. The "B"s in the chemical name should read "ß" (beta).

   b. See comment 2 under Container.

c. Change "empirical" to "molecular".

3. CLINICAL PHARMACOLOGY

Pharmacokinetics, Paragraph 1 - "(See DOSAGE AND ADMINISTRATION section)" should appear on the same line as the last sentence.

4. INDICATIONS AND USAGE

Delete the extra line spaces from this section.

5. PRECAUTIONS

a. Information for Patients - Delete the first paragraph (This information...intended effects.).

b. Pregnancy - The subsection heading should read as follows:

Pregnancy: *Teratogenic Effects*: Pregnancy Category C:

c. You have inserted paragraph breaks before some of your subsection headings but not all of them. Please be consistent. Please revise accordingly.

6. OVERDOSAGE

This section heading should appear in bold print to be consistent with the other section headings.

7. DOSAGE AND ADMINISTRATION

It becomes very difficult to read this information with the product title capitalized in so many places. Please revise to promote readability. In addition, delete the second bold in the dosage form.

8. HOW SUPPLIED

a. Your format should be consistent with regard to paragraph breaks. See General Comments (b).

b. The storage temperatures with units should appear on one line.

c. Delete the hyphen after "NDC".

RECOMMENDATIONS:

1. Inform the firm of the above comments.

2. Request the firm revise their labels and labeling, then prepare and submit final print container labels and carton labeling and draft insert labeling.

NOTES TO THE CHEMIST:

1. Please note GENERAL COMMENTS.

2. Please note comment 2 under Container. Do you concur?

FOR THE RECORD:

1. Review based on the listed drug (Diprosone; Schering Corp.; Approved 12/2/82; Revised 4/82). This is the latest approved labeling as of 3/16/95. We are aware that the labeling with revision date of 12/85, was submitted in an annual report, however, the text remains the same.

2. Storage/Dispensing

   ANDA: Store between 2° and 30° C (36° and 86° F).

   NDA: Same as ANDA

   USP: Preserve in collapsible tubes or in tight containers.

3. Inactive ingredients found on page 1737 (vol 1.1).

4. This firm submitted only container labels as an example of what the cartons would look like. We have ask them submit the appropriate number of labels and labeling at the time of final print.

5. We have asked the firm to delete all references to the ointment formulation because we have no record of approving or record of a new submission. The Lotion is already approved (ANDA

Angela Payne

cc:

ANDA CHECKLIST FOR COMPLETENESS AND ACCEPTABILITY OF THE APPLICATION

AADA/ANDA# 74-579

DRUG NAME Betamethasone Dipropionate

E FORM Cream USP 0.05%

SUPERVISORY CHEMIST /S/

RANDOM ASSIGNMENT (Random IV 4)
*If high potency, 1 mg/dosage unit or less, assign to Branch 2

Therapeutic Code (4020600 / Steroidal Skin Products) On Cards ✓
Comments ECI ✓

	YES	NO
Methods Validation package (3 copies) (__) Required for Non-USP drugs		
Cover Letter	12/1/94 12/2/94	
Letters of Authorization		
U.S. Agent (If Needed, Countersignature on 356h)		
DMF Referral(s)		
356h Form - Completed/Original Signature	✓	
Table of Contents	✓	
Listed Drug/Firm Diprosone Cream/Schering	✓	
AADA Monograph	✓	
Information to show proposed product is the same as the listed product: (i)(a) indications (ii) active ingredient(s) (iii) (a) route (b) dosage form (c) strength (iv) labeling -- side by side comparison - insert: 91 differences 918 + 1734	—	
container: 91 different 92 different all written IIG rouge		✓
Same Formulation? (Ophthalmics/Otics/Externals/Parenterals)		✓
Parenterals: Same Size Container (strength/volume)		✓
Petition Required	—	
Debarment Certification Page 1972	—	
List of Convictions		
Third Copy Certification NYK-DO	✓	
Patent Certification page 13	✓	
Use Patent Statement?	✓	
Exclude Use in labeling/indications?		
Exclusivity Addressed (If Applicable)		
Five year exclusivity? If yes, cannot be filed until expiration or after 4 years if challenged.	✓	
Labeling: 4 copies of draft (✓) or 12 copies of FPL ( )	✓	
Statement re Rx/OTC Status	✓	
Components & Composition (Unit Composition)	✓	
Manufacturing Controls	✓	
Batch Formulation	✓	
Master Production Batch Record for largest batch size intended for production. (No more than 10x pilot batch)	✓	
Certification of GMP.	✓	
Description of Facilities	✓	
Address of Manufacturing Site for Production Batches	✓	
Manufacturing Procedures (Batch Records) 2725	✓	
Page entire exhibit bio batch.	✓	
Batch Number(s)/Mfg. Facility		
If Sterile product:		
Aseptic Fill____ Terminal Sterilization____		

Specifications and Tests for Active Ingredient and Dosage Form . . . . . ✓

- Source of Active Ingredient ✓
- COA from Manufacturer of Active Ingredient ✓
- Applicant COA ✓
- COA for finished product ✓

Specifications and Tests for Inactive Ingredients ✓

- Source of Inactive Ingredients Identified ✓
- COA from Manufacturer of Inactive Ingredient ✓
- Applicant COA for Inactive Ingredients ✓

Stability Profile Including Stability Data (Use of Stability Indicating Method) . . . . . ✓

- 3 mo. Accelerated Stability Data (50-75% RH) . . . . . ✓
- Batch Numbers Listed on Stability Records ✓
- Samples Statement Plus Data ✓

Bioavailability/Bioequivalence needs to go on consult

- Study . . . . . Vasoconstrictor Bioassay
- In Vivo Study/Waiver Request ✓ New methodology
- Comparative Dissolution Data . . . . . N/A
- Paragraph IV bio study acceptable for filing N/A
  - Date acceptable for filing N/A

Environmental Impact Analysis . . . . . ✓

- Compliance Statement . . . . . ✓

Reviewing CSO (William Russell)

Date 12/6/94

Recommendation: (File) Refuse to File

Supervisory Concurrence/Date ____

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MEMORANDUM OF MEETINGS
December 2 and 3, 1992

Present:

Dec. 2 Albert Rothschild, Douglas I. Ellsworth, Marilyn L. Watson, Diane M. Sullivan.

Dec. 3 Albert Rothschild, Douglas I. Ellsworth, Marilyn L. Watson, Thomas Kuchenberg, Deborah Wolf

Subject:

Applicability of Section 306(k) Certification and Conviction Information Requirements to Supplements to Certain Drug Product Applications

I. ISSUES RESOLVED

1. When are supplements to NDA's, NADA's, and ANADA's subject to the section 306(k)(1) certification requirements?

2. What is a supplement to an ANDA or an AADA for a "new or additional use" subject to the section 306(k)(1) certification and section 306(k)(2) conviction information requirements?

II. DISCUSSION

The Generic Drug Enforcement Act of 1992 ("Act") at section 306(k)(1)[1] requires that any application for approval of a drug product submitted on or after June 1, 1992, include a certification that the applicant did not and will not use in any capacity the services of any person debarred under the Act, in connection with such application. This certification requirement applies to the following drug product applications. NDA's, ANDA's, AADA's, NADA's, ANADA's, Export applications for certain unapproved products, and PLA's. [2] The Act at section 306(k)(2) establishes the

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[1] (21 U.S.C 335a(k)(1))

[2] The Act specifically defines the term "drug product" to mean "a drug subject to regulation under section 505, 507, 512, or 802 of this act or under section 351 of the Public Heath Service Act." See section 201(ee) of the Act. (21 U.S.C. 321(ee)). Thus, the following drug product applications submitted on or after June 1, 1992, are required to comply with the certification requirements of section 306(k)(1): NDA's, ANDA's, AADA's, NADA's, ANADA's, Export applications for certain unapproved

additional requirement that an applicant provide conviction information for the following applications submitted on or after June 1, 1992: original ANDA's, original AADA's, and certain supplements to ANDA's and AADA's.

The 306(k)(1) and 306(k)(2) requirements as they apply to original applications are relatively straightforward, however, these requirements as they apply to supplements are not so clear. For example, the Act does not address 306(k)(1) requirements for supplements to NDA's, NADA's, and ANADA's[3]. In addition, while the Act sets a standard for requiring supplements to ANDA's and AADA's to comply with 306(k) (i.e. those providing for a *different or additional use of the drug)*, there has been some confusion as to specifically what types of supplemental abbreviated drug applications the standard encompasses. The following discussion addresses these ambiguities and outlines the determinations made during the 12/2-3 meetings.

1. Supplements to NDA's, NADA's, and ANADA's:

306(k)(1) certification requirement applies to all supplements.

As mentioned above, the Act is silent as to 306(k)(1) requirements for supplements to NDA's, NADA's, and ANADA's. As noted by the Office of General Counsel, the agency has consistently interpreted a supplement to be an application for approval of a drug product. Thus, because certification applies to all drug product applications and because all supplements to NDA's, NADA's, and ANADA's are considered drug product applications such supplements require the 306(k)(1) certification.

2. Supplements to ANDA's and AADA's:

30(k)(1) certification and 306(k)(2) conviction information requirements apply each time the supplement provides for a use (1) not covered by the listed drug and (2) supported by clinical data.

The Act requires that supplements to ANDA's and AADA's submitted on or after June 1, 1992, providing for a *different or additional use of the drug* contain a certification and a list of all convictions, occurring within the last 5 years, for which a person can be debarred, of the applicant and affiliated persons responsible for the development or submission of such application.

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products, and PLA's.

[3] Supplements to export applications for certain unapproved products, and PLA's are not adressed because they do not exist.

The Office of Generic Drugs has advocated that the section 306(k)(1) requirement for certification and section 306(k)(2) requirement for conviction information in ANDA and AADA supplements for a *different or additional use* be limited to those supplements that provide for a new use (1) not covered by the listed drug and (2) supported by clinical data (i.e. supplements providing for a new indication, dosage form or strength that requires supporting clinical data.) Under this interpretation, only applications submitted under 21 CFR 314.54 (previously referred to as 505(b)(2) supplements to ANDA's)[4] and AADA supplements providing for a use not covered by the reference antibiotic drug and supported by clinical data, require certification and conviction information. Note that a supplement to an ANDA or an AADA that adds an indication to the labelling of the generic drug because exclusivity has expired for that indication need not contain the certification and conviction information.

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[4] The requirements of 306(k)(1) and 306(k)(2) are applicable to an "abbreviated drug applications", defined in the Act as follows:

> ...an application *submitted under section 505j or 507* for the approval of a drug that relies on the approval application of another drug with the same active ingredient to establish safety and efficacy, and...in the case of section 306, includes a supplement to such an application for a different or additional use of the drug but does not include a supplement to such an application for other than a different or additional use of the drug...

21 U.S.C. 335(ee).

Under this definition, abbreviated drug applications for a different or additional use submitted under section 505(j) or 507 for the approval of a drug that relies on the approval application of another drug with the same active ingredient must comply with 306(k) requirements.

Applications submitted under 21 CFR 314.54 are subject to the 306(k) requirements, notwithstanding that such applications are approved under 505(b)(2), are classified as NDA's under FDA regulations, and must establish safety and efficacy for the new use independently. These applications are submitted under 505(j) as supplements to an original application for approval of a drug that relies on the approval of another drug with the same active ingredient to establish safety and efficacy. Accordingly, applications submitted under 21 CFR 314.54 come within the purview of the definition of abbreviated drug application for purposes of complying with 306(k)(1) and 306(k)(2) requirements.

III. CONCLUSION

1. Supplements submitted on or after June 1, 1992, to NDA's, NADA's, and ANADA's must comply with the section 306(k)(1) certification requirements.

2. Supplements submitted on or after June 1, 1992, under 21 CFR 314.54 and AADA supplements providing for a use not covered by the reference antibiotic drug and supported by clinical data, are supplements for "new or additional use" subject to the section 306(k)(1) certification and section 306(k)(2) conviction information requirements.

Diane M. Sullivan

cc: