CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 74-579

CORRESPONDENCE

CLAY-PARK LABS, INC.

AGIS GROUP

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

NEW CORRES.
NC

Mr. Joseph Buccine
Program Manager, FDA/OGD, Chemistry - I
FDA Document Control Room #150
Metro Park North-II
7500 Cavendish Place
Rockville, MD 20855

November 10, 1997
Via FAX (301) 594-0180

Re: ANDA #74-579, Bethamethasone Dipropionate, USP, 0.05% Cream

MINOR AMENDMENT

Dear Mr. Buccine,

As a follow-up to your telephone request of Monday, November 10, 1997, Clay-Park Labs, Inc. is making a commitment to make the viscosity a part of the Clay-Park Quality Control release and the stability specifications for our Bethamethasone Dipropionate, USP, 0.05% Cream, ANDA #74-579.

Sincerely,

Gabriel Lebovic

Gabriel Lebovic
Director, Regulatory Affairs

PS You may reach me by phone at (718)-960-0142 or via FAX at (718)-960-0120.

CLAY-PARK LABS, INC.

AGIS GROUP

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

October 17, 1997

ORIG AMENDMENT

N/A2

Dr. Rashmikant M. Patel, PhD
Director of Division of Chemistry I
Office of Generic Drugs/CDER
FDA Document Control Room #150
Metro Park North-II
7500 Cavendish Place
Rockville, MD 20855

MINOR AMENDMENT

RE: ANDA # 74-579
Betamethasone Dipropionate Cream USP, 0.05%

Dear Dr. Patel,

In reference to your letter of May 20,1997, related to our ANDA # 74-579 for Betamethasone Dipropionate Cream USP, 0.05%, we would like to inform that Clay-Park Labs,Inc. was inspected for CGMP Compliance on June 1997.

On Sept 30,1997, Mr. Bill Friederich, the FDA Compliance Officer at Brooklyn, New York District Office, faxed a letter to the FDA Compliance headquarters in Rockville, MD, stating that all CGMP issues were resolved, and Clay-Park is in compliance with CGMP in regards to methods used in the manufacturing, purchasing, QC testing and stability testing of Betamethasone Dipropionate Cream USP, 0.05%.

Therefore, I would like to request that OGD issues an approvable letter to Clay-Park Lab's ANDA # 74-579, pending the forthcoming validation of the three (3) sequential batches which would confirm the homogeneity of this product.

Respectfully,
Clay-Park Labs,Inc.

Gabriel Lebovic
Director of Regulatory Affairs

/S/ 10/20/97

RECEIVED

OCT 20 1997

GENERIC DRUGS

CLAY-PARK LABS, INC.

AGIS GROUP

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

ORIG AMENDMENT

September 12, 1997

N/A

Mr. Joe Buccine
Office of Generic Drugs
CDER, Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room #150
Rockville, MD 20855-2773

RE: AMENDMENT OF PENDING APPLICATION
ANDA # 74-579
Betamethasone Dipropionate Cream USP, 0.05%

Dear Mr. Buccine,

As a follow up of Clay-Park's letter to FDA dated 12/18/1996, I am herely enclosing the results of the antimicrobial preservative effectiveness test for Betamethasone Dipropionate Cream, 0.05%, USP, Lot # P-725, tested by eport # FA 886 of 11/18/92.

In addition, I am also submitting to you the results of the antimicrobial preservative effectiveness testing of BMD Cream, 0.05% USP, for the preservative levels of 0%, 50%, 80% & 100% which clearly show that our product is effectively preserved.

Respectfully,

Gabriel Lebovic
Director of Regulatory Affairs

CLAY-PARK LABS, INC.

AGIS GROUP

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

6/17/97

Mr. Alonzo Cruse
Acting District Director
Food and Drug Administration
850 Third Ave. 7th Floor
Brooklyn, New York 11232

Dear Mr. Cruse:

As a follow-up to the FDA's pre-approval inspection of Clay Park Labs, Inc., of 05/20/97 - 06/04/97, related to Betamethasone Dipropionate 0.05% Cream, USP, ANDA # 74-579, we would like to respond to the FDA - 483 observations:

Page(s) _____

Contain Trade Secret, Commercial/Confidential Information and are not releasable.

In conclusion, we believe that the above batch of Betamethasone Dipropionate 0.05% Cream, USP, Lot # **P725** was made in accordance with FDA's 1992 requirements.

Therefore, we can assure you that the 1997 validation of the three (3) consecutive bathes will be done as per FDA's 1997 level of expectations.

Respectfully,
Gabe Lebovic
Director of Regulatory Affairs

cc: Mr. Tej Pouai
FDA Investigator
Food and Drug Administration
300 Hamilton Avenue room #309
White Plains, N.Y. 10601

ANDA 74-579

Clay-Park Labs, Inc.
Attention: Tsion Bellete
1700 Bathgate Avenue
Bronx, NY 10457

MAY 20 1997

Dear Ms. Bellete:

This is in reference to your abbreviated new drug application dated December 1, 1994, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act, for Betamethasone Dipropionate Cream USP, 0.05% (base).

Reference is also made to your amendments dated October 29, November 1, November 21, and December 12 and 18, 1996, and January 10, 15 and 17, 1997.

This application is deficient and, therefore, not approvable under 21 CFR 314.125(b)(13) because the Center for Drug Evaluation and Research is unable to find that the methods used in, and the facilities and controls used for, the manufacturing, packaging, testing, and stability testing of Betamethasone Dipropionate Cream USP, 0.05% (base) comply with current good manufacturing practice (cGMP) regulations.

Firms referenced in your application relative to the manufacturing and testing of the drug substance and drug product must be in compliance with cGMP at the time of approval. The Clay-Park Labs facility in Bronx, NY has not received an acceptable cGMP evaluation with respect to this application. Our Office of Compliance has informed us that your firm has informed the New York district that it is not ready for inspection.

Reference is further made to the telephone conversation on April 22, 1997, between your associate Gene Ander and Robert L. West of this Office. During that conversation, it was confirmed that Clay-Park will notify the district to schedule an inspection once an internal assessment of the marketability of this drug product has been completed.

Until such time when you can demonstrate to the agency that the Bronx facility complies with cGMP, your application cannot be approved. Please note that the local District Office is willing to inspect your facility upon your readiness.

You should amend this application when cGMP have been evaluated and found satisfactory. Your amendment submitted in response to this not approvable letter will be considered as a MINOR

AMENDMENT provided that the amendment contains no significant additional information. Your amendment should include a statement from a responsible company official informing the agency that this application has been recommended for approval by representatives of the local District Office. If, as a result of follow-up inspections related to the ongoing evaluation of this or other applications, it is necessary for you to significantly revise your procedures, controls or practices to correct your deficiencies, then the amendment will be considered to represent a MAJOR AMENDMENT.

The file on this application is now closed. You are required to take an action described under 21 CFR 314.120 which will either amend or withdraw the application. If you have substantial disagreement with our reasons for not approving this application, you may request an opportunity for a hearing.

Sincerely yours,

5/97

/S/

Rashmikant M. Patel, Ph.D.
Director
Division of Chemistry I
Office of Generic Drugs
Center for Drug Evaluation and Research

CLAY-PARK LABS, INC.

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

January 17, 1997

AMENDMENT
N/AM

Mr. Paul Schwartz
Office of Generic Drugs
CDER, Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room #150
Rockville, MD 20855-2773

RE: ANDA #74-579
Betamethasone Dipropionate Cream USP, 0.05%

TELEPHONE AMENDMENT

Dear Mr. Schwartz:

This refers to our telecon this morning concerning our abbreviated new drug application dated December 1, 1994 and our amendments dated October 11, 1995, November 12, 1995, October 29, 1996 and telephone amendments dated November 21, 1996, December 12, 1996, December 18, 1996, January 10, 1997 and January 15, 1997.

You indicated the following:

1. The Finished product specification submitted on January 15, 1997 must include limits for impurities ;
   and Total Degradants.
2. The specification for drug substance must include limit for Ordinary Impurities as individual and total.

Our response is as follows:

Clay-Park will provide the agency with a revised Finished Product and Drug Substance specifications after approval as we gain experience with the product. A commitment l letter is enclosed.

Should you have any question, please feel free to contact me at (718) 960-9952, fax (718) 960-0111.

Sincerely,
CLAY PARK LABS

Tsion Bellete
Manager of Regulatory Affairs

RECEIVED
JAN 21 1997
GENERIC DRUGS

CLAY-PARK LABS, INC.
1700 BATHGATE AVE. BRONX, NY 10457 (718)901-2800

November1, 1996

Mr. Douglas Sporn, Director
Office of Generic Drugs
CDER, Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room #150
Rockville, MD 20855-2773

NDA ORIG AMENDMENT

RE: ANDA #74-579
Betamethasone Dipropionate Cream USP, 0.05%

TELEPHONE AMENDMENT

Dear Mr. Sporn:

This refers to my telephone conversation with Ms. Lily Golson (FDA) on Thursday October 31, 1996 concerning our abbreviated new drug application dated December 1, 1994 and our amendments dated October 11, 1995, November 12, 1995, and October 29, 1996.

During reviewing our amendment dated October 11, 1995, we have discovered a typographical error on the color printed carton labeling. Please refer to pages 21 and 22 of this amendment. The product name is written as "Betamethasone Dipropionate Cream, **0.5%**". This was corrected to read "Betamethasone Dipropionate Cream, **0.05**%"

Enclosed for review in support of this telephone amendment are the following:

1. A form 356h
2. Revised color printed 15 and 45 g carton labelings.

Your prompt response to this communication is appreciated

Sincerely,
CLAY PARK LABS

Tsion Bellete
Asso. Mgr. of Regulatory Affairs

RECEIVED
NOV 0 4 1996
GENERIC DRUGS

CLAY-PARK LABS, INC.

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

NDA ORIG AMENDMENT

RECEIVED

NOV 01 1996

GENERIC DRUGS

October 29, 1996

Mr. Douglas Sporn, Director
Office of Generic Drugs
CDER, Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room #150
Rockville, MD 20855-2773

RE: ANDA #74-579
Betamethasone Dipropionate Cream USP, 0.05%

MINOR AMENDMENT

Dear Mr. Sporn:

Reference is made to your letter dated January 25, 1996 (copy attached) concerning our abbreviated new drug application dated December 1, 1994 and our amendments dated October 11, 1995 and November 12, 1995.

The administration's comments have been restated and our responses follow:

1. **Additional justification is needed for your reasons for the overage of the active ingredient.**

   a. **Please provide data which demonstrate actual manufacturing transfer loss, if this data is available.**

   b. **The formula could be rewritten to require the weighing of the raw material on basis of assay.**

   c. **We note that you have resubmitted stability data for the 15 g tube (page 1963 of the original ANDA), but not for the 45 g tube (page 1964 of the original ANDA), which showed a (possibly) smaller decrease of potency.**

   d. **There may be a decrease in potency, or the possible trend in the results may be due to analytical variation.**

   e. **The assay result for the bulk drug was 100.4% (page 1748 of the original ANDA) and the Clay-Park result was 99.3% (page 1754). The initial results for the drug product were all close to 101%. The lowest result at 24 months was 93.6%, which is still above the lower limit of 90.0%.**

Alternatively, you may reconsider and drop the overage prior to approval of the ANDA, or you may submit a written commitment that after you have accumulated stability data for at least three production lots, you will do the following:

a. Subject the stability data to regression analysis, including 95% confidence bands and tests for non-zero slope.

b. Use the statistical conclusions to reconsider whether an overage is needed or not.

c. If you decide an overage is not needed, supplement the ANDA to provide for removal of the overage and include manufacturing and stability data to support the change.

Response:

From statement number 1 above we have elected to use the alternative method i.e. issue a commitment letter if we chose to kee overage. A commitment letter is provided as attachment 1.

2. **The test and limits for p-chloro-m-cresol have been omitted from the finished product specifications on page 15 of the amendment of October 11, 1995.**

Response:

The test and limits for p-chloro-m-cresol have been deleted from the finished product specifications. It is becoming our practice not to test preservatives on finished product samples. Preservative testing for bulk and stability samples is sufficient from a quality control perspectives. We believe that the preservative would not change during the filling operation.. Clay-Park is in a process of conducting a PET (Preservative Effectiveness Test) for this product.

3. **The formal stability specifications which you have provided are incomplete. Please add individuals limits for the two degradants you have identified , L , as well as any other individual degradant, plus a limit on total degrandants.**

Response:

The stability specifications and stability protocol has been revised to provide the monitoring of degradation products. See attachment 2. Based upon available data limits are established for
and total degradants.

NOTE: The following changes are found to be necessary to the bulk and finished product specifications:

1. The method for microbial limit test for both specifications has been changed from USP<61>.
2. The method for p-Chloro-m-Cresol in the Bulk specifications was found to be a typographical error and is corrected to be read

The revised specifications for both bulk and finished products along with the analytical methods are enclosed. (Attachment 3)

Pursuant to 21 CFR 314.70(a), Clay Park Labs certifies that a field copy of this minor amendment has been sent to the FDA district office.

Sincerely,
CLAY PARK LABS

Tsion Bellete
Asso. Mgr. of Regulatory Affairs

CC: Mr. Edward Warner - NY District Office, FDA

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

ANDA 74-579

Clay-Park Labs, Inc.
Attention: Tsion Bellete
1700 Bathgate Avenue
Bronx, NY 10457

JAN 25 1996

Dear Madam:

This is in reference to your abbreviated new drug application dated December 1, 1994, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act, for Betamethasone Dipropionate Cream USP, 0.05% (base).

Reference is also made to your amendments dated October 11 and November 12, 1995.

The application is deficient and, therefore, not approvable under Section 505 of the Act for the following reasons:

1. Additional justification is needed for your reasons for the overage of the active ingredient.

   a. Please provide data which demonstrate actual manufacturing transfer loss, if this data is available.

   b. The formula could be rewritten to require the weighing of the raw material on basis of assay.

   c. We note that you have resubmitted stability data for the 15 g tube (page 1963 of the original ANDA), but not for the 45 g tube (page 1964 of the original ANDA), which showed a (possibly) smaller decrease of potency.

   d. There may be a decrease in potency, or the possible trend in the results may be due to analytical variation.

   e. The ssay result for the bulk drug was 100.4% (page 1748 of the original ANDA) and the Clay-Park result was 99.3% (page 1754). The initial results for the drug product were all close to 101%. The lowest result at 24 months was 93.6%, which is still above the lower limit of 90.0%.

Alternatively, you may reconsider and drop the overage prior to approval of the ANDA, or you may submit a written

commitment that after you have accumulated stability data for at least three production lots, you will do the following:

a. Subject the stability data to regression analysis, including 95% confidence bands and tests for non-zero slope.

b. Use the statistical conclusions to reconsider whether an overage is needed or not.

c. If you decide an overage is not needed, supplement the ANDA to provide for removal of the overage and include manufacturing and stability data to support the change.

2. The test and limits for p-chloro-m-cresol have been omitted from the finished product specifications on page 15 of the amendment of October 11, 1995.

3. The formal stability specifications which you have provided are incomplete. Please add individual limits for the two degradants you have identified,

propionate, as well as any other individual degradant, plus a limit on total degradants.

The file on this application is now closed. You are required to take an action described under 21 CFR 314.120 which will either amend or withdraw the application. Your amendment should respond to all the deficiencies listed. A partial reply will not be considered for review, nor will the review clock be reactivated until all deficiencies have been addressed. Your response to this letter will be considered a MINOR AMENDMENT and should be plainly marked as such in your cover letter. Please note that if the pending bioequivalence review is not received prior to completion of the chemistry and/or labeling review of your amendment, issuance of our subsequent action letter may be delayed. Further, if a major deficiency is cited in the bioequivalence review, the subsequent Not Approvable letter will request that the reply be declared a MAJOR AMENDMENT. If you have substantial disagreement with our reasons for not approving this application, you may request an opportunity for a hearing.

Sincerely yours,

/S/

Rashmikant M. Patel, Ph.D.
Director
Division of Chemistry I
Office of Generic Drugs
Center for Drug Evaluation and Research

CLAY-PARK LABS, INC.
1700 BATHGATE AVE. BRONX, NY 10457 (718)901-2800

November 12, 1995

Angela Payne
Office of Generic Drugs
CDER, Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room #150
Rockville, MD 20855-2773

RE: ANDA #74-579
Betamethasone Dipropionate Cream, USP 0.05%

MINOR AMENDMENT

Dear Ms Payne:

Per your request during our telephone conversation on October 25, 1995, Clay Park Labs is herewith submitting 12 final printed inserts for the above mentioned product.

Should you have any question please feel free to contact me at (718) 901-2800.

Sincerely
CLAY PARK LABS

Tsion Bellete
Asso. Mgr. of Regulatory Affairs

CLAY-PARK LABS, INC.

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

January 15, 1997

NDA ORIG AMENDMENT

N/Am

Mr. Joe Buccine
Office of Generic Drugs
CDER, Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room #150
Rockville, MD 20855-2773

RE: ANDA #74-579
Betamethasone Dipropionate Cream USP, 0.05%

TELEPHONE AMENDMENT

Dear Mr. Buccine:

This refers to your facsimile dated January 13, 1997 (copy attached) and a teleconference on January 14, 1997, between yourself and Gene Schaffer from the agency and Gene Ander, David Fell and myself from Clay-Park, concerning our abbreviated new drug application dated December 1, 1994 and our amendments dated October 11, 1995, November 12, 1995, October 29, 1996 and telephone amendments dated November 21, 1996, December 12, 1996, December 18, 1996 and January 10, 1997.

We have revised the analytical procedure to reflect the changes you indicated in the faxed letter. Copies of the revised procedures for Bulk, Finished and Stability samples are enclosed.

Should you have any question, please feel free to call me at (718) 960-9952.

Sincerely,
CLAY PARK LABS

Tsion Bellete
Manager of Regulatory Affairs

RECEIVED

JAN 16 1997

GENERIC DRUGS

RECORD OF TELEPHONE CONVERSATION/MEETING

In going over the approval package for this product, I noticed that release limits for impurities had never been requested. I called Ms. Bellette and asked her to include individual and total limits for release of the drug product. She said they had not tested for them and was reluctant to set a specific limit without data. She asked if we would accept a commitment to add the limits post approval after they tested the validation batches. I agreed that that would be acceptable and suggested that she should provide limits in a changes being effected supplement.
I also asked her to add individual limits to release of the drug substance. They currently only do the ordinary impurities USP test with a limit of 2% total.
She agreed to fax in the commitment today.

DATE Jan 17, 1997

ANDA NUMBER
74-579

IND NUMBER

TELECON

INITIATED BY _ APPLICANT/ SPONSOR
MADE BY TELE.

X FDA
_ IN PERSON

PRODUCT Betamethasone dipropionate cream, 0.05%

FIRM NAME
Clay Park

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

TELEPHONE NUMBER
+-(718) 960-9952-

SIGNATURE
/S/
1/17/97

1/13/97 ESS 1/14/97 1/16/97

~~1/10/97~~

RECORD OF TELEPHONE CONVERSATION

Reference is made to FDA's fax dated 1/13/97. The sponsor called to discuss comments in the fax.

FDA and the sponsor reached agreement on the following issues:

*The sponsor agrees to abide by the following USP standard for Betamethasone Dipropionate. "In a suitable chromatogram, the lowest and highest peak area ratios (R_s) of three successive injections of the *Standard preparation* agree within 2%" (USP 23, page 191).

*For the system suitability test, the resolution factor R, between the Betamethasone Diproprionate and Beclomethasone Dipropionate peaks, are not less than

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

cc:

ons\7457

DATE 1/14/97

ANDA NUMBER 74-579

FDA PARTICIPANTS
Dr. Gene Schaefer
Joseph Buccine

INITIATED BY SPONSOR

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

FIRM NAME
Clay-Park

NAME AND TITLE OF PERSON WITH WHOM CONVERSATION WAS HELD
Dr. David Fell
Gene Anders
Tsion Bellete

TELEPHONE NUMBER
(718)960-9952

SIGNATURE
/S/
Joseph Buccine

CLAY-PARK LABS, INC.

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

January 10, 1997

Mr. Joe Buccine
Office of Generic Drugs
CDER, Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room #150
Rockville, MD 20855-2773

NDA ORIG AMENDMENT
N/A rm

RE: ANDA #74-579
Betamethasone Dipropionate Cream USP, 0.05%

TELEPHONE AMENDMENT

Dear Mr. Buccine:

This refers to our telephone communication on January 9, 1997 concerning our abbreviated new drug application dated December 1, 1994 and our amendments dated October 11, 1995, November 12, 1995, October 29, 1996 and telephone amendments dated November 21, 1996, December 12, 1996 and December 18, 1996.

You indicated that a review chemist discovered differences in the system suitability requirements between the October 29, 1996 and December 18, 1996 amendments.

As we were in the process of revising the stability specification, it was discovered that while the reagents, conditions and internal standard preparation for the assay of betamethasone dipropionate were consistent with directives appearing in the USP monograph, several inconsistencies with that monograph existed. Since the ANDA designates this USP procedure for product testing, all of the test monographs (bulk, finished and stability) were revised so that each now complies with the compendial source. Therefore, the system suitability requirements are replaced with those given in the USP monograph.

Should you have any question, please feel free to call me at (718) 960-9952.

Sincerely,
CLAY PARK LABS

Tsion Bellete
Manager of Regulatory Affairs

RECEIVED
JAN 15 1997
GENERIC DRUGS

ANDA 74-579

Betamethasone Dipropionate Cream USP, 0.05%

Clay-Park Labs, Inc.

There are two comments regarding your response of January 10, 1997:

1. The system suitability requirement proposed in your December 16 amendment does not comply with the compendial source. Three numbers, of which the lowest and highest differ by more than , can have a relative standard deviation less than For example, the set 1.00, 1.01, 1.03 would meet your proposed test, but would fail the USP test, if rounding errors are avoided.

2. A USP monograph is a minimum set of requirements. The agency has the authority to set a higher standard. Many, perhaps most, of the USP assay methods are not stability indicating. A stability-indicating method should include one or more system suitability tests that guarantee specificity.

If you wish to discuss these comments further, let me know and I'll schedule a telecon with the review chemist.

Thank you,

Joe

1/13/97

CLAY-PARK LABS, INC.
1700 BATHGATE AVE. BRONX, NY 10457 (718)901-2800

December 18, 1996

NDA ORIG AMENDMENT
N/A??

Mr. Joe Buccine
Office of Generic Drugs
CDER, Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room #150
Rockville, MD 20855-2773

TELEPHONE AMENDMENT

RE: ANDA #74-579
Betamethasone Dipropionate Cream USP, 0.05%

Dear Mr. Buccine:

This refers to the telephone communication on December 17, 1996 between Gene Ander and myself from Clay-Park and Gene Schaffer, Paul Schwartz and yourself from the agency, concerning our abbreviated new drug application dated December 1, 1994 and our amendments dated October 11, 1995, November 12, 1995, October 29, 1996 and telephone amendment dated November 21, 1996 and December 12, 1996. It is our understanding that the approval letter will be forthcoming based on our commitment below:

The issues discussed were as follows:

1. Clay-Park to provide a Preservative Effectiveness Test at lower concentration of preservative.
2. Long-term stability data to support the pH limit must be provided. The pH limit should be revised based on the long-term stability data.
3. The limits for the degradants must be revised based on the data provided on November 21, 1996 amendment.

1. Clay-Park is committed to perform Preservative Effectiveness test at different concentrations of preservative (0, 50, and 80%) and submit the results before marketing the product. Based on our discussion yesterday, we are submitting a commitment letter that we will perform PET before marketing.

2. Based on the available stability data, we have revised the Bulk and Finished products specifications to change the pH limit and stability protocol have been revised to change the addition, the stability specifications

DEC 20 1996

GENERIC DRUGS

3. The limits for degradants have been changed as follows:

-
-
-

Enclosed please find the following materials in support of this telephone amendment:

1. A 356 h form
2. A commitment letter to perform Preservative Effectiveness Test.
3. Long-term stability data for lot # P725, 15 and 45 g tubes.
4. Revised specifications along with the analytical methods for bulk, finished and stability samples.
5. Revised stability protocol

Pursuant to 21 CFR 314.70(a), Clay Park Labs certifies that a field copy of this telephone amendment has been sent to the FDA district office.

Should you have any question please feel free to call at (718) 960-9952.

Sincerely,
CLAY PARK LABS

Tsion Bellete
Manager of Regulatory Affairs

cc: Edward Warner (NY District Office)

CLAY-PARK LABS, INC.
AGIS GROUP
1700 BATHGATE AVE. BRONX, NY 10457 (718)901-2800

December 12, 1996

Mr. Joe Buccino
Office of Generic Drugs
CDER, Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room #150
Rockville, MD 20855-2773

RE: ANDA #74-579
Betamethasone Dipropionate Cream USP, 0.05%

Dear Mr. Buccino:

This refers to my telephone communication with you this morning and with Mr. Tim Ames on December 6, 1996 concerning our abbreviated new drug application dated December 1, 1994 and our amendments dated October 11, 1995, November 12, 1995, October 29, 1996 and telephone amendment dated November 21, 1996.

On November 20, 1996, the agency requested that we provide Preservative Effectiveness Test results to support the stability data for p-Chloro-m-cresol and also to submit the missing pages from Bulk and Finished product specifications.

In our response to November 20th request, we stated that "The Anti-Microbial Preservative Effectiveness result demonstrated that the product was adequately preserved and the product is found to be stable over a 42 month period. The product is still adequately preserved since the concentration (100%) of the preservative did not decrease over a 42 month test period." Concerning the pH. Since stability samples are showing lower pH results, we revised our specifications from .

Mr. Ames in his telephone communication on December 6, 1996, stated that, we are required to make a batch with a lower level of p-Chloro-m-cresol and submit the results. In addition the pH limit from the Bulk and Finished product specifications has to be set back fror to the original specification which was

Since this application is two years old, we suggest a solution to these technical issues whereby an approval letter from the agency would request that we commit to the following <u>before</u> marketing:

1. Clay-Park will commit to perform the PET test and submit the results after approval.

2. Clay-Park will commit to change the pH limit to

I understand that this will be resolved early next week. We are available for a conference call so we can resolve this to our mutual benefit.

Should you have any question please feel free to call at (718) 960-9952.

Sincerely,
CLAY PARK LABS

Tsion Bellete
Manager of Regulatory Affairs

CLAY-PARK LABS, INC.

AGIS GROUP

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

ORIG AMENDMENT

N/AM

November 21, 1996

Mr. Joe Buccine
Office of Generic Drugs
CDER, Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room #150
Rockville, MD 20855-2773

RECEIVED
NOV 2 3
FEDERAL DRUG

RE: ANDA #74-579
Betamethasone Dipropionate Cream USP, 0.05%

TELEPHONE AMENDMENT

Dear Mr. Buccine:

This refers to our telephone communication on November 20, 1996 concerning our abbreviated new drug application dated December 1, 1994 and our amendments dated October 11, 1995, November 12, 1995 and October 29, 1996.

Your comments have been restated and our responses follow:

1. **Provide Preservative Effectiveness Test results to support the stability data for p-Chloro-m-Cresol.**

Response:

The Anti-microbial Preservative Effectiveness test was performed by Industries on Betamethasone Dipropionate Cream, 0.05% at full strength and was submitted with the Original Application as pages 1974 - 1976. A copy of the result is attached with this amendment. (attachment 1)

The result demonstrated that the product was adequately preserved. The preservative, p-Chloro-m-cresol was found to be stable over a 42 month period. The product is still adequately preserved since the concentration (100%) of the preservative did not decrease over a 42 month test period.

2. **Provide the missing pages from Bulk and Finished product specifications which are Page 6 of and page**

Response:

Page d page enclosed as attachments 2 and 3.

3. Provide a stability data to support the proposed limit for the degradation products, [redacted]c products.

Response:

The proposed limits for Degradation products in Betamethasone Dipropionate Cream is as follows:

[redacted]

Total Related Substances

The specifications for degradation products was based on the analyses of a 15 g metal tube and a 45 metal tube samples at 42 month. The samples were tested from the cap and crimp of the tubes.

The results of the analyses for related substances is shown below:

								Total
15 g tube	Cap #1							2.407%
	Cap #2							2.384%
	Crimp #1							2.425%
	Crimp #2							2.451%
45 g tube	Cap #1							2.795%
	Cap #2							2.821%
	Crimp #1							2.948%
	Crimp #2							2.891%

Pursuant to 21 CFR 314.70(a), Clay Park Labs certifies that a field copy of this telephone amendment has been sent to the FDA district office.

Sincerely,
CLAY PARK LABS

Tsion Bellete
Asso. Mgr. of Regulatory Affairs

CC: Mr. Edward Warner - NY District Office, FDA

ANDA 74-579

Clay-Park Labs, Inc.
Attention: Tsion Bellete
1700 Bathgate Avenue
Bronx, NY 10457

Dear Madam:

This is in reference to your abbreviated new drug application dated December 1, 1994, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act, for Betamethasone Dipropionate Cream USP, 0.05% (base).

Reference is also made to your amendments dated October 29 and November 1, 1996.

The application is deficient and, therefore, not approvable under Section 505 of the Act for the following reasons:

1. Please submit Preservative Effectiveness Test results which will support your stability limits for p-chloro-m-cresol.

2. Please provide page 6 of and page 5 of

3. Please submit stability data to support your proposed limits for , and Total Related Substances.

Joseph and Maureen: The labeling was previously found to be satisfactory, but the firm submitted an amendment on 11/1/96. The strength on the carton labeling was corrected from 0.5% to 0.05%. As far as I know there were no other changes, so the labeling should still be satisfactory. Lillie needs to update the Labeling Review Worksheet, so please check with her.

The file on this application is now closed. You are required to take an action described under 21 CFR 314.120 which will either amend or withdraw the application. Your amendment should respond to all the deficiencies listed. A partial reply will not be considered for review, nor will the review clock be reactivated until all deficiencies have been addressed. Your response to this letter will be considered a MINOR AMENDMENT and should be plainly marked as such in your cover letter. If you have substantial disagreement with our reasons for not approving this application, you may request an opportunity for a hearing.

X:\NEW\FIRMSAM\CLAYPARK\LTRS&REV\74579NA3.D

CLAY-PARK LABS, INC.

AGIS GROUP

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

NDA ORIG AMENDMENT

October 11, 1995

Dr. Charles Ganley, Acting Director
Office of Generic Drugs
CDER, Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room #150
Rockville, MD 20855-2773

Noted
10/19/95

RE: ANDA #74-579
Betamethasone Dipropionate Cream USP, 0.05%

MINOR AMENDMENT

Dear Mr. Sporn:

Reference is made to your letter dated April 20, 1995 (copy attached) concerning our abbreviated new drug application dated December 1, 1994.

The administration's comments have been restated and our responses follow:

A. Chemistry Deficiencies:

1. Please provide justification for the verage of the active ingredient, or remove the overage from the formulation.

Response: During the development of the product a excess was added for the following reasons:

1. To compensate for potential
2. The USP assay range for Betamethasone Dipropionate is 97-103%. The formula requires the weighing of the raw material on basis.
3. The stability data that was previously submitted (page 2 of this amendment) shows a drop of potency.
4. To assure label claim throughout the product expiration period.

Therefore, Clay Park would like to keep the verage of the active ingredient in the formulation.

2. **The lot of monobasic sodium phosphate for which you have provided test results (106755, pages 1788 and 1789) is not the lot which you used to make exhibit batch of drug product (106527, page 1838).**

Also, please explain why your pH limits (page 1787) are broader than the USP limits (4.1 to 4.5)

Response: Clay Park's test result and supplier's certificate of analysis for Monobasic Sodium Phosphate (lot # 106755) which were provided on pages 1788 and 1789 of the original application were submitted by mistake. The correct test result for lot #106527 along with the supplier's certificate of analysis are enclosed as pages 3-4.

The pH limits for previously submitted material (lot # 106755) is broader because it is an F.C.C grade material. Enclosed please find a copy of the USP specification for monobasic sodium phosphate, USP (page 5-6). The pH limits for the monobasic sodium phosphate is 4.1 to 4.5.

3. **Please add the test for organic volatile impurities to your specifications for monobasic sodium phosphate and for propylene glycol, to comply with the monographs in USP 23.**

Response: The test for Organc Volatile Impurities has been added to the specifications for Monobasic Sodium Phosphate and Propylene Glycol to comply with USP 23 monograph. Please refer to pages 5-8 for the specifications.

4. **Please provide extraction data which demonstrate that the components of the will not be drawn from the tubes into the product, to satisfy the requirements of 21 CFR 175.300 (c).**

Please note that we have previously determined, in reviewing correspondence with W . regarding other ANDAs, that provision of such extraction data is the responsibility of the ANDA applicant, not the DMF holder. The reason is that the supplier of the tube coating does not know the composition of the drug product that will be put into the tube, or the condition of use of the tube containing product.

Response: A test for determining the amount of extractives from the components of the internal coating was conducted to satisfy the requirements of 21 CFR 175.300 (c). The result for determining the extraction data is enclosed as pages 9-10. The amount of extractives was found to be

5. **Please provide chromatograms (and any other evidence) which demonstrate the lack of interference of degradation products with the betamethasone dipropionate and beclomethasone dipropionate peaks in the validation for the analytical method for the active ingredient in the drug product, pages 1929 and 1920.**

Response: Enclosed as pages 11-13 ar omatograms which proof the lack of interference of degradation products with the products with the betamethasone dipropionate and beclomethasone dipropionate peaks in validation for the analytical method for the active ingredient in the drug product.

6. **Your stability reports (page 1952, 1954, 1956, 1958, and 1958B) state that the pH test is "for informational purpose only." We believe that pH limits should be set for bulk product, final product, and stability testing, since the product is a semi-aqueous dosage form which will be applied to the skin.**

Please submit revised bulk product and final product specifications. Also submit a formal set of stability specifications, which you have not yet provided.

Response: The pH limits of s being set for the bulk product, final product and stability testing.

Revised specifications for bulk products and finished products are being enclosed as pages 14-15. In addition a formal set of stability specifications, and a revised stability protocol are also provided as pages 16-18.

B. **Labeling Deficiencies:**

Please revise your labels and labeling, then prepare and submit final printed container labels and carton labeling and draft insert labeling.

Container:
The revision has been made per the agency's comment. 12 final printed labels are enclosed
15 g page 19
45 g page 20

Carton:
The revision has been made per the agency's comment. Enclosed are for each sizes one (1) overlay board and 11 colored copies.
15 g page 21
45 g page 22

Insert: As per the agency's comment a revision has been made to the insert. Enclosed is 12 draft insert labeling. (page 23)

In addition to responsing to these deficiencies, please note and acknowledge the following in your response:

1. **Please acknowledge that the USP test for consistency will be the regulatory method for white petrolatum USP, and will prevail in case of a dispute, and your viscosity method will be the alternate method.**

   Response: Clay Park Labs acknowledges the administration's comment.

2. **Please acknowledge that future exhibit batches, for other abbreviated new drug applications, will be 100% filled into market containers.**

   Response: Clay Park Labs acknowledges the administration's comment.

3. **The firms referenced in the application relative to the manufacture and testing of the product must be in compliance with current GMPs at the time of approval. We will request an evaluation from the Division of Manufacturing and product quality at the appropriate time.**

   Response: Clay Park Labs acknowledges the administration's comment.

Pursuant to 21 CFR 314.70(a), Clay Park Labs certifies that a field copy of this minor amendment has been sent to the FDA district office.

Sincerely,
CLAY PARK LABS

/S/

Tsion Bellete
Asso. Mgr. of Regulatory Affairs

CC: Mr. Edward Warner - NY District Office, FDA

a:\bmdcr.doc

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

ANDA 74-579

Clay-Park Labs, Inc.
Attention: Jay Jadeja
1700 Bathgate Avenue
Bronx, NY 10457

APR 20 1995

Dear Sir:

This is in reference to your abbreviated new drug application dated December 1, 1994, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act, for Betamethasone Dipropionate Cream USP, 0.05% (base).

The application is deficient and, therefore, not approvable under Section 505 of the Act for the following reasons:

A. Chemistry Deficiencies:

B. Labeling Deficiencies:

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, and/or 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".

Please revise your labels and labeling, then prepare and submit final print container labels and carton labeling and draft insert labeling.

In addition to responding to these deficiencies, please note and acknowledge the following in your response:

1. Please acknowledge that the USP test for consistency will be be the regulatory method for White Petrolatum USP, and will prevail in case of a dispute, and your viscosity method will be the alternate method.

2. Please acknowledge that future exhibit batches, for other abbreviated new drug applications, will be 100% filled into market containers.

3. The firms referenced in the application relative to the manufacture and testing of the product must be in compliance with current GMPs at the time of approval. We will request an evaluation from the Division of Manufacturing and Product Quality at the appropriate time.

The file on this application is now closed. You are required to take an action described under 21 CFR 314.120 which will either amend or withdraw the application. Your amendment should respond to all the deficiencies listed. A partial reply will not be considered for review, nor will the review clock be reactivated until all deficiencies have been addressed. Your response to this letter will be considered a MINOR AMENDMENT and should be plainly marked as such in your cover letter. Please note that if the pending bioequivalence review is not received prior to completion of the chemistry and/or labeling review of your amendment, issuance of our subsequent action letter may be delayed. Further, if a major deficiency is cited in the

bioequivalence review, the subsequent Not Approvable letter will request that the reply be declared a MAJOR AMENDMENT. If you have substantial disagreement with our reasons for not approving this application, you may request an opportunity for a hearing.

Sincerely yours,

/S/

Rashmikant M. Patel, Ph.D.
Director
Division of Chemistry I
Office of Generic Drugs
Center for Drug Evaluation and Research

ANDA 74-579

Clay-Park Labs, Inc.
Attention: Jay Jadeja
1700 Bathgate Avenue
Bronx, NY 10457

APR 20 1995

Dear Sir:

This is in reference to your abbreviated new drug application dated December 1, 1994, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act, for Betamethasone Dipropionate Cream USP, 0.05% (base).

The application is deficient and, therefore, not approvable under Section 505 of the Act for the following reasons:

A. Chemistry Deficiencies:

B. Labeling Deficiencies:

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, and/or 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 "β" (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.

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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".

Please revise your labels and labeling, then prepare and submit final print container labels and carton labeling and draft insert labeling.

In addition to responding to these deficiencies, please note and acknowledge the following in your response:

1. Please acknowledge that the USP test for consistency will be be the regulatory method for White Petrolatum USP, and will prevail in case of a dispute, and your viscosity method will be the alternate method.

2. Please acknowledge that future exhibit batches, for other abbreviated new drug applications, will be 100% filled into market containers.

3. The firms referenced in the application relative to the manufacture and testing of the product must be in compliance with current GMPs at the time of approval. We will request an evaluation from the Division of Manufacturing and Product Quality at the appropriate time.

The file on this application is now closed. You are required to take an action described under 21 CFR 314.120 which will either amend or withdraw the application. Your amendment should respond to all the deficiencies listed. A partial reply will not be considered for review, nor will the review clock be reactivated until all deficiencies have been addressed. Your response to this letter will be considered a MINOR AMENDMENT and should be plainly marked as such in your cover letter. Please note that if the pending bioequivalence review is not received prior to completion of the chemistry and/or labeling review of your amendment, issuance of our subsequent action letter may be delayed. Further, if a major deficiency is cited in the

bioequivalence review, the subsequent Not Approvable letter will request that the reply be declared a MAJOR AMENDMENT. If you have substantial disagreement with our reasons for not approving this application, you may request an opportunity for a hearing.

Sincerely yours,

/S/

Rashmikant M. Patel, Ph.D.
Director
Division of Chemistry I
Office of Generic Drugs
Center for Drug Evaluation and Research

cc:

HFD-Schaefer 4/19/95

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bioequivalence review, the subsequent Not Approvable letter will request that the reply be declared a MAJOR AMENDMENT. If you have substantial disagreement with our reasons for not approving this application, you may request an opportunity for a hearing.

Sincerely yours,

Rashmikant M. Patel, Ph.D.
Director
Division of Chemistry I
Office of Generic Drugs
Center for Drug Evaluation and Research

cc:

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Endc

ANDA 74-579

Clay-Park Labs, Inc.
Attention: Jay Jadeja
1700 Bathgate Avenue
Bronx, NY 10457

DEC 23 1994

Dear Sir:

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

NAME OF DRUG: Betamethasone Dipropionate Cream USP, 0.05%.

DATE OF APPLICATION: December 1, 1994

DATE OF RECEIPT: December 2, 1994

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

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

Should you have questions concerning this application, contact:

Robert West
Consumer Safety Officer
(301) 594-0375

Sincerely yours,

12/23/94

Gordon R. Johnston
Acting Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

ANDA 74-579
cc:

12/21/94

2/57

CLAY-PARK LABS, INC.

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

12/6/94

505(j)(2)(A)(i)

12/14/94

Dec. 1st, 1994

To:

Douglas Sporn,
Acting Director,
Office of Generic Drugs, CDER
Metro Park North II,
7500 Standish Place, Rm. 150
Rockville, MD 20855-2773

Re: Betamethasone Dipropionate Cream USP, 0.05%

Dear Mr. Sporn;

Please find enclosed documents and data that are being submitted to support Abbreviated New Drug Application for the above referenced drug product. This submission includes:-

1. Four volumes of Archival copy (Blue)
2. Four volumes of Review copy divided into two sections:-
   a. Chemistry, manufacturing and control section (Red).
   b. Pharmacokinetic section (Orange). A 5 1/4" disket is in vol. 2.

Four volumes of Archival copy are also being send to our local New York District Office for their reference. A true copy certification can be found on the next page.

Should any question arise please feel free to contact the under signed.
Thank you.

Sincerely,

Jay Jadeja,
Director, Regulatory Affairs.