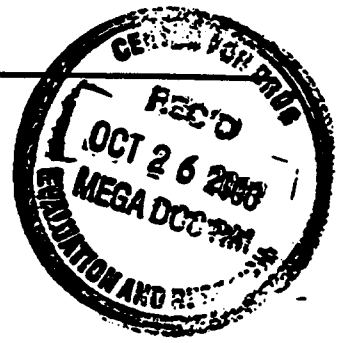
DERMIK LABORATORIES, INC.

1050 WESTLAKES DRIVE
BERWYN, PA 19312
484-595-2700



NDA ORIG AMENDMENT

October 25, 2000

Jonathan K. Wilkin, MD, Director
Division of Dermatologic and Dental Drug Products (HFD-540)
Center for Drug Evaluation and Research
Food and Drug Administration
9201 corporate Boulevard
Building No. 2, Second Floor, Room N115
Rockville, MD 20850

SU

NDA No. 20-985
fluorouracil Topical Cream 0.5%

SAFETY UPDATE REPORT

Dear Mr. Wilkin:

Reference is made to an October 25 telephone call from Division of Dermatological and Dental Drug Products Product Manager, Ms. Vickey Lutwak during which Dermik Laboratories, Inc. was requested to submit an updated safety report to this application. This letter serves as a Safety Update Report for our fluorouracil Topical Cream application.

Please be informed that no clinical trials have been conducted with fluorouracil Topical Cream that were not included in the original October 28, 1999 NDA submission. Therefore, there is no additional clinical study safety information to provide at this time. Additionally, Dermik is not aware of any other safety information that may reasonably affect the statement of contraindications, warnings, precautions, and adverse reactions included in the draft labeling included in our fluorouracil Topical Cream New Drug Application.

We believe that this submission fully responds to Ms. Lutwak's request. If you have any questions regarding this submission, please contact me at (610) 595-2795.

Sincereiy,

James P. Thompson

James P. Thompson
Manager, Regulatory Affairs

ORIGINAL

Enc.

BEST POSSIBLE COPY

DERMIK LABORATORIES, INC.

1050 WESTLAKES DRIVE
BERWYN, PA 19312
484-595-2700

October 25, 2000

Jonathan Wilkin, MD, Director
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Dermatologic and Dental Drug Products (HFD-540)
9201 Corporate Boulevard
Building No. 2, Second Floor, Room N115
Rockville, MD 20850

NDA No. 20-985
fluorouracil Topical Cream, 0.5%

Amendment to a Pending Application
Response to FDA Request for Information
Phase IV Clinical Study Commitment

Dear Dr. Wilkin:

Reference is made to an October 13, 2000 facsimile transmission from Division of Dermatological and Dental Drug Products (DDDP) Project Manager Ms. Vickey Lutwak recommending that Dermik commit to a Phase IV study to assess post-treatment safety and efficacy of our fluorouracil Topical Cream product. This commitment was submitted October 24, 2000.

Reference is also made to an October 24, 2000 voice mail message from Ms. Lutwak, requesting the re-submission of a revised Phase IV clinical study commitment by Dermik Laboratories, Inc. The requested commitment follows:

As recommended by DDDDP, Dermik commits to a Phase IV study or studies that, together with the patients already treated equal to or greater than two weeks with our fluorouracil Topical Cream product in controlled clinical trials, will enable Dermik to reach the number of patients treated for actinic keratosis of the face and/or scalp as recommended in the ICH E1A safety guidance. In adequately sized long term studies, Dermik will also address the additional safety and efficacy issues delineated in the reference facsimile (common skin areas not previously treated, recurrence, re-treatment, eye irritation, etc.).

The study protocol or protocols will be submitted to the Agency for review prior to the conduct of said study or studies to assure that the study or studies will address the concerns of the Agency with regard to the use of the product for the treatment of actinic keratosis. Dermik will initiate the study or studies within one year following the approval of our application. The study or studies will be completed no later than three years after it's (their) initiation, and the results submitted to the Agency within one year after completion.

BEST POSSIBLE COPY

NDA 20-985
Phase IV Commitment
October 25, 2000

If you have any questions, please contact us at 484-595-2795.

Sincerely,

James P. Thompson

James P. Thompson
Regulatory Manager
Worldwide Regulatory Affairs

Enc

APPEARS THIS WAY
ON ORIGINAL

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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, Parts 314 & 601)

Form Approved: OMB No. 0910-0338
Expiration Date: March 31, 2003
See OMB Statement on page 2.

FOR FDA USE ONLY

APPLICATION NUMBER

APPLICATION INFORMATION

NAME OF APPLICANT	DATE OF SUBMISSION
Dermik Laboratories, Inc.	October 25, 2000
TELEPHONE NO. *(Include Area Code)*	FACSIMILE (FAX) Number *(Include Area Code)*
(484) 595-2795	(484) 595-2785
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
1050 Westlakes Drive Berwyn, PA 19312-2421	

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER *(If previously issued)* NDA 20-985

ESTABLISHED NAME *(e.g., Proper name, USP/USAN name)*	PROPRIETARY NAME *(trade name)* IF ANY
(fluorouracil cream)	N/A

CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME *(If any)*	CODE NAME *(If any)*
5-fluoro-2,4 (1H, 3H) - pyrimidinedione	DL-6025

DOSAGE FORM:	STRENGTHS:	ROUTE OF ADMINISTRATION:
Topical Cream	0.5%	Topical

(PROPOSED) INDICATION(S) FOR USE: Topical treatment of actinic keratosis

APPLICATION INFORMATION

APPLICATION TYPE *(check one)* X NEW DRUG APPLICATION (21 CFR 314.50) ☐ ABBREVIATED NEW DRUG APPLICATION (ANDA, 21 CFR 314.94)
☐ BIOLOGICS LICENSE APPLICATION (21 CFR Part 601)

IF AN NDA, IDENTIFY THE APPROPRIATE TYPE X 505 (b)(1) ☐ 505 (b)(2)

IF AN ANDA, OR 505(b)(2), 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 ☐ EFFICACY SUPPLEMENT
☐ LABELING SUPPLEMENT ☐ CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT X OTHER

IF A SUBMISSION OF PARTIAL APPLICATION, PROVIDE LETTER DATE OF AGREEMENT TO PARTIAL SUBMISSION: _____

IF A SUPPLEMENT, IDENTIFY THE APPROPRIATE CATEGORY ☐ CBE ☐ CBE-30 ☐ Prior Approval (PA)

REASON FOR SUBMISSION Sponsor's Phase IV Commitment

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

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

ESTABLISHMENT INFORMATION (Full establishment information should be provided in the body of the Application.)
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.

See Original Application

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

See Original Application

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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 report 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)
	19. Financial Information (21 CFR Part 54)
X	20. OTHER *(Specify:)* Sponsor's Phase IV Clinical Study Commitment

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 Parts 210, 211 or applicable regulations, Parts 606, and/or 820.
2. Biological establishment standards in 21 CFR Part 600.
3. Labeling regulations in 21 CFR Parts 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 Part 202.
5. Regulations on making changes in application in FD&C Act Section 506A, 21 CFR 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
James P. Thompson	James T. Thompson, Manager Worldwide Regulatory Affairs	October 25, 2000

ADDRESS *(Street, City, State, and ZIP Code)*	Telephone Number
1050 Westlakes Drive Berwyn, PA 19312	(484) 595-2795

Public reporting burden for this collection of information is estimated to average 24 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:

Department of Health and Human Services
Food and Drug Administration
CBER, HFM-99
1401 Rockville Pike
Rockville, MD 20852-1448

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.

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DERMIK LABORATORIES, INC.

1050 WESTLAKES DRIVE
BERWYN. PA 19312
484-595-2700

October 26, 2000

Jonathan K. Wilkin, MD, Director
Division of Dermatologic and Dental Drug Products (HFD-540)
Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Boulevard
Building No. 2, Second Floor, Room N115
Rockville, MD 20850

NDA No. 20-985
fluorouracil Topical Cream 0.5%

Amendment to a Pending Application
Draft Labeling

Dear Mr. Wilkin:

Reference is made to a Labeling teleconference meeting held earlier today at which the proposed draft labeling submitted to the Division of Dermatological and Dental Drug Products (DDDDP) by Dermik Laboratories, Inc., October 25, 2000 was discussed by representatives of DDDDP and Dermik.

Concerning the footnote issue, the footnotes contain information on the trademarks referenced in the Package Insert. Dermik has been legally advised that including registered trademarks in the package insert implies that those trademark registrations are owned by Dermik. However, since neither trademark is owned by Dermik, the statements included in the footnotes are required to designate the true source or sponsorship of the marks.

Please be informed that Dermik is in full agreement with the negotiated labeling, a copy of which is enclosed.

If you have any questions, please contact me at 484-595-2795.

Sincerely,

James P. Thompson

James P. Thompson
Manager, Regulatory Affairs

BEST POSSIBLE COPY

DERMIK LABORATORIES, INC. A RHÔNE-POULENC RORER COMPANY
Dedicated to Dermatology

1050 Westlakes Drive
Berwyn, PA 19312

Alicia Cabrelli
Regulatory Analyst

TEL. ++ 484-595-2775
FAX: ++ 484-595-2785

FAX TRANSMISSION

DATE & TIME:	10/27/00
TO:	Vickey Lutwak, Project Manager
COMPANY:	Food and Drug Administration
FAX:	301-827-2075
RE:	**NDA 20-985** **TRADENAME 0.5% fluorouracil cream**
PAGES:	2

Confidential: For Your Eyes Only

Dear Vickey-

Attached is the signed letter from Dermik referencing our agreement to the label and the rationale for the trademarks.

If you have any questions, please feel free to contact me at 484-595-2775 or Jim at 484-595-2795.

Kind regards,

Alicia Cabrelli
Regulatory Analyst

APPEARS THIS WAY
ON ORIGINAL

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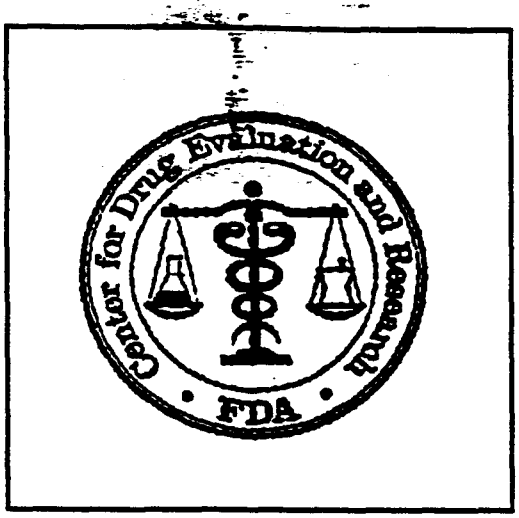
FACSIMILE TRANSMISSION RECORD



From: Vickey Lutwak, Project Manager

Division of Dermatologic and
Dental Drug Products, HFD-540
Center for Drug Evaluation & Research
Food & Drug Administration
9201 Corporate Blvd.
Rockville, MD 20850

Phone 301-827-2020
Fax 301-827-2075

Date: Dec 1, 1999

To:

Name Jim Thompson
Company Damik Laboratories Inc
City _____ State ____
Phone # 610-454-3227

FAX # 610-454-5287

Number of Pages (INCLUDING COVER PAGE) 1

Please telephone (301) 827-2020 IMMEDIATELY if re-transmission is necessary.

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NOTE: We are providing the attached information via telephone facsimile for your convenience. This material should be viewed as unofficial correspondence. Please feel free to contact me if you have any questions regarding the contents of this transmission.

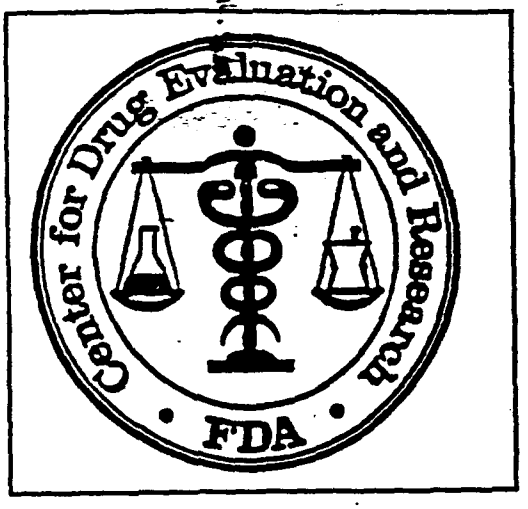
Additional message: NDA 20-985

Jim - Per our conversation Pharm/Tox

It is requested that the sponsor provide the full references referred to in the annotated label. Reference numbers are listed in the annotated label, but there is no reference list provided to match the numbers. In addition, it is requested that the sponsor annotate and provide the full references used for the description of the teratogenicity associated with 5-fluorouracil provided in the label. Also, it is requested that the sponsor annotate and provide the full references used for the information provided in the carcinogenesis, mutagenesis and impairment of fertility section of the label. It is requested that the sponsor provide the estimate of maximum daily human topical dose in mg/kg and mg/m^2 that was used for calculating fold exposure levels in the label.

Regards - Vickey

FACSIMILE TRANSMISSION RECORD



From: Vickey Lutwak

Division of Dermatologic and Dental Drug Products, HFD-540

Phone 301-827-2073
Fax 301-827-2075

Date: March 8, 2000

To: Name Jim Thompson
Company Dermik
City _____ State ____
Phone # 610 454 3057

FAX # 610 454-3057

Number of Pages (INCLUDING COVER PAGE) 2

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NOTE: We are providing the attached information via telephone facsimile for your convenience. This material should be viewed as unofficial correspondence. Please feel free to contact me it you have any questions regarding the contents of this transmission.

Additional message: NDA 20-485

Dear Jim,

We need the following in electronic format - DISK or CD, whichever is faster - Any question? Please call - Also, would you let me know approximately when to expect this request.

Thanks & Regards
Vickey

BEST POSSIBLE COPY

NDA 20-985 [redacted]

Please provide the following:

1. Protocols and final study reports for the following studies:
   - DL-6025-9508
   - DL-6025-9509
   - DL-6025-9713
   - DL-6025-9714
   - DL-6025-9715
   - DL-6025-9815
   - DL-6025-9720
   - DL-6025-9518
   - DL-6025-9625

2. Protocols for the following studies:
   - DL-6025-9721
   - DL-6025-9722

3. Section 3.7, Clinical Data Summary and Results of Statistical Analysis (pages 3-1-82 to 3-1-122)

4. The corrected replacement table for Volume 1.1, page 3-1-85, 8-1-4,8-1-1, and 8-1-32 (as per amendment dated 12-10-99).

Please indicate when we may expect this information. CD or disc.
Thank you,

VL

Vickey Lutwak

[redacted]

APPEARS THIS WAY
ON ORIGINAL

NDA 20-985 (fluorouracil cream, 0.5%) Sponsor – Dermik Labs.

1. Please provide a copy of the detailed patient instruction sheet for application of drug product referenced in Vol. 1.18, pg. 8-2-166 for Protocol DL-6025-9721. Aslo, describe the [redacted] used in the clinical studies.

2. Were actinic keratosis lesions located on the ears counted and treated during conduct of clinical trials for Protocols DL-6025-9721 and DL-6025-9722? The facial diagram provided for Regional Count of Visible and Palpable Actinic Lesions (Vol. 1.18, pg. 8-2-167) for Protocol DL-6025-9721 has ears depicted. The facial diagrams provided with Case Report Forms (e.g., Baseline Actinic Lesion Count, Vol. 1.18, pg. 8-2-200, and Final Actinic Lesion Count, Vol. 1.18, pg. 8-2-210) used by investigators to record the actual regional counts for Protocol DL-6025-9721 do not have ears depicted ears.

3. Actinic keratoses occur on sun exposed areas. The rationale for limiting therapy with the Sponsor's drug product for treatment of actinic keratoses on the face and scalp as per Indication and Usage Section of the proposed label (Vol.1.1, pg. 2-1-22) is requested? Is there a safety concern with use of the Sponsor's 5-FU formulation on areas other than face and anterior bald scalp?

4. For PK Study DL-6025-9720, where in the submission are baseline line listings for actinic lesion counts per patient or range of numbers for baseline actinic lesions located? According to the submission (Vol. 1.14, Pg. 6-1-82)..."On average, patients in each treatment group had 8-9 actinic keratosis lesions at baseline."

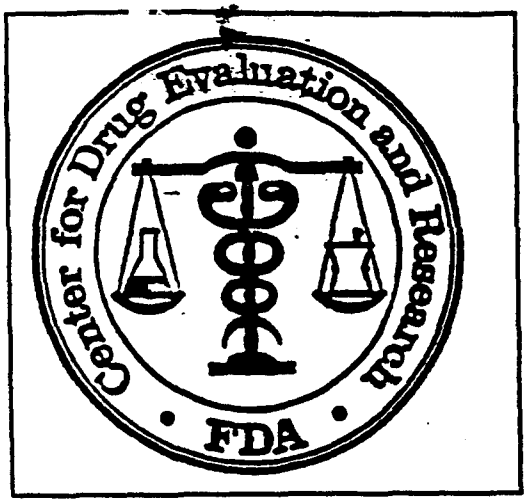
Would you let us know when we can expect this information.
Please send one desk copy to Vickey Lutwak when making the formal submissison to the NDA 20-985.

Thank you,

[redacted]

APPEARS THIS WAY
ON ORIGINAL

FACSIMILE TRANSMISSION RECORD



From: Vickey Lutwak

Division of Dermatologic and Dental Drug Products, HFD-540

Phone 301-827-2073
Fax 301-827-2075

Date: June 20, 2000

To: Name Jim Thompson
Company _____
City _____ State ____
Phone # 610-454-3027

FAX # 610-454-5287

Number of Pages (INCLUDING COVER PAGE) 2

Please telephone (301) 827-2020 IMMEDIATELY if re-transmission is necessary.

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Additional message:

Dear Jim -
Request for information - Please respond in a timely fashion -
In addition - anything about a TRADENAME?
Regards Vickey

DERMIK LABORATORIES, INC.
Dedicated to Dermatology
A RHÔNE-POULENC RORER COMPANY

500 ARCOLA ROAD
P.O. BOX 1200
COLLEGEVILLE, PA 19426-0107
TEL. [illegible]

NDA ORIG AMENDMENT

CENTER FOR DRUG
REC'D
JUL 27 2000
MEGA
EVALUATION AND RESEARCH

July 25, 2000

Jonathan Wilkin, MD, Director
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Dermatologic and Dental Drug Products (HFD-540)
Attention: Document Control Room
9201 Corporate Boulevard
Rockville, MD 20850

NDA No. 20-985

[redacted] Cream, 0.5%
(fluorouracil cream)

Amendment to a Pending Application
Response to FDA Request for Information

Dear Dr. Wilkin:

Reference is made to the facsimile dated July 25, 2000 we received from DDDDP Project Manager Ms. Victoria Lutwak requesting additional information for the [redacted] (fluorouracil cream) Cream 0.5% clinical reviewer.

Included in this submission is Dermik's response to Ms. Lutwak's request.

Thank you for your attention. Please contact me at (610) 454-3027 if you have any questions.

Sincerely,

James P. Thompson

James P. Thompson
Regulatory Manager
Worldwide Regulatory Affairs

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DUPLICATE

Desk Copy: Victoria Lutwak, Project Manager

DERMIK LABORATORIES, INC.
Dedicated to Dermatology
A RHÔNE-POULENC RORER COMPANY

500 ARCOLA ROAD
P.O. BOX 1200
COLLEGEVILLE, PA 19426-0107
TEL. 610-454-8000

July 14, 2000

Jonathan K. Wilkin, M.D., Director
Division of Dermatologic and Dental Drug Products
Center for Drug Evaluation and Research
Office of Drug Evaluation V
Food and Drug Administration
9201 Corporate Boulevard
Building No. 2, Second Floor, Room N115
Rockville, MD 20850

NDA No. 20-985
[redacted] Cream, 0.5%
(fluorouracil cream)

INFORMATION AMENDMENT:
Chemistry, Manufacturing and Controls

Dear Dr. Wilkin,

Reference is made to our New Drug Application dated October 28, 1999 which contained, in part, CMC information for [redacted] Cream, 0.5% (fluorouracil cream).

[redacted], the supplier of the [redacted] has informed Dermik in a March 31, 2000 letter that their Drug Master File No. [redacted] was amended. We have been told that this DMF amendment provides for a [redacted] The resulting [redacted] product meets all specifications required by USP.

This letter serves as an amendment to the Chemistry, Manufacturing and Controls section of the [redacted] Cream NDA No. 20-985.

If you have any questions or comments regarding this submission, please contact me at (610) 454-3027.

Sincerely,

James P. Thompson

James P. Thompson
Manager
Worldwide Regulatory Affairs

cc: Debra L. Pagano
Philadelphia District Pre-Approval Manager
U.S. Food and Drug Administration
Room 900, U.S. Customhouse
2nd and Chestnut Streets
Philadelphia, PA 19106-2973

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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, Parts 314 & 601)

Form Approved: OMB No. 0910-0338
Expiration Date: March 31, 200?
See OMB Statement on page 2.

FOR FDA USE ONLY

APPLICATION NUMBER

APPLICATION INFORMATION

NAME OF APPLICANT	DATE OF SUBMISSION
Dermik Laboratories, Inc.	July 14, 2000
TELEPHONE NO. *(Include Area Code)*	FACSIMILE (FAX) Number *(Include Area Code)*
(610) 454-3027	(610) 454-5287
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
500 Arcola Road Collegeville, PA 19426	

PRODUCT DESCRIPTION: synthetic antifungal agent

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER *(if previously issued)* NDA 20-985

ESTABLISHED NAME *(e.g., Proper name, USP/USAN name)*	PROPRIETARY NAME *(trade name)* IF ANY
(fluorouracil cream)	Cream 0.5%

CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME *(If any)*	CODE NAME *(If any)*
5-fluoro-2,4(1H,3H)-pyrimidinedione	DL-6025

DOSAGE FORM:	STRENGTHS:	ROUTE OF ADMINISTRATION:
topical gel	0.5%	topical

(PROPOSED) INDICATION(S) FOR USE: Topical treatment of [redacted]

APPLICATION INFORMATION

APPLICATION TYPE *(check one)* X NEW DRUG APPLICATION (21 CFR 314.50) ☐ ABBREVIATED NEW DRUG APPLICATION (ANDA, 21 CFR 314.94)
☐ BIOLOGICS LICENSE APPLICATION (21 CFR Part 601)

IF AN NDA, IDENTIFY THE APPROPRIATE TYPE X 505 (b)(1) ☐ 505 (b)(2)

IF AN ANDA, OR 505(b)(2), 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 ☐ EFFICACY SUPPLEMENT
☐ LABELING SUPPLEMENT ☐ CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT x OTHER

IF A SUBMISSION OF PARTIAL APPLICATION, PROVIDE LETTER DATE OF AGREEMENT TO PARTIAL SUBMISSION:

IF A SUPPLEMENT, IDENTIFY THE APPROPRIATE CATEGORY ☐ CBE ☐ CBE-30 ☐ Prior Approval (PA)

REASON FOR SUBMISSION Information Amendment: Chemistry, Manufacturing and Controls

PROPOSED MARKETING STATUS *(check one)* X PRESCRIPTION PRODUCT (Rx) ☐ OVER THE COUNTER PRODUCT (OTC)

NUMBER OF VOLUMES SUBMITTED: 1 — THIS APPLICATION IS x PAPER ☐ PAPER AND ELECTRONIC ☐ ELECTRONIC

ESTABLISHMENT INFORMATION: (Full establishment information should be provided in the body of the Application.)
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.

See Original Application

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

See Original Application

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	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)
	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 report 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)
	19. Financial Information (21 CFR Part 54)
X	20. OTHER *(Specify) Information Amendment: Chemistry, Manufacturing and Controls*

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 Parts 210, 211 or applicable regulations, Parts 606, and/or 820.
2. Biological establishment standards in 21 CFR Part 600.
3. Labeling regulations in 21 CFR Parts 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 Part 202.
5. Regulations on making changes in application in FD&C Act Section 506A, 21 CFR 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
James P. Thompson	James P. Thompson, Manager Worldwide Regulatory Affairs	7/14/00

ADDRESS *(Street, City, State, and ZIP Code)*	Telephone Number
500 Arcola Road Collegeville, PA 19426	(610) 454-3027

Public reporting burden for this collection of information is estimated to average 24 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:

Department of Health and Human Services
Food and Drug Administration
CBER, HFM-99
1401 Rockville Pike
Rockville, MD 20852-1448

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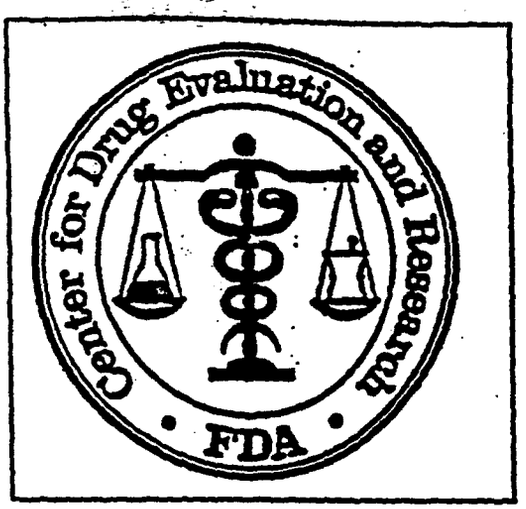

From: Vickey Lutwak

Division of Dermatologic and Dental Drug Products, HFD-540

Phone 301-827-2073
Fax 301-827-2075

Date: July 25, 2000

To: Name Jim Thompson
Company Dermik
City _____ State ____
Phone # 610-454-3327

FAX # 610.454.5287

Number of Pages (INCLUDING COVER PAGE) 2

Please telephone (301) 827-2020 IMMEDIATELY if re-transmission is necessary.

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NOTE: We are providing the attached information via telephone facsimile for your convenience. This material should be viewed as unofficial correspondence. Please feel free to contact me it you have any questions regarding the contents of this transmission.

Additional message:

Dear Jim—

Please provide as soon as possible—
let me know when you Fed Ex the
disk as a desk copy - Thanks—

Vickey

DERMIK LABORATORIES, INC.
Dedicated to Dermatology

A RHÔNE-POULENC RORER COMPANY

500 ARCOLA ROAD
P.O. BOX 5093
COLLEGEVILLE, P.A. 19426-0997
U. S. A.

Alicia Cabrelli
Regulatory Analyst

TEL. ++ 610-454-2690
FAX: ++ 610-454-2283

FAX TRANSMISSION

DATE & TIME:	07/25/00 5:27 5:30 PM
TO:	Vickey Lutwak, Project Manager
COMPANY:	Food and Drug Administration
FAX:	301-827-2075
RE:	[redacted] **Cream, 0.5%** **(fluorouracil cream)** 6 pgs.

Confidential: For Your Eyes Only

Dear Vickey-

Attached is a copy of the Sponsor's Response to the Division's request sent via facsimile on July 25, 2000. This will also be officially submitted to the Division today via FedEx.

If you have any questions, please feel free to contact me at 610-454-2690.

Kind regards,

Alicia Cabrelli

Alicia Cabrelli

APPEARS THIS WAY
ON ORIGINAL

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DERMIK LABORATORIES, INC.
Dedicated to Dermatology
A RHÔNE-POULENC RORER COMPANY

500 ARCOLA ROAD
P.O. BOX 1200
COLLEGEVILLE, PA 19426-0107
TEL. 610-454-8000

July 25, 2000

Jonathan Wilkin, MD, Director
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Dermatologic and Dental Drug Products (HFD-540)
Attention: Document Control Room
9201 Corporate Boulevard
Rockville, MD 20850

NDA No. 20-985

[redacted] Cream, 0.5%
(fluorouracil cream)

Amendment to a Pending Application
Response to FDA Request for Information

Dear Dr. Wilkin:

Reference is made to the facsimile dated July 25, 2000 we received from DDDDP Project Manager Ms. Victoria Lutwak requesting additional information for the [redacted] (fluorouracil cream) Cream 0.5% clinical reviewer.

Included in this submission is Dermik's response to Ms. Lutwak's request.

Thank you for your attention. Please contact me at (610) 454-3027 if you have any questions.

Sincerely,

James P. Thompson

James P. Thompson
Regulatory Manager
Worldwide Regulatory Affairs

Desk Copy: Victoria Lutwak, Project Manager

BEST POSSIBLE COPY

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, Parts 314 & 601)

Form Approved: OMB No. 0910-0338
Expiration Date: March 31, 2003
See OMB Statement on page 2.

FOR FDA USE ONLY

APPLICATION NUMBER

APPLICATION INFORMATION

NAME OF APPLICANT	DATE OF SUBMISSION
Dermik Laboratories, Inc.	July 25, 2000
TELEPHONE NO. *(Include Area Code)*	FACSIMILE (FAX) Number *(Include Area Code)*
(610) 454-3027	(610) 454-5287
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
500 Arcola Road Collegeville, PA 19426	

PRODUCT DESCRIPTION topical fluorouracil

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER *(If previously issued)* NDA 20-985

ESTABLISHED NAME *(e.g., Proper name, USP/USAN name)*	PROPRIETARY NAME *(trade name)* IF ANY
(fluorouracil cream)	Cream 0.5%
CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME *(If any)*	CODE NAME *(If any)*
5-fluoro-2,4(1H,3H)-pyrimidinedione	DL-6025

DOSAGE FORM:	STRENGTHS:	ROUTE OF ADMINISTRATION:
Topical Cream	0.5%	topical

(PROPOSED) INDICATION(S) FOR USE: Topical Treatment of actinic keratosis

APPLICATION INFORMATION

APPLICATION TYPE *(check one)*

X NEW DRUG APPLICATION (21 CFR 314.50) ☐ ABBREVIATED NEW DRUG APPLICATION (ANDA, 21 CFR 314.94)
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Name of Drug	Holder of Approved Application

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PRESUBMISSION ☐ ANNUAL REPORT ☐ ESTABLISHMENT DESCRIPTION SUPPLEMENT ☐ EFFICACY SUPPLEMENT

☐ LABELING SUPPLEMENT ☐ CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT X OTHER

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REASON FOR SUBMISSION FDA Request for Additional Information

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

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See Original Application

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SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT	TYPED NAME AND TITLE	DATE
James P. Thompson	James P. Thompson, Manager Worldwide Regulatory Affairs	July 25, 2000

ADDRESS *(Street, City, State, and ZIP Code)*	Telephone Number
500 Arcola Road Collegeville, PA 19426	(610) 454-3027

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Department of Health and Human Services
Food and Drug Administration
CBER, HFM-99
1401 Rockville Pike
Rockville, MD 20852-1448

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NDA 20-985
Dermik DL-6025
(Fluorouracil Cream) Cream 0.5%

FDA Requested Additional Table – Fax Request Date 7/25/00

Summary of All Adverse Events Reported in ≥ 1% of Patients in the Combined Active Treatment and Vehicle Groups – Pooled Phase III Studies

	9721 and 9722 Combined				
Body System AE COSTART Term*	Active One Week N= 86	Active Two Week N= 87	Active Four Week N= 85	ALL Active Treatments N=257	Vehicle Treatments N=127
	n (%)	n (%)	n (%)	n (%)	n (%)
BODY AS A WHOLE	7 (8.2)	8 (8.9)	12 (14.1)	25 (9.7)	15 (11.8)
Headache	3 (3.5)	2 (2.3)	3 (3.5)	8 (3.1)	3 (2.4)
Common Cold	4 (4.7)	0	2 (2.4)	6 (2.3)	3 (2.4)
Allergy	0	2 (2.3)	1 (1.2)	3 (1.2)	2 (1.6)
Infection Upper Respirator	0	0	0	0	2 (1.6)
MUSCULOSKELETAL	1 (1.2)	1 (1.1)	1 (1.2)	3 (1.2)	5 (3.9)
Muscle Soreness	0	0	0	0	2 (1.6)
RESPIRATORY	5 (5.9)	0	1 (1.2)	6 (2.3)	6 (4.7)
Sinusitis	4 (4.7)	0	0	4 (1.6)	2 (1.6)
SKIN & APPENDAGES	78 (91.8)	83 (95.4)	82 (96.5)	243 (94.6)	85 (66.9)
Application Site Reaction	78 (91.8)	83 (95.4)	82 (96.5)	243 (94.6)	83 (65.4)
Irritation Skin	1 (1.2)	0	2 (2.4)	3 (1.2)	0
SPECIAL SENSES	6 (7.1)	4 (4.6)	6 (7.1)	16 (6.2)	6 (4.7)
Eye Irritation	5 (5.9)	3 (3.4)	6 (7.1)	14 (5.4)	3 (2.4)

Source: extracted from ISS- Table 24: Summary of All Adverse Events - Pooled Phase III Studies (NDA Vol. 1.28, page 8-12-120) and Appendix A.5 (NDA Vol. 1.28, page 8-12-156)

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7-25-00 FDA requested table word 6.0version

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FACSIMILE TRANSMISSION RECORD

From: Vickey Lutwak

Division of Dermatologic and Dental Drug Products, HFD-540

Phone 301-827-2073
Fax 301-827-2075

Date: July 31, 2000

To: Name Jim Thompson
Company _____
City _____ State ____
Phone # 610 454 3027

FAX # 610 454 5287

Number of Pages (INCLUDING COVER PAGE) 2

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NOTE: We are providing the attached information via telephone facsimile for your convenience. This material should be viewed as unofficial correspondence. Please feel free to contact me it you have any questions regarding the contents of this transmission.

Additional message:

NDA - 20-975

Dear Jim -

Would you please respond to the attached list of questions from the medical officer - Thank you - Regards, Vickey

Dermik Laboratories, Inc.
Facsimile Cover Page

Date: August 14, 2000

To: Ms. Victoria Lutwak
Project Manager
Fax Number: 301 827-2075

From: James P. Thompson
Manager, Regulatory Affairs
Phone #: 610 454-3027
Fax Number: 610 454-5287

Pages Sent: 1

Vicky,

The names that follow are the trade names we are proposing for our fluorouracil product in order of preference

1. [ ]
2. [ ]

Please call me at 610 454-3027 if you have any questions. I can be reached at this number tomorrow also.

James P. Thompson

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ON ORIGINAL

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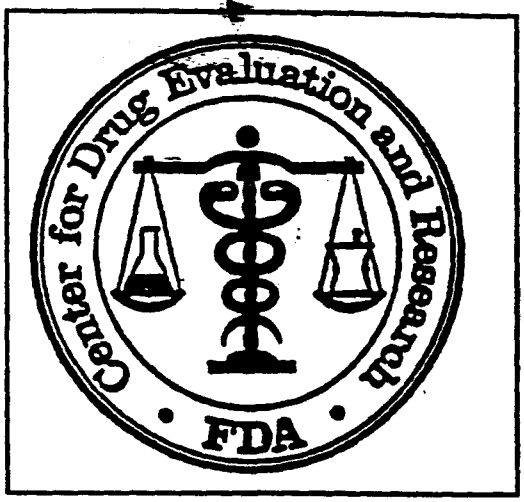

From: Vickey Lutwak

Division of Dermatologic and Dental Drug Products, HFD-540

Phone 301-827-2073
Fax 301-827-2075

Date: October 13, 2000

To: Name Jim Thompson
Company Dermik
City _____ State _____
Phone # 484-595-2795

FAX # 484-595-2785

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Additional message:

Dear Jim -

The phase 4 -

Regards,
Vickey

DERMIK LABORATORIES, INC.

1050 WESTLAKES DRIVE
BERWYN, PA 19312
484-595-2700

October 25, 2000

Jonathan K. Wilkin, MD, Director
Division of Dermatologic and Dental Drug Products (HFD-540)
Center for Drug Evaluation and Research
Food and Drug Administration
9201 corporate Boulevard
Building No. 2, Second Floor, Room N115
Rockville, MD 20850

NDA No. 20-985
fluorouracil Topical Cream 0.5%

SAFETY UPDATE REPORT

Dear Mr. Wilkin:

Reference is made to an October 25 telephone call from Division of Dermatological and Dental Drug Products Product Manager, Ms. Vickey Lutwak during which Dermik Laboratories, Inc. was requested to submit an updated safety report to this application. This letter serves as a Safety Update Report for our fluorouracil Topical Cream application.

Please be informed that no clinical trials have been conducted with fluorouracil Topical Cream that were not included in the original October 28, 1999 NDA submission. Therefore, there is no additional clinical study safety information to provide at this time. Additionally, Dermik is not aware of any other safety information that may reasonably affect the statement of contraindications, warnings, precautions, and adverse reactions included in the draft labeling included in our fluorouracil Topical Cream New Drug Application.

We believe that this submission fully responds to Ms. Lutwak's request. If you have any questions regarding this submission, please contact me at (610) 595-2795.

Sincerely,

James P. Thompson

James P. Thompson
Manager, Regulatory Affairs

BEST POSSIBLE COPY

Inc.

DERMIK LABORATORIES, INC.
Dedicated to Dermatology
A RHÔNE-POULENC RORER COMPANY

500 ARCOLA ROAD
P.O. BOX 1200
COLLEGEVILLE, PA 19426-0107
TEL. 610-454-8000

June 21, 2000

Ms. Victoria Lutwak
Project Manager
Division of Dermatologic and
Dental Drug Products (HFD-540)
Center for Drug Evaluation and Research
Office of Drug Evaluation V
Food and Drug Administration
9201 Corporate Boulevard
Building No. 2, Second Floor, Room N115
Rockville, MD 20850

RE: DL-6025 (5-FU) NDA #20-985 Response to FDA request for Clinical Information dated 6/20/00 from Vicky Lutwak

The following responses are provided to the four clinical questions faxed to us by Vicky Lutwak on 6/20/00. The questions are summarized below followed by Dermik's response to each question:

1. **QUESTION-** Provide a copy of the detailed patient instruction sheet for application of drug product reference in Vol. 1.18, pg. 8-2-166 for Protocol DL6025-9721. Also describe the [redacted] used in the clinical studies.

   RESPONSE- Attached please find a sample detailed patient instruction sheet from study DL-6025-9721 which provides instructions consistent with those listed in the study protocol (NDA Vol. 1.18, pg. 8-2-165, section E. Application of Drug). Patients were not provided with, nor instructed to use a [redacted] to apply study medication in studies DL-6025-9721 and DL-6025-9722.

2. **QUESTION-** Were actinic keratosis lesions located on the ears counted and treated during conduct of the clinical trials for Protocols DL-6025-9721 and DL-6025-9722? The facial diagram provided for Regional Count of Visible and Palpable Actinic Lesions (Vol. 1.18, pg. 8-2-167) for Protocol DL-6025-9721 has ears depicted. The facial diagrams provided with Case Report Forms (e.g., Baseline Actinic Lesion Count, Vol. 1.18, pg. 8-2-200, and Final Actinic Lesion Count, Vol. 1.18, pg. 8-2-210)

used by investigators to record the actual regional counts for Protocol DL-6025-9721 do not have ears depicted.

RESPONSE- Actinic keratosis lesions located on the ears were not counted during conduct of the clinical trials for Protocols DL-6025-9721 and DL-6025-9722.

The reviewer is correct that the facial diagram located in the protocol depicts ears (NDA Vol. 1.18, pg. 8-2-167). However, the protocol (Section VI.A., subsection 2. Regional Count of Visible and Palpable Actinic Lesions; Vol 1.18, pg. 8-2-167), specifically stated that only lesions on the face and frontal scalp were to be counted. Because ears were not included in the lesion count, the case report form did not include ears as part of the facial image (NDA Vol. 1.18, pg. 8-2-200 and pg. 8-2-210).

3. **QUESTION-** Actinic keratoses occur on sun exposed areas. The rationale for limiting therapy with the Sponsor's drug product for treatment of actinic keratoses on the face and scalp as per Indication and Usage Section of the proposed label (Vol. 1.1, pg. 2-1-22) is requested? Is there a safety concern with use of the Sponsor's 5-FU formulation on areas other than face and anterior bald scalp?

   RESPONSE- The rationale for limiting therapy with Dermik's 5-FU formulation to the face and (anterior bald scalp when present) was that these areas tend to have the greatest sun exposure. Sun exposure is an important determinant in the presentation of actinic keratosis lesions. Therefore, limiting the investigative site to the face (and anterior bald scalp) allowed for evaluation of the study drug at a body site that would have a relatively high density of lesions. Additionally, facial actinic keratoses are often very noticeable to both patient and physician. Patients frequently present to the physician for diagnosis and treatment of these lesions.

   Dermik sees no specific safety concerns with treatment of other body sites beyond the face and anterior bald scalp. In fact, from a safety standpoint, treatment of facial AKs (versus for example arm lesions) most likely presents a 'worst case' safety assessment of the study drug. The facial skin is relatively thinner than that of other body sites (e.g., arms). Both skin irritation responses and systemic exposure to the study drug are likely enhanced with treatment of the face relative to other body sites. Facial irritation with study drug treatment was fully assessed within the clinical efficacy/safety studies (DL-6025-9721, DL-6025-9722). The 5-FU product was also evaluated in special dermal safety studies involving applications to the skin of the back and arms. As determined in a specific pharmacokinetic study of patients with facial actinic keratoses (DL 6025-9720), systemic exposure to fluorouracil is very minimal, even with daily treatments for four weeks.

4. **QUESTION-** For PK Study DL-6025-9720, where in the submission are baseline line listings for actinic lesion counts per patient or range of numbers for baseline actinic lesions located? According to the submission (Vol. 1.14, pg. 6-1-82)..."On average, patients in each treatment group had 8-9 actinic keratosis lesions at baseline."

RESPONSE- The baseline line listings for PK Study DL-6025-9720 actinic lesion counts are located in the Final Study Report, Appendix 16.2.7.2 (NDA Vol. 1.15, pgs. 6-2-157 through 6-2-166). For ease of reference Appendix 16.2.7.2, pages 6-2-157 through 6-2-166 are included with this document.

APPEARS THIS WAY
ON ORIGINAL

DERMIK LABORATORIES, INC.
Dedicated to Dermatology

500 ARCOLA ROAD
P.O. BOX 1200
COLLEGEVILLE, P.A. 19426-0107
U. S. A.

Katharine W. Furst
Sr. Clinical Research Specialist
Clinical Research and Medical Affairs

TEL: ++ 610-454-5223
FAX: ++ 610-454-2283

FAX TRANSMISSION

DATE:	6/30/00
TO:	Vickey Lutwak
COMPANY:	FDA, Division of Dermatologic and Dental Drug Products, HFD-540
PHONE:	301-827-2073
FAX:	301-827-2075
Total number of pages including this cover:	2
SUBJECT:	**NDA 20-985, Patient Instructions**

Vickey,

As per your request, attached please find patient instructions for Dermik's 5-fluorouracil product (NDA 20-985). We will forward this document to you under formal cover next week with an electronic disk copy. Please do not hesitate to contact us should you have questions or require additional information.

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NDA 20-985

[redacted] (fluorouracil cream) Cream 0.5%

PATIENT INFORMATION AND INSTRUCTIONS FOR APPLYING [redacted]

[redacted] should be used as directed by your health care professional and should not be used for any disorder other than that for which you are being treated. Read the information and instructions below before applying [redacted] (fluorouracil cream) Cream 0.5%.

BEFORE USING THIS MEDICATION, TELL YOUR DOCTOR IF YOU:

- are pregnant or lactating (breast feeding)
- are a female of childbearing potential
- know you have dihydropyrimidine dehydrogenase (DPD) enzyme deficiency

INSTRUCTIONS FOR APPLYING [redacted]

1. [redacted] cream is for use only on your skin.
2. Cleanse the area where you are going to apply [redacted] Rinse the area thoroughly and dry with a clean towel.
3. Apply [redacted] to affected areas once daily as instructed by your health care professional. Only use this product as directed by your health care professional.
4. Avoid contact with your eyes, nostrils, and mouth when applying [redacted]
5. [redacted] should be applied with your fingers in an amount sufficient to cover the affected area. Wash your hands immediately after applying the product.
6. If irritation becomes intolerable or you experience any adverse reaction, contact your health care professional.

WHAT SHOULD YOU AVOID WHILE USING [redacted] CREAM?

You should avoid excessive exposure to sunlight while you are using [redacted] as the intensity of your skin reactions may be increased. During any sun exposure, wear a hat, and use sunscreen. Women should not breast feed or become pregnant while using this product.

WHAT ARE THE POSSIBLE OR REASONABLY LIKELY SIDE EFFECTS OF [redacted] ?

Treated areas may be unsightly during therapy. Irritation at the application site during treatment may include redness, dryness, burning, erosion (skin ulceration), pain and /or swelling. Some irritation at the application site may persist for two or more weeks after therapy is discontinued.

STORAGE: Keep this medication out of the reach of children. Store [redacted] at controlled room temperature 68 to 77° F (20 to 25° C). Do not keep this medication past the expiration date on the tube. Be sure to discard [redacted] out of the reach of children.

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1. Please provide a table for the following:

Summary of All Adverse Events Reported in ≥ 1% of Patients in the Combined Active Treatment and Vehicle Groups, by Body System, and COSTART Term pooled for Phase 3 studies.

Body System AE COSTART Term	Active One Week	Active Two Week	Active Four Week	All Active	Vehicle

To facilitate the review process, also submit the table as an electronic file in MS Word.
— as a desk copy— Hard copy to the NDA

2. (Vol. 1.18, pg. 8-2-165) According to the protocol, patients applied the study drug morning or evenings at 12-hour intervals. Who decided whether the study drug application was to be applied AM or PM?
3. According to the protocol, patients with clinically significant abnormalities should not be entered into the study. Were any patients excluded from Study DL-6025-9722 due to abnormal baseline clinical laboratory abnormalities?

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NDA 20-985
— (fluorouracil) Cream 0.5%

Response to FDA request for Clinical Information – July 25, 2000

1. **REQUEST-** Please provide a table summarizing all adverse events reported in ≥ 1% of patients in the Combined Active Treatment and Vehicle Groups, by Body System, and COSTART Term pooled for Phase 3 Studies. Additionally, submit the table as an electronic file in MS Word.

   RESPONSE- Attached please find a table entitled "Summary of All Adverse Events Reported in ≥ 1% of Patients in the Combined Active Treatment and Vehicle Groups – Pooled Phase III Studies". The table presents the adverse events by Body System, and COSTART Term. This table was extracted from the Integrated Summary of Safety (ISS), Table 24, entitled "Summary of All Adverse Events – Pooled Phase III Studies" (NDA Vol. 1.28, page # 8-12-120) and the ISS Appendix A.5 (NDA Vol. 1.28, Page #8-12-156). An electronic copy of the table is provided on disk in Word 6.0. The disk has been scanned for viruses using ——— virus scan software, version — and no viruses have been detected.

2. **QUESTION-** (Vol. 1.18, pg. 8-2-165) According to the protocol, patients applied the study drug morning or evenings at 12-hour intervals. Who decided whether the study drug application was to be applied AM or PM?

   RESPONSE- The assigned treatment schedule for each patient was determined by the Investigator and patient.

3. **QUESTION-** According to the protocol, patients with clinically significant abnormalities should not be entered into the study. Were any patients excluded from study DL-6025-9722 due to abnormal baseline clinical laboratory abnormalities?

   RESPONSE- According to the DL-6025-9722 patient screening logs, no patients were excluded from participation in the study due to abnormal baseline clinical laboratory abnormalities.

NDA 20-985 (fluorouracil cream, 0.5%) Sponsor – Dermik Labs.

1. How was treatment compliance (Vol. 1.18, Section 5.3.4, page 8-2-45) evaluated (e.g., were the returned tubes of study medication weighed?

2. (Vol. 1.18, Section 5.2.4, page 8-2-43) Were patients provided with sun/screen moisturizer at baseline? According to the protocol, a sun/screen moisturizer (Eucerin, SPF25) was provided by the sponsor, if needed. There are differences between use of sun/screen moisturizer in the Phase 3 studies as indicated in Table 24 (Concomitant Medications for Skin Irritation, Sun Protection, or Eye Irritation) for Study 9721 (Vol. 1.18, pg. 8-2-127) and Study 9722 (Vol. 1.20, pg. 8-4-318). For example, in Study 9721, 36.2% of patients in Active One-Week, 45.7% of patients in the Active Two-Week, and 42.2% in the Active 4-Week treatment arms predominately used sun/screen moisturizers (also includes use of topical steroid, etc.) vs. 5.3%, 12.2%, and 20% respectively for Study 9722. Is there a rationale for this difference?

3. Please provide the following details regarding eye irritation in the Phase 3 studies:
   - Onset
   - Duration
   - Severity
   - Treatment (s) used for eye irritation during the study
   - Is there any correlation between AM or PM application of study medication and eye irritation? Is there a rationale?

4. Section E, Application of Drug (Vol. 1.18, pg. 8-2-165) of the protocol indicates that study medication was to be applied morning or evening at 24 hour intervals in accordance with assigned treatment schedule.
   - Who decided whether the study medication was to be applied morning or evening?
   - Where in the NDA is the line listing indicating the morning or evening application schedule?
   - Was there a difference between timing (AM or PM) of the study medication application across the Phase 3 studies?

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NDA 20-985

FAX

Dermik Laboratories, Inc.
Attention: Mr. James Thompson
Manager, Regulatory Affairs
1050 Westlake Drive
Berwyn, PA 19312

Dear Mr. Thompson:

Please refer to your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for NDA 20-985.

As a condition of approval the Division recommends a study to assess post-treatment safety and efficacy of TRADENAME cream, 0.5%. We would like your commitment to perform a Phase 4 Study, to initiate it within one year after approval, and to complete it no later than three years after initiation, and to submit the results to the Agency within one year after completion.

The Phase 4 study should include the following:

1. Because the number of subjects studied with the to-be-marketed formulation under labeled conditions does not reach the numbers recommended in the ICH E1A guidance, additional safety data for the treatment of actinic keratosis lesions located on the face is needed. In addition, because the safety and efficacy of TRADENAME has not been characterized for some common skin surface areas at risk for development of actinic keratosis (e.g., ears, scalp (other than anterior), and other sun-exposed areas), an appropriate study to address these informational needs should be conducted.
2. The study should include no less than one year safety and efficacy post-treatment and follow-up for incidence of recurrence,
3. The study should include an assessment of the safety and efficacy of re-treatment of actinic keratoses with TRADENAME cream
4. Particular attention should be paid to an assessment of the potential for eye irritation and the actions patients can take to minimize this potential.

If you have any questions or wish to schedule a teleconference to discuss these conditions, please call Victoria Lutwak, Project Manager, at 301-827-2073.

cc:
Archival NDA 20-985
HFD-540 Division Files
HFD-540/ Vaughan/Okun
HFD-540/Lutwak

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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

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

FACSIMILE TRANSMISSION

DATE: July 27, 1999 Number of Pages (including cover sheet) - 10

TO: James P. Thompson, Manager, Worldwide Regulatory Affairs
COMPANY: Dermik Laboratories
FAX #: 610-454-5287

MESSAGE: Please find attached to this facsimile transmission our meeting minutes for our July 26, 1999, pre-NDA Meeting for IND —— , DL-6025, fluorouracil topical cream, 0.5%.

Thank you.

FROM: Frank H. Cross, Jr., M.A., CDR
TITLE: Senior Regulatory Management Officer
PHONE #: 301-827-2063
FAX #: 301-827-2075/2091

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feeting Date: July 26, 1999 Time: 1000 Location: N225
Meeting ID# 4441

IND — DL-6025, fluorouracil topical cream, 0.5%

Indication: Actinic (solar) Keratosis

Sponsor: Dermik Laboratories, Inc.

Pre-NDA Meeting

Meeting Chair: Jonathan K. Wilkin, M.D.

Meeting Recorder (CSO/Project Manager): Frank H. Cross, Jr., M.A., CDR

FDA Attendees, titles and offices:

Jonathan K. Wilkin, M.D., Division Director, DDDDP, HFD-540
Bonnie Dunn, Ph.D., Deputy Division Director, DNDCIII, HFD-830
Jim Vidra, Ph.D., Acting Chemistry Team Leader, DNDCIII, HFD-830
William Timmer, Ph.D., Chemist, DNDCIII, HFD-830
Barbara Hill, Ph.D., Pharmacologist/Toxicologist, DDDDP, HFD-540
Dennis Bashaw, Pharm.D., Biopharmaceutics Team Leader, DPEIII, HFD-880
bi Adebowale, Ph.D., Biopharmaceutist, DPEIII, HFD-880
san Walker, M.D., Dermatology Team Leader, DDDDP, HFD-540
R. Srinivasan, Ph.D., Biostatistics Team Leader, DOBIV, HFD-725
Shahla Farr, M.S., Biostatistician, DOBIV, HFD-725
Frank H. Cross, Jr., M.A., CDR, Senior Regulatory Management Officer, DDDDP, HFD-540
Victoria Lutwak, Project Manager, DDDDP, HFD-540

Sponsor Attendees, titles and offices:

Kim A. Forbes-McKean, Ph.D., Director, Regulatory Affairs and Project Management
Gary L. Feiss, M.S., Senior Manager, Regulatory Affairs
Wendy H. Chem, Ph.D., Department Manager, Dermatological Product Development
Jay E. Dorrell, Associate Research Fellow
Lee Geiger, Ph.D., Director, Toxicology U.S.
Sharon F. Levy, M.D., Director, Clinical Research and Medical Affairs
Katherine W. Furst, Senior Clinical Research Specialist
James P. Thompson, Manager, Regulatory Affairs
Margaret Connolly, Ph.D., Statistician

Meeting Objectives:

Pre-NDA Meeting

"th reference to the Meeting Request submitted June 16, 1999, and to the Meeting Briefing Package submitted June 24, 9, the following discussion took place:

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Agency:

With regard to the 5-fluorouracil Microsponge® formulation, the Agency asked if the Sponsor will be making any labeling or marketing claims.

Sponsor:

The Sponsor said no.

Chemistry, Manufacturing and Controls:

The primary CMC issue is the ——————————. The Sponsor has 18 months of stability data with — and 6 months without —

1. Question 1a of the June 24, 1999, Meeting Briefing Package - Chemistry, Manufacturing and Controls (CMC), Are the data requirements at the time of NDA filing satisfied by:

   a. Eighteen months of stability data from 3 batches manufactured with —

   b. Six months of stability data from 3 batches manufactured without —

   c. Executed batch records for all stability batches,

   d. The degradation pathway of fluorouracil.

Agency:

The information is sufficient for filing a NDA. The Agency could accept the amount of stability data as proposed for filing; but the Sponsor should not expect an —— month shelf life even after it provides updated 9 and 12 months stability data with satisfactory statistical analysis. The Agency would prefer to receive at least 9 months of data at the time of NDA submission with the expectation of receiving 18 months data during the first 9 months of the review clock.

2. Question 1b of the June 24, 1999, Meeting Briefing Package - Chemistry, Manufacturing and Controls (CMC), The Sponsor is seeking input that...expiration dating will be established from real time stability data...which will be provided in updates during the review cycle.

Agency:

This is acceptable. We further suggest that the Sponsor perform a pooling test of the stability data from batches manufactured without — as part of the statistical analysis. This statistical analysis should be provided both in the original NDA and in the amendment when the last updated stability data are submitted.

3. Other comments:

   a. The Agency would like to make sure that the pivotal clinical trials were performed with DP that was within specification for 5-FU.

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b. All facilities must be ready for inspection at the time of the NDA submission. The last GMP inspection for ——— was in January 1997; a new inspection will be required. ——— should also ascertain that the DMF is current.

c. The Agency want to reiterate from the End of Phase 2 Meeting Minutes of January 29, 1997. The Agency is requesting the ——— from ——— of both the drug substance and the drug product. From an analytical perspective, the CMC reviewer is interested in the ——— from ——— From a photobiology perspective, the Clinical reviewer is interested in the ——— from ———

d. On pg. 9 of the June 24, 1999, Meeting Briefing Package, the %w/w of the formulation is presented. The ——— and dimethicone concentration must be ——— This is a fairly precise formula.

The Agency would like to know how these numbers were derived. Please provide the batch formula in units of weight.

e. The Agency would also like to know under what conditions ——— of the DP is performed.

Pharmacology/Toxicology:

Question 2a of the June 24, 1999, Meeting Briefing Package:

The Sponsor's proposal for submission of nonclinical toxicity studies to the NDA is acceptable. It is requested that the full study reports for all nonclincal studies conducted with the 5-fluorouracil Microsponge® formulation and the Microsponge® formulation alone be submitted with the NDA. The Agency is particularly interested in seeing any full study reports that are available concerning the mutagenicity of the Microsponge® formulation alone.

2. Question 2b of the June 24, 1999, Meeting Briefing Package:

As stated in the previous discussion point, it is requested that the full study reports for all nonclinical studies with the Microsponge® formulation alone be submitted with the NDA. If no mutagenicity studies have been conducted with the Microsponge® formulation used for the 5-fluorouracil cream product, then it is requested that full mutagenicity study reports for any Microsponge® formulation be submitted with the NDA. This would be more useful to the Pharmacology/Toxicology reviewer than a "Letter of Authorization" to allow reference to specific studies in other NDAs that may have used these Microsponge® formulations.

3. Question 2c of the June 24, 1999, Meeting Briefing Package:

It is requested that the Sponsor submit the full referenced article for any labeling statements that the Sponsor may make concerning general toxicity, genotoxicity, carcinogenicity and reproductive toxicity associated with 5-Fluorouracil. The full referenced article will be important to support information included in the label under these sections. The summary proposed by the Sponsor would be helpful in the review of nonclinical literature studies. In addition, it would be helpful to the Pharmacology/Toxicology reviewer if full referenced articles would be included in the NDA for information that the Sponsor feels is important to support the safety of the 5-fluorouracil Microsponge® formulation. It is requested that the Sponsor provide the rationale used to select key articles from the literature that will be summarized and provided in the NDA to support the safety of the 5-

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fluorouracil Microsponge® formulation (There may be an abundance of literature, and we are interested in any potential selection bias).

4. Question 2d of the June 24, 1999, Meeting Briefing Package: "As agreed upon at the End of Phase 2 Meeting with FDA, a [redacted] study is not planned."

The Sponsor's proposal is acceptable based on the previous discussion with the Sponsor concerning anticipated duration of therapy. However, if the Sponsor should plan to [redacted], then this topic will need to re-visited at that time.

Biopharmaceutics:

1. The Sponsor appears to have done the studies requested by the Agency in the January 29, 1997, End of Phase 2 meeting.

2. The Pk studies as designed and performed will not support, nor were they intended to support, a finding of bioequivalency between Dermik's product and Efudex. The results of these studies represent a stand-alone PK package for this product and will not suport a 505(b)(2) application.

Clinical:

esponses to Clinical questions:

1. Based on the material submitted in the briefing package, it appears that the nature and scope of the clinical studies are appropriate to support filing of the NDA for the treatment of actinic keratosis of the face and scalp.

The primary efficacy assessment should only be the proportion of patients with treated lesions totally cured vs. the similar proportion in the placebo group (other efficacy comparisons should be considered secondary endpoints). The Sponsor should consider an adjustment for multiple comparisons when multiple dosing durations are included in a clinical trial (see statistical comments also). The approval of any treatment regimen is data driven and labeling should reflect the clinical trial data. Elements of both safety and efficacy should be considered.

2. Integration of the efficacy data from the two pivotal Phase 3 studies is acceptable in the integrated summary of efficacy (ISE). However, the studies should also be presented separately, with detailed information about the results in each individual study center. The data presented in each study should give enough information to make it possible for the reviewer to trace it back to the study center and the individual patient.

3. The planned presentation of the integrated summary of safety (ISS) is acceptable. It is important to emphasize that all adverse events be listed and counted regardless of causality relationships. The adverse events of the pivotal trials should be analyzed by the individual regimen used, i.e., 1 week vs. 2 weeks vs. 4 weeks in additional to any combined analysis.

The general format, overall scope and extent of data planned for provision in the ISS and ISE appear to be acceptable.

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Additional comment:

To facilitate the review process, it is helpful to submit ISS, ISE, and the pivotal Phase 3 clinical protocols with their full reports (including tables) as electronic files in MS Word format.

Biostatistics:

1. Since the Sponsor desires to demonstrate the superiority of any or all three duration of treatments vs. Vehicle (i.e. 1-Week vs. Vehicle, 2-Week vs. Vehicle, and/or 4-Week vs. Vehicle), these constitute three separate possibilities for a win. Hence, the Sponsor needs to adjust the level using Bonferroni or any other appropriate multiple adjustment procedure.

2. Request for data: please see attachment.

Divisional Comments:

Pediatric Rule:

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

: 21CFR 314.50(d)(7), NDA applications are required to 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 (d)(3) and (d)(5) of this section, and information required to be submitted under Section 314.55."

In addition, per 21CFR 314.55(a), each NDA "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 drug is safe and effective...." Under 21CFR 314.55(d) "this section does not apply to any drug for an indication or indications for which orphan designation has been granted under part 316, subpart C, of this chapter."

A waiver can be requested in accordance with 21CFR 314.55(c).

Financial Disclosure:

For applications submitted after February 2, 1999, per 21CFR 54.3 and 21CFR 54.4, an NDA applicant is required either to certify to the absence of certain financial interests of clinical investigators or disclose those financial interests.

Labeling:

.e Applicant has an Information for Patients leaflet/labeling, please submit it with the NDA.

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Decisions (agreements) reached:

Unresolved issues or issues requiring further discussion:

None.

Signature, minutes preparer: /S/

Concurrence Chair (or designated signatory): /S/ 7/27/99

Handout: Briefing Package, dated June 24, 1999
Attachment: FDA Division of Biometrics Request For Data

cc:

IND —
HFD-540 HFD-540/DIV DIR/Wilkin
HFD-830/DIV DIR/Chen
HFD-830/DEP DIV DIR/Dunn
HFD-540/CHEM TL/DeCamp
HFD-540/ACTING CHEM TL/Vidra
D-540/CHEM/Timmer/7.26.99
HFD-540/PHARM TOX TL/Jacobs
HFD-540/PHARM TOX/Hill/7.26.99
HFD-880/BIOPHARM TL/Bashaw
HFD-880/BIOPHARM/Adebowalea/7.26.99
HFD-540/DERM TL/Walker/7.26.99
HFD-540/MO/Labib
HFD-725/BIOSTAT TL/Srinivasan/7.26.99
HFD-725/BIOSTAT/Farr/7.26.99
HFD-540/PROJ MGR/Cross
Drafted by: fhc/July 26, 1999
c: \word\ind\ind— .min
Initialed by:
final:

MEMORANDUM OF MEETING

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FDA Division of Biometrics

IND# — (Fluorouracil Topical Cream)
REQUEST FOR DATA
DATE: 7/26/1999

The followings are some suggestions and general recommendations to expedite the data evaluation procedure. These are not official policy statements and should not be construed as such. It is to be noted that FDA does not encourage submissions in one statistical package over another, this note is not meant to endorse SAS.

We would like to thank you in advance for cooperating in this matter, also to remind you that adhering to these simple instructions will only accelerate the review process which in turn will benefit you as a sponsor.

REQUEST FOR TRANSFER OF DATA:

Please provide the data for pivotal studies only.

1. Data Submission by Study Number:

   Efficacy and safety data sets should be submitted by study. Study number is to be carried as a common variable to facilitate pooling of the data across studies.

   A listing from PROC CONTENTS from each data library should be provided which lists all the data sets, clearly labeled for each study and variable type. *For each study only two data sets should be provided.*

   For example:
   Study # 1, Demographic Data & Efficacy Data
   Study # 1, Safety Data

   Study # 2, Demographic Data & Efficacy Data
   Study # 2, Safety Data

2. Uniformity of Data and Data Layout:

   All data should be named, coded and described in the same manner for all studies throughout the NDA.

   All files should include patient number, investigator number and treatment group as common variables. **A useful data layout is to have one record per patient, with all visit information available in a single record.**

   The patient numbers in all the data sets should be unique, so it would be possible to merge the data sets if necessary.

3. Description of Data:

   - A data dictionary which lists and describes the key safety and efficacy variables. Example: TRT =treatment, INVID =investigator id#.

   - A description of the values of the variables. Example: TRT (A=Investigational Drug, B=Placebo), SEX (1=male, 2=female).

   Data Formats:

   All format libraries and variable labels should be provided, along with step-by-step outline of attaching the format catalogs to SAS data sets.

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If SAS transport files or compressed files are submitted, a step-by-step instruction set should be attached for conversion to SSD or SD2. As of now, we are using PC-SAS version 6.12 for Windows as our primary platform.

5. SAS Programs:
The programs used to generate the results, and a description of their intended use, for each of the studies separately (no need for programs that create tables or pages.)

For each study please provide:

Demographic Data:

Example:

Patient Id
Investigator Id
Treatment Group
Age
Race
Gender
Baseline Clinical Evaluability
Any Concomitant Drug Use & Drug Type
Past History of Sickness
Smoker
Drinker
Number of Days in Study
Number of Days on Therapy

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(All available related demographic variables)

Efficacy Data:

Example:

Patient Id
Investigator Id
Treatment Group
Visit Number
Days from start of treatment
Losses: (Culture, LTFU, ...)
Signs & Symptoms
Clinical Response at test of cure

(All the variables needed for the efficacy analyses)
Safety Data:

Example:

Patient Id
'nvestigator Id
.reatment Group
Visit Number
Days from Start of Treatment to Adverse Event
Adverse Event

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List of Adverse Events
Death
Date of Death

(All the variables needed for the safety analyses)

Other comments:

Comments and Action Taken are not needed in the data sets. At this time, lab results are not needed.

APPEARS THIS WAY
ON ORIGINAL

MESSAGE: Please find attached to this facsimile transmission our meeting minutes for our July 26, 1999, pre-NDA Meeting for IND — DL-6025, fluorouracil topical cream, 0.5%.

Thank you.

FROM: Frank H. Cross, Jr., M.A., CDR
TITLE: Senior Regulatory Management Officer
PHONE #: 301-827-2063
FAX #: 301-827-2075/2091

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MESSAGE CONFIRMATION

07/27/99 17:19

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Rockville MD 20857

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

FACSIMILE TRANSMISSION

DATE: July 27, 1999 Number of Pages (including cover sheet) - 10

TO: James P. Thompson, Manager, Worldwide Regulatory Affairs
COMPANY: Dermik Laboratories
FAX #: 610-454-5287

MESSAGE: Please find attached to this facsimile transmission our meeting minutes for our July 26, 1999, pre-NDA Meeting for IND — DL-6025, fluorouracil topical cream, 0.5%.

Thank you.

FROM: Frank H. Cross, Jr., M.A., CDR
TITLE: Senior Regulatory Management Officer
PHONE #: 301-827-2063
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MEMORANDUM OF MEETING MINUTES

Date: October 23, 2000
NDA 20-985
Sponsor: Dermik Laboratories, Inc.
Type: teleconference
Purpose: A request for information

FDA Attendees:
Wilson DeCamp, Ph.D, Chemsitry Teamleader
Victoria Lutwak, Project Manager

Dermik Attendees:
Kim Forbes-McKean, M.D., Sr. Director
Alicia Cabrelli, Regulatory Analyst
Jim Thompson, Manager, Regulatory
Wendy Chern, Dept Mgr, Product Development
Ken Balaji, Research Fellow

The t-con was requested by us to ask the sponsor to supply certain information to the NDA.

1. It was noted during the review that there was no provision to limit storage of the bulk product between manufacturing and filling. We requested the sponsor to provide a post-approval commitment to either (1) limit the storage of the bulk product to — or less, or (2) submit stability data to support the storage of the bulk product for a longer period of time.

2. It was noted during the review that there was no statement about ——— product. We requested the sponsor to provide a commitment that ——— product will be done without submission of a prior approval supplement.

The sponsor agreed to the above and would send in their commitment to the NDA today along with a fax copy to the Division.

cc:
NDA 20-985
Div File
HFD-540/DeCamp/S/10/24/00
HFD-540/Lutwak