ARCHIVAL

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. 0910-0338
Expiration Date: April 30, 2000
See OMB Statement on page 2.

FOR FDA USE ONLY

APPLICATION NUMBER

CENTER FOR DRUG EVALUATION RECD MAR 20 2000 MEGA DOC RM

APPLICANT INFORMATION

NAME OF APPLICANT	DATE OF SUBMISSION
Fujisawa Healthcare, Inc.	03/17/00
TELEPHONE NO. *(Include Area Code)*	**FACSIMILE (FAX) Number *(Include Area***
(847) 317-8872	(847)317-7286

APPLICANT ADDRESS *(Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued)*:

Parkway North Center
Three Parkway North
Deerfield, IL 60015-2548

AUTHORIZED U.S. AGENT NAME & ADDRESS *(Number, Street, City, State, ZIP Code, telephone & FAX number)* IF APPLICABLE

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER (If previously issued) NDA 50-777

ESTABLISHED NAME *(e.g., Proper name, USP/USAN name)*	PROPRIETARY NAME *(trade name)* IF ANY
tacrolimus ointment	PROTOPIC

CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME *(If any)*	CODE NAME *(If any)*
Please refer to package insert	FK506, FK 506, FK-506, FR900506

DOSAGE FORM:	STRENGTHS:	ROUTE OF ADMINISTRATION:
Ointment	0.03% and 0.1%	Topical

(PROPOSED) INDICATION(S) FOR USE: Short and long term treatment of the signs and symptoms of atopic dermatitis.

APPLICATION INFORMATION

APPLICATION TYPE (check one)
☒ NEW DRUG APPLICATION (21 CFR 314.50) ☐ ABBREVIATED APPLICATION (ANDA, AADA, 21 CFR 314.94)
☐ BIOLOGICS LICENSE APPLICATION (21 CFR part 601)

IF AN NDA, IDENTIFY THE APPROPRIATE TYPE ☒ 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

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☐ ORIGINAL APPLICATION ☒ AMENDMENT TO A PENDING APPLICATION ☐ RESUBMISSION
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☐ EFFICACY SUPPLEMENT ☐ LABELING SUPPLEMENT ☐ CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT ☐ OTHER

REASON FOR SUBMISSION CMC Amendment: Notification of additional supplier

PROPOSED MARKETING STATUS (check one) ☒ PRESCRIPTION PRODUCT (Rx) ☐ OVER-THE-COUNTER PRODUCT (OTC)

NUMBER OF VOLUMES SUBMITTED 1 THIS APPLICATION IS ☒ PAPER ☐ PAPER AND ELECTRONIC ☐ ELECTRONIC

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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 type 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.

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NDA 50-708
NDA 50-709

This application contains the following items: *(Check all that apply)*	
	1. Index
	2. Labeling (check one) ☐ Draft Labeling ☐ Final Printed Labeling
	3. Summary (21 CFR 314.50 (c))
	4. Chemistry section
X	A. Chemistry, manufacturing, and controls information (e.g. 21 CFR 314.50 (d) (1), 21 CFR 601.2)
	B. Samples (21 CFR 314.50 (e) (1), 21 CFR 601.2 (a)) (Submit only upon FDA's request)
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	16. Debarment certification (FD&C Act 306 (k)(1))
X	17. Field copy certification (21 CFR 314.50 (k) (3))
	18. User Fee Cover Sheet (Form FDA 3397)
	19. OTHER (Specify)

CERTIFICATION

I agree to update this application with new safety information about the product 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 21 CFR 201, 606, 610, 660 and/or 809.
4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR 202.
5. Regulations on making changes in application in 21 CFR 314.70, 314.71, 314.72, 314.97, 314.99, 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, to the best of my knowledge 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
Donald E. Baker	Donald E. Baker, JD Senior Director, Regulatory Affairs	3/17/2000

ADDRESS *(Street, City, State, and ZIP Code)*	Telephone Number
3 Parkway Center North Deerfield, IL 60015-2548	(847) 317-8872

Public reporting burden for this collection of information is estimated to average 40 hours 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:

DHHS, Reports Clearance Officer
Paperwork Reduction Project (0910-0338)
Hubert H. Humphrey Building, Room 531-H
200 Independence Avenue, S.W.
Washington, DC 20201

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

Please DO NOT RETURN this form to this address.

(422)

Fujisawa Healthcare, Inc.
Parkway North Center, Three Parkway North
Deerfield, Illinois 60015-2548
Tel. (847) 317-8800 • Telefax (847) 317-7286

Fujisawa

Donald E. Baker, J.D.
Senior Director
Regulatory Affairs

March 13, 2000

Jonathan Wilkin, M. D., Director
Division of Dermatologic and Dental Drug Products
Food and Drug Administration (HFD-540)
Center for Drug Evaluation and Research
9201 Corporate Blvd. 2nd Fl., N-214
Rockville, Maryland 20850-3202

REVIEW

NDA ORIG AMENDMENT

RE: NDA 50-777 BB
Protopic® (tacrolimus 0.03% and 0.1%) Ointment

AMENDMENT: Response to PK Question

Dear Dr. Wilkin:

Reference is made to Fujisawa Healthcare, Inc.'s (FHI) new drug application (NDA 50-777) submitted under Section 505(b) to the FDA on September 8, 1999 for Protopic (tacrolimus 0.03% and 0.1%) Ointment.

Reference is also made to a FDA Fax Memo dated February 29, 2000 from Ms. Millie Wright regarding a question from the PK reviewer (see attached). FHI was asked to provide an answer to a question regarding blood levels in Study FG-06-04. Furthermore, FHI was asked to provide this information via fax, as well as submit a hard copy explanation to NDA 50-777. A response to the question was provided via fax to Ms. Millie Wright on March 10, 2000.

Accordingly, we are providing below our official response to the FDA Fax Memo dated February 29, 2000.

> In Table no. 6 of study FG-06-04 the bracketed values were below — pg/mL (i.e. the LOQ), but were above the limit of detection (i.e. LOD) of the assay. Thus the values in brackets were not quantifiable but the concentration was estimated based on the chromatogram. At the time of this study, the convention in Europe was to report concentrations which were not detectable as " — pg/mL" whereas concentrations which were above the limit of detection but below the limit of quantitation were reported as the concentration in brackets. For the purposes of our analyses, all concentrations which were below the limit of quantitation — pg/mL) were assigned a value of 0.

Should you have any questions or require further information regarding this submission, please do not hesitate to contact me at **(847) 317-8872** or Jerry D. Johnson, Ph.D. at **(847) 317-8898.**

Sincerely,

Laura C Navarre for

Donald E. Baker
Senior Director, Regulatory Affairs

cc: Millie Wright, Project Manager (desk copy)

K:\kim\protopic\nda\FG04 Blood Levels
NDA_Dev\archive\protopic\nda\subm\000313.pdf

FDA Fax Memo

Date: February 29, 2000

Subject: NDA 50-777/Protopic (Tacrolimus Ointment)

Hi Don,

The PK reviewer has the following question:

Re: Blood Levels in Study FG-06-04 (Relative bioavailability of 0.03, 0.1, and 0.3% tacrolimus ointment in healthy Volunteers)

The limit of quantitation of tacrolimus used in this study is — pg/mL. Table no. 6 on pages 48-51 of volume 43 of the submission has several values that are reported in brackets. These values are below the — pg/mL level. There are some as low as 1 pg/mL. Most others are reported as — pg/mL. It is unclear how the bracketed values were accounted for. The Sponsor needs to provide an explanation for the criteria used in estimating the blood levels and how were these low levels quantifiable based on the assay validation range.

Don, once you have obtained an explanation, please submit it the NDA. It would be helpful if you would fax a copy to me and I will forward it to the PK reviewer. While the hard copy is being submitted, the reviewer can review the faxed copy.

If you have questions, please call.

Respectfully,
Millie

CC:
Orig NDA 50-777
HFD-540/Div File
HFD-540/Wright

APPEARS THIS WAY
ON ORIGINAL

DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

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tacrolimus ointment	PROTOPIC

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Please refer to package insert

CODE NAME *(If any)* FK506, FK 506, FK-506, FR900506

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REASON FOR SUBMISSION Response to FDA Fax Memo dated February 29, 2000

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Laura Chavarre for	Donald E. Baker, JD Senior Director, Regulatory Affairs	3/13/2000

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Paperwork Reduction Project (0910-0338)
Hubert H. Humphrey Building, Room 531-H
200 Independence Aver ue, S.W
Washington, DC 20201

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Parkway North Center, Three Parkway North
Deerfield, Illinois 60015-2548
Tel. (847) 317-8800 • Telefax (847) 317-7286

Fujisawa

Donald E. Baker, J.D.
Senior Director
Regulatory Affairs

February 11, 2000

NEW CORRESPONDENCE

ARCHIVAL

Jonathan Wilkin, M.D., Director
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Dermatologic and Dental Drug Products, HFD-540
9201 Corporate Blvd., 2nd Fl., N-214
Rockville, Maryland 20850-3202

Re: NDA 50-777
Protopic® (tacrolimus 0.03% and 0.1%) Ointment

GENERAL CORRESPONDENCE

Dear Dr. Wilkin:

Reference is made to Fujisawa Healthcare, Inc.'s (FHI) new drug application (NDA 50-777) submitted under Section 505(b) to the FDA on September 8, 1999 for Protopic® (tacrolimus 0.03% and 0.1%) Ointment.

Reference is also made to the 120-day safety update to NDA 50-777 for Protopic® (tacrolimus 0.03% and 0.1%) Ointment, which was submitted to the Division on January 10, 2000.

In our Protopic (tacrolimus ointment) 120-day safety update, we described preliminary findings from a European/Canadian clinical study (FG-06-19) that was conducted in pediatric patients. In this study, a small proportion of blood samples showed high tacrolimus concentrations that were inconsistent with previous studies. In the 120-day safety update it was stated that further investigation of these samples was underway. We now have further information from this investigation, which is summarized in the attached report **(Attachment 1).** This information is being shared with Japanese as well as some European Regulatory Authorities during preliminary meetings to appoint the Rapporteur/Co-Rapporteur. As you will see from your review of the attached report, the blood concentrations reported in FG-06-19 in the low volume sample subset are highly suspect, since they are inconsistent with the large body of blood concentration data obtained in 10 previous studies involving 1660 patients and are, in many cases, biologically implausible given the known systemic pharmacokinetic profile of tacrolimus.

We are confident that the elevated tacrolimus concentrations were the result of contamination due to the finger stick sampling technique that was used in sampling blood from children in this study and therefore, are not a safety concern. We are providing this summary report to the Division to ensure that the FDA has the most recent information from this investigation and is kept apprised of information which has been shown to some other Regulatory Authorities around the world.

ORIGINAL

An electronic archive copy and a paper desk copy have been included in this submission. The electronic archive copy of this information is contained on one diskette (approximately 500KB). The electronic archive copy was checked with Norton Antivirus (version 4.04) and is virus-free. The electronic archive copy and the paper desk copy are identical.

We would be willing to answer any questions or further discuss this matter with the Division should you so desire. Should you have any questions or require additional information concerning this summary report, please do not hesitate to contact the undersigned at **(847) 317-8872** or Jerry D. Johnson, Ph.D. at **(847) 317-8898**.

Sincerely,

Donald E. Baker
Senior Directory. Regulatory Affairs

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L:\RA\Dbaker NDA50-777 Protopic Update.doc

APPEARS THIS WAY
ON ORIGINAL

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FOOD AND DRUG ADMINISTRATION

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REASON FOR SUBMISSION General Correspondence: Amendment to the 120-Day Safety Update for NDA 50-777

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	18. User Fee Cover Sheet (Form FDA 3397)
X	19. OTHER (Specify) Further information for Safety Update for NDA 50-777

CERTIFICATION

I agree to update this application with new safety information about the product 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 21 CFR 201, 606, 610, 660 and/or 809.
4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR 202.
5. Regulations on making changes in application in 21 CFR 314.70, 314.71, 314.72, 314.97, 314.99, 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, to the best of my knowledge are certified to be true and accurate.

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SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT	TYPED NAME AND TITLE	DATE
Donna E. Baker	Donald E. Baker, JD Senior Director, Regulatory Affairs	2/11/2000

ADDRESS *(Street, City, State, and ZIP Code)*	Telephone Number
3 Parkway Center North Deerfield, IL 60015-2548	(847 317-8872

Public reporting burden for this collection of information is estimated to average 40 hours 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:

DHHS, Reports Clearance Officer
Paperwork Reduction Project (0910-0338)
Hubert H. Humphrey Building, Room 531-H
200 Independence Avenue, S.W.
Washington, DC 20201

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Please **DO NOT RETURN** this form to this address.

(379)

Fujisawa Healthcare, Inc.
Parkway North Center, Three Parkway North
Deerfield, Illinois 60015-2548
Tel. (847) 317-8800 • Telefax (847) 317-7286

Fujisawa

Donald E. Baker, J.D.
Senior Director
Regulatory Affairs

NEW CORRESP

January 31. 2000

Jonathan Wilkin, M.D., Director
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Dermatologic and Dental Drug Products, HFD-540
9201 Corporate Blvd., 2nd Fl., N-214
Rockville, Maryland 20850-3202

Re: NDA 50-777
Protopic® (tacrolimus 0.03% and 0.1%) Ointment

GENERAL CORRESPONDENCE

Dear Dr. Wilkin:

Reference is made to Fujisawa Healthcare, Inc.'s (FHI) new drug application (NDA 50-777) submitted under Section 505(b) to the FDA on September 8, 1999 for Protopic® (tacrolimus 0.03% and 0.1%) Ointment.

Reference is also made to the pre-NDA meeting with your Division on April 6, 1999 and the pre-NDA briefing package which contained a list of issues and specific questions for which we requested answers during the meeting.

One of the questions included in the pre-NDA briefing package pertained to vendor lead times for pre-printed laminate tubes. The specific question posed by FHI and the answer provided by the Division are reflected in the Division's minutes of the meeting as follows:

Sponsor's Question:

1. Based on vendor lead times for pre-printed laminate tubes, would the Division be willing to provide general acceptance early in the review process of the printed content of the laminate tube?

Division's Answer:

2. Not early in the review process; however, it might be possible to provide a draft version within the last three months of the review cycle. Sponsor acknowledged that they would be assuming a risk in sending draft container labeling to vendor.

During the pre-NDA meeting, Dr. Wilson DeCamp (Chemistry Team Leader) indicated that he may be able to undertake a preliminary review of the content of the pre-printed laminate tube label.

Accordingly, we are providing for the Division's review and comment draft copies of the proposed laminate tube label and artwork for Protopic (tacrolimus 0.03% and 0.1%) Ointment **(Attachment 1)**. A color copy of the proposed draft tube label artwork has been provided with the review copy of this submission.

In addition, we are also requesting that the Division evaluate the Protopic tradename, and if required, request a trademark consultation from the FDA's Labeling and Nomenclature Committee (LNC) as soon as possible.

We have carefully reviewed our vendor lead times, our internal manufacturing cycle times, and the time required to test and release product as soon as possible following approval of the NDA. Therefore, in order to facilitate the earliest possible launch, we would need to order printing of the 0.03% laminate tubes during [redacted] and the 0.1% tubes during [redacted]

As you are aware, the Division's comments on the pre-printed laminate tube label and artwork are desirable, in order to minimize expenditure associated with revisions to the proposed version. Therefore, since time is of the essence, we respectfully request that the Division provide us with comments at the earliest possible time.

We look forward to continued communication with the Division during the review of this NDA. Should you have any questions or require additional information concerning this matter, please do not hesitate to contact the undersigned at **(847) 317-8872** or Laura C. Navarre at (847) **317-1340**.

Sincerely,

Donald E. Baker
Senior Director, Regulatory Affairs

APPEARS THIS WAY
ON ORIGINAL

cc: Ms. Millie Wright, Project Manager, FDA-HFD 540

Kim\Protopic NDA Gen Corres Label.doc
NDA_Dev\Archive NDA\Subm\000201

ORIGINAL

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. 0910-0338
Expiration Date: April 30, 2000
See OMB Statement on page 2.

FOR FDA USE ONLY

APPLICATION NUMBER

APPLICANT INFORMATION

NAME OF APPLICANT	DATE OF SUBMISSION
Fujisawa Healthcare, Inc.	01/31/00
TELEPHONE NO. (Include Area Code)	**FACSIMILE (FAX) Number (Include Area Code)**
(847) 317-8872	(847)317-7286

APPLICANT ADDRESS *(Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued)*
Parkway North Center
Three Parkway North
Deerfield, IL 60015-2548

AUTHORIZED U.S. AGENT NAME & ADDRESS *(Number, Street, City, State, ZIP Code, telephone & FAX number)* IF APPLICABLE

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER (If previously issued) NDA 50-777

ESTABLISHED NAME *(e.g., Proper name, USP/USAN name)*	PROPRIETARY NAME *(trade name)* IF ANY
tacrolimus ointment	PROTOPIC

CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME *(If any)*
Please refer to package insert

CODE NAME *(If any)* FK506, FK 506, FK-506, FR900506

DOSAGE FORM:	STRENGTHS:	ROUTE OF ADMINISTRATION:
Ointment	0.03% and 0.1%	Topical

(PROPOSED) INDICATION(S) FOR USE Short and long term treatment of the signs and symptoms of atopic dermatitis.

APPLICATION INFORMATION

APPLICATION TYPE (check one)
☒ NEW DRUG APPLICATION (21 CFR 314.50) ☐ ABBREVIATED APPLICATION (ANDA, AADA, 21 CFR 314.94)
☐ BIOLOGICS LICENSE APPLICATION (21 CFR part 601)

IF AN NDA, IDENTIFY THE APPROPRIATE TYPE ☒ 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)
☐ ORIGINAL APPLICATION ☐ AMENDMENT TO A PENDING APPLICATION ☐ RESUBMISSION
☐ PRESUBMISSION ☐ ANNUAL REPORT ☐ ESTABLISHMENT DESCRIPTION SUPPLEMENT ☐ SUPAC SUPPLEMENT
☐ EFFICACY SUPPLEMENT ☐ LABELING SUPPLEMENT ☐ CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT ☒ OTHER

REASON FOR SUBMISSION General Correspondence (Draft Tube Artwork)

PROPOSED MARKETING STATUS (check one) ☒ PRESCRIPTION PRODUCT (Rx) ☐ OVER-THE-COUNTER PRODUCT (OTC)

NUMBER OF VOLUMES SUBMITTED _____ THIS APPLICATION IS ☒ PAPER ☐ PAPER AND ELECTRONIC ☐ 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 type 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.

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

[ ]

NDA 50-708
NDA 50-709

ORIGINAL

This application contains the following items: *(Check all that apply)*	
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	A. Chemistry, manufacturing, and controls information (e.g. 21 CFR 314.50 (d) (1), 21 CFR 601.2)
	B. Samples (21 CFR 314.50 (e) (1), 21 CFR 601.2 (a)) (Submit only upon FDA's request)
	C. Methods validation package (e.g. 21 CFR 314.50 (e) (2) (i), 21 CFR 601.2)
	5. Nonclinical pharmacology and toxicology section (e.g. 21 CFR 314.50 (d) (2), 21 CFR 601.2)
	6. Human pharmacokinetics and bioavailability section (e.g. 21 CFR 314.50 (d) (3), 21 CFR 601.2)
	7. Clinical Microbiology (e.g. 21 CFR 314.50 (d) (4))
	8. Clinical data section (e.g. 21 CFR 314.50 (d) (5), 21 CFR 601.2)
	9. Safety update report (e.g. 21 CFR 314.50 (d) (5) (vi) (b), 21 CFR 601.2)
	10. Statistical section (e.g. 21 CFR 314.50 (d) (6), 21 CFR 601.2)
	11. Case report tabulations (e.g. 21 CFR 314.50 (f) (1), 21 CFR 601.2)
	12. Case reports forms (e.g. 21 CFR 314.50 (f) (2), 21 CFR 601.2)
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	14. A patent certification with respect to any patent which claims the drug (21 U.S.C. 355 (b) (2) or (j) (2) (A))
	15. Establishment description (21 CFR Part 600, if applicable)
	16. Debarment certification (FD&C Act 306 (k)(1))
	17. Field copy certification (21 CFR 314.50 (k) (3))
	18. User Fee Cover Sheet (Form FDA 3397)
X	19. OTHER (Specify) Letter & Attachment requesting comments on draft tube artwork

CERTIFICATION

I agree to update this application with new safety information about the product 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:

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2. Biological establishment standards in 21 CFR Part 600.
3. Labeling regulations 21 CFR 201, 606, 610, 660 and/or 809.
4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR 202.
5. Regulations on making changes in application in 21 CFR 314.70, 314.71, 314.72, 314.97, 314.99, and 601.12.
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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, to the best of my knowledge 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
Donald E. Baker	Donald E. Baker, JD Senior Director, Regulatory Affairs	1/31/2000

ADDRESS *(Street, City, State, and ZIP Code)*	Telephone Number
3 Parkway Center North Deerfield, IL 60015-2548	(847) 317-8872

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Washington, DC 20201

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Fujisawa Healthcare, Inc.
Parkway North Center, Three Parkway North
Deerfield, Illinois 60015-2548
Tel. (847) 317-8800 Telefax (847) 317-7286

Fujisawa

NDA

January 10, 2000

ARCHIVAL

Jonathan Wilkin, M. D., Director
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Dermatologic and Dental Drug Products, HFD-540
9201 Corporate Blvd. 2nd Fl., N-214
Rockville, Maryland 20850-3202

Re: NDA 50-777
Protopic® (tacrolimus 0.03% and 0.1%) Ointment

SUBMISSION OF 120-DAY SAFETY UPDATE

Dear Dr. Wilkin:

Reference is made to Fujisawa Healthcare, Inc.'s (FHI) new drug application (NDA 50-777) submitted under Section 505(b) to the FDA on September 8, 1999 for Protopic (tacrolimus 0.03% and 0.1%) Ointment.

We are herewith submitting the 120-day safety update for NDA 50-777.

An electronic archive copy and a paper desk copy have been included in this submission. The electronic archive copy of this NDA safety update is contained on one CDROM (approximately 12 megabytes). The electronic archive copy was checked with Norton Antivirus (version 4.04) and is virus-free. The electronic archive copy and the paper desk copy are identical.

Please feel free to contact me at 847/317-8872 or Robert M. Reed at 847/317-8985 if you have any questions or concerns.

Sincerely,

Robert M. Reed for

APPEARS THIS WAY
ON ORIGINAL

Donald E. Baker
Senior Director, Regulatory Affairs

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ORIGINAL

ARCHIVAL

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. 0910-0338
Expiration Date: April 30, 2000
See OMB Statement on page 2.

FOR FDA USE ONLY

APPLICATION NUMBER

CENTER FOR DRUG EVALUATION AND RESEARCH
JAN 12 2000
MEGA DIVISION

APPLICANT INFORMATION

NAME OF APPLICANT	DATE OF SUBMISSION
Fujisawa Healthcare, Inc.	01/10/00
TELEPHONE NO. (Include Area Code)	**FACSIMILE (FAX) Number (Include Area Code)**
(847) 317-8872	(847)317-7286

APPLICANT ADDRESS (Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued):	AUTHORIZED U.S. AGENT NAME & ADDRESS (Number, Street, City, State, ZIP Code, telephone & FAX number) IF APPLICABLE
Parkway North Center Three Parkway North Deerfield, IL 60015-2548	

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER (If previously issued) NDA 50-777

ESTABLISHED NAME (e.g., Proper name, USP/USAN name)	PROPRIETARY NAME (trade name) IF ANY
tacrolimus ointment	PROTOPIC

CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME (If any)	CODE NAME (If any)
Please refer to package insert	FK506, FK 506, FK-506, FR900506

DOSAGE FORM:	STRENGTHS:	ROUTE OF ADMINISTRATION:
Ointment	0.03% and 0.1%	Topical

(PROPOSED) INDICATION(S) FOR USE: Short and long term treatment of the signs and symptoms of atopic dermatitis.

APPLICATION INFORMATION

CENTER FOR DRUG EVALUATION AND RESEARCH
REC'D
JAN 11 2000
CDR

APPLICATION TYPE (check one)
☒ NEW DRUG APPLICATION (21 CFR 314.50) ☐ ABBREVIATED APPLICATION (ANDA, AADA, 21 CFR 314.94)
☐ BIOLOGICS LICENSE APPLICATION (21 CFR part 601)

IF AN NDA, IDENTIFY THE APPROPRIATE TYPE ☒ 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)
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☐ PRESUBMISSION ☐ ANNUAL REPORT ☐ ESTABLISHMENT DESCRIPTION SUPPLEMENT ☐ SUPAC SUPPLEMENT
☐ EFFICACY SUPPLEMENT ☐ LABELING SUPPLEMENT ☐ CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT ☒ OTHER

REASON FOR SUBMISSION Submission of Section 9 (120-Day Safety Update) to NDA 50-777

PROPOSED MARKETING STATUS (check one) ☒ PRESCRIPTION PRODUCT (Rx) ☐ OVER-THE-COUNTER PRODUCT (OTC)

NUMBER OF VOLUMES SUBMITTED 2 — THIS APPLICATION IS ☐ PAPER ☒ PAPER AND ELECTRONIC ☐ ELECTRONIC

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NDA 50-709

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	19. OTHER (Specify)

CERTIFICATION

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6. Regulations on reports in 21 CFR 314.80, 314.81, 600.80 and 600.81.
7. Local, state and Federal environmental impact laws.

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The data and information in this submission have been reviewed and, to the best of my knowledge are certified to be true and accurate.

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SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT	TYPED NAME AND TITLE	DATE
[signature] for Don Baker	Donald E. Baker, JD Senior Director, Regulatory Affairs	1/10/00

ADDRESS *(Street, City, State, and ZIP Code)*	Telephone Number
3 Parkway Center North Deerfield, IL 60015-2548	(847 317-8872

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Fujisawa Healthcare, Inc.
Parkway North Center, Three Parkway North
Deerfield, Illinois 60015-2548
Tel. (847) 317-8800 • Telefax (847) 317-7286

Fujisawa

Donald E. Baker, J.D.
Senior Director
Regulatory Affairs

ARCHIVAL

December 9, 1999

Jonathan Wilkin, M. D., Director
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Dermatologic and Dental Drug Products, HFD-540
9201 Corporate Blvd. 2nd Fl., N-214
Rockville, Maryland 20850-3202

RE: NDA 50-777
Protopic® (tacrolimus 0.03% and 0.1%) Ointment

AMENDMENT: Pharmacology/Toxicology

Dear Dr. Wilkin:

Reference is made to Fujisawa Healthcare, Inc.'s (FHI) new drug application (NDA 50-777) submitted under Section 505(b) to the FDA on September 8, 1999 for Protopic (tacrolimus 0.03% and 0.1%) Ointment.

Reference is also made to a FDA Fax Memo dated December 8, 1999 from Ms. Millie Wright regarding a request from Dr. Freidlin. FHI was asked to re-submit the SAS transport file for the tumor dataset (tumor.xpt) from the two (2) year dermal oncogenicity study of Protopic ointment to revise the variable ANUMLNUM to be a character variable instead of a numerical variable. This information was previously submitted to the FDA on October 21, 1999 as an amendment to NDA 50-777 and to ———— (Amendment Serial No. 132).

Accordingly, we are re-submitting the SAS transport file for the tumor dataset provided by the contract lab,———————————— in the format as requested above. This electronic submission was checked with Norton Antivirus (version 4.04) and is virus free.

Should you have any question or require further information regarding this submission, please do not hesitate to contact me at **(847) 317-8872** or Jerry D. Johnson, Ph.D. at **(847) 317-8898.**

Sincerely,

Donald E. Baker
Senior Director, Regulatory Affairs

ORIGINAL

APPEARS THIS WAY
ON ORIGINAL

cc: Millie Wright, Project Manager (desk copy)

K:\kim\protopic\nda\tumor dataset.doc
NDA_Dev\archive\protopic\nda\subm\991209.pdf

ARCHIVAL

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. 0910-0338
Expiration Date: April 30, 2000
See OMB Statement on page 2.

FOR FDA USE ONLY

APPLICATION NUMBER

APPLICANT INFORMATION

NAME OF APPLICANT	DATE OF SUBMISSION
Fujisawa Healthcare, Inc.	12/09/99
TELEPHONE NO. *(Include Area Code)* (847) 317-8872	FACSIMILE (FAX) Number *(Include Area Code)* (847)317-7286

APPLICANT ADDRESS *(Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued)*:	AUTHORIZED U.S. AGENT NAME & ADDRESS *(Number, Street, City, State, ZIP Code, telephone & FAX number)* IF APPLICABLE
Parkway North Center Three Parkway North Deerfield, IL 60015-2548	

PRODUCT DESCRIPTION

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tacrolimus ointment	PROTOPIC

CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME *(If any)*	CODE NAME *(If any)*
Please refer to package insert	FK506, FK 506, FK-506, FR900506

DOSAGE FORM:	STRENGTHS:	ROUTE OF ADMINISTRATION:
Ointment	0.03% and 0.1%	Topical

(PROPOSED) INDICATION(S) FOR USE: Short and long term treatment of the signs and symptoms of atopic dermatitis.

APPLICATION INFORMATION

APPLICATION TYPE (check one)

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☐ BIOLOGICS LICENSE APPLICATION (21 CFR part 601)

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Name of Drug — Holder of Approved Application

TYPE OF SUBMISSION (check one)

☐ ORIGINAL APPLICATION ☒ AMENDMENT TO A PENDING APPLICATION ☐ RESUBMISSION

☐ PRESUBMISSION ☐ ANNUAL REPORT ☐ ESTABLISHMENT DESCRIPTION SUPPLEMENT ☐ SUPAC SUPPLEMENT

☐ EFFICACY SUPPLEMENT ☐ LABELING SUPPLEMENT ☐ CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT ☐ OTHER

REASON FOR SUBMISSION Resubmission of revised tumor dataset for Study 9-0055 (revised variable)

PROPOSED MARKETING STATUS (check one) ☒ PRESCRIPTION PRODUCT (Rx) ☐ OVER-THE-COUNTER PRODUCT (OTC)

NUMBER OF VOLUMES SUBMITTED 1

THIS APPLICATION IS ☐ PAPER ☒ PAPER AND ELECTRONIC ☐ 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 type 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.

CENTER FOR DRUG REC'D DEC 10 1999 DOCRM EVALUATION AND RESEARCH

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

[ ] NDA 50-708
NDA 50-709

This application contains the following items: *(Check all that apply)*	
	1. Index
	2. Labeling (check one) ☐ Draft Labeling ☐ Final Printed Labeling
	3. Summary (21 CFR 314.50 (c))
	4. Chemistry section
	A. Chemistry, manufacturing, and controls information (e.g. 21 CFR 314.50 (d) (1), 21 CFR 601.2)
	B. Samples (21 CFR 314.50 (e) (1), 21 CFR 601.2 (a)) (Submit only upon FDA's request)
	C. Methods validation package (e.g. 21 CFR 314.50 (e) (2) (i), 21 CFR 601.2)
	5. Nonclinical pharmacology and toxicology section (e.g. 21 CFR 314.50 (d) (2), 21 CFR 601.2)
	6. Human pharmacokinetics and bioavailability section (e.g. 21 CFR 314.50 (d) (3), 21 CFR 601.2)
	7. Clinical Microbiology (e.g. 21 CFR 314.50 (d) (4))
	8. Clinical data section (e.g. 21 CFR 314.50 (d) (5), 21 CFR 601.2)
	9. Safety update report (e.g. 21 CFR 314.50 (d) (5) (vi) (b), 21 CFR 601.2)
	10. Statistical section (e.g. 21 CFR 314.50 (d) (6), 21 CFR 601.2)
	11. Case report tabulations (e.g. 21 CFR 314.50 (f) (1), 21 CFR 601.2)
	12. Case reports forms (e.g. 21 CFR 314.50 (f) (2), 21 CFR 601.2)
	13. Patent information on any patent which claims the drug (21 U.S.C. 355 (b) or (c))
	14. A patent certification with respect to any patent which claims the drug (21 U.S.C. 355 (b) (2) or (j) (2) (A))
	15. Establishment description (21 CFR Part 600, if applicable)
	16. Debarment certification (FD&C Act 306 (k)(1))
	17. Field copy certification (21 CFR 314.50 (k) (3))
	18. User Fee Cover Sheet (Form FDA 3397)
X	19. OTHER (Specify) Resubmission of revised tumor dataset for Study 9-0055 (revised variable)

CERTIFICATION

I agree to update this application with new safety information about the product 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 21 CFR 201, 606, 610, 660 and/or 809.
4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR 202.
5. Regulations on making changes in application in 21 CFR 314.70, 314.71, 314.72, 314.97, 314.99, 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, to the best of my knowledge 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
Donald E. Baker	Donald E. Baker, JD Senior Director, Regulatory Affairs	12/9/99

ADDRESS *(Street, City, State, and ZIP Code)*	Telephone Number
3 Parkway Center North Deerfield, IL 60015-2548	(847) 317-8872

Public reporting burden for this collection of information is estimated to average 40 hours 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:

DHHS, Reports Clearance Officer
Paperwork Reduction Project (0910-0338)
Hubert H. Humphrey Building, Room 531-H
200 Independence Avenue, S.W.
Washington, DC 20201

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

Please **DO NOT RETURN** this form to this address.

ORIGINAL

BS

Fujisawa Healthcare, Inc.
Parkway North Center, Three Parkway North
Deerfield, Illinois 60015-2548
Tel. (847) 317-8800 • Telefax (847) 317-7286

Fujisawa

Donald E. Baker, J.D.
Senior Director
Regulatc Affairs

NDA ORIG AMENDMENT

ARCHIVAL

November 9, 1999

Jonathan Wilkin, M.D., Director
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Dermatologic and Dental Drug Products, HFD-540
9201 Corporate Blvd., 2nd Fl., N-214
Rockville, Maryland 20850-3202

Re: NDA 50-777
Protopic® (tacrolimus 0.03% and 0.1%) Ointment

AMENDMENT
Clinical

Dear Dr. Wilkin:

Reference is made to Fujisawa Healthcare, Inc.'s (FHI) new drug application (NDA 50-777) submitted under Section 505(b) to the FDA on September 8, 1999 for Protopic® (tacrolimus 0.03% and 0.1%) Ointment.

Reference is also made to a telephone conference on November 8, 1999 with Ms. Millie Wright, the Division's Biostatistics reviewers, Dr. Srinivasan and Dr. Freidlim, and the Medical Reviewer, Dr. Ramzy Labib. During the teleconference, the Biostatistics reviewers requested that FHI provide the efficacy analysis for the intent-to-treat (ITT) population following the format used for Tables No. 8, 9, and 10 in the Summary Report for Study 97-0-036 (pages 41-44 of Volume 68 of the Protopic® NDA) for all three pivotal clinical studies.

Accordingly, we are providing in **Attachment 1**, the information in the format requested. In addition, one electronic archival copy (pdf format) and two electronic desk copies (pdf format and Word 97 format) of this submission are also being provided. The electronic files were checked with Norton Antivirus (version 4.04) and found to be virus free.

APPEARS THIS WAY
ON ORIGINAL

We look forward to continued communication with the Division during the review of the data presented in this NDA. Should you have any questions or require additional information concerning this submission, please do not hesitate to contact the undersigned at (847) 317-8872 or Jerry D. Johnson, Ph.D. at (847) 317-8898.

Sincerely,

Donald E. Baker
Senior Director, Regulatory Affairs

cc: Millie Wright

NDA_Dev Archive\Protopic\NDA\Subm\991109.pdf
K. Kim Protopic\NDA\11-9-99 Amendment.doc

APPEARS THIS WAY
ON ORIGINAL

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ORIG AMENDMENT

ORIGINAL

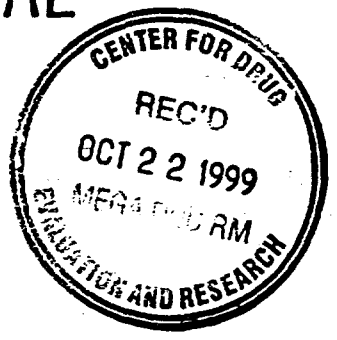
Fujisawa Healthcare, Inc.
Parkway North Center, Three Parkway North
Deerfield, Illinois 60015-2548
Tel. (847) 317-8800 • Telefax (847) 317-7286

Fujisawa

Donald E. Baker, J.D.
Senior Director
Regulatory Affairs

October 21, 1999

ARCHIVAL



Jonathan Wilkin, M. D., Director
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Dermatologic and Dental Drug Products, HFD-540
9201 Corporate Blvd. 2nd Fl., N-214
Rockville, Maryland 20850-3202

RE: NDA 50-777
Protopic® (tacrolimus 0.03% and 0.1%) Ointment

AMENDMENT
Pharmacology/Toxicology

Dear Dr. Wilkin:

Reference is made to Fujisawa Healthcare, Inc.'s (FHI) new drug application (NDA 50-777) submitted under Section 505(b) to the FDA on September 8, 1999 for Protopic (tacrolimus 0.03% and 0.1%) Ointment.

Reference is also made to a telephone conference on September 29, 1999, with Ms. Millie Wright and the Division's Biostatistics reviewers, Dr. Srinivasan and Dr. Freidlim. During that teleconference, the Biostatistics reviewers requested that FHI re-submit the SAS transport file for the tumor dataset (tumor.xpt) from the two (2) year dermal oncogenicity study of Protopic ointment, in the format described in the FDA's Electronic Submissions Guidance. This information was previously submitted to the FDA on February 3, 1999, in IND ——— (Amendment Serial No. 122), and was also included in NDA 50-777, which was submitted to FDA on September 8, 1999.

Accordingly, we are re-submitting the SAS transport file for the tumor dataset provided by the contract lab, ——————————— which is in the format requested. This electronic submission was checked with Norton Antivirus (version 4.04) and is virus free.

Please note that this Amendment is also being submitted as an Information Amendment to IND ——— Serial No. 132).

Should you have any question or require further information regarding this submission, please do not hesitate to contact me at **(847) 317-8872** or Jerry D. Johnson, Ph.D. at **(847) 317-8898.**

Sincerely,

Donald E. Baker
Senior Director, Regulatory Affairs

K:\kim\protopic\nda\tumor dataset.doc
NDA_Dev\archive\protopic\nda\amend\991021.pdf

APPEARS THIS WAY
ON ORIGINAL

Fujisawa Healthcare, Inc.
Parkway North Center, Three Parkway North
Deerfield, Illinois 60015-2548
Tel. (847) 317-8800 • Telefax (847) 317-7286

Fujisawa

Donald E. Baker, J.D.
Senior Director
Regulatory Affairs

September 8, 1999

Jonathan Wilkin, M.D., Director
Division of Dermatologic and Dental Drug Products
Food and Drug Administration
CDER – HFD-540
9201 Corporate Blvd., 2nd Fl. N-214
Rockville, MD 20850

RE: NDA 50-777
PROTOPIC® (tacrolimus ointment)
Ointment 0.03%
Ointment 0.1%

SUBMISSION: ORIGINAL NEW DRUG APPLICATION

Dear Dr. Wilkin:

Fujisawa Healthcare, Inc. (FHI) is hereby submitting an original new drug application (NDA) pursuant to section 505(b) of the Federal Food, Drug and Cosmetic Act for PROTOPIC® (tacrolimus) ointment, 0.03% and 0.1% for the treatment of atopic dermatitis.

This NDA is being submitted in electronic format pursuant to the general requirements provided in the FDA's IT3 guidance. This NDA electronic archive copy consists of one DLT tape III (approximately 4 gigabytes). The electronic submission was checked with Norton Antivirus (version 4.04) and is virus free. Both the review (hard copies) and electronic archival copies are identical. A description of those portions of the submission presented in paper as desk copies (including number of copies provided), as well as a directory tree can be found in **Attachment I** of this cover letter.

Included as **Attachment II** and **III** of this cover letter are relevant Patent Information (Section 13) and Patent Certification (Section 14) for tacrolimus (FK506) drug substance.

Provided in **Attachment IV** and **V** of this cover letter are the Debarment Certification (Section 16) and the Field Copy Certification (Section 17).

The User Fee cover sheet (Section 18) for the FY 1999 assessed user fee is provided as **Attachment VI** and the Financial Disclosure (Section 19) is included as **Attachment VII** of this cover letter.

As requested during the April 6, 1999 Pre-NDA meeting, also included as **Attachment VIII** are copies of the overall and section tables of contents.

As agreed to at the April 6, 1999 Pre-NDA meeting, please cross-reference NDA 50-708 for information on the drug substance, tacrolimus (FK506) for this NDA, Section 4 – Chemistry, Manufacturing and Controls (CMC).

The drug substance tacrolimus, also known as FK506, is an immunosuppressant which inhibits the early activation of T-lymphocytes and was originally approved in the United States on April 8, 1994 in Prograf® Capsules (NDA 50-708) and Injection (NDA 50-709) for the prophylaxis of organ rejection in patients receiving allogeneic liver transplants. Since atopic dermatitis is considered an immunologic disorder believed to be modified by T-lymphocyte activation, a topical formulation of tacrolimus, PROTOPIC® (tacrolimus) ointment, 0.03% and 0.1% has been developed by Fujisawa for dermatologic use.

On December 15, 1994, Fujisawa Healthcare, Inc. (FHI), (formerly Fujisawa USA, Inc.) submitted an Investigational New Drug Application (IND ——— to the FDA to study the use of Tacrolimus (FK506) ointment ——————————————— for the treatment of atopic dermatitis.

A new manufacturing facility in Grand Island, New York was constructed by Fujisawa Healthcare, Inc. to produce tacrolimus ointment for Phase 3 U.S. studies and commercial use. Phase 3 clinical supplies were manufactured at the new Grand Island, New York facility in a —— scale (commercial) batch size and packaged in 30 g and 60 g laminate tubes.

A total of 17 clinical studies are included in this submission. However, the following five Phase 3 clinical studies form the core of this submission:

- *Pivotal Studies:* Three multicenter, randomized, double-blind, parallel group, vehicle controlled 12-week studies were conducted in the United States; one in pediatric patients (Study 97-0-037) and two in adult patients (Studies 97-0-035 and 97-0-036). These three 12-week pivotal studies (pediatric Study 97-0-037, adult Study 97-0-035 and adult Study 97-0-036) were similarly designed with respect to objective, procedures, treatment duration, endpoints and analyses.

- *Long-Term Safety Studies:* Two multicenter, open-label, single concentration (0.1% tacrolimus ointment), long-term (up to 12 months) studies were conducted; one in the United States in pediatric patients (Study 96-0-025) and one in Europe in adult patients (Study FG-06-12).

At the October 28, 1996 End-of-Phase 2 meeting between Fujisawa Healthcare, Inc. and the FDA, it was agreed that these five core studies would be adequate to support the indication. In addition to these five core studies, 12 clinical (Phase 2 and Phase 3) studies are included in this submission in support of the safety and efficacy of tacrolimus ointment in the treatment of atopic dermatitis.

Request for Priority Review

Tacrolimus ointment represents the first in a new therapeutic class of nonsteroidal agents for the topical treatment of atopic dermatitis. Atopic dermatitis has a significant negative impact on a patient's quality of life, hindering social interaction, lowering self-esteem, leading to work/school absenteeism, negatively affecting family interactions, and producing sleep disturbances and emotional distress. Poorly controlled atopic dermatitis can increase patient risk, rendering patients susceptible to opportunistic bacterial and viral infections and other co-morbidities. Tacrolimus ointment therapy has demonstrated excellent clinical results for both pediatric and adult atopic dermatitis patients, including those patients who are the most difficult to treat (e.g., severe disease, extensive body surface involvement, long-standing/chronic disease, facial lesions, and disease recalcitrant to steroidal therapy). These results have been obtained without the adverse events associated with steroidal therapy.

Priority review of NDA 50-777, Tacrolimus Ointment For The Treatment Of Atopic Dermatitis, is requested for the following reasons:

- No safe topical therapy currently exists for the chronic treatment of facial or intertriginous area lesions of atopic dermatitis. Tacrolimus ointment presents a significant therapeutic advance for the treatment of these types of lesions without the adverse effects (e.g., cutaneous atrophy, striae, hypopigmentation) associated with currently available treatment.

- Tacrolimus ointment presents a safer alternative to currently available therapies for patients with severe disease or disease recalcitrant to topical steroidal therapy. For these patients, tacrolimus ointment may represent the only effective topical therapy available for the treatment of their atopic dermatitis.

- As stated in the Pediatric Use Guidance, pediatric labeling is inadequate for steroids. Children treated with topical steroids are at particular risk for adverse effects. Tacrolimus ointment was safe and effective in a large pediatric population (>600 patients less than 16 years of age, nearly 300 of whom were 2 to 6 years of age), including those with severe disease and/or extensive body surface area involvement.

- Atopic dermatitis is a recurring disease. Tacrolimus ointment presents a safer option for chronic treatment than currently available therapies. The results of multiple clinical trials have demonstrated that there is no loss of effectiveness; no rebound phenomena, no skin atrophy, striae, hypopigmentation or other skin disorders; and no increase in adverse events, including infections, with prolonged daily use of tacrolimus ointment.

In summary, priority review of NDA 50-777, Tacrolimus Ointment For The Treatment Of Atopic Dermatitis, is requested in view of the significant negative impact of atopic dermatitis on people's lives and the clinical evidence that tacrolimus ointment presents a significant therapeutic advance, especially for patients with facial or other thin skin area lesions, severe disease, disease recalcitrant to topical steroidal therapy, and atopic dermatitis refractory to all other therapies.

This new drug application (NDA) provides data that supports the safety and efficacy of a topical formulation of Tacrolimus (FK506) ointment, 0.03% and 0.1%, a prescription drug that is intended for the treatment of atopic dermatitis in adult and pediatric patients. We are confident in the data included in this NDA and are hopeful that the FDA will reach a favorable conclusion at the end of their review. We look forward to a collaborative review of the data presented in this NDA.

Should you have any questions or require additional information concerning this application, please do not hesitate to contact the undersigned at (847) 317-8872 or Jerry D. Johnson, Ph.D. at (847) 317-8898.

Sincerely,

Donald E. Baker
Senior Director, Regulatory Affairs

cc: Millie Wright, Project Manager

a:\baker\ltr2\jw50777

APPEARS THIS WAY
ON ORIGINAL

APR 6 1999

MEMORANDUM OF MEETING

Date: April 6, 1999 **Meeting Number:** 3840

Time: 2 PM

Location: S200

Topic: IND —— Protopic (tacrolimus ointment), 0.03% and 0.1%

Subject: Pre-NDA Meeting

Meeting Chair: Dr. Jonathan Wilkin

Meeting Recorder: Millie Wright, Project Manager

FDA Attendees:
Division of Dermatologic & Dental Drug Products/HFD-540
Jonathan Wilkin, M.D., Division Director
Susan Walker, M.D., Dermatology Team Leader
Ramzy Labib, M.D., Medical Reviewer
Barbara Hill, Ph.D., Pharmacology/Toxicology Reviewer
Wilson DeCamp, Ph.D., Chemistry Team Leader
William Timmer, Ph.D., Chemistry Reviewer
Ping Gao, Ph.D., Biostatistics Reviewer
Rajagopolan Srinivasan, Ph.D., Biostatistics Team Leader
Veneeta Tandon, Ph.D., Biopharmaceutic Reviewer
Millie Wright, RN, MSN, Project Manager

Fujisawa Healthcare, Inc. Attendees:
Jerry D. Johnson, Ph.D., Vice President, Regulatory Affairs, Quality Assurance and Safety
Donald E. Baker, J.D., Senior Director, Regulatory Affairs
William Fitzsimmons, Pharm.D., M.S., Senior Director, Drug Development Project Planning
Rochelle Maher, Assistant Director, Drug Development and Project Management
Ira Lawrence, M.D., Vice President, Research and Development
Steven Carrier, Ph. D., Senior Director, Research Data Operations
Yoichi Satoi, Assistant Director, Research Data Operations

Fujisawa Healthcare, Inc. Attendees: (cont):
Robert Reed, Assistant Director, Regulatory Affairs
Jan Logan, Clinical Projects Manager
Dr. med. Michael Reusch, Manager, Clinical Research
Mr. Yoichi Sato, Assistant Director, Research Data Operations
Mr. Jay Erdman, Assistant Director of Statistical Analytical Services
Ihor Bekersky, Ph.D., Senior Director, Biopharmaceutical Sciences

Chemistry

Sponsor's Question:
FK 506 (tacrolimus) drug substance in Prograf® was originally approved on April 8, 1994 (NDA 50-708) and the drug substance remains unchanged. The drug substance remains unchanged. The drug substance utilized in Protopic Ointment) is tacrolimus, and the chemistry, manufacturing & control (CMC) for tacrolimus remains unchanged from that previously approved. Therefore, Fujisawa Healthcare, Inc. (FHI) is proposing to cross-reference the information previously submitted in NDA 50-708 for the tacrolimus drug substance.

Answer:
1. NDA 50-708 can be cross-referenced for the drug substance. They should state on the 356h form that no letter of reference is included in the submission since they are the NDA holder.

Sponsor's Question:
Please review and comment on the adequacy of the proposed Post-Approval Stability Protocol for Protopic (tacrolimus ointment) provided in Attachment 2.

Answer:
2. The stability protocol is acceptable. However, they should consider the following. They plan to market the 30 gm tube size — It would be to their advantage to include stability data for the 60 gm tube size in the NDA, since any [stability] data submitted later would require a prior approval supplement.

Sponsor's Question:
Based on the techincal rationale provided, Does FHI meet the current FDA criteria for its claim of a categorical exclusion from the requirement to prepare an environmental assessment (EA) as part of the new drug application (NDA) for Protopic™ (tacrolimus ointment)? (See Attachment 5.)

Answer:
3. Based on the information submitted it would appear that they are eligible for a categorical exclusion.

Sponsor's Question:
As a result of the End-of-Phase 2 meeting, FHI has attempted to develop the ——— ——— method to establish a viscosity test and specification for viscosity for tacrolimus ointment. However, the ——— method was further evaluated, and so far we have been unable to standardize this method. We will continue our development of the ——— method and, as back up, will develop a ——— method to establish a viscosity specification for tacrolimus ointment. However, as previously indicated in our response following the EOP2 meeting, viscosity obtained from ——— method for ——— materials has some limitations. This summarized in Attachment 3. Therefore, would FDA reconsider "consistency" as the regulatory specification in lieu of a viscosity specification?

Answer:
4. We can't determine a priori which viscosity method will be acceptable for them. Whatever they submit we will evaluate. What might aid them is that a viscosity spec does not have to be limited to ±10% around a nominal value. FDA wants a viscosity spec.

Sponsor's Question:
We plan to submit the NDA for Protopic (tacrolimus ointment) electronically in compliance with FDA Guidance IT3. This guidance states that the methods validations section need not be submitted as a review copy (hard copy). Are there any other sections (e.g., environmental assessment, publications) that need not be provided in hard copy? Are there any specific requirements for reviewer's aids?

Answer:
5. No. There are no additional reviewer requirements. The submission must be well organized with the appropriate hyper-links as required in the IT3 Guidance document.

Sponsor's Question:
How many desk copies (hardcopies) of the CMC section should be provided with this submission?

Answer:
6. One.

Additional CMC Comments:

1. Please include a table listing batch formulations used in the nonclinical and clinical trials.

2. Please include the ——— of each component of the drug product, from ———

3. The Sponsor should inform the Division how the —— impurity forms.

Pharmacology/Toxicology

Sponsor's Question:
We plan to submit the NDA for Protopic (tacrolimus ointment) electronically in compliance with FDA Guidance IT3. This guidance states that animal line listings need not be submitted as a review copy (hard copy). Are there any other sections (e.g., publications) that need not be provided in hard copy? Are there any specific requirements for reviewers' aids?

Answer:

1. It is acceptable to the pharmacology reviewer that the entire pharmacology/toxicology section be submitted electronically for the NDA. I would like to emphasize that a well integrated pharmacology/toxicology summary section with summary tables and hypertext links to the location of the appropriate nonclinical studies to support the summary information is highly recommended to aid in the review of the application. If the sponsor intends to rely on nonclinical data submitted to previous NDAs (i.e., oral or intravenous nonclinical toxicity studies), it is recommended that the sponsor provide a thorough summary of this data in the NDA and provide cross references to the complete nonclinical study reports in previous NDAs. No additional reviewer aids are required as long as the sponsor follows the guidelines provided in the electronic NDA guidance document (IT3) posted on the CDER website in January, 1999.

   If electronic nonclinical datasets are to be submitted to the NDA, they should be submitted in SAS transport 5 format as outlined in the electronic NDA guidance document. I would be willing to look at an example of an electronic data set for a chronic toxicity study for comment purposes if the sponsor submits it to the current IND prior to formally submitting the NDA.

   It is requested that the sponsor include a description of the drug substance, drug product and impurity profile for the drug product in the pharmacology/toxicology section. Access to the Clinical and Clinical Biopharmacology summary sections for the pharmacology reviewer would be helpful for review purposes. It is recommended that the sponsor provide an electronic copy of the proposed label in Microsoft Word '97 for ease of review.

Sponsor's Question:
We have performed all the studies requested by the agency and believe we have a complete package to support the chronic use of tacrolimus in adults and children. Does the agency concur?

Answer:

2. The sponsor's plan for nonclinical studies to support the chronic use of tacrolimus in adults and children is adequate. There remain two outstanding studies that are recommended to be included in the NDA submission. The first study is a 28 day repeat dose toxicity study comparing the toxicity of the impurity —— and tacrolimus ointment in rats. The second study is titled "Four-week toxicokinetic study of FR900506 (FK506, Tacrolimus) ointment administered topically in combination with ultraviolet radiation in hairless mice".

Sponsor's Question:

How many desk copies (hardcopies) of the pharmacology/toxicology section should be provided with this submission?

Answer:

3. It is requested that a desk copy of Volume 1.1 of the NDA be provided to the pharmacology reviewer if it is decided to submit the pharmacology/toxicology section electronically. In addition to the summary information normally contained in Volume 1.1, the proposed label for the drug product and the table of contents for the entire NDA should be included in Volume 1.1. If this information is not included in Volume 1.1, then it is requested that a desk copy of this information be provided to the pharmacology reviewer. It is not necessary to provide a desk copy of the entire pharmacology/toxicology section of the NDA.

   If it is decided to submit the entire pharmacology/toxicology section of the NDA in paper, then it will not be necessary to provide a desk copy of Volume 1.1 or of the pharmacology/toxicology section.

Preliminary Comments concerning the Submitted Label for Protopic:

1. It is recommended that the doses in the nonclinical section be expressed as mg/kg and mg/m^2 in addition to the concentration (%) currently stated in the label. It is recommended that a comparison of the fold level of the nonclinical dose to the estimated maximum human dose be included in the appropriate sections of the label.

2. It is recommended that the sponsor include the information contained in the Prograf label under the Pregnancy Category section in the Protopic label. In particular, the description of the teratogenic effects of tacrolimus contained in the Prograf label should be incorporated into the Protopic label. If the sponsor should choose to conduct a dermal reproductive toxicity study with the tacrolimus ointment, then the results of this study may then also be incorporated into the Protopic label.

Biopharmaceutics

Sponsor's Question:
We plan to submit the NDA for Protopic (tacrolimus ointment) electronically in compliance with FDA Guidance IT3. This guidance states that the study report appendices need not be submitted as a review copy (hard copy). We intend to provide hard copies of the study protocol and the annotated case report form for each study report. Are there any other sections (e.g., publications) that need not be provided in hard copy? Are there any specific requirements for reviewers' aids?

Answer:
1. In addition to hard copies of the protocol, the supportive pk data, i.e., demographic tables, individual raw data, analytical validation, and statistical files should be provided in hard copy form. In addition the most relevant publications should also be included in hard copy form, although background or collateral publications may be included by reference only. Individual case report forms, investigator CV's, and tabulated safety data from the pk trials may be submitted electronically only.

Sponsor's Question:
How many desk copies (hardcopies) of the biopharm section should be provided with this submission?

Answer:
2. One review copy of the biopharm section is sufficient.

Clinical

Sponsor's Question:
Based on discussions during the IND and at the EPO2 meeting, and as outlined in this pre-NDA package, support for the indication of atopic dermatitis will be provided by three Phase 3, 12-week pivotal studies conducted in the United States (pediatric Study 97-0-037; adult Studies 97-0-035, 97-0-036) as well as two additional long-term Phase 3 safety studies, once conducted in children in the United States (Study 96-0-025) and one conducted in adults in Europe (FG-06-12), which are presented as fulfilling the International Conference on Harmonization recommendations for long-term exposure. Does the Division agree that these studies are adequate to support the indication?

Answer:
1. The Division agrees that these 5 studies are adequate for NDA filing. Please notice that the topical safety studies (Patch test studies) and mechanism of action studies should be included in the clinical section.

Sponsor's Question:
FHI is proposing to present data to support the use of both 0.03% and 0.1% tacrolimus ointment in the treatment of atopic dermatitis in adult and pediatric patients. Is this acceptable to the Division?

Answer:
2. Submission of data supporting the use of both 0.03% and 0.1% ointments is acceptable. However, if there is no significant advantage for the use of a higher concentration in children or adult patients, then the lower concentration will be the only approvable product.

Sponsor's Question:
Foreign data, with the exception of the long-term safety study FG-06-12, will be presented in the NDA for Protopic in "Other Studies and Information" section in the form of publications. Is this acceptable to the Division?

Answer:
3. Submission of all data and full reports of foreign studies (rather than publications) is recommended.

Sponsor's Question:
Experience with concentrations not intended for commercial development (0.3%, 0.5%) will be briefly summarized, primarily based on information from publications. Is this acceptable to the Division?

Answer:
4. Submission of all available data on higher concentrations is recommended for their implications on safety evaluation.

Sponsor's Question:
In the NDA for Protopic, the core of the integrated summaries of safety and efficacy will be the three randomized, double-blind, 12 week studies. The results of the two open-label long-term (up to 12 months) safety studies will be presented separately. Is this acceptable to the Division?

Answer:
5. It is acceptable to present the long-term safety studies separately from the 3 pivotal studies. However, an ISS including all safety data from all available studies should be also submitted.

Sponsor's Question:

In the integrated summaries of safety and efficacy, the results of the three pivotal studies will be explored with respect to possible relationship to:

- Age-The primary age cut for the integrated summaries of safety and efficacy
- will be 2-15 years (pediatric) and ≥16 years (adult).

  An additional pediatric age split will be ages 2-6 and 7-15. This second age split was chosen based on the age dichotomy of dermatological evaluation tools used in the studies (e.g., EASI score, percent BSA affected); the lack of previous data collected for ages >7 years; and current thinking that atopic dermatitis disease modality may be different for children under 7 years of age compared with older children.

  The overall incidence of adverse events will also be presented for the 31 patients in the three pivotal studies ≥65 years of age.

- Race-The primary analysis will be of blacks and whites. Approximately 25%
- of the patients in the pivotal studies were black, providing the opportunity to explore this subpopulation with known physiological differences in skin properties and responsiveness to topical drugs. The number of patients who do not fit into either of these two race categories in the pivotal studies is small (45 Oriental, 16 Other).

-Gender
-Baseline disease severity
-Percent body surface area affected

Is this acceptable to the Division? Are there any other specific factors of interest to the Division?

Answer:

6. As mentioned above the ISS is not limited to three pivotal studies. The relationships to be explored in the ISS and ISE are acceptable. An additional analysis of ages 2-6 years for each year of age is strongly recommended.

Sponsor's Question:

Photographic documentation of disease status was performed on a subset of patients in the three pivotal studies. Representative photographs with accompanying patient narratives will be provided as an appendix to the integrated summary of efficacy. The remaining photographs, digitized onto a CD, will be available upon request. Is this acceptable to the Division?

Answer:

7. Photographic documentation is acceptable as outlined, but the CD should be submitted with the NDA together with the software required for its visualization if it is not readily available in the Division.

Sponsor's Question:

The presentation of results that will be included in the overall summary documents of the NDA will be similar to that used in Section 5. Is this acceptable to the Division?

Answer:

8. The overall summary presentation is acceptable.

Additional comments:

1. The pivotal and the long-term safety studies should show the data by individual study sites to allow comparison of sites within each study. Also, the scores for individual signs and symptoms, before combining as EASI Scores, should be available in these studies.

2. Adverse event tabulations should include all causalities, i.e. irrespective of whether they are thought to be related or unrelated to the drug.

3. Pediatric Rule implementation: The immunological parameters studied in the long-term adult study were not studied in the log-term pediatric study. The safety of the drug in the pediatric group has to be thoroughly assessed before making any decision regarding the adequacy of the pediatric development program.

4. Full reports of the pivotal and long-term safety studies as well as the ISS and ISE should be additionally presented as MS Word 97 electronic documents, because the current Adobe software does not allow copying and modification of tables which are needed in the clinical review.

5. Prior to submission of the NDA, Mr. Baker and Ms. Wright will determine the desk copies required by the medical and biostatistical reviewers.

Statistical Questions

Sponsor's Question:

The SAS datasets used for analysis in the phase 3 studies are presented in Section 6. Note, these data sets are standardized across all five protocols in terms of variable names, common COSTART coding, common laboratory units, etc. Are these variables and data structures sufficient for the medical/statistical review team?

Answer:

1. Primary evaluation population: ITT, all randomized patients who were dispensed the treatment medication. NOT the efficacy evaluable population, which is defined as all randomized patients who receive study drug for at least 3 consecutive days (minimum of five applications);
   Data set: each data set should have patient ID so the data sets can be merged easily. Data as SAS transport files are acceptable. Please submit the data in SAS 6.12 for windows.

General Questions

Sponsor's Question:
Protopic (tacrolimus ointment) would provide a clinically significant alternative to conventional therapy for the treatment of atopic dermatitis, especially in children. This is of particular note, in light of recent data suggesting that topically applied corticoseriods may have detrimental effect on growth and maturity of children. Therefore, would the Division consider the NDA for Protopic (tacrolimus ointment) eligible for priority review?

Answer:

1. No. The Division would need a stronger argument than we currently have before committing to a priority review.

Sponsor's Question:
Based on vendor lead times for pre-printed laminate tubes, would the Division be willing to provide general acceptance early in the review process of the printed content of the laminate tube?

Answer:

2. Not early in the review process; however, it might be possible to provide a draft version within the last three months of the review cycle. Sponsor acknowledged that they would be assuming a risk in sending draft container labeling to vendor.

Sponsor's Question
Regarding procedures for communication between FHI and the Division during the NDA review process, would the use of Fax and E-mail be acceptable?

Answer:

3. Absolutely NO to E-mail. In situations where the reviewer and Project Manager determine that a shorter response time from FHI is necessary to facilitate the review process, a Fax, followed by submission to the NDA would be acceptable.

Sponsor's Question:
FHI will submit the Section 6 (pre-NDA package) domain data sets for the three pivotal studies and the two long-term safety studies as per the IT3 guidelines as SAS transport files for the electronic archive copy. FHI does not believe that case report tabulations for the phase 1 and phase 2 studies provide additional safety information above that which is available for the phase 3 studies. Is this sufficient for the Division?

Answer:
4. No. Include case report tabulations for the phase 1 and phase 2 studies.

Divisional Comments
Pediatric Rule
The Food and Drug Administration Modernization Act [FDAMA] of 1997, Section 111, Pediatric Studies of Drugs, became effective April 1, 1999, requires the following:

For pre-NDA meetings

1. Under 21CFR, Section 312.47, the Sponsor is required to inform the Agency about the status of ongoing or needed studies adequate to assess pediatric safety and effectiveness. The meeting package submitted for the pre-NDA meeting must now included the status of needed or ongoing pediatric studies.

For NDA applications

2. Under 21 CFR, Section 314.50, the NDA application is required to included the following:

   (d) (7) Pediatric Use Section. Requires that an NDA contain "a section describing the investigation of the drug for use in pediatric populations, including an integrated summary of the information (the clinical pharmacology studies, controlled clinical studies, or uncontrolled clinical studies, or other data or information) that is relevant to the safety and effectiveness and benefits and risks of the drug in pediatric populations for the claimed indications, a reference to the full descriptions of such studies provided under paragraphs (3) and (5), and information required to be submitted under Section 314.55."

3. Under 21 CFR, Section 314.55 Pediatric Use Information.

   (a) Required assessment. "Except as provided in paragraphs (b), (c), and (d), each application for a new active ingredient, new indication, new dosage form, new dosing regimen, or new route of administration shall contain data that are adequate to assess the safety and effectiveness of the product for the claimed indications in all relevant pediatric subpopulations, and to support dosing and administration for each pediatric subpopulation for which the product is safe and effective...." Orphan drugs are exempted from this requirement.

4. For additional information, please refer to the following CDER web site, www.fda.gov/cder/pediatric

Financial Disclosure

For applications submitted after February 2, 1999, the applicant is required either to certify to the absence of certain financial interests of clinical investigators or disclose those financial interests. For additional information, please refer to the following CDER web site, www.fda.gov/cdrh/modact/fr112098a.html

Labeling

If you have an Information for Patients leaflet/labeling, please submit with the NDA.

Signature, minutes preparer: /S/ 4/6/99

Chair concurrence (or designated signatory): /S/ 4/6/99

APPEARS THIS WAY
ON ORIGINAL

CC:
Orig IND [redacted]
Div File
HFL-540/Wilkin/4/6/99
HFD-540/Walker
HFD-540/Labib4/6/99
HFD-540/Hill/4/6/99
HFD-540/Timmer/4/6/99
HFD-540/DeCamp/4/6/99
HFD-540/Gao/4/6/99
HFD-540/Srinivasan/4/6/99
HFD-540/Bashaw
HFD/540/Tandom/4/6/99
HFD-540/Wright

Meeting Minutes
Minutes drafted 4/6/99 by M.Wright
Final Type: 4/6/99
Doc: [redacted] preNDA (word)

APPEARS THIS WAY
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FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Dermatologic and Ophthalmic Drugs Advisory Committee
Meeting # 54

AGENDA
November 16, 2000

CDER Advisory Committee, Conference Room 1066
Rockville, Maryland

November 16, 2000

NDA 50-777, (tacrolimus) ointment, Fujisawa Healthcare, for short and long term treatment of the signs and symptoms of atopic dermatitis in adults and pediatric patients 2 years of age or older

10:00	Call to Order and Welcome Conflict of Interest Statement Overview of Issues	Robert Stern, M.D., Acting Chair Jaime Henriquez, Executive Secretary Jonathan Wilkin, M.D.
10:10	Sponsor Presentation:	
	• Introduction	Jerry D. Johnson, Ph.D.
	• Pharmacology of Tacrolimus Ointment	William Fitzsimmons, Pharm.D.
	• Efficacy and Safety of Tacrolimus Ointment	Ira D. Lawrence, M.D., F.A.C.P.
11:10	FDA Presentation:	
	• Nonclinical Pharmacology/ Toxicology Data for Protopic	Barbara Hill, Ph.D.
	• Systemic Exposure of Topical Tacrolimus	Veneeta Tandon, Ph.D.
	• Clinical Review of Protopic Ointment Safety, Potential Risk and Efficacy	Martin Okun, M.D., Ph.D.
12:25	Lunch	
2:00	Open Public Hearing – The meeting will proceed when last open public hearing participant has spoken.	
3:00	Questions to the Committee	Jonathan Wilkin, M.D.
3:10	Committee Discussion	
3:30	Break	
3:45	Committee Discussion Continue	
5:00	Adjournment	

Dermatologic and Ophthalmic Drugs Advisory Committee
Meeting # 54

QUESTIONS

1. Is there sufficient evidence for effectiveness of Protopic, 0.03%, in the treatment of atopic dermatitis?

2. Is there sufficient evidence for superior effectiveness of Protopic 0.1% compared to 0.03%...
a. ...in adults?
b. ...in children?

3. Has the safety profile of Protopic in the treatment of atopic dermatitis been adequately determined for unrestricted chronic therapy as a first-line treatment...
a. ...in adults for both 0.03% and 0.1%?
b. ...in children for both 0.03% and 0.1%?

4. The proposed indication for Protopic, which would allow for both 0.03% and 0.1%, for unrestricted chronic therapy, as a first-line treatment of atopic dermatitis, in adults and children 2 years and older, may be decomposed into the following elements which may be reconstructed into indication(s):

DECISION TABLE

	Adults	Children 2 years and up
Unrestricted chronic therapy vs time-limited acute therapy?	?	?
First-line vs second-line treatment?	?	?
0.03%, 0.1%, both, or neither	?	?

Is approval of Protopic recommended and, if so, under what conditions [concentration(s), first- vs second-line, chronic vs (time-limited) acute therapy] in which age groups?

5. Are there additional studies needed to provide information important for the labeling of Protopic? If so, what studies are recommended? (Consider the issues of lymphoma, local suppression of immunity, photocarcinogenesis, etc.)

FDA Fax Memo

Date: December 8, 1999

Subject: NDA 50-777/Carc. Data sets

Hi Don,

This is the comment from Dr. Freidlin:

The SAS transport file for the tumor data set (tumor.xpt, of 10/21/99) is not in the format requested. The variable ANUMLNUM should be a character variable instead of numerical variable. Please ask the Sponsor to submit the tumor data set in the requested format.

If you have questions, please give MaryJean Kozma-Fornaro a call.

Thanks,

Millie

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ON ORIGINAL

will be available for listening in the Board's Freedom of Information Office, and copies may be ordered for $6 per cassette by calling 202–452–3684 or by writing to: Freedom of Information Office, Board of Governors of the Federal Reserve System, Washington, DC 20551.

CONTACT PERSON FOR MORE INFORMATION: Lynn S. Fox, Assistant to the Board, 202–452–3204.

SUPPLEMENTARY INFORMATION: You may call 202–452–3206 for a recorded announcement of this meeting; or you may contact the Board's Web site at http://www.federalreserve.gov for an electronic announcement. (The Web site also includes procedural and other information about the open meeting.)

Dated: November 1, 2000.

Robert deV. Frierson,

Associate Secretary of the Board.

[FR Doc. 00–28346 Filed 11–1–00; 10:55 am]

BILLING CODE 6210–01–P

FEDERAL RESERVE SYSTEM

Sunshine Act Meeting

AGENCY HOLDING THE MEETING: Board of Governors of the Federal Reserve System.

TIME AND DATE: Approximately 10:30 a.m., Wednesday, November 8, 2000, following a recess at the conclusion of the open meeting.

PLACE: Marriner S. Eccles Federal Reserve Board Building, 20th and C Streets, NW., Washington, DC 20551.

STATUS: Closed.

MATTERS TO BE CONSIDERED:

1. Personnel actions (appointments, promotions, assignments, reassignments, and salary actions) involving individual Federal Reserve System employees.

2. Any matters carried forward from a previously announced meeting.

CONTACT PERSON FOR MORE INFORMATION: Lynn S. Fox. Assistant to the Board, 202–452–3204.

SUPPLEMENTARY INFORMATION: You may call 202–452–3206 beginning at approximately 5 p.m. two business days before the meeting for a recorded announcement of bank and bank holding company applications scheduled for the meeting; or you may contact the Board's Web site at http://www.federalreserve.gov for an electronic announcement that not only lists applications, but also indicates procedural and other information about the meeting.

Dated: November 1, 2000.

Robert deV. Frierson,

Associate Secretary of the Board.

[FR Doc. 00–28347 Filed 11–1–00; 10:56 am]

BILLING CODE 6210–01–P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

Dermatologic and Ophthalmic Drugs Advisory Committee; Notice of Meeting; Correction

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice; correction.

SUMMARY: The Food and Drug Administration (FDA) is correcting a notice that appeared in the **Federal Register** of October 19, 2000 (65 FR 62722). The notice announced a meeting of the Dermatologic and Ophthalmic Drugs Advisory Committee, which was scheduled for November 16, 2000. The document was published with an error. This document corrects that error.

FOR FURTHER INFORMATION CONTACT: Anita Prout, Committee Management Office (HFA–306), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301–827–5503.

SUPPLEMENTARY INFORMATION: In FR Doc. 00–26787, appearing on page 62722 in the **Federal Register** of Thursday, October 19, 2000, the following correction is made:

1. On page 62722, in the first column, under the "Location" caption, "Holiday Inn, Grand Ballroom, Two Montgomery Village Ave., Gaithersburg, MD." is corrected to read "CDER Advisory Committee, conference room 1066, 5630 Fishers Lane, Rockville, MD."

Dated: October 31, 2000.

Linda A. Suydam,

Senior Associate Commissioner.

[FR Doc. 00–28349 Filed 11–01–00; 2:45 pm]

BILLING CODE 4160–01–F

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

Clinical Chemistry and Clinical Toxicology Devices Panel of the Medical Devices Advisory Committee; Notice of Meeting

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

This notice announces a forthcoming meeting of a public advisory committee of the Food and Drug Administration (FDA). At least one portion of the meeting will be closed to the public.

Name of Committee: Clinical Chemistry and Clinical Toxicology Devices Panel of the Medical Devices Advisory Committee.

General Function of the Committee: To provide advice and recommendations to the agency on FDA's regulatory issues.

Date and Time: The meeting will be held on November 13, 2000, 10 a.m. to 4:30 p.m., and November 14, 2000, 8:30 a.m. to 4 p.m.

Location: Hilton, Salons C, D, and E, 620 Perry Pkwy., Gaithersburg, MD.

Contact Person: Veronica J. Calvin, Center for Devices and Radiological Health (HFZ–440), Food and Drug Administration, 2098 Gaither Rd., Rockville, MD 20850, 301–594–1243, or FDA Advisory Committee Information Line, 1–800–741–8138 (301–443–0572 in the Washington, DC area), code 12514. Please call the Information Line for up-to-date information on this meeting.

Agenda: On November 13, 2000, the committee will discuss two draft guidances: "Guidance for Prescription Use Drugs of Abuse Assays Premarket Notifications" and "Over the Counter (OTC) Screening Tests for Drugs of Abuse: Guidance for Premarket Notifications." The prescription use guidance will be available to the public on the Internet at http://www.fda.gov/cdrh/ode/odecl052.html and supersedes the document entitled "Review Criteria for Assessment of In Vitro Diagnostic Devices for Drugs of Abuse Assays Using Various Methodologies." The OTC use guidance will be available to the public on the Internet at http://www.fda.gov/cdrh/ode/91.html and supersedes the document entitled "Guidance for Premarket Submissions for Kits for Screening Drugs of Abuse To Be Used by the Consumer." Draft questions for the committee regarding these guidances will be available to the public on the Internet at http://www.fda.gov/cdrh/panelmtg.html. On November 14, 2000, the committee will discuss and make recommendations on a premarket notification (510(k)) for a first-of-a-kind prescription use screening device for heroin in human hair.

Procedure: On November 13, 2000, from 10 a.m. to 4:30 p.m., and on November 14, 2000, from 9 a.m. to 4 p.m., the meeting is open to the public. Interested persons may present data, information, or views, orally or in writing, on issues pending before the

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

Dermatologic and Ophthalmic Drugs Advisory Committee; Notice of Meeting

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

This notice announces a forthcoming meeting of a public advisory committee of the Food and Drug Administration (FDA). At least one portion of the meeting will be closed to the public.

Name of Committee: Dermatologic and Ophthalmic Drugs Advisory Committee.

General Function of the Committee: To provide advice and recommendations to the agency on FDA's regulatory issues.

Date and Time: The meeting will be held on November 16, 2000, 9 a.m. to 5:30 p.m.

Location: Holiday Inn, Grand Ballroom, Two Montgomery Village Ave., Gaithersburg, MD.

Contact: Jaime Henriquez, Center for Drug Evaluation and Research (HFD–21), Food and Drug Administration, 5600 Fishers Lane (for express delivery, 5630 Fishers Lane, rm. 1066), Rockville, MD 20857, 301–827–7001, or FDA Advisory Committee Information Line, 1–800–741–8138 (301–443–0572 in the Washington, DC area), code 12534. Please call the Information Line for up-to-date information on this meeting.

Agenda: On November 16, 2000, the committee will discuss new drug application (NDA) 50–777, Protopic® (tacrolimus) Ointment, Fujisawa Healthcare, Inc., for short- and long-term treatment of the signs and symptoms of atopic dermatitis in adult and pediatric patients 2 years of age or older.

Procedure: Interested persons may present data, information, or views, orally or in writing, on issues pending before the committee. Written submissions may be made to the contact person by November 6, 2000. Oral presentations from the public will be scheduled between approximately 1:30 p.m. and 2:30 p.m. Time allotted for each presentation may be limited. Those desiring to make formal oral presentations should notify the contact person before November 6, 2000, and submit a brief statement of the general nature of the evidence or arguments they wish to present, the names and addresses of proposed participants, and an indication of the approximate time requested to make their presentation.

Closed Committee Deliberations: On November 16, 2000, from 9 a.m. to 10 a.m., the meeting will be closed to permit discussion and review of trade secret and/or confidential information regarding NDA issues (5 U.S.C. 552b(c)(4)).

Notice of this meeting is given under the Federal Advisory Committee Act (5 U.S.C. app. 2).

Dated: October 11, 2000.

Linda A. Suydam,

Senior Associate Commissioner.

[FR Doc. 00–26787 Filed 10–18–00; 8:45 am]

BILLING CODE 4160–01–F

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

Radiological Devices Panel of the Medical Devices Advisory Committee; Notice of Meeting

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

This notice announces a forthcoming meeting of a public advisory committee of the Food and Drug Administration (FDA). At least one portion of the meeting will be closed to the public.

Name of Committee: Radiological Devices Panel of the Medical Devices Advisory Committee.

General Function of the Committee: To provide advice and recommendations to the agency on FDA's regulatory issues.

Date and Time: The meeting will be held on November 6, 2000, 10 a.m. to 4:30 p.m.

Location: Corporate Bldg., conference room 020B, 9200 Corporate Blvd., Rockville, MD.

Contact Person: Robert J. Doyle, Center for Devices and Radiological Health (HFZ–470), Food and Drug Administration, 9200 Corporate Blvd., Rockville, MD 20850, 301–594–1212, or FDA Advisory Committee Information Line, 1–800–741–8138 (301–443–0572 in the Washington, DC area), code 12526. Please call the Information Line for up-to-date information on this meeting.

Agenda: The committee will discuss, make recommendations, and vote on a premarket approval application for an embolic radiation therapy device.

Procedure: On November 6, 2000, from 10 a.m. to 12:30 p.m., and from 1 p.m. to 4:30 p.m., the meeting is open to the public. Interested persons may present data, information, or views, orally or in writing, on issues pending before the committee. Written submissions may be made to the contact person by October 26, 2000. Oral presentations from the public will be scheduled between approximately 10:15 a.m. and 10:45 a.m., and for an additional 30 minutes near the end of the committee deliberations. Time allotted for each presentation may be limited. Those desiring to make formal oral presentations should notify the contact person before October 26, 2000, and submit a brief statement of the general nature of the evidence or arguments they wish to present, the names and addresses of proposed participants, and an indication of the approximate time requested to make their presentation.

Closed Committee Deliberations: On November 6, 2000, from 12:30 p.m. to 1 p.m., the meeting will be closed to the public to permit discussion and review of trade secret and/or confidential commercial information (5 U.S.C. 552b(c)(4)) regarding pending and future agency issues.

Notice of this meeting is given under the Federal Advisory Committee Act (5 U.S.C. app. 2).

Dated: October 13, 2000.

Linda A. Suydam,

Senior Associate Commissioner.

[FR Doc. 00–26899 Filed 10–18–00; 8:45 am]

BILLING CODE 4160–01–F

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

Joint Meeting of the Advisory Committee for Pharmaceutical Science and the Dermatologic and Ophthalmic Drugs Advisory Committee; Notice of Meeting

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

This notice announces a forthcoming meeting of a public advisory committee of the Food and Drug Administration (FDA). The meeting will be open to the public.

Name of Committee: Advisory Committee for Pharmaceutical Science and the Dermatologic and Ophthalmic Drugs Advisory Committee.

General Function of the Committee: To provide advice and recommendations to the agency on FDA's regulatory issues.

Date and Time: The meeting will be held on November 17, 2000, from 8:30 a.m. to 12:30 p.m.

cc:
Archival NDA 50-777
HFD-540/Div. Files
HFD-540/M.Wright
HFD-540/Wilkin
HFD-540/Okun
HFD-540/Labib
HFD-540/Jacobs
HFD-540/Hill
HFD-725/Al-Osh
HFD-725/Lu
HFD-880/Tandon
HFD-880/Bashaw

Drafted by:MAW /March 29, 2000
Initialed by MKF/3/29/00:
final:3/29/00/MAW
filename: N50777IR

INFORMATION REQUEST (IR)

APPEARS THIS WAY
ON ORIGINAL

FDA Fax Memo

Date: March 15, 2000

FAXED 3/15/00

To: Donald Baker
Senior Director, Regulatory Affairs
Fujisawa Healthcare, Inc.
Phone: (847) 317-8872
Fax: (847) 317-7286

APPEARS THIS WAY
ON ORIGINAL

From: Millie Wright, Project Manager
Phone: (301) 827-2020
Fax: (301) 827-2091

This transmission includes 3 pages (including this page)

Center for Drug Evaluation and Research
Division of Dermatologic and Dental
Drug Products, HFD-540
9201 Corporate Blvd
Building 2, 2nd Floor
Rockville, MD 20850

301-827-2020, fax 301-827-2091

APPEARS THIS WAY
ON ORIGINAL

FDA Fax Memo

Date: March 15, 2000

Subject: NDA 50-777/Protopic (Tacrolimus Ointment)

Hi Don,

During an internal meeting, the following information requests were identified:

Please provide the following information:

Safety analysis:

1. Compare the AE rates between different dose groups: 0.03% vs. 0.1% with combined 12 week data (studies 97-0-035, 97-0-036, and 97-0-037).

2. Provide p-values for comparison for AE rates in Appendix 8.4.13.6.1.1 for 0.03% vs. 0.1%.

3. Compare long term vs. short term AE rate of dose 0.1%, as shown in the following table.

COSTART boy system	COSTART term	AE in FG-06-12 (#/%)	AE in 96-0-025 (#/%)	Total long-term AE+ (#/%)	Total short term++ AE (#/%)	p-value+++ for long term vs short term AE

+: long term AE are those found in studies FG-06-12 and 96-0-025

++: short term AE are those found in the three 12 week pivotal studies (97-0-035, 97-0-036, 97-0-037)

+++: p-value by Cochran-Mantel Haenszel test stratified by age (2-15 years, >15 years)

Please provide the result tables requested in 1) (Appendix 8.4.13.6.1.1 with one extra column of p-values) and 2) to be submitted in MS word version. Also, the Sponsor should provide the SAS programs for these safety analyses and detailed documentation if more than one program is involved for each analysis.

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ON ORIGINAL

Efficacy information:

4. The sponsor to submit a by-patient (one record per patient) ITT efficacy SAS 6.12 dataset for each of the pivotal efficacy studies (97-0-035, 97-0-036 and 97-0-037). Each dataset should include patient number, treatment code, investigator, demographic variables, reason for terminating study, all primary and secondary efficacy variables at each visit and final result by last-observation-carried-forward method, and indicator for efficacy evaluable patient. The formats for characteristic variables such as investigator site, treatment, gender, race, and reason for terminating study should be provided.

5. The Sponsor should provide summary of efficacy results for MITT population for studies 97-0-035, 97-0-036 and 97-0-037 in the same way as for the evaluable patient population (Tables 3, and 8-13 for studies 035 and 036, Tables 3 and 9-14 for study 037. Additionally, the results for individual signs, pruritus evaluations, and subgroup analysis (if any) should also be included.). These results should be submitted in MS word documents.

If you have questions, please call.
Respectfully,
Millie

CC:
Orig NDA 50-777
HFD-540/Div File
HFD-540/Wright

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ON ORIGINAL

MESSAGE CONFIRMATION

03/15/00 16:48

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03/15 16:48	00'44"	8473177286	003/003	OK		0000

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ON ORIGINAL

FDA Fax Memo

Date: March 15, 2000

To: Donald Baker
Senior Director, Regulatory Affairs
Fujisawa Healthcare, Inc.
Phone: (847) 317-8872
Fax: (847) 317-7286

APPEARS THIS WAY
ON ORIGINAL

From: Millie Wright, Project Manager
Phone: (301) 827-2020
Fax: (301) 827-2091

This transmission includes 3 pages (including this page)

FDA Fax Memo

Date: February 29, 2000

To: Donald Baker
Senior Director, Regulatory Affairs
Fujisawa Healthcare, Inc.
Phone: (847) 317-8872
Fax: (847) 317-7286

FAXED 2/29/00

From: Millie Wright, Project Manager
Phone: (301) 827-2020
Fax: (301) 827-2091

APPEARS THIS WAY
ON ORIGINAL

This transmission includes 2 pages (including this page)

Center for Drug Evaluation and Research
Division of Dermatologic and Dental
Drug Products, HFD-540
9201 Corporate Blvd
Building 2, 2nd Floor
Rockville, MD 20850

301-827-2020, fax 301-827-2091

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FDA Fax Memo

Date: February 29, 2000

Subject: NDA 50-777/Protopic (Tacrolimus Ointment)

Hi Don,

The PK reviewer has the following question:

Re: Blood Levels in Study FG-06-04 (Relative bioaviailability of 0.03, 0.1, and 0.3% tacrolimus ointment in healthy Volunteers)

The limit of quantitation of tacrolimus used in this study is — pg/mL. Table no. 6 on pages 48-51 of volume 43 of the submission has several values that are reported in brackets. These values are below the — pg/mL level. There are some as low as 1 pg/mL. Most others are reported as — pg/mL. It is unclear how the bracketed values were accounted for. The Sponsor needs to provide an explanation for the criteria used in estimating the blood levels and how were these low levels quantifiable based on the assay validation range.

Don, once you have obtained an explanation, please submit it the NDA. It would be helpful if you would fax a copy to me and I will forward it to the PK reviewer. While the hard copy is being submitted, the reviewer can review the faxed copy.

If you have questions, please call.

Respectfully,
Millie

CC:
Orig NDA 50-777
HFD-540/Div File
HFD-540/Wright

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FDA Fax Memo

e: February 29, 2000

Donald Baker
Senior Director, Regulatory Affairs
Fujisawa Healthcare, Inc.
Phone: (847) 317-8872
Fax: (847) 317-7286

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m: Millie Wright, Project Manager
Phone: (301) 827-2020
Fax: (301) 827-2091

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FDA Fax Memo

Date: December 8, 1999

FAXED 12/8/99

To: Donald Baker
Senior Director, Regulatory Affairs
Fujisawa Healthcare, Inc.
Phone: (847) 317-8872
Fax: (847) 317-7286

From: Millie Wright, Project Manager
Phone: (301) 827-2020
Fax: (301) 827-2091

This transmission includes 2 pages (including this page)

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Center for Drug Evaluation and Research
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301-827-2020, fax 301-827-2091

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Date December 8, 1999

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Senior Director, Regulatory Affairs
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Phone: (847) 317-8872
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From Millie Wright, Project Manager
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