CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20-400

CHEMISTRY REVIEW(S)

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JAN 2 1998

DIVISION OF DERMATOLOGIC AND DENTAL DRUG PRODUCTS

Review of Chemistry, Manufacturing, and Controls

NDA#: 20-400 **CHEM.REVIEW#**: 5 **REVIEW DATE**: 26-NOV-97

SUBMISSION/TYPE	**DOCUMENT DATE**	**CDER DATE**	**DOCUMENT**
ORIGINAL	24-SEP-93	24-SEP-93	Review #1
RESUBMISSION	28-MAR-94	29-MAR-94	
AMENDMENT/AC	16-DEC-94	16-DEC-94	
AMENDMENT/BC	17-JAN-95	17-JAN-95	
AMENDMENT/BC	24-MAY-96	24-MAY-96	Review #2
AMENDMENT/BC	13-JUN-96	14-JUN-96	Review #3
AMENDMENT/AC	12-JUL-96	15-JUL-96	
AMENDMENT/BC	20-JUN-96	21-JUN-96	
AMENDMENT/NC	13-DEC-96	16-DEC-96	Review #4
AMENDMENT/AM	28-OCT-97	29-OCT-97	
EER SUMMARY	N/A	02-DEC-97	Review #5

NAME & ADDRESS OF APPLICANT: Penderm Incorporated
320 Lakeside Drive
Suite A
Foster City, CA 94404
(415) 378-6479

DRUG PRODUCT NAME

Proprietary: Avita Gel
Nonproprietary/USAN: *trans*-retinoic acid
Code Names/#'s:
Chemical Type/
Therapeutic Class: **5 S**

PHARMACOLOGICAL CATEGORY/INDICATION: Acne vulgaris

DOSAGE FORM: gel
STRENGTHS: 0.025%
ROUTE OF ADMINISTRATION: topical
DISPENSED: _X_ **Rx** ____ **OTC**

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Refer to previous chemistry reviews.

SUPPORTING DOCUMENTS: See previous chemistry reviews.

RELATED DOCUMENTS: None

CONSULTS: None

REMARKS/COMMENTS:

NDA 20-400, Avita (tretinoin) Gel was given a tentative approval on 14-Jan-97 pending expiration of a patent. A full approval is scheduled to be issued on 27-Jan-98.

The GMP inspections were acceptable as of 28-May-96. As this date was greater than one year from the full approval date, the manufacturing facilities were re-submitted for inspection.

As of 17-Nov-97, all manufacturing facilities were within GMP compliance per the attached EER.

CONCLUSIONS & RECOMMENDATIONS:

The NDA is approvable for manufacturing and controls under section 505 of the Act. All manufacturing facilities are currently in acceptable GMP compliance as of 11/17/97.

/S/

William C. Timmer, Ph.D.
Review Chemist

cc: Orig. NDA 20-400
HFD-540/Division File
HFD-540/Chem/WTimmer
HFD-540/TmLdr/WHDeCamp WD 1/2/98
HFD-540/CSO/OCintron

filename: c:\wpwin61\wpdocs\cder\nda\nda20400.doc

DIVISION OF DERMATOLOGIC AND DENTAL DRUG PRODUCTS
Review of Chemistry, Manufacturing, and Controls

NDA #: 20-400 **CHEM.REVIEW #:** 4 **REVIEW DATE:** 12-19-96

SUBMISSION/TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
ORIGINAL	9-24-93	9-24-93	
RESUBMISSION	3-28-94	3-29-94	
AMENDMENT/NC	12-13-96	12-16-96	

DEC 20 1996

NAME & ADDRESS OF APPLICANT: Penederm Incorporated
320 Lakeside Drive, Suite A
Foster City, CA 94404
Tel: (415)-378-6479

DRUG PRODUCT NAME

Proprietary: Avita Gel
Nonproprietary/USAN: Retinoic acid/all-trans
Retinoid acid/Vitamin A

Code Names/#'s:
Chemical Type/
Therapeutic Class: 5 S

ANDA Suitability Petition/DESI/Patent Status: N/A

PHARMACOLOGICAL CATEGORY/INDICATION:
Retinoid/Topical treatment of acne vulgaris

DOSAGE FORM: Gel
STRENGTHS: 0.025%,
ROUTE OF ADMINISTRATION: Topical application
DISPENSED: X **Rx** _____ **OTC**

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOL.WT:
USP
(all-E)-3,7-dimethyl-9-(2,6,6-trimethyl-1-cyclohexen-1-yl)-2,4,6,8-nonatetraenoic acid

$C_{20}H_{28}O_2$ Mol.weight:344.44
CAS# [302-79-4]

PATENT STATUS:

3,729,568; expired April 24, 1990

4,247,547; expired January 27, 1998; no exclusivity exists.

SUPPORTING DOCUMENTS:

IND
DMF

DMF

DMF

DMF

DMF

NDA 17-340 Retin A Cream, 0.1%
NDA 17-522 Retin A Cream, 0.05%
NDA 19-049 Retin A Cream, 0.025%
NDA 20-404 Avita (tretinoin) Cream 0.025%.

AMENDMENTS:

Dated: December 13, 1996, commitment to add "avoid freezing" to storage condition.
Received: December 16, 1996.

Dated: December 10, 1996, signed Fonsi by Nancy Sager
Received: December 13, 1996.

CONSULTS:

The updated environmental assessment package suitable for release under FOI found to be acceptable. The prepared FONSI was sent to Nancy Sager (HFD-357) on November 25, 1996. The Fonsi was issued on December 10, 1996 by Nancy Sager. The trade

name "Avita" was found acceptable by the Labeling and Nomenclature Committee on May 28, 1996.

REMARKS/COMMENTS:

This is the final chemistry review for Avita 0.025% Gel. The only pending issues on this application were EA and final labeling information. The information regarding signed Fonsi by Nancy Sager dated December 10, 1996 is included (Attachment 1). The following comments address our concerns regarding labeling issues:

1. The applicant's commitment to modify the storage condition by including the statement on the labeling. For more information, please see Attachment I, the MEMO TELECONFERENCE between the Review Chemist, Nahid Mokhtari-Rejali, Ph.D., Robin Anderson, Project Manager and Bhaskar Chaudhuri, Ph.D., of Penederm dated December 12, 1996. This information was requested based on chemistry review #2. The applicant had indicated in this review that they have no plan to freeze the product for storage; therefore, no data was submitted for storage under temperature. See commitment of December 13, 1996.

2. A draft copy of the container label and the box for shelf use is provided.

3. In the package insert all the requirement for DESCRIPTION Section and HOW SUPPLIED Section are satisfactory. The applicant has adequately responded to our labeling concerns.

Satisfactory EER (#9999) has been received from the Office of Compliance on 5/20/96.

Method validation remains pending, see Chem. Review #3.

CONCLUSIONS:

This application is APPROVABLE from a manufacturing and control standpoint.

/S/

Nahid Mokhtari-Rejali, Ph.D.,
Review Chemist, HFD-540

cc: Orig. NDA 20-400
HFD-540/Division File
HFD-540/Rejali/12/19/96
HFD-540/Labib
HFD-540/Jacobs
HFD-540/Blay
HFD-540/WHDeCamp
HFD-830/Eric Sheinin
HFD-354/Yana Mille
R/D Init by: SUPERVISOR WD 12/20/96

filename: **NDA20400.rv4**

12/31/96

DIVISION OF DERMATOLOGIC AND DENTAL DRUG PRODUCTS
Review of Chemistry, Manufacturing, and Controls

NDA #: 20-400 CHEM.REVIEW #: 3 REVIEW DATE: 11-29-96

SUBMISSION/TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
ORIGINAL	9-24-93	9-24-93	
RESUBMISSION	3-28-94	3-29-94	
AMENDMENT/AC	7-12-96	7-15-96	
AMENDMENT/BC	6-13-96	6-14-96	
AMENDMENT/BC	11-20-96	11-21-96	

DEC 3 1996

NAME & ADDRESS OF APPLICANT: Penederm Incorporated
320 Lakeside Drive, Suite A
Foster City, CA 94404
Tel: (415)-378-6479

DRUG PRODUCT NAME

Proprietary: Avita Gel
Nonproprietary/USAN: Retinoic acid/all-trans
Retinoid acid/Vitamin A

Code Names/#'s:
Chemical Type/
Therapeutic Class: 5 S

ANDA Suitability Petition/DESI/Patent Status: N/A

PHARMACOLOGICAL CATEGORY/INDICATION:
Retinoid/Topical treatment of acne vulgaris

DOSAGE FORM: Gel
STRENGTHS: 0.025%,
ROUTE OF ADMINISTRATION: Topical application
DISPENSED: __X__ Rx _____ OTC

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOL.WT:
USP
(all-E)-3,7-dimethyl-9-(2,6,6-trimethyl-1-cyclohexen-1-yl)-2,4,6,8-nonatetraenoic acid

$C_{20}H_{28}O_2$ Mol.weight:344.44
CAS# [302-79-4]

PATENT STATUS:

3,729,568; expired April 24, 1990
4,247,547; expired January 27, 1998; no exclusivity exists.

SUPPORTING DOCUMENTS:

IND
DMF

DMF

DMF

DMF

DMF

NDA 17-340 Retin A Cream, 0.1%
NDA 17-522 Retin A Cream, 0.05%
NDA 19-049 Retin A Cream, 0.025%
NDA 20-404 Avita (tretinoin) Cream 0.025%, 0.05% & 0.1%.

AMENDMENTS:

Dated: June 3, 1996, the official copy of information faxed on May 31, 1996, regarding specifications for degradants.
Received: June 4, 1996, this information was reviewed in chemistry review #2.

Dated: June 13, 1996, upon my request, three copies of updated method validation including method with revised specifications to be forwarded to LA District.
Received: June 14, 1996, this information was reviewed in chemistry review #2.

Dated: November 20, 1996, Updated EA was submitted upon my request.
Received: November 21, 1996.

CONSULTS:

The updated environmental assessment package suitable for release under FOI found to be acceptable. The prepared FONSI was sent to Nancy Sager (HFD-357) on November 25, 1996. The trade name "Avita" was found acceptable by the Labeling and

Nomenclature Committee on May 28, 1996.

REMARKS/COMMENTS:

The applicant has responded to our nonapprovable letter of June 26, 1996 regarding the deficiencies found in chemistry review #2.

From a manufacturing and control standpoint, the data and information submitted to this application are currently adequate to recommend that this application is approvable. The major concern was the impurity profile for the degradants. There is no new information regarding the degradation products since previous review. However, as we suggested, Penederm has committed to further develop the analytical method to cover all the tretinoin degradation products in the finished drug products and aged products. This should include specifications for all the products in tretinoin gel.

It should also be noted that the current in-process Revision in the First Supplement, USP 23, NF 18, July-August 1995, page 2511 proposes limit of 90-120% label claim for tretinoin gel. The proposal method and assay limit for tretinoin in official monograph, USP 23 is different from this application. Penederm may choose to request that their own procedure be adopted. The Compendial Operation Branch has been notified of the different specification (%) and procedure for tretinoin assay and method than USP. When the method is found acceptable by FDA Laboratory, this issue should be pursed.

The 18 months stability data support the two-year expiry date for tretinoin gel 0.025%.

Method validation remains pending. Updated method validation package including method (variable wavelength) and revised specifications for and other degradants was sent to the LA District on November 29, 1996.

An FUR was sent to the office of compliance on April 17, 1996 (Cirts, EER #9999). The satisfactory response was received from the Office of Compliance on May 20, 1996. Another FUR will be requested in future if is appropriate.

The updated environmental assessment package was amended on November 20, 1996. The EA is acceptable. The prepared FONSI was

sent to Nancy Sager (HFD-357) on November 29, 1996. No response has been received as of today.

CONCLUSIONS:

This application is APPROVABLE from a manufacturing and control standpoint pending acceptable EA .

/S/

Nahid Mokhtari-Rejali, Ph.D.,
Review Chemist, HFD-540

cc: Orig. NDA 20-400
HFD-540/Division File
HFD-540/Mokhtari-Rejali/11/29/96
HFD-540/MO
HFD-540/Jacobs
HFD-520/Utrup
HFD-540/Blay
HFD-540/WHDeCamp
HFD-830/Eric Sheinin
HFD-354/Yana Mille
R/D Init by: SUPERVISOR 12/3/96

filename: **NDA20400.rv3**

12/30/96

JUN 1 1 [illegible]

DIVISION OF TOPICAL DRUG PRODUCTS
Review of Chemistry, Manufacturing, and Controls

NDA #: 20-400 **CHEM.REVIEW #:** 2 **REVIEW DATE:** 6-2-96

SUBMISSION/TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
ORIGINAL	9-24-93	09-24-93	
RESUBMISSION	3-28-94	03-29-94	
AMENDMENT/AC	12-22-95	12-26-96	
AMENDMENT/BC	5-24-96	05-24-96	

NAME & ADDRESS OF APPLICANT: Penederm Incorporated
320 Lakeside Drive, Suite A
Foster City, CA 94404
Tel: (415)-378-6479

DRUG PRODUCT NAME

Proprietary: Acticin Gel

Nonproprietary/USAN: Retinoic acid/all-trans
Retinoic acid/Vitamin A

Code Names/#'s:

Chemical Type/
Therapeutic Class: 5 S

ANDA Suitability Petition/DESI/Patent Status: N/A

PHARMACOLOGICAL CATEGORY/INDICATION:
Retinoid/Topical treatment of acne vulgaris

DOSAGE FORM: Gel
STRENGTHS: 0.025%,
ROUTE OF ADMINISTRATION: Topical application
DISPENSED: __X__ Rx _____ OTC

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOL.WT:
USP
(all-E)-3,7-dimethyl-9-(2,6,6-trimethyl-1-cyclohexen-1-yl)-2,4,6,8-nonatetraenoic acid

$C_{20}H_{28}O_2$ Mol.weight:344.44
CAS# [302-79-4]

PATENT STATUS:

3,729,568; expired April 24, 1990
4,247,547; expired January 27, 1998; no exclusivity exists.

SUPPORTING DOCUMENTS:

IND
DMF

DMF

DMF

DMF

DMF

NDA 17-340 Retin A Cream, 0.1%
NDA 17-522 Retin A Cream, 0.05%
NDA 19-049 Retin A Cream, 0.025%
NDA 20-404 Acticin (tretinoin) Cream 0.025%, 0.05% & 0.1%.

AMENDMENTS:

Dated: May 24, 1996, response to my request, see MEMORANDUM of TELEPHONE CONVERSATION on May 23, 1996, regarding the EA, (Appendix D).
Received: May 24, 1996, received By fax.

Dated: May 31, 1996, response to telephone conversation, see MEMORANDUM of TELEPHONE CONVERSATION on May 31, 1996, regarding specifications for degradants, (Appendix E).
Received: May 31, 1996, received By fax.

CONSULTS:

The environmental assessment package suitable for release under FOI found to be acceptable (NDA 20-404, Appendix A). The prepared FONSI was sent to Nancy Sager (HFD-357) on May 24, 1996. The consult on the drug product was sent to Rita Hassal (HFD-350) on 5/27/96. A Request for Trademark Review of "Avita" was sent to the Labeling and Nomenclature Committee on April 16, 1996, (NDA 20-404, Appendix B).

REMARKS/COMMENTS:

The applicant has responded to the not approvable letter of March 29, 1995 regarding the deficiencies found in chemistry review #1. This amendment contains the new information: The impurity profile for the drug substance and the drug product, report of degradation pathways for the tretinoin, six months stability at 40°C and 12 months stability at 27°C for batches made at . Additional six months stability data at 27°C was received by fax on May 31, 1996.

as the original contract facility for the manufacture and testing of Tretinoin gel 0.025%, has been withdrawn from the application. is the only manufacturing site for this product. It should be noted that the current procedure at is to collect the representative samples of the product for in process, release and stability testing. The representative samples then will be shipped overnight to Penederm (California), where they are analyzed and the results returned to Due to the instability of tretinoin considerable attention should be given to the handling and storage during the manufacturing process. It is advisable to perform the assay as soon as possible and samples should not stand longer than overnight. The in-process and release testing should be performed by

From a manufacturing and control standpoint, the data and information submitted to this application are currently adequate to recommend that this application is approvable pending resolving additional concerns. The major manufacturing and control concerns were the inadequacy of stability data from the new manufacturing site and impurity profile for the

tretinoin gel.

The overage of *trans* retinoic acid had been lowered to % (from % in Retin-A). The proposed assay for tretinoin (90-120%) is according to the monograph, first Supplement, USP 23/NF 18, July-august 1195, page 2511. The assay specification is acceptable. However, it is recommended that both finished release and finished stability be revised to % of label amount of tretinoin. The stability data support the proposed specifications.

Penederm has done an extensive literature research on tretinoin. The revised method, with photodiode array UV detection at multiple wavelengths, ranging from nm and was capable of detecting other impurities besides . These studies confirm that not all degradants of tretinoin (and isotretinoin) will be detected at a single wavelength during analysis, whether the Penederm or USP methods are used. The proposal method in official monograph, USP 23 is different from this application. Penederm may choose to request that their own procedure be adopted.When specifications for all the impurities are estabilshed and the method is found acceptable by our laboratory, this issue will be perused. The compendial Operation Branch, has been notified of these differences.

Based on degradation study of tretinoin raw material by and tretinoin gel products by applicant, three key degradation products, in addition to have been identified as occurring at low levels on stability storage. These are:

The proposed tretinoin degradation pathways are also provided.

The stability data for the lots manufactured at are provided. These data include six months stability data at 40°C and 12 months stability data at room temperature, 27°C. Limits for and total degradation are not according to values obtained in the stability studies. These limits do not comply with the USP 23/NF 18 monograph.

According to USP monograph, the isotretinoin specifications for finished drug product and stability specification cannot exceed % of the tretinoin. The total degradation product cannot exceed % of the amount of tretinoin based on % overage in the formulation.

On May 31, 1996, the applicant has submitted [received by fax on May 31, 1996 (Appendix E)] a new limit for degradation products including 18 months supporting stability data for tretinoin gel (Appendix E)]. The new limits have been established based on the modification of the method, . The of isotretinoin was originally found to be %wt, and has now been revised to %wt, page 124. The new specifications are in accordance with USP monograph. The 18 months stability data at 27°C for lots SP-94-29, SP-94-30 & SP-94-31 support the new specifications for Tretinoin gel 0.025%. The new specifications for isotretinoin and other degradants are acceptable. However, the individual specification for other degradants should be provided. Identical specifications for finished product stability and finished product release should be submitted.

The 18 months stability data support the two-year expiry date for tretinoin gel 0.025%. It is recommended that as a post-approval commitment the applicant attempt to develop a new analytical methodology to identify all the impurities. This should include specifications for all the photo-isomerization, autoxidation, and photo-oxidation product in tretinoin gel.

Method validation remains pending. The method validation package for revised method has been requested. Upon the recipt of this package, the method will be forwarded to the LA District for evaluation.

A Request for Trademark Review of "Avita" was sent to the Labeling and Nomenclature Committee (LNC) April 16, 1996. An acceptable response was received on May 28, 1996. Therefore, the tradename "Avita" is acceptable. However, the statement should be added to the Section of the labeling.

A joint pre-approval inspection was conducted by Review

Chemist (myself) and Wilson DeCamp, Ph.D., Supervisory Chemist with participation of Jim Robinson (San Antonio Residents Post CSO) and Jerome Elkins (Dal-Do Chemist) at on April 10-11, 1995 (NDA 20-404, Appendix C). During this inspection, we found that Penederm is currently engaged in the process of qualifying for QC testing. It was found that the facilities were not currently performing all operations identified in the NDA, and initial QC testing and stability tests were being performed only at Penederm facility. A limited GMP inspection of the manufacturing, packaging and analytical laboratory at did not reveal any GMP deficiencies and no 483 was issued. An FUR was sent to the office of compliance on April 17, 1996 (Cirts, EER #9999). The satisfactory response was received from the Office of Compliance on May 20, 1996.

The environmental assessment package suitable for release under FOI found to be acceptable. The prepared FONSI was sent to Nancy Sager (HFD-357) on May 29, 1996. The response was reviewed and received with comments on June 10, 1996.

CONCLUSIONS:

This application is APPROVABLE from a manufacturing and control standpoint pending acceptable EA report. However, before final approval the applicant is to provide the following information:

1. Revise the assay limit to not less than percent and not more than percent of the labeled amount of tretinoin.

2. Modify all the specification of degradants to the percent of labeled amount of tretinoin.

3. Provide identical specifications for finished product stability and finished product release.

4. Provide individual specification for

5. States which tests (in-process and/or regulatory) are performed by as compare to Penederm. Please include time frames for testing and release.

6. It is recommended that the future stability studies be performed at either C/ambient humidity or C/ %RH.

7. In addition, it is recommended that as a post-approval commitment, the applicant attempt to develop a new analytical methodology to identify all the impurities. This should include specifications for all the photo-isomerization, autoxidation, and photo-oxidation product in tretinoin gel.

8. Regarding the environmental assessment: (a) information has to be provided for the drug substance site (format item 6), since it is a foreign manufacturer, a certification of compliance is sufficient (see Industry Guidance for appropriate certification language); (b) on page 8 of the EA (last sentence) a compliance statement for is referenced but the compliance statement is not included; (c) there are no format items 12, 13 or 14 which are required for the abbreviated EA format for topical drugs [25.31a(b)(3)].

/S/

Nahid Mokhtari-Rejali,
Ph.D., Review Chemist

c: Orig. NDA 20-400
HFD-540/Division File
HFD-540/Mokhtari-Rejali/6/10/96
HFD-540/Slifman
HFD-540/Jacobs
HFD-520/Utrup
HFD-540/Blay
HFD-540/WHDeCamp
HFD-830/Eric Sheinin
R/D Init by: SUPERVISOR

filename: NDA20400.rv2

MAR 3 1995

DIVISION OF TOPICAL DRUG PRODUCTS
Review of Chemistry, Manufacturing, and Controls

NDA #: 20-400 **CHEM.REVIEW #:** 1 **REVIEW DATE:** 10-25-94

SUBMISSION/TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
ORIGINAL	9-24-93	9-24-93	
RESUBMISSION	3-28-94	3-29-94	
AMENDMENT/AC	12-16-94	12-16-94	
AMENDMENT/BC	1-17-95	1-19-95	

NAME & ADDRESS OF APPLICANT: Penederm Incorporated
320 Lakeside Drive, Suite A
Foster City, CA 94404
Tel: (415)-378-6479

DRUG PRODUCT NAME
Proprietary: Acticin Gel

Nonproprietary/USAN: Retinoic acid/all-trans
Retinoic acid/Vitamin A

Code Names/#'s:
Chemical Type/
Therapeutic Class: 5 S

ANDA Suitability Petition/DESI/Patent Status: N/A

PHARMACOLOGICAL CATEGORY/INDICATION:
Retinoid/Topical treatment of acne vulgaris

DOSAGE FORM: Gel
STRENGTHS: 0.025%,
ROUTE OF ADMINISTRATION: Topical application
DISPENSED: __X__ Rx _____ OTC

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOL.WT:
USP
(all-E)-3,7-dimethyl-9-(2,6,6-trimethyl-1-cyclohexen-1-yl)-2,4,6,8-nonatetraenoic acid

$C_{20}H_{28}O_2$ Mol.weight:344.44
CAS# [302-79-4]

PATENT STATUS:

3,729,568; expired April 24, 1990
4,247,547; expired January 27, 1998; no exclusivity exists.

SUPPORTING DOCUMENTS:

IND
DMF

DMF

DMF

DMF

DMF

NDA 17-340 Retin A Cream, 0.1%
NDA 17-522 Retin A Cream, 0.05%
NDA 19-049 Retin A Cream, 0.025%
NDA 20-404 Acticin (tretinoin) Cream 0.025%, 0.05% & 0.1%.

AMENDMENTS:

Dated: March 28, 1994, response to our deficiencies found at the time of fileability of the application.

Dated: December 16, 1994, CMC information on new manufacturing site, including one month accelerated stability data.

Dated: January 17, 1995, addresses the information on the changes in amendment of December 16 from the original application.

CONSULTS:

Environmental Impact Assessment consult for tretinoin, drug substance, was requested from HFD-102 on 1/27/95. The consult has not been received as of today. Trade name consult is deferred; the applicant intends to propose a new trade name.

REMARKS/COMMENTS:

This application was first submitted as ANDA (generic equivalence of Retin-A) in May 1991.

The entire application was submitted as Acticin gel NDA on September 24, 1994. The deficiencies found at the time of fileability of the NDA was responded on March 28, 1994.

The synthesis of tretinoin is not a concern because tretinoin is a compendial item, and the source of new drug substance (NDS) are being used for the Retin-A and Renova products and the synthesis has been reviewed.

All manufacturing operations for this product are at Penederm conducts confirmatory QC lot release testing and stability program. However, the current contract manufacturer for both NDAs, gel and cream was found not to be in GMP compliance as stated below, Thus, Penederm has selected a new manufacturing site, and amended their application on December 16, 1994. This amendment includes the similar CMC information on new manufacturing site with % overage of tretinoin and one months accelerated stability data.

The EER was requested from the Office of Compliance on May 17, 1994 (CIRTS, EER #6383). A product specific pre-approval inspection was conducted by Gregory Bobrowicz, SAN-DO Inspector, with participation of Ruth Johnson, the analyst Chemist from Seattle DO, on July 11-15, 1994 (Appendix B). A 483 was issued by SAN-DO for contract manufacturer of Acticin gel on July 15, 1994. A copy of recommendation from SAN-DO to withhold approval of this NDA was issued on July 21, 1994. Several deficiencies and inconsistency have been observed by the inspector and participant chemist. According to the inspectors,

The applicant has responded to the 483 items on August 22, 1994. The firm's response was reviewed by the inspector, and found to be inadequate on August 24, 1994. A copy of recommendation to withhold approval from Office of Compliance, PCA EIR FD-483, Penederm's response to the FD 483, and inspector's evaluation are attached (Appendix B).

The applicant has request a pre-approval inspection for the

new manufacturing site, in amendment of December 16, 1994. A Final Update Request was sent to the Office of Compliance for Penederm on January 18, 1995 (CIRTS, EER #7510).

Method validation packages were sent to LA District Laboratories on February 23, 1995 (Appendix C). The report will be reviewed when is found acceptable by our laboratory.

CONCLUSIONS:

This application is NOT APPROVABLE from a manufacturing and control standpoint and GMP compliance. The major manufacturing and control concerns are the inadequacy of stability data from the new manufacturing site and impurity profile for the tretinoin gel.

The one months accelerated stability data at cannot justify the proposed two years expiry date. Therefore, the evaluation of the stability data will be deferred until the receipt of three months accelerated stability data at and satisfactory GMP inspection.

In addition, a chromatographic impurity specification should be added to the finished drug products and stability specifications. The new regulatory specification for the total degradants is not adequate. The applicant should attempt to develop an impurity profile for the drug substance and drug product. This should include specifications for all the photo-isomerization, autoxidation, and photo-oxidation products in tretinoin gel.

Deficiencies are outlined in the Draft Letter to the applicant. The CSO is to convey these deficiencies to the Applicant.

/S/

Nahid Mokhtari-Rejali,
Ph.D., Review Chemist

cc: Orig. NDA 20-400
HFD-540/Division File
HFD-540/Mokhtari-Rejali/2/4/95
HFD-540/Slifman
HFD-540/Sheevers
HFD-520/King
HFD-540/Chapman
HFD-540/WHDeCamp WD 2/23/95
R/D Init by: SUPERVISOR
filename:NDA20400.rv1 gw 3/3/95