CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20-769

CORRESPONDENCE

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

OCT - 8 1996

NDA 20-769

PHARMAQUEST
Attention: Richard D'Agostino
4470 Redwood Highway
Suite 101
San Rafael, California 94903

Dear Mr. D'Agostino:

We have received your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of the Drug Product: Locoid® Lipocream (hydrocortisone butyrate), 0.1%

Therapeutic Classification: 3S

Date of Application: August 30, 1996

Date of receipt: September 3, 1996

Our Reference Number: NDA 20-769

As per our telephone conversation on September 27, 1996, the User Fee Payment was not received until September 12, 1996. Therefore, the application was unacceptable for filing until receipt of payment which was September 12, 1996.

Unless we notify you within 60 days of the receipt date of User Fee Payment that the application is not sufficiently complete to permit substantive review, this application will be filed under section 505(b) of the Act on November 12, 1996 in accordance with 21 CFR 314.101(a).

Please cite the NDA number listed above at the top of the first page of any communications concerning this application.

Sincerely yours,

Mary Jean Kozma-Fornaro, R.N., M.S.A.
Acting Supervisory Project Manager
Division of Dermatologic and Dental
Drug Products
Office of Drug Evaluation V
Center for Drug Evaluation and Research

cc:
Original NDA 20-769
HFD-540/DIV FILE
HFD-540/PROJ MGR/Kozma-Fornaro
DISTRICT OFFICE

ACKNOWLEDGEMENT - AC

MEMORANDUM OF A MEETING AND TELEPHONE CONVERSATION

Date: August 28, 1997

Between: Nancy Sager, HFD-357

Jean Harvey
Inveresk
1-415-446-1922

AUG 29 1997

And: Wilson H. De Camp, Ph.D.
HFD-540

Subject: Environmental Assessment, NDA 20-769, Locoid (hydrocortisone butyrate) Lipocream

On August 28, 1997, I took Dr. Hathaway's EA review to Dr. Sager for concurrence with the FONSI that had been prepared. Several items of missing information were identified. However, rather than delay action on the NDA, Dr. Sager suggested withdrawal of the EA in accordance with the Final Rule that became effective on this date.

Following her suggestion, I called Ms. Harvey later that afternoon. She is the U.S. agent for Yamanouchi for NDA 20-769. Her supervisor, Dick D'Agostino also participated in the telephone call. I asked them to withdraw the existing EA, including the revised one submitted 97/08/25, and to submit a claim for a categorical exclusion. My suggestion included the exact wording for the claim, as discussed by Dr. Sager. This wording is:

> The requested action, approval of NDA 20-769, qualifies for a categorical exclusion from the requirement to prepare an environmental assessment under 21 CFR §25.31(b). To the applicant's knowledge, no extraordinary circumstances exist that would warrant the preparation of an environmental assessment.

A substantially similar claim was received by fax today, and should be in our hands shortly as a hard copy. Therefore, the recommendation for the environmental assessment section of Dr. Hathaway's review is changed to "ACCEPTABLE". The NDA may be approved without a FONSI.

cc: Orig: NDA 20-769
HFD-540/DivFile
HFD-520/Sheldon
HFD-880/Lee
HFD-540/Hathaway
HFD-540/Huene
HFD-540/Avalos
HFD-540/Cintron
HFD-540/DeCamp
filename:N20769.mem

MAY 20 1997

TELECONFERENCE MINUTES

meeting ID # 972

Meeting Date: 4/21/97 **Time:** 2:30pm **Location:** N-225
Sponsor: Inveresk Research
NDA: 20-769 (Locoid Lipocream)
Meeting Type: Telecon regarding HPA axis studies
Meeting Chair: Dr. Jonathan Wilkin/Division Director/HFD-540
Meeting Recorder: Robin Anderson/Project Manager/HFD-540
FDA Attendees:
Dr. Jonathan Wilkin/Division Director/HFD-540
Robin Anderson/Project Manager/HFD-540
Dr. Dennis Bashaw/Biopharmaceutics Team Leader/HFD-880
Dr. Sue-Chih Lee/Biopharmaceutics Reviewer/HFD-880
Sponsor Attendees:
Richard D'Agostino/President, Inveresk Research N. A.
Jean Harvey, Regulatory Affairs

Background:
Applicant had previously committed to doing additional adrenal suppression studies as a phase 4 commitment for this NDA.

Discussion Topics/Agreements Reached:

Clinical:

- The Division Director stated that the medical review of this NDA is currently in progress, and it has been noted that Locoid Lipocream is more potent than Locoid Cream. This conclusion was based on results of the vasoconstrictor studies. Because of the higher potency, the lack of results of the HPA axis studies currently planned for phase 4 could potentially affect the wording of the label for this drug. The applicant is encouraged to do the HPA axis studies sooner, and to submit the results before an approval decision is made.

- The restrictive factor for the current adrenal axis studies is that they were done on normal volunteers. Since diseased skin is known to be more permeable with enhanced absorption of drug, HPA axis studies should be conducted in the population in which the proposed label was indicated. The maximal surface area and duration of treatment consistent with labeling should also be used in the adrenal axis studies.

- The applicant questioned whether the adrenal axis studies could be done in foreign countries. The Division responded that this would be acceptable, providing the subjects are representative of the target population in the proposed label.

Minutes Preparer:

Chair Concurrence:

NDA 20-769

cc: NDA 20-769
HFD-540/Division file
HFD-540/Wilkin
HFD-540/Huene
HFD-540/Anderson
HFD-880/Bashaw 4/22/97
HFD-880/Lee 4/22/97

ITP 54
M.J. Fornaro

SEP 27 1996

MEMORANDUM OF TELECON

DATE: September 27, 1996

NDA: 20-769
Locoid (hydrocortisone butyrate lipocream) Lipocream, 0.1%

SPONSOR: Yamanouchi Europe B.V.
Pharmaquest Corporation (U.S. Representative)
Mr. Richard D'Agostino
415 491-6460

FDA: Mary Jean Kozma Fornaro
Acting Supervisory Project Manager
HFD-540

SUBJECT: NDA 20-769 User Fee Payment

Mr. D'Agostino was notified that NDA 20-279 was received on September 3, 1996. However, as of September 9, 1996, no User Fee Payment was received therefore the application was unacceptable for filing.

Receipt of the Use Fee was September 12, 1996. Therefore the application was considered acceptable for filing as of September 12, 1996.

Conversation ended amicably.

cc:

NDA 20-769
HFD-540-Division File
HFD-540-Kozma-Fornaro
HFD-005-HassallT

UN: 9/9/96
AR: 9/12/96

Yamanouchi

Yamanouchi Europe B.V.

Elisabethhof 19
P.O. Box 108
2350 AC Leiderdorp
The Netherlands
Telephone +31 71 5455745
Telefax +31 71 5455800

Direct line (071) 545 5 722

Direct fax (071) 545 5 840

Our ref. APM/cmb

Your ref.

Date Autust 15, 1996

Food & Drug Administration
Center for Drug Evaluation & Research
5600 Fishers Lane
ROCKVILLE, Maryland 20852
UNITED STATES OF AMERICA

Subject: Authorization

Dear Sirs,

We herewith authorize Pharmaquest Corporation, San Rafael, California, to act as our representative in submitting a New Drug Application (NDA) on Locoid Lipocream® (hydrocortisone butyrate 0.1%) on behalf of Yamanouchi Europe B.V. in maintaining liaison with the FDA in matters pertaining to this NDA and in referencing the three previous Locoid NDA's (NDA Nos. 18-514, 18-652 and 19-116) for all information pertinent to this NDA.

YAMANOUCHI EUROPE B.V.

A.P. Morgenstern, Ph.D.
Director Regulatory Affairs

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

APPLICATION TO MARKET A NEW DRUG, BIOLOGIC, OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations, 314 & 601)

Form Approved: OMB No. 0910-0316
Expiration Date: December 31, 1997
See OMB Statement on last page.

FOR FDA USE ONLY

APPLICATION NUMBER

APPLICATION INFORMATION

NAME OF APPLICANT Yamanouchi Europe B.V.

DATE OF SUBMISSION Augsut 30, 1996

TELEPHONE NO. *(Include Area Code)* 011-71-45-57-45

FACSIMILE (FAX) number *(Include Area Code)* 011-71-45-58-00

APPLICANT ADDRESS *(Number, Street, City, State and Zip Code or Mail Code):*
Elisabethhof 19 (P.O. Box 108)
2350 AC Leiderdorp
The Netherlands

AUTHORIZED U.S. AGENT NAME & ADDRESS *(Number, Street, State, and ZIP Code telephone & FAX number)* IF APPLICABLE
Pharmaquest Corporation
4470 Redwood Highway, Suite101
San Rafael, CA 94903
Phone: 415-491-6460
Fax: 415-491-6464

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE NUMBER (if previously issued) n/a

PRODUCT DESCRIPTION

ESTABLISHED NAME *(e.g., Proper name, USP/USAN name)* hydrocortisone butyrate USP

PROPRIETARY NAME *(trade name)* IF ANY Locoid Lipocream®

CHEMICAL/BIOCHEMICAL NAME *(If any)* pregn-4-ene-3,20-dione,11,21-dihydroxy-17-(1-oxobutoxy)-,(11β)-

CODE NAME *(If any)*

DOSAGE FORM: topical cream

STRENGTHS: 0.1%

ROUTE OF ADMINISTRATION topical

PROPOSED INDICATIONS FOR USE Relief of the inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses

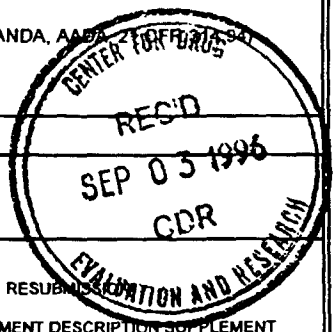
APPLICATION INFORMATION

APPLICATION TYPE
(check one)

XXX NEW DRUG APPLICATION (21 CFR 314.50)

___ ABBREVIATED APPLICATION (ANDA, AADA 21 CFR 314.94)

___ BIOLOGIC APPLICATION (21 CFR part 601)



IF A NDA, IDENTIFY THE APPROPRIATE TYPE XXX 505 (b) (1) ___ 505 (b) (2) ___ 507

IF AN ANDA, OR AADA, IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION
Name of Drug Holder of Approved Application

TYPE OF SUBMISSION
(check one)

XXX ORIGINAL APPLICATION ___ AMENDMENT TO A PENDING APPLICATION ___ RESUBMISSION

___ PRESUBMISSION ___ NOTIFICATION ___ ESTABLISHMENT DESCRIPTION SUPPLEMENT

___ SUPAC SUPPLEMENT ___ EFFICACY SUPPLEMENT ___ LABELING SUPPLEMENT ___ CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT

REASON FOR SUBMISSION: To obtain FDA approval for marketing Locoid Lipocream® (a new drug) in the United States.

PROPOSED MARKETING STATUS (Check one) XXX PRESCRIPTION PRODUCT (Rx) ___ OVER-THE-COUNTER PRODUCT (OTC)

NUMBER OF VOLUMES SUBMITTED ___

THIS APPLICATION IS XXX PAPER ___ PAPER AND ELECTRONIC

ESTABLISHMENT INFORMATION

Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or types of testing (e.g. Final dosage form, Stability testing conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.

Drug subtance: DMF
Drug Product: Yamanouchi Europe B.V., Meppel, The Netherlands. Contact: Dr. A.P. Morgenstern, Director of Regulatory Affairs.
Complete manufacture of final dosage form, stability testing, and packaging is conducted at this site. The site was inspected by the FDA on May 20, 1996

Cross References (list related License Application, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMFs referenced in the current application)

INDs:
NDAs: No 18-514 (Locoid® Cream 0.1%), No. 18-652 (Locoid® Ointment 0.1%), No. 19-116 (Locoid® Lotion 0.1%).
DMF:

This application contains the following items: *(Check all that apply)*	
X	1. Index
	2. Labeling (check one) XXX Draft Labeling ___ Final Printed Labeling
	3. Summary (21 CFR 314.50 (c))
X	4. Chemistry section
X	A. Chemistry, manufacturing, and control information (e.g. 21 CFR 314.50 (d) (1))
X	B. Samples (21 CFR 314.50 (e) (1), 21 CFR 601.2 (a)) (Submit only upon FDA's request)
X	C. Methods validation package (e.g. 21 CFR 314.50 (e) (2) (i))
X	5. Nonclinical pharmacology and toxicology section (21 CFR 314.50(d)(2))
X	6. Human pharmacokinetics and bioavailability section (21 CFR 314.50 (d)(3))
N/A	7. Clinical Microbiology section (21 CFR 314.50(d)(4))
X	8. Clinical data section (21 CFR 314.50(d)(5))
N/A	9. Safety update report (21 CFR 314.50 (d)(5)(vi)(b))
X	10. Statistical section (21 CFR 314.50 (d)(6))
X	11. Case report tabulations (21 CFR 314.50 (f)(1))
X	12. Case report forms (21 CFR 314.50 (f) (1))
N/A	13. Patent information on any patent which claims the drug (21 U.S.C. 355 (b) or (c))
N/A	14. A patent certification with respect to any patent which claims the drug (21 U.S.C. 355 (b) (2) or (j) (2) (A))
N/A	15. Establishment description (21 CFR Part 600, if applicable)
X	16. Debarment certification
X	17. Field copy certification
	18. User Fee Cover Sheet (Form FDA 3397)
N/A	19. OTHER (Specify)

CERTIFICATION

I agree to update this application with new safety information about the drug that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including, but not limited to the following:

1. Good manufacturing practice regulations in 21 CFR 210 and 211, 606, and/or 820.
2. Biological establishment standards in 21 CFR Part 600.
3. Labeling regulations in 21 CFR 201, 606, 610 and/or 809
4. In the case of a prescription drug product, prescription drug advertising regulations in 21 CFR 202.
5. Regulations on making changes in application in 21 CFR 314.70, 314.71, and 314.72 and 601.12.
6. Regulations on reports in 21 CFR 314.80, 314.81, 600.80 and 600.81.
7. Local, state and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the controlled substances act, I agree not to market the product until the drug enforcement administration makes a final scheduling decision.

The data and information in this submission have been reviewed and are certified to be true and accurate.

Warning: a willfully false statement is a criminal offense, U.S. Code, title 18, section 1001.

SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT	TYPED NAME AND TITLE	DATE
	Leon Freeman, Ph.D. Chairman and CEO Pharmaquest Corporation	August 30, 1996

Public reporting burden for this collection of information is estimated to average 20 minutes per response including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to

s Clearance Officer, PHS
H Humphrey Building, Room 721B
dependence Avenue, S W
ington D C 20201
Attn: PRA

and to

Office of Management and Budget
Paperwork Reduction Project (0910 8014)
Washington D.C. 20503

Please DO NOT RETURN this application to either of these addresses

DUPLICATE

Inveresk Research
4470 REDWOOD HIGHWAY SUITE 101
SAN RAFAEL CALIFORNIA 94903
TELEPHONE: 415 491 6460

VIA FEDERAL EXPRESS

July 2, 1997

BL
NDA ORIG AMENDMENT

Document Control Room (HFD-540)
Food and Drug Administration
Department of Health and Human Services
Center for Drug Evaluation and Research
Division of Dermatologic and Dental Drug Products
9201 Corporate Blvd.
Rockville, MD 20850

Re: NDA 20-769 LOCOID LIPOCREAM®
LOCOID LIPOCREAM® (hydrocortisone butyrate 0.1%)

As discussed during a teleconference with the Division on June 16, 1997, we have revised the labeling submitted to this NDA. Attached is revised labeling for NDA 20-769. One copy is redlined to show the changes from that submitted in the original NDA.

We have amended the labeling to remove reference to the other dosage forms of Locoid (ointment and cream) separating the Locoid Lipocream. We have also removed all references to occlusion in this new labeling.

As discussed in the teleconference, we are making plans to conduct the HPA-Axis study required. However, due to various constraints we will not be able to conduct this study and submit the results before approval of NDA 20-769. Thus, we request approval based on the data already submitted, including the revised labeling.

This submission is made in duplicate.

Sincerely.

R.V. D'Agostino
President

Enclosures: 2 copies revised labeling, June 1997 (1 redlined)

cc:A.P. Morgenstern, Ph.D., Yamanouchi Europe B.V.
Jean Harvey

JH/

REVIEWS COMPLETED
CSO ACTION:
☐ LETTER ☐ N.A.I. ☐ MEMO
CSO INITIALS DATE

FAX: 415 491 6464
INTERNET: inveresk@aol.com
INVERESK RESEARCH (NORTH AMERICA) INC

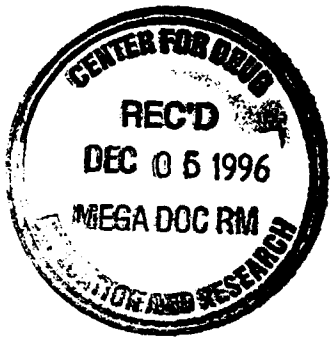
Inveresk Research
4470 REDWOOD HIGHWAY SUITE 101
SAN RAFAEL CALIFORNIA 94903
TELEPHONE: 415 491 6460

NEW CORRESPONDENCE

VIA FEDERAL EXPRESS

December 5, 1996

Attn: Ms. Mary Jane Kozma-Fornaro
HFD-540, Room N-115
Food and Drug Administration
Department of Health and Human Services
Center for Drug Evaluation and Research
Division of Dermatologic and Dental Drug Products
9201 Corporate Blvd.
Rockville, MD 20850



Re: NDA 20-769 LOCOID LIPOCREAM®

Dear Ms. Kozma-Fornaro,

This letter will respond to your telephone call today.

Copies of the tube and carton labels for Locoid Lipocream 15 gm and 45 gm were faxed to you today. Enclosed are three additional copies for the NDA.

Please let us know if you require any additional information.

Sincerely,

Jean Harvey
Manager of Regulatory Affairs

Encl: above

cc:A.P. Morgenstern, Ph.D., Yamanouchi Europe B.V.
R. J. D'Agostino

JH/

REVIEWS COMPLETED
CSO ACTION:
☐ LETTER ☐ N.A.I. ☐ MEMO
CSO INITIALS DATE

FAX: 415 491 6464
INTERNET: inveresk@aol.com
INVERESK RESEARCH (NORTH AMERICA) INC

ORIGINAL

Inveresk Research
4470 REDWOOD HIGHWAY SUITE 101
SAN RAFAEL CALIFORNIA 94903
TELEPHONE: 415 491 6460

VIA FEDERAL EXPRESS

January 16, 1997

Michael Weintraub, MD
Director
Division of Dermatologic and Dental Drug Products
Office of Drug Evaluation V
Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Boulevard, HFD-540
Rockville, MD 20850

RE: SAFETY UPDATE REPORT: 001
NDA 29-769
LOCOID LIPOCREAM® (hydrocortisone butyrate 0.1%)

This constitutes the first Safety Update Report under 21 CFR §314.50 (d) (5) (vi) (b).

The Sponsor of this NDA, Yamanouchi Europe B.V., Leiderdorp, The Netherlands, reports that there is no new animal or human data to add to that included in the NDA, submitted September 12, 1996. They have received no additional reports of adverse events connected with the use of Locoid Lipocream® since the NDA was submitted.

Sincerely,

Richard J. D'Agostino
President

Enclosures: Form FDA 3439

cc: A. P. Morgenstern, Ph.D., Director of Regulatory Affairs
Yamanouchi Europe B.V., Leiderdorp
The Netherlands

REVIEWS COMPLETED
CSO ACTION
☐ LETTER ☐ N.A.L. ☐ MEMO
CSO INITIALS DATE

FAX: 415 491 6464
INTERNET: inveresk@aol.com
INVERESK RESEARCH (NORTH AMERICA) INC

Inveresk Research
4470 REDWOOD HIGHWAY SUITE 101
SAN RAFAEL CALIFORNIA 94903
TELEPHONE: 415 491 6460

VIA FAX and DHL

August 28, 1997

Jonathan K. Wilkin, MD, Director
Division of Dermatologic and Dental Drug Products
Document Control Room (HFD-540)
Center for Drug Evaluation and Research
Food and Drug Administration
Department of Health and Human Services
9201 Corporate Blvd.
Rockville, MD 20850

Re: NDA 20-769 LOCOID LIPOCREAM® Cream
Environmental Assessment

Dear Dr. Wilkin,

This letter will formally withdraw the Environmental Assessment submitted in NDA No. 29-769, per the National Environmental Policy Act, Revision of Policies and Procedures Final Rule published in the Federal Register dated July 29, 1997. This will also constitute the withdrawal of the revised Environmental Assessment, along with certification and statements, both faxed to Ms. Olga Cintron on August 22, and sent via courier on August 25.

The sponsor submits a claim of Categorical Exclusion in accordance with 21 CFR 25.15 (d) of this Final Rule.

Sincerely

Richard J. D'Agostino
President

JH/
cc: A.P. Morgenstern, Ph.D., Yamanouchi Europe B.V. (fax)
G. Yingling, Esq., McKenna & Cuneo (fax)
S. Goldner, Ferndale Laboratories Inc. (fax)
R. J. D'Agostino, Inveresk Research

ORIGINAL

Inveresk Research
4470 REDWOOD HIGHWAY SUITE 101
SAN RAFAEL CALIFORNIA 94903
TELEPHONE: 415 491 6460

VIA FEDERAL EXPRESS

May 15, 1997

BC

Document Control Room (HFD-540) NDA ORIG AMENDMENT
Food and Drug Administration
Department of Health and Human Services
Center for Drug Evaluation and Research
Division of Dermatologic and Dental Drug Products
9201 Corporate Blvd.
Rockville, MD 20850

Re: NDA 20-769 LOCOID LIPOCREAM®
LOCOID LIPOCREAM® (hydrocortisone butyrate 0.1%)
Additional Information to Address CMC Deficiencies

At the request of Ms.Robin Anderson, we are attaching an official copy of additional information regarding Environmental Assessment and Chemistry data to this NDA. This information was sent as a Desk Copy to Ms. Mary Jane Kozma-Fornaro on November 26, 1996.

This submission is made in duplicate.

Sincerely,

R. J. D'Agostino
President

Encl: Environmental Assessment 11/25/96
Expanded Table of Contents, CMC section
9 mos. stability data

cc: A.P. Morgenstern, Ph.D., Yamanouchi Europe B.V.
Jean Harvey, Inveresk Research

JH/

REVIEWS COMPLETED
OSO ACTION:
☐ LETTER ☐ N.A.I. ☐ MEMO
OSO INITIALS DATE

FAX: 415 491 6464
INTERNET: inveresk@aol.com
INVERESK RESEARCH (NORTH AMERICA) INC

ORIGINAL

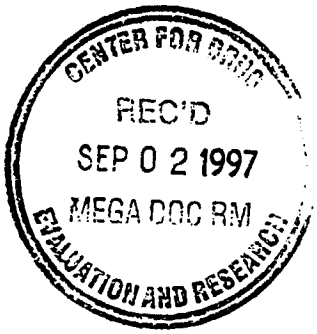
Inveresk Research

4470 REDWOOD HIGHWAY SUITE 101
SAN RAFAEL CALIFORNIA 94903
TELEPHONE: 415 491 6460

NEW CORRESP

VIA FAX AND COURIER

August 29, 1997



Jonathan K. Wilkin, M.D.
Director
Division of Dermatologic and Dental Drug Products
Document Control Room (HFD-540)
Center for Drug Evaluation and Research
Food and Drug Administration
Department of Health and Human Services
9201 Corporate Blvd.
Rockville, MD 20850

Re: NDA 20-769 LOCOID LIPOCREAM® Cream
Phase IV Commitments

Dear Dr. Wilkin:

This letter will confirm Yamanouchi Europe's commitment to the following in Phase IV.

Sincerely,

Richard J. D'Agostino
President

cc: A. P. Morgenstern, Ph.D., Yamanouchi Europe B.V. (fax)
G. Yingling, Esq., McKenna & Cuneo (fax)
S. Goldner, Ferndale Laboratories, Inc. (fax)

FAX: 415 491 6464
INTERNET: inveresk@aol.com
INVERESK RESEARCH (NORTH AMERICA) INC

NC

NEW CORRESP

DUPLICATE

Inveresk Research

4470 REDWOOD HIGHWAY SUITE 101
SAN RAFAEL CALIFORNIA 94903
TELEPHONE: 415 491 6460

VIA DHL

August 25, 1997

Jonathan K. Wilkin, MD, Director
Division of Dermatologic and Dental Drug Products
Document Control Room (HFD-540)
Center for Drug Evaluation and Research
Food and Drug Administration
Department of Health and Human Services
9201 Corporate Blvd.
Rockville, MD 20850

Re: NDA 20-769 LOCOID LIPOCREAM® Cream
Carton and Tube Labels
Environmental Assessment Statement and Certificate

Dear Dr. Wilkin,

We are enclosing a letter from the sponsor, Yamanouchi Europe, B.V., dated August 20, 1997 committing to revised carton and tube labels. Copies of these labels are also attached. Faxed notification of this commitment, along with a copy of the draft labels, was sent to the Consumer Safety Officer, Ms. Olga Cintron, on August 22, 1997.

We are also enclosing a complete copy of the revised Environmental Assessment Report, including new Statement and Certificate, dated August 20, 1997. A copy of the revised Environmental Assessment Report was faxed to Ms. Cintron on August 22, 1997.

We believe that this satisfies all the documentation requirements for this NDA review but please do not hesitate to let us know if we can assist in any way.

Sincerely.

Richard J. D'Agostino
President

Encl: Letter 8/20/97, EA Statement & Certificate 8/20/97

cc:A.P. Morgenstern, Ph.D., Yamanouchi Europe B.V. (air mail)
G. Yingling, Esq., McKenna & Cuneo (fax)
S. Goldner, Ferndale Laboratories Inc. (fax)
R. J. D'Agostino, Inveresk Research

FAX: 415 491 6464
INTERNET: inveresk@aol.com
INVERESK RESEARCH (NORTH AMERICA) INC

Yamanouchi

Yamanouchi Europe B.V.

Elisabethhof 19
P.O. Box 108
2350 AC Leiderdorp
The Netherlands
Telephone +31 71 5455745
Telefax +31 71 5455800

Direct line (071) 545 5 722
Direct fax (071) 545 5 840

Our ref.
Your ref. APM/lg/0820b1
Date August 20, 1997

Jonathan K. Wilkin, M.D.
Director, Division of Dermatologic and Dental
Drug Products (HFD-540)
Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Blvd.
Rockville, MD 20850
United States of America

Re: Locoid Lipocream Cream, NDA No. 20-769
Commitment to Revise and Submit New Labels of Carton and Tube

Dear Dr. Wilkin,

Recently Yamanouchi Europe B.V. accepted the suggested labeling changes for the Locoid Lipocream Cream 1% which had been recommended by the Center. Based on that acceptance, it will be necessary for Yamanouchi Europe B.V. to revise the labels of carton and tube to reflect the changes.

This letter is to notify the Center that Yamanouchi Europe B.V. is committed to making the changes in the labels as quickly as possible and will hope to submit to the agency during the week of August 25 the new labels that Yamanouchi Europe B.V. will use on the marketed product.

Very truly yours,
YAMANOUCHI EUROPE B.V.

A.P. Morgenstern, Ph.D
Director Regulatory Affairs

c.c. Olga Cintron, FDA CDER
Inveresk Research (North America), Inc.

YEH 0695 B

NEW CORRESP

ORIGINAL

Inveresk Research
4470 REDWOOD HIGHWAY SUITE 101
SAN RAFAEL CALIFORNIA 94903
TELEPHONE: 415 491 6460

VIA DHL

August 25, 1997

Jonathan K. Wilkin, MD, Director
Division of Dermatologic and Dental Drug Products
Document Control Room (HFD-540)
Center for Drug Evaluation and Research
Food and Drug Administration
Department of Health and Human Services
9201 Corporate Blvd.
Rockville, MD 20850

Re: NDA 20-769 LOCOID LIPOCREAM® Cream
Stability Commitment

Dear Dr. Wilkin,

We are enclosing a letter from the sponsor, Yamanouchi Europe, B.V., dated August 20, 1997 This letter states their commitment to a revised stability program post-approval, per the reviewing chemist's comments which we received via fax from Ms. Olga Cintron, Consumer Safety Officer, on August 19, 1997. Also enclosed is a letter dated August 22, 1997 which gives the details of their stability program, including a reference copy from the protocol for batch 95K06/33. The sponsor officially withdraws the submitted in the NDA. A revised stability protocol will be sent as soon as it is prepared. Data from the stability studies will be submitted in the Annual Report. Faxed notification of this commitment was sent to the Consumer Safety Officer, Ms. Olga Cintron, on August 22, 1997.

Sincerely,

Richard D'Agostino
President

Encl: Letters 8/20/97, 8/22/97

cc:A.P. Morgenstern, Ph.D., Yamanouchi Europe B.V. (air mail)
G. Yingling, Esq., McKenna & Cuneo (fax)
S. Goldner, Ferndale Laboratories Inc. (fax)
R. J. D'Agostino, Inveresk Research

FAX: 415 491 6464
INTERNET: inveresk@aol.com
INVERESK RESEARCH (NORTH AMERICA) INC

Yamanouchi

Yamanouchi Europe B.V.

Elisabethhof 19
P.O. Box 108
2350 AC Leiderdorp
The Netherlands
Telephone +31 71 5455745
Telefax +31 71 5455800

Direct line (071) 545 5 722

Direct fax (071) 545 5 840

Our ref.

Your ref. APM/lg/0820b2

Date August 20, 1997

Jonathan K. Wilkin, M.D.
Director, Division of Dermatologic and Dental
Drug Products (HFD-540)
Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Blvd.
Rockville, MD 20850
United States of America

Re: Locoid Lipocream Cream, NDA No. 20-769
Stability Commitment

Dear Dr. Wilkin,

This letter is to inform you that Yamanouchi Europe B.V. is prepared to submit a revised stability program for post approval batches based on the ICH Q1A Stability Guidelines.

By this letter we are officially withdrawing the submitted in the NDA application 20-769 and will submit for the Agency's review a new protocol following the ICH Q1A Stability Guidelines that will include:

1. Samples from the first 3 production batches.

2. Sample testing upon manufacture/introduction and at 3, 6, 9, 12, 18 and 24 months.

3. Sample analysis from the top, middle and bottom of each tube with reports of any variation being provided to FDA.

4. A commitment to remove from the market any product that fails to meet all specifications.

../2

YEH 0695 B

5. A commitment to submit the data from the stability studies in the annual report.

We will submit the revised stability protocol as soon as possible.

Very truly yours,
YAMANOUCHI EUROPE B.V.

A.P. Morgenstern, Ph.D
Director Regulatory Affairs

c.c. Olga Cintron, FDA CDER
Steve Hathaway, CDER
Inveresk Research (North America), Inc.

Yamanouchi

Yamanouchi Europe B.V.

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Direct fax (071) 545 5 840

Our ref. JV/em/0822b1

Your ref.

Date August 22, 1997

Jonathan K. Wilkin, M.D.
Director, Division of Dermatologic and Dental
Drug Products (HFD-540)
Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Blvd.
ROCKVILLE, MD 20850
UNITED STATES OF AMERICA

Re: Locoid Lipocream Cream, NDA No. 20769
Stability Commitment, revision of commitment dated August 20, 1997

Dear Dr. Wilkin,

This letter is to inform you that Yamanouchi Europe B.V. commits to execute the following stability program for post approval batches.

1. Samples from the first 3 production batches, and one batch per year (minimum) thereafter will be shelved under the following storage conditions: C and C/ % Rel.hum., in conformity with the labeled storage instructions.

2. Sample testing will be executed upon manufacture/introduction and at 3, 6, 9, 12, 18, 24, 30 and 36 months and annually thereafter until at least one time point past expiration.

3. According to the protocol to be used, in analysis, samples will be taken from the top, middle and bottom of each tube and all results will be reported.

4. The protocols to be used for these stability studies are the same as the protocols used in the current stability studies with stability batches 95K06/32, 95K07/32 and 95K08/32 (15 g tubes) and 95K06/33, 95K07/33 and 95K08/33 (45 g tubes), with the exception that no storage at elevated temperature is planned.

..2

Yamanouchi Europe B.V., Trade register Leiden nr: 53775, Established at Leiderdorp, The Netherlands.

Inveresk Research
4470 REDWOOD HIGHWAY SUITE 101
SAN RAFAEL CALIFORNIA 94903
TELEPHONE: 415 491 6460

VIA COURIER

August 20, 1997

Jonathan K. Wilkin, MD, Director
Division of Dermatologic and Dental Drug Products
Document Control Room (HFD-540)
Center for Drug Evaluation and Research
Food and Drug Administration
Department of Health and Human Services
9201 Corporate Blvd.
Rockville, MD 20850

Re: NDA 20-769 LOCOID LIPOCREAM® CREAM
(hydrocortisone butyrate 0.1% cream)

Dear Dr. Wilkin

Enclosed is a letter from the sponsor, Yamanouchi Europe B.V., in which they commit to conducting an HPA axis suppression study post-approval. A study protocol will be submitted for review shortly.

This letter was originally sent as requested to Ms. Olga Cintron, Consumer Safety Officer, via fax, on August 18, 1997.

Sincerely,

Richard J. D'Agostino
President

Enclosure: Yamanouchi letter 8/18/97 re HPA Axis study

cc: A. P. Morgenstern, Ph.D., Yamanouchi Europe B.V. (cover letter via fax only)
G. Yingling, Esq., McKenna & Cuneo (cover letter via fax only)
S. Goldner, Ferndale Laboratories (fax)
J. Harvey, Inveresk Research

JH/

FAX: 415 491 6464
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INVERESK RESEARCH (NORTH AMERICA) INC

Yamanouchi

Yamanouchi Europe B.V.

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Direct line (071) 545 5 722
Direct fax (071) 545 5 840

Our ref.

Your ref. APM/lg/0818b1

Date August 18, 1997

Jonathan K. Wilkin, M.D.
Director, Division of Dermatologic and Dental
Drug Products (HFD-540)
Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Blvd.
Rockville, MD 20850
United States of America

Re: Locoid Lipocream Cream, NDA No. 20-769
HPA Axis Suppression Study Commitment

Dear Dr. Wilkin,

Yamanouchi Europe B.V. ("Yamanouchi"), the sponsor of NDA 20-769, commits to conducting an HPA axis suppression study in a target patient population with maximal disease surface area and duration of treatment consistent with the approved product labelling.

Yamanouchi is in the final stages of completing a study protocol that will be submitted to the agency for its review. The work on the HPA axis study will be commenced as expeditiously as possible.

Very truly yours,
YAMANOUCHI EUROPE B.V.

A.P. Morgenstern, Ph.D
Director Regulatory Affairs

c.c. Olga Cintron, FDA CDER
Inveresk Research (North America), Inc.

DUPLICATE

NEW CORRESP

Inveresk Research

4470 REDWOOD HIGHWAY SUITE 101
SAN RAFAEL CALIFORNIA 94903
TELEPHONE: 415 491 6460

VIA COURIER

August 20, 1997

Jonathan K. Wilkin, MD, Director
Division of Dermatologic and Dental Drug Products
Document Control Room (HFD-540)
Center for Drug Evaluation and Research
Food and Drug Administration
Department of Health and Human Services
9201 Corporate Blvd.
Rockville, MD 20850

Re: NDA 20-769 LOCOID LIPOCREAM[7] CREAM (hydrocortisone butyrate 0.1% cream)

Dear Dr. Wilkin

This letter constitutes the formal acceptance of the Division's revised labeling, as received via fax on August 11, 1997. Faxed acceptance was sent to Ms. Olga Cintron, Consumer Safety Officer, on August 15, 1997.

Sincerely,

Richard J. D'Agostino
President

cc: A. P. Morgenstern, Ph.D., Yamanouchi Europe B.V. (air mail)
G. Yingling, Esq., McKenna & Cuneo (fax)
S. Goldner, Ferndale Laboratories (fax)
J. Harvey, Inveresk Research

JH/

FAX: 415 491 6464
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INVERESK RESEARCH (NORTH AMERICA) INC

McKenna & Cuneo, L.L.P.
Attorneys at Law

Washington, D.C.
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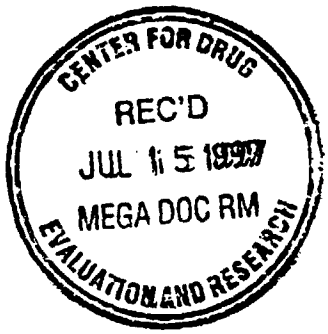
Denver
Dallas
Brussels
London

NEW CORRESP

July 8, 1997

Gary L. Yingling
202-496-7645
gary_yingling@mckennacuneo.com

Jonathan K. Wilkin, M.D.
Division of Dermatologic and
Dental Drug Products (HFD-540)
Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Blvd.
Rockville, MD 20850



Re: Locoid Lipocream®, NDA No. 20-769

Dear Dr. Wilkin:

We are writing this letter on behalf of our client, Yamanouchi Europe B.V. ("Yamanouchi"), to respond to requests from the Food and Drug Administration's ("FDA's") Division of Dermatologic and Dental Drug Products (the "Division") for additional HPA axis data confirming that Yamanouchi's Locoid Lipocream® ("LLC") product is a mid-potency steroid and does not produce more adrenal suppression than described for products of the same potency classification. LLC is the subject of New Drug Approval application ("NDA") number 20-769.

From our August 29, 1995 meeting with FDA, Ms. Kozma Fornaro's January 25, 1996 letter, and the April 21 and June 16, 1997 conference calls, it is our understanding that pre-approval submission of the HPA axis data will prevent post-approval issues, but that the Division will accept the HPA axis study as a post-approval, phase IV study, in order to complete the review of the NDA by the August 8, 1997 deadline. While Yamanouchi is anxious to have the review of the NDA completed without any post-approval issues, it is impossible to complete the HPA axis study within that time frame. Yamanouchi does have the capability to perform the HPA axis study on healthy volunteers with occluded normal skin within a reasonable time frame; however, the Division is requesting that the HPA axis study be conducted using patients with

diseased, rather than normal, skin. Arranging and conducting such a study will take a significant amount of time.

It will take at least a month, perhaps more, for Yamanouchi to locate a clinical investigator with a statistically significant number of patients (minimum 12 to 15) with the requisite level of psoriasis (15 to 20% upper surface involvement) who are willing to enroll in the study. This is in part due to the potency of the product. While the vasoconstriction data suggests a higher potency, all the clinical data on LLC document that it is a mid-potency steroid. We have been told that because patients that would qualify for the study will be foregoing more effective methods of treatment by agreeing to be treated with a mid-potency steroid, it will be difficult to obtain a patient population.

Yamanouchi realizes that it is possible to find an adequate number of diseased patients to conduct the HPA axis study; however, for the reasons discussed above, it is nearly impossible to conduct such a study within the next month. Nevertheless, Yamanouchi is committed to conducting the study at the earliest possible date. The company wishes to cooperate with the Division to develop a protocol that will provide the data that the Division seeks, and will be providing a protocol for the agency's comments and/or recommendations within the next couple of weeks.

Very truly yours,

Gary L. Yingling

GLY/mhh
cc: Yamanouchi Europe B.V.
Inveresk Research (North America) Inc.

DUPLICATE - file

Inveresk Research
4470 REDWOOD HIGHWAY SUITE 101
SAN RAFAEL CALIFORNIA 94903
TELEPHONE: 415 491 6460

VIA FEDERAL EXPRESS

June 30, 1997 ✓ NEW CORRESPONDENCE

stamp date 7/1/97

Document Control Room (HFD-540)
Food and Drug Administration
Department of Health and Human Services
Center for Drug Evaluation and Research
Division of Dermatologic and Dental Drug Products
9201 Corporate Blvd.
Rockville, MD 20850

Re: NDA 20-769 LOCOID LIPOCREAM®
LOCOID LIPOCREAM® (hydrocortisone butyrate 0.1%)

At the request of Ms. Robin Anderson, we are attaching official copies of two communications recently faxed to the Division.

1. Copy of fax from McKenna & Cuneo dated June 12,1997 with agenda for teleconference on June 16, 1997.

2. Copy of position paper on additonal HPA axis studies by Daniel Piacquadio, M.D. dated June 16, 1997.

This submission is made in duplicate.

Sincerely,

R. J. D'Agostino
President

Enclosures (above)

cc: A.P. Morgenstern, Ph.D., Yamanouchi Europe B.V.
Jean Harvey

JH/

REVIEWS COMPLETED
CSO ACTION:
☐ LETTER ☐ N.A.L. ☐ N.E.C.
CSO INITIALS DATE

FAX: 415 491 6464
INTERNET: inveresk@aol.com
INVERESK RESEARCH (NORTH AMERICA) INC

ORIGINAL

Inveresk Research
4470 REDWOOD HIGHWAY SUITE 101
SAN RAFAEL CALIFORNIA 94903
TELEPHONE: 415 491 6460

VIA FEDERAL EXPRESS

February 18, 1997

Attn: Ms. Robin Anderson, RN, MBA
HFD-540, Room N-115
Food and Drug Administration
Department of Health and Human Services
Center for Drug Evaluation and Research
Division of Dermatologic and Dental Drug Products
9201 Corporate Blvd.
Rockville, MD 20850

BZ

Re: NDA 20-769 LOCOID LIPOCREAM®
Addendum to Integrated Clinical/Statistical Study Report No. 607 (92-LOC-04)
Subset Analysis of Protocol No. BRO 3800-03

Dear Ms. Anderson,

As requested in your fax of January 28, 1997, we are enclosing two copies of the subset analysis for Protocol No. BRO 3800-03 (Study No. 92-LOC-04). This analysis was conducted on the Locoid Lipocream® patient population only.

As expected, this analysis does not show any statistical significance between groups, either gender (male/female) or age (less than 50 years compared to over 50 years, or less than 65 years compared to over 65 years old).

Please let us know if you require anything else for this NDA review.

Sincerely,

Jean Harvey
Manager of Regulatory Affairs

Encl: Subset Analysis BRO 3800-03 2/17/97

cc: A.P. Morgenstern, Ph.D., Yamanouchi Europe B.V.
M. Thomas, Priority Statistics,. Inc.
S. Goldner, Ferndale Laboratories Inc.
G. Yingling, Esq., McKenna & Cuneo (cover letter via fax only)
R. J. D'Agostino, Inveresk Research

JH/

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ORIGINAL
NEW CORRESP
NC

Inveresk Research
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TELEPHONE: 415 491 6460

VIA FEDERAL EXPRESS

December 20, 1996

Ms. Mary Jane Kozma-Fornaro
HFD-540, Room N-115
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Dermatologic and Dental Drug Products
9201 Corporate Blvd.
Rockville, MD 20850

RE: **NDA No. 20-769**
LOCOID LIPOCREAM® (hydrocortisone butyrate 0.1%)
CMC: English Translations of Master Batch Records

Dear Ms. Fornaro,

The enclosed information will address your request of November 6, 1996, and is in addition to our response of November 26 (Item 3.)

English translations of the following Attachments to the Chemistry, Manufacturing & Controls Section of NDA No. 20-769, Volume 3.1 are enclosed:

Attachment 8-5, pages 88-164
Attachment 8-6, pages 165-189
Attachment 8-7, pages 190-206
Attachment 8-8, pages 207-296
Attachment 8-9, pages 297-317
Attachment 8-10, pages 1-19
Attachment 8-11, pages 20-50
Attachment 8-12, pages 51-82
Attachment 8-13, pages 83-106

REVIEWS COMPLETED
CSO ACTION:
☐ LETTER ☐ N.A.I. ☐ MEMO
CSO INITIALS DATE

RECD
DEC 23 1996
HFD
EVALUATION AND RESEARCH

Sincerely,

Jean Harvey
Manager of Regulatory Affairs

cc: A. P. Morgenstern, Ph.D., Director of Regulatory Affairs
Yamanouchi Europe B.V., Leiderdorp, The Netherlands

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INVERESK RESEARCH (NORTH AMERICA) INC

PHARMAQUEST / Inveresk Research

N

VIA FEDERAL EXPRESS

CENTER FOR DRUG EVALUATION AND RESEARCH
REC'D
SEP 5 1996
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CENTER FOR DRUG EVALUATION AND RESEARCH
REC'D
SEP 03 1996
CDR

August 30, 1996

Food and Drug Administration
Center for Drug Evaluation and Research
Central Document Room
Park Building, Room 214
12420 Parklawn Drive
Rockville, MD 20852

RE: **NEW DRUG APPLICATION**
LOCOID LIPOCREAM® (hydrocortisone butyrate 0.1%)

Enclosed is a New Drug Application for Locoid Lipocream® 0.1% (hydrocortisone butyrate). This Application conforms to the regulations contained in 21 CFR §314.50.

This new drug is a topical formulation of 0.1% hydrocortisone butyrate for the relief of inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses. This formulation has been marketed in Europe for many years. One controlled, efficacy study was conducted in the United States under IND

The Sponsor of this NDA, Yamanouchi Europe B.V., Leiderdorp, The Netherlands, is the holder of three approved NDAs for other topical formulations of Locoid® (hydrocortisone butyrate) 0.1%. The approved NDAs are:

- NDA No. 18-514, Locoid® Cream formulation, approved March 3, 1982
- NDA No. 18-652, Locoid® Ointment formulation, approved October 29, 1982
- NDA No. 19-116, Locoid® Lotion formulation, approved February 25, 1987

The strength of hydrocortisone butyrate in all of these formulations is 0.1%, the same strength as in the Locoid Lipocream® formulation. All of the pertinent material on the drug substance, hydrocortisone butyrate, in these approved NDAs, and their annual updates, is incorporated into this NDA by reference.

Pharmaquest Corporation · 4470 Redwood Highway · Suite 101 · San Rafael, CA 94903 · phone (415) 491-6460 · fax (415) 491-6464

A letter of authorization from Yamanouchi Europe B.V., naming Pharmaquest Corporation as their representative in the United States is attached.

A Debarment Certification, signed by Dr. A.P. Morgenstern, Directory of Regulatory Affairs, Yamanouchi B.V. Europe is also attached.

The User Fee Cover Sheet (Form FDA 3397) is attached to this letter. The sponsor has made arrangements to wire transfer the amount of to the designated FDA Demand Deposit bank account

Sincerely,

Leon Freeman, Ph.D.
Chairman and CEO

Enclosures: Locoid Lipocream® (hydrocortisone butyrate 0.1%) NDA
Authorization letter
Debarment Certification
User Fee Cover Sheet (Form FDA 3397)
Application Sheet (Form FDA 3439)

cc: A. P. Morgenstern, Ph.D., Director of Regulatory Affairs
Yamanouchi Europe B.V., Leiderdorp
The Netherlands