CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

75733

CORRESPONDENCE

ANDA 75-733

Stiefel Laboratories, Inc.
Attention: Mary Jane Carr
Route 145
Oak Hill, NY 12460

JAN 3 2000

Dear Madam:

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

Reference is also made to the telephone conversation dated December 9, 1999 and your correspondence dated December 10, 1999.

NAME OF DRUG: Clobetasol Propionate Emollient Cream, 0.05%

DATE OF APPLICATION: November 8, 1999

DATE (RECEIVED) ACCEPTABLE FOR FILING: November 12, 1999

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:

Joe Buccine
Project Manager
(301) 827-5848

Sincerely yours,

/S/

Robert L. West, M.S., R.Ph.
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

ANDA 75-733
cc: DUP/Jacket
Division File
Field Copy
HFD-610/R.West
HFD-610/P.Rickman
HFD-92
HFD-615/M.Bennett
HFD-330
Endorsement:
HFD-615, NMahmud, Chief, RSB /S/ date 1/3/00
HFD-615, EThomas, CSO _____ date 12/29/99
HFD-629, PSchwartz, Sup. Chem. _____ date
Word File V:\firmsnz\Stiefel\ltrs&rev\75733.ack
F/T mjl/12/29/99
ANDA Acknowledgment Letter!

Research in Dermatology

STIEFEL LABORATORIES, INC., OAK HILL, NY 12460 • TEL. 518-239-6901 • FAX. 518-239-6341

November 8, 1999

Director
Office of Generic Drugs
Center for Drug Evaluation
and Research
U.S. Food and Drug Administration
Metro Park North II, HFD-600
7500 Standish Place, Room 150
Rockville, MD 20855

Dear Sir/Madam:

We are here submitting an Abbreviated New Drug Application for Clobetasol Propionate Emollient Cream, 0.05% in accordance with the provisions of 21 CFR§314.94.

Please direct all communications concerning this application to:

Mary Jane Carr
Senior Manager
Regulatory Affairs
Stiefel Laboratories, Inc.
Route 145
Oak Hill, New York 12460

We here commit to resolve any issues identified in the method validation process after approval.

Please note that a portion of this submission, specifically information associated with the bioavailability/bioequivalence section, is submitted in electronic format.

This submission is complete in five (5) volumes, not including additional copies which are also included as required.

Sincerely,
STIEFEL LABORATORIES, INC.

Mary Jane Carr

Mary Jane Carr
Senior Manager
Regulatory Affairs

NOV 12

MJC:cdf

0002

1 - 1 ORG

Research in Dermatology

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ORIG AMENDMENT
N/AB

June 20, 2000

Ms. Patty Nguyen
Division of Bioequivalence
Office of Generic Drugs, CDER, FDA
Metro Park North II, HFD-600
7500 Standish Place, Room 150
Rockville, MD 20850

RE: ANDA 75-733
Clobetasol Propionate
Emollient Cream, 0.05%

Dear Ms. Nguyen:

Reference is made to our June 20, 2000 telephone conversation specific to our pending Abbreviated New Drug Application for Clobetasol Propionate Emollient Cream, 0.05%.

Reference is also made to OGD's Policy and Procedure Guide #41-95: Guidance on the Packaging of Test Batches.

We are currently preparing to manufacture a second kg. pilot batch which will be utilized to perform another pivotal bioequivalence study utilizing an ED_{50} of 15 minutes to comply with FDA's 14 April 2000 bioequivalence deficiency communication.

We plan to fill a portion of the above referenced pilot batch into approximately seven hundred (700) - 30 gram tubes which are identical to those submitted in support of our ANDA. The number of units filled is limited by available inventory of subject tubes.

We plan to fill the remainder of the pilot batch into an alternate tube size of - which may be utilized to support a post approval change following anticipated approval of the ANDA.

FDA has previously advised us that the guidance at Policy and Procedure Guide #41-95 specific to filling the same number of units for each container is no longer applicable.

In light of the above, and recognizing that we have previously (lot # D0738, #D0739 and #D0740; submission dated November 8, 1999) filled approximately equal numbers of three (3)

submitted container sizes that were appropriately uniform, we question the requirement to package equal numbers of the referenced 30 gram containers for this pilot batch.

May we proceed as planned?

Thank you in advance for your guidance.

Sincerely,
STIEFEL LABORATOIRES, INC.

Mary Jane Carr

Mary Jane Carr
Senior Manager
Regulatory Affairs

Research in Dermatology

STIEFEL LABORATORIES, INC., OAK HILL, NY 12460 • TEL. 518-239-6901 • FAX. 518-239-6341

BIOAVAILABILITY

April 20, 2000

NEW CORR.

NC

Dale P. Conner, Pharm.D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II, HFD-600
7500 Standish Place, Room 150
Rockville, MD 20850

RE: **New Correspondence**
ANDA 75-733
Clobetasol Propionate
Emollient Cream, 0.05%

Dr. Dr. Conner:

We acknowledge your communication dated 14 April 2000 specific to bioequivalence deficiencies with our ANDA 75-733.

Despite significant effort we are unable to confirm the 11.25 minute ED_{50} calculated by the Division of Bioequivalence using our pilot study data.

We therefore request FDA's assistance in determining the nature of our apparent error or errors and have several questions and requests in this regard.

1. Stiefel Laboratories, Inc. utilizes software for data analyis and pharmacokinetic modeling. Is this consistent with software utilized by FDA?

2. Assuming)software is utilized by FDA, please provide the model code (.prc file) used for fitting the E_{max} model, a copy of the .xpd data file used for the pilot study, and copies of printouts.

3. Please provide the initial settings for the fit. Specifically, please clarify whether normal or log-normal distributions were assumed for the parameters, which setting was assumed for sigma, and what values were used for starting the iterations.

CENTER FOR DRUG EVALUATION AND RESEARCH
RECD
APR 21 2000
OGD

4. What measures were used to assess the fit of the resulting model?

5. Was the model checking given in the pilot study report adequate? If not, can you point to the deficiencies.

We look forward to your response and assistance.

Sincerely,
STIEFEL LABORATORIES, INC.

Mary Jane Carr
Senior Manager
Regulatory Affairs

Research in Dermatology

STIEFEL LABORATORIES, INC., OAK HILL, NY 12460 • TEL. 518-239-6901 • FAX. 518-239-6341

November 14, 2000

Director
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II, HFD-600
7500 Standish Place, Room 150
Rockville, MD 20855

NDA ORIG AMENDMENT
N/AC

RE: **MAJOR AMENDMENT**
ANDA 75-733
Clobetasol Propionate Cream
USP, 0.05% (Emollient)

Dear Sir/Madam:

Reference is made to our Abbreviated New Drug Application for Clobetasol Propionate Cream USP, 0.05% (Emollient).

Reference is also made to FDA's 5 April 2000 not approvable communication specific to subject application.

We are here responding to FDA's 5 April communication via this MAJOR AMENDMENT to the ANDA.

Our response is numerically keyed to FDA's comments for ease of review. Additional supporting data, referenced by tab and page, is also included in this submission as required.

A. Chemistry Deficiencies:

FDA Comment

1. Please justify the reason for having a % overage of the drug substance in your formulation.

Stiefel Response

Data generated on the reference listed drug, Temovate E®/Glaxo Wellcome; (NDA 20-340) suggests an overage in the range of % (please refer to Volume 1 of 5; page 0046 of our original November 12, 1999 ANDA submission).

Additional data generated on the very closely related Temovate® Cream/Glaxo Wellcome (NDA 19-322) suggests an overage in the range o

CORPORATE OFFICES: 255 ALHAMBRA CIRCLE, CORAL GABLES, FLORIDA 33134
TLANTA, GEORGIA • RENO, NEVADA • ROCKVILLE, MARYLAND • BAYAMON, PUERTO RICO • BUENOS AIRES, ARGENTINA • CASTLE HILL, NSW, AUSTRALIA • BRUXELLES, BELGIUM • SAO PAULO, BRAZIL • MONTREAL, CANADA
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We have, based upon the above, formulated our product to contain a › overage – which is within the range utilized by Glaxo Wellcome.

FDA Comment

2. Please provide integrity testing for the tube liner.

Stiefel Response

Please find following liner integrity testing performed on the 15 gram (Tube, Aluminum 4 -⅛" x ¾", IC# 88959) and the 30 gram (Tube, Aluminum 4 - ½" x 1", IC# 88982) blank (i.e. no regulatory (label) copy) tubes which were utilized in the submitted exhibit batch(es). Please note that at the time of testing there were no available 60 gram tubes to perform the referenced testing. [see TAB 1]

We have incorporated tube liner integrity testing into the inspection program for incoming packaging. All future testing will be performed in accordance with QC Component Inspection Sheets specific to the 15 gram, 30 gram and 60 gram tubes (see attached).

Please note that the above referenced QC Component Inspection Sheets are specific to tubes which contain proposed regulatory (label) copy, hence the difference in inventory control (IC) numbers.

Methodology for the above referenced liner integrity testing also follows.

FDA Comment

3. Please explain the difference between certificates of analysis on page 1202 and page 1225 regarding the individual and total related substances. In addition, revise your limits based on your data.

Stiefel Response

The Certificate of Analysis referenced at page 1202 is specific to bulk drug product, i.e. drug product which has not completed filling/packaging operations, and incorporate in-house tests and specifications (i.e. Bulk Product Tests and Specifications) which are designed to assure the finished packaged drug product will meet all established in-house packaged product tests and specifications.

The Certificate of Analysis referenced at page 1225 is specific to finished packaged (i.e. filled) drug product. In-house tests and specifications (i.e. Release Packaged Product Tests and Specifications) are designed to assure the marketed drug product will meet all marketed product specifications (i.e. Stability Tests and Specifications) throughout the expiration dating period of the product.

Specifications, to include those established for related substances, are – in general - more conservative for bulk product to provide an adequate level of assurance that packaged/filled product will meet the established Release Packaged Product Tests and Specifications referenced above.

We have, in accordance with FDA's request, revised our drug product specifications specific to related substances – individual largest and total.

Please find enclosed updated Bulk Product Tests and Specifications which reflect a reduction in limits for Related Substances – Individual Largest to(%, and Related Substances – Total to( )%. [see TAB 2]

Also enclosed please find Release Packaged Product Tests and Specifications, which reflect a reduction in limits for Related Substances– Individual Largest to (%, and Related Substances – Total to( )%.

FDA Comment

4. Please revise your specifications for bulk and finished drug product to include limits and specifications for specific gravity and viscosity.

Stiefel Response

We recognize physical properties, such as viscosity and specific gravity, of any semi-solid dosage form are critical parameters which must be controlled to confirm product performance and release characteristics remain consistent from batch to batch during production operations.

We also recognize slight variation may be encountered which – although well within an acceptable range – must be considered prior to establishing regulatory specifications.

Lacking necessary data to establish reliable specifications – we are here proposing to establish specifications for viscosity and specific gravity following completion of the first three (3) commercial production batches (i.e. process validation batches) with submission of established specifications to FDA via a Changes Being Effected Supplement to the ANDA.

FDA Comment

5. Please revise your stability specifications to include limits and specifications for specific gravity and viscosity.

Stiefel Response

As noted at point 4. above, lacking necessary data to establish reli specifications - we are here proposing to establish specifications for viscosity and

specific gravity following completion of the first three (3) commercial production batches (i.e. process validation batches) with submission of established specifications to FDA via a Changes Being Effected Supplement to the ANDA.

FDA Comment

6. Please revise your stability specifications for individual and total related substances based on your data.

Stiefel Response

Please find enclosed updated Stability Tests and Specifications which reflect a reduction in limits for Related Substances – Individual Largest to %, and Related Substances – Total to %. [see TAB 3]

For convenience of review we are also here providing updated eighteen (18) month long-term stability data for the 15 gram, 30 gram and 60 gram tubes.

FDA Comment

7. Please explain the reason for having three tests for related substances for the drug substance.

Stiefel Response

Methodology specific to chromatographic purity is derived from the USP monograph specific to clobetasol propionate drug substance.

Additional related substance testing specific to Clobetasol Propionate and Clobetasol Propionate is derived from the drug substance manufacturer's tests and specifications.

All of the above is simply intended to assure compliance to the USP monograph, as well as confirm data generated by the drug substance manufacturer.

FDA Comment

8. Please revise your organic volatile impurities for the drug substance according to the current USP 24.

Stiefel Response

Our original Raw Material Tests and Specifications established for clobetasol propionate drug substance did specify testing in accordance with the USP test requirement for organic volatile impurities (OVIs) (included in our original Clobetasol Propionate Gel ANDA submission dated December 13, 1996).

Subject tests and specifications were revised – to include all residual solvents specific to the manufacturing process for the drug substance – in response to a not approvable communication received for the related ANDA, Clobetasol Propionate Gel, 0.05% (ANDA 75-027, Facsimile Amendment dated 11 August 1997).

Based upon this communication – and recognizing that the USP specified OVI's specific to( )are not used in the manufacturing process for the drug substance - we respectfully request that OVI testing for the drug substance continue as referenced.

FDA Comment

9. Please define the objectionable microorganisms.

Stiefel Response

Objectionable Microorganisms are defined as any Gram negative rods, *Staphylococcus* species, *Streptococcus* species, or any other known or opportunistic pathogen, which may adversely affect the safety of the intended user or the product's stability.

Subject testing goes beyond testing referenced at USP <61> Microbial Limits Tests which simply "provides for the estimation of viable aerobic microorganisms present and for freedom from designated microbial species in pharmaceutical articles of all kinds" (i.e. *Staphylococcus aureus, Escherichia coli, Pseudomonas aeruginosa, Salmonella* species), by also including as objectionable – Gram negative rods, *Staphylococcus* species, *Streptococcus* species, or any other known or opportunistic pathogen which may adversely affect the safety of the intended user or the product's stability.

Subject testing is intended to assure compliance with the above referenced USP <61> microbial requirements and to the provisions of 21 CFR§211.113 – Control of microbiological contamination.

FDA Comment

10. Please provide an in-process bulk test and specification including RSD limits.

Stiefel Response

We are here providing an in-process test specification for(% with a RSD of %, as requested.

Enclosed please find Bulk Product Tests and Specifications specific to(analysis. [see TAB 4]

B. In addition to responding to the deficiencies presented above, please note and acknowledge the following comments in your response:

FDA Comment

1. The firms referenced in your application regarding the manufacturing and testing of the drug product should be in compliance with CGMP's at the time of the approval.

Stiefel Response

We confirm that all manufacturing performed by Stiefel Laboratories, Inc. and all testing performed by Stiefel Research Institute, Inc. for Clobetasol Propionate Cream USP, 0.05% (Emollient) is, and will remain, in conformance with current Good Manufacturing Practice as defined at 21 CFR§210 and 211.

FDA Comment

2. The methods validation for the drug product has been submitted to an FDA District Laboratory for validation.

Stiefel Response

We acknowledge that the methods validation for the drug product, to include samples and required documentation, has been submitted to FDA's Northeast Regional Laboratory, Brooklyn, New York.

FDA Comment

3. Your bioequivalence section is under review.

Stiefel Response

We acknowledge that the bioequivalence section is under review.

Labeling Deficiencies:

Enclosed please find twelve (12) copies of 'final printed' labeling revised in exact accordance with FDA's recommendations. [see TAB 5]

Also enclosed please find a side-by-side comparison of previously submitted draft copy vs. final printed labeling, as requested. [see TAB 6]

We here confirm that we will routinely monitor the labeling review branch web site for any approved changes to the reference listed drug, and incorporate such changes, as required.

We look forward to FDA's timely review of this submission.

Sincerely,
STIEFEL LABORATORIES, INC.

Mary Jane Carr
Senior Manager
Regulatory Affairs

MJC:cdf

Research in Dermatology

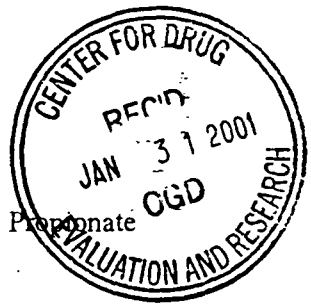
STIEFEL LABORATORIES, INC., OAK HILL, NY 12460 • TEL. 518-239-6901 • FAX. 518-239-6341

January 30, 2001

Director
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II
7500 Standish Place
Rockville, MD 20855

ORIG AMENDMENT
N/AB

RE: **BIOEQUIVALENCY AMENDMENT**
ANDA 75-733
Clobetasol Propionate
Emollient Cream, 0.05%



Dear Sir/Madam:

Reference is made to our Abbreviated New Drug Application for Clobetasol Propionate Emollient Cream, 0.05%.

Reference is also made to FDA's 14 April 2000 facsimile communication specific to subject ANDA.

We are here responding to FDA's 14 April communication via this Bioequivalency Amendment to the ANDA.

Our response is keyed to FDA's comment for ease of review. Additional supporting data referenced by tab and by page is also included in this submission as required.

FDA Comment

From analysis of the pilot study data, the Division of Bioequivalence calculated an ED_{50} value of 11.25 minutes, which is one fourth of the ED_{50} value which you reported. Based on your ED_{50} value, you have used a dose duration of 45 minutes to compare the test and reference products in the pivotal bioequivalence study.

Based on the Agency research, sensitivity of the vasoconstrictor assay to detect potential difference in bioavailability of test and reference products is markedly reduced at dose durations greater than the population ED_{50} (Singh et al, *Clin Pharmacol Ther* 1999; 66: 346-357).

Comparison of the test and reference products at dose durations greater than the population ED_{50} is not appropriate. Therefore, the pivotal bioequivalence study is not

acceptable, due to the lack of sensitivity to detect potential differences between test and reference products.

You should conduct another pivotal bioequivalence study based on ED_{50} of approximately 11 minutes.

Stiefel Response

We have conducted the pivotal element of the bioequivalence study utilizing a nominal ED_{50} of approximately 11 minutes as instructed. For practical purposes, and in accordance with FDA's Guidance "Topical Dermatological Corticosteroids: *In Vivo* Bioequivalence (June 1995), the ED_{50} was rounded to 15 minutes.

Please find enclosed, study report - Pivotal Bioequivalence of 0.05% Clobetasol Propionate Emollient Cream, Protocol #0005, Study #932 - conducted utilizing D_1, ED_{50} and D_2 values of 8 minutes, 15 minutes, and 30 minutes, respectively. Excel spreadsheets are provided on diskette.

Case Report Forms are also provided. (please see Volume 2 of 2)

We look forward to your timely review.

Sincerely,
STIEFEL LABORATORIES, INC.

Mary Jane Carr

Mary Jane Carr
Senior Manager
Regulatory Affairs

MJC:cdf

Research in Dermatology

STIEFEL LABORATORIES, INC., OAK HILL, NY 12460 • TEL. 518-239-6901 • FAX. 518-239-6341

August 7, 2001

Director
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II, HFD-600
7500 Standish Place, Room 150
Rockville, MD 20855

ORIG AMENDMENT
N/Am

RE: MINOR AMENDMENT
ANDA 75-733
Clobetasol Propionate Cream
USP, 0.05% (Emollient)

Dear Sir/Madam:

Reference is made to our Abbreviated New Drug Application for Clobetasol Propionate Cream USP, 0.05% (Emollient).

Reference is also made to FDA's 19 June 2001 not approvable communication specific to subject application.

We are here responding to FDA's 19 June not approvable communication via this MINOR AMENDMENT to the ANDA.

Our response is numerically keyed to FDA's comments for ease of review. Additional supporting data, referenced by tab and by page, is also included in this submission as required.

A. Deficiencies:

FDA comment

1. Please propose limits for viscosity and specific gravity based on the available data for bulk, finished drug product and stability.

Stiefel Response

1. Please find enclosed updated Bulk Product Tests and Specifications, Release Packaged Product Tests and Specifications and Stability Tests and Specifications which incorporate limits for viscosity and specific gravity, as requested. [see TAB 1]

FDA Comment

2. In addition to responding to the deficiencies presented above, please note and respond to the FDA district laboratory comments regarding your methods validation:

   a. For the related substances test, response factor was not used in the calculation. The absorptivity of the related substances may not be the same as that of clobetasol propionate at nm.

   b. The sample preparation for the assay analysis was also used for the related substances determination, however, an internal standard was used for the assay analysis. The presence of an internal standard in the solution used for related substance determination rendered the determination inaccurate. In this case, the internal standard, contains some impurities with retention times that are very similar to the retention times of the related substances of clobetasol propionate. If the sample preparation is to be used for the assay and related substances determination, an internal standard should not be used.

   c. Page 5 of the method states "consult your supervisor if peaks appear after the internal standard peak". Review of the company's worksheet found that peaks eluted after the internal standard peak were not calculated. If these peaks are to be excluded in the calculation of the related substances, the method should state so clearly.

   d. The method calls for the preparation of the limit of detection preparation only for the analysis of the placebo. In addition, the procedure of the preparation only states to prepare an appropriate dilution of "standard A". The limit of detection test is mandatory for every related substances determination.

   e. The specifications used were from page 1377 of the submission. These specifications were approved in August, 1999. The specifications indicated on the firm's worksheet were slightly different for assay as compare to the limits of % that used). The district laboratory could not determine which are the current specifications.

Stiefel Response

2.a. Available 2-year (730 day) long-term stability data (please see TAB 4) specific to subject product indicates the active compound, clobetasol propionate, exhibits very minimal degradation relative to initial results. Data reported specific to total related substances supports the degradation profile of the active compound with results in the range of % of label during the stability program.

Based upon the above, an analytical assumption of equivalent detector response of related substances relative to clobetasol propionate is incorporated into the methodology. (i.e. relative response factor of 1.000).

2(b-d.) We agree with FDA district laboratory's comments specific to points 2.b, c, and d.

We have developed a separate method specific to the determination of related substances in subject product. This method (please refer to Tab 2 – Clobetasol Propionate Degradates - 3) retains the chromatographic conditions utilized in the assay method (Clobetasol Propionate – 3), but differs in respect to the incorporation of points 2.b. specific to the removal of internal standard; 2.c. specific to eliminating the statement "consult..." at page 5; and, 2.d. specific to the inclusion of a LOD standard for each run. Additional minor editorial/procedural modifications have also been incorporated.

We have also – based upon the above – reissued Clobetasol Propionate – 3 (specific to assay and identification) to remove reference to the determination of related substances. (please see TAB 3 – Clobetasol Propionate – 3)

In light of all the above – product tests and specifications have also been revised to reflect the above method, Clobetasol Propionate Degradates – 3, under the "Procedures" section for the determination of Related Substances (tests and specifications provided at TAB 1).

2.e. The tests and specifications referenced at page 1377 of the submission are specific to (in-process) Bulk Product Tests and Specifications, i.e. drug product which has not completed filling/packaging operations, and are designed to assure the finished packaged drug product will meet all established in-house packaged product tests and specifications.

Release Packaged Product Tests and Specifications (page 1492 of the method validation package) are specific to the drug product which has completed filling operations.

The worksheet (page 1283 of our 13 March 2000 submission to FDA Northeast Regional Laboratory) erroneously referenced a specification of (% w/w for clobetasol propionate for package lot #D0739. The correct specification should read % w/w for clobetasol propionate (as specified on the Release Packaged Product Tests and Specifications).

Certificate(s) of Analysis for package lot #D0739 (page 1266 of our 13 March submission) do reference the correct specification of % w/w for clobetasol propionate.

Product tests and specifications are provided at TAB 1 of this submission.

B. In addition to the above deficiencies, please note and acknowledge the following:

FDA Comment

1. Your bioequivalence amendment of Jan 30, 2001 is under review.

Stiefel Response

We acknowledge that our bioequivalence amendment of 30 January 2001 is under review.

FDA Comment

2. Please provide any additional long-term stability data.

Stiefel Response

Enclosed please find available 2-year (730 day) long-term stability data for the 15 gram (Package lot #D0738), 30 gram (Package lot #D0739) and 60 gram (Package lot #D0740) tubes. [see TAB 4]

Additional supportive 9 month (273 day) long-term stability is also enclosed for Package lot #H0611, 30 gram tube.

We look forward to your timely review.

Sincerely,
STIEFEL LABORATORIES, INC.

Mary Jane Carr
Senior Manager
Regulatory Affairs

MJC:cdf