

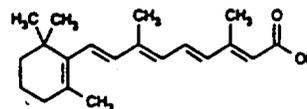
CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 21-112

CHEMISTRY REVIEW(S)

(all-E)-3, 7-Dimethyl-9-(2,6,6-trimethyl-1-yl)-2,4,6,8
nonatetraenoic acid

Molecular Weight: 300.14
Structural Formula:

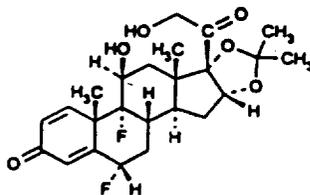


(2) Fluocinolone Acetonide Anhydrous USP

Chemical Name: 6a,9-Difluoro-11b, 16a,17,21-
tetrahydroypregna-1,4-diene-3,20-dione cycle
16,17-acetal with acetone

Molecular Weight: 452.50

Structural Formula:

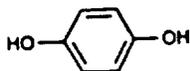


(3) Hydroquinone USP

Chemical Name: 1,4-Benzenediol
Hydroquinone
p-dihydroxybenzene

Molecular Weight: 110.11

Structural Formula:



SUPPORTING DOCUMENTS:

Document Type & Number	Subject	Holder	Status	Review Date	Letter Date
			Review found acceptable	Aug. 1993	
			Amend. under review		
			Amend. Acceptable	2/2/93	

Letters of authorization were given to the following drug product components:

LOA dated 1/13/99 for _____
LOA dated 12/22/98 for _____

Note: There is no DMF number for Hydroquinone. _____ has provided Hill with a reference letter for compliance with cGMPS. :

RELATED DOCUMENTS (if applicable):

CONSULTS:

Microbiology consult was requested 8/27/99. See Micro Review dated 9/24/99.

Labeling consult was requested from the Labeling and Nomenclature Committee on 8/16/99. See L&NC reviews dated

9/24/99 and 11/10/99.

REMARKS/COMMENTS:

The applicant has provided a New Drug Application for a combination drug product, _____. This combination drug product contains three active ingredients in the formulation, Tretinoin USP, Fluocinolone acetonide USP and Hydroquinone USP. Two of these drug substances are subjects of approved NDAs for topical products and are used in the manufacture of Renova (tretinoin) Cream, 0.05% (NDA 19-963) by Johnson and Johnson and by Syntex for Synalar (fluocinolone acetonide) Cream, 0.025%, & 0.1% (NDA 12-787). Fluocinolone acetonide USP is also used in the manufacture of other marketed NDAs and many generic equivalents.

Basically, this NDA was found unacceptable from a CMC standpoint because the applicant has not demonstrated the chemical compatibility of the triple combination drug product. In this regard, the applicant is using the individual USP monograph methods for testing tretinoin, fluocinolone acetonide and hydroquinone and their degradation products. Until validation data have been submitted to show that fluocinolone acetonide, hydroquinone and tretinoin and their degradation products do not interfere in any of the assay methods, the stability of _____ Cream is of question.

The NDA was also found unacceptable because it failed to provide adequate information for the drug substance, finished product specifications, container/closure, and stability studies. Refer to chemist review notes for details regarding these CMC deficiencies.

The establishment inspection of the manufacturing facilities is presently under review by the Office of Compliance for Hill Dermaceuticals Inc., _____. Acceptable EERs were received for _____ (see Chemist's Review Notes; Item G, pg. 39 for details).

Draft labeling was submitted and found acceptable from a technical standpoint with one exception (see Chemist's Review Notes; Item F, pg. 38 for details). Microbiology Review dated 9/24/99 found the NDA in an approvable state.

CONCLUSIONS & RECOMMENDATIONS:

The application is not approvable for manufacturing and controls under section 505 of the Act. See " DRAFT OF CHEMIST'S PORTION OF LETTER TO APPLICANT" attached to Chemist's Review.

ISI 12/16/99

Review Chemist

cc: Orig. NDA 21-112
HFD-540/Division File
HFD-540/Pappas
HFD-540/Ko
HFD-540/Nostrandt
HFD-850/Riley
HFD-540/Lutwak
R/D Init by: Team Leader

ISI

As above. Distinction between MA issues and deficiencies will need further discussion. ISI 12/20/00

**APPEARS THIS WAY
ON ORIGINAL**

**THIS SECTION
WAS
DETERMINED
NOT
TO BE
RELEASABLE**

36 pages

CHEMISTRY REVIEW

NDA 21-112

TRI-LUMA Cream

Hill Dermaceuticals, Inc.

Ernest G. Pappas
Division of Dermatological and Dental Drug Products

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APPEARS THIS WAY
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CHEMISTRY REVIEW

Chemistry Review Data Sheet

Chemistry Review Data Sheet

1. NDA 21-112
2. REVIEW #: 2
3. REVIEW DATE: 10-Dec-01
4. REVIEWER: Ernest G. Pappas
5. PREVIOUS DOCUMENTS:

Previous Documents

Original
Amendment (BC)
Amendment (NC)
Amendment (NC)
Amendment (NC)
Amendment (BC)
Amendment (NC)
Amendment (NC)
Amendment (NC)

Document Date

19-Mar-1999
29-Apr-1999
29-Apr-1999
07-May-1999
04-Jun-1999
23-Jun-1999
19-Aug-1999
24-Sept-1999
08-Nov-1999

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed

Amendment (BC)
Amendment (BC)
Amendment (NC)
Amendment (AZ)
Amendment (BL)
Amendment (BC)
Amendment (BZ)
Amendment (BC)
Amendment (IN)
Amendment (BC)

Document Date

25-Oct-1999
16-Dec-1999
21-Feb-2000
20-Jul-2001
16-Aug-2001
26-Sept-2001
22-Nov-2001
18-Dec-2001
28-Dec-2001
8-Jan-2002

CHEMISTRY REVIEW

Chemistry Review Data Sheet

7. NAME & ADDRESS OF APPLICANT:

Name: Hill Dermaceuticals, Inc.
Address: 2650 South Mellonville Avenue
Sanford, Florida 32773
Representative: Rosario G. Ramirez, MD
Telephone: (407)323-1887

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: Tri-Luma
- b) Non-Proprietary Name (USAN): fluocinolone acetonide; hydroquinone; tretinoin
- c) Code Name/# (ONDC only): None
- d) Chem. Type/Submission Priority (ONDC only):
 - Chem. Type: 4
 - Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: 505(b)(1)

10. PHARMACOL. CATEGORY: Cutaneous melanosis

11. DOSAGE FORM: Cream

12. STRENGTH/POTENCY: (0.01%) fluocinolone acetonide; (4.0%) hydroquinone;
(0.05%) tretinoin

13. ROUTE OF ADMINISTRATION: topical

14. Rx/OTC DISPENSED: Rx OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM)[Note27]:

SPOTS product – Form Completed

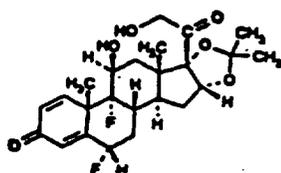
Not a SPOTS product

CHEMISTRY REVIEW

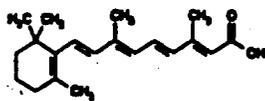
Chemistry Review Data Sheet

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

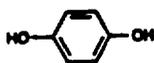
(1) Fluocinolone acetonide



(2) Tretinoin



(3) Hydroquinone



**APPEARS THIS WAY
ON ORIGINAL**

CHEMISTRY REVIEW

Chemistry Review Data Sheet

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS
				3	Adequate	Aug. 1993	
				3	Adequate	2/22/01	
				3	Adequate	2/2/93	
				7	Adequate	12/18/01	
				7	Not reviewed	N/A	Item not used; see II.8

¹ Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 – Type 1 DMF

3 – Reviewed previously and no revision since last review

4 – Sufficient information in application

5 – Authority to reference not granted

6 – DMF not available

7 – Other (explain under "Comments")

² Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION

**APPEARS THIS WAY
ON ORIGINAL**

CHEMISTRY REVIEW

Chemistry Review Data Sheet

18. STATUS:

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
EES	Acceptable	29-Feb-2000	
Methods Validation	To be sent	4-Jan-2002	Pappas
OPDRA	Acceptable	11-Sept-2001	Mahmud
Microbiology	Acceptable	24-Sept-1999	Riley

APPEARS THIS WAY
ON ORIGINAL

CHEMISTRY REVIEW

Executive Summary Section

The Chemistry Review for NDA 21-112

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

This NDA can be **approved** from a Chemistry standpoint.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if approvable

None

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

(1) Drug Product:

The drug product, Tri-Luma Cream, is packaged in _____ with a white, _____ piercing screw cap. This product is a combination drug product, which contains Fluocinolone Acetonide, USP, Hydroquinone, USP, and Tretinoin, USP, as the active components.

A critical manufacturing parameter for Tri-Luma Cream occurs during the _____

_____, fluocinolone acetonide, tretinoin and hydroquinone, is added to _____ (see steps 9 - 13, Review #1, pg. 17). It is at these steps it is critical that fluocinolone acetonide, tretinoin and hydroquinone _____ . This is controlled by microscopic examination. However, particles were observed in the cream resulting from the insolubility of the inactive ingredient, magnesium aluminum silicate. These particles are controlled by a _____

The release specifications have been established following the principles of ICH Q6A, and give adequate assurance of identity, strength, quality and purity of the finished product. The validation of the assay methods adequately demonstrate that the methods are stability indicating. Each of the three active ingredients and their five known major degradation products can be assayed without interference from the other active ingredients and their related degradation products. In order to have this assurance, it was necessary to ask the applicant to carry out more extensive validation studies than are normally required.

CHEMISTRY REVIEW

Executive Summary Section

C. Basis for Approvability or Not-Approval Recommendation

The manufacturing and controls identified above are sufficient to assure the consistent identity, strength, quality and purity of the drug.

III. Administrative

A. Reviewer's Signature

B. Endorsement Block

ChemistName/Date: Same date as draft review
ChemistryTeamLeaderName/Date
ProjectManagerName/Date

C. CC Block

**APPEARS THIS WAY
ON ORIGINAL**

**THIS SECTION
WAS
DETERMINED
NOT
TO BE
RELEASABLE**

12 pages

CHEMISTRY REVIEW

Chemistry Assessment Section

31-DEC-2001

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST

Page 1 of 2

SUMMARY REPORT

Application: **NDA 21112/000** Priority: **4S** Org Code: **540**
Stamp: **22-MAR-1999** Regulatory Due: **25-JAN-2002** Action Goal: District Goal:
23-NOV-1999
Applicant: **HILL DERMAC** Brand Name: **TRI-LUMA CREAM**
2650 MELLONVILLE AVE Established Name:
SANFORD, FL 327739311 Generic Name: **FLUOCINOLONE**
ACETONIDE/HYDROQUINONE/TRET
Dosage Form: **CRM (CREAM)**
Strength: **0.01%, 4.0%, 0.05%** FDA Contacts:

M. KOZMA-FORNARO (HFD-540) 301-827-2020, Project Manager
E. PAPPAS (HFD-540) 301-827-2066, Review Chemist
W. DECAMP II (HFD-540) 301-827-2041, Team Leader

Overall Recommendation:
ACCEPTABLE on 29-FEB-2000 by J. D AMBROGIO (HFD-324) 301-827-0062

Establishment: _____ DMF No:
_____ AADA No:

Profile: **CTL** OAI Status: **NONE**
Tester Last Milestone: **OC RECOMMENDATION**
Milestone Date: **19-OCT-1999**
Decision: **ACCEPTABLE**
Reason: **DISTRICT RECOMMENDATION**

Responsibilities: _____

Establishment: **1036365**
HILL DERMACEUTICALS INC
2650 MELLONVILLE AVE
SANFORD, FL 327739311

DMF No:
AADA No:

Profile: **OIN** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Milestone Date: **29-FEB-2000**
Decision: **ACCEPTABLE**
Reason: **DISTRICT RECOMMENDATION**

Responsibilities: **FINISHED DOSAGE
MANUFACTURER**

Establishment: _____ DMF No: _____
_____ AADA No:

Profile: **CSN** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Milestone Date: **19-MAY-1999**

Responsibilities: _____

CHEMISTRY REVIEW

Chemistry Assessment Section

31-DEC-2001

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST

Page 2 of 2

SUMMARY REPORT

Decision: **ACCEPTABLE** Reason: **BASED ON PROFILE**

Establishment: _____

DMF No:
AADA No:

Profile: **CTL** OAI Status: **NONE**
TESTER Last Milestone: **OC RECOMMENDATION**
Milestone Date: **22-OCT-1999**

Responsibilities: _____

Decision: **ACCEPTABLE** Reason: **BASED ON PROFILE**

Establishment: _____

DMF No:
AADA No:

VIA TERRAZZANO 77 RHO, IT

Profile: **CSN** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Milestone Date: **19-MAY-1999**

Responsibilities: _____

Decision: **ACCEPTABLE** Reason: **BASED ON PROFILE**

Establishment: _____

DMF No:
AADA No:

Profile: **CSN** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Milestone Date: **14-JAN-2000**

Responsibilities: _____

Decision: **ACCEPTABLE**
Reason: **DISTRICT RECOMMENDATION**

**APPEARS THIS WAY
ON ORIGINAL**

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Ernest G. Pappas
1/9/02 01:02:30 PM
CHEMIST
Chemist Reveiw #2 is completed; recommend approval.

Wilson H. DeCamp
1/9/02 01:16:27 PM
CHEMIST
concur with review

**APPEARS THIS WAY
ON ORIGINAL**

CHEMISTRY REVIEW

Chemistry Review Data Sheet

NDA 21-112

TRI-LUMA Cream

Hill Dermaceuticals, Inc.

Ernest G. Pappas
Division of Dermatological and Dental Drug Products

CHEMISTRY REVIEW

Chemistry Review Data Sheet

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V. METHODS VALIDATION	12
VI. LABELING.....	12

CHEMISTRY REVIEW

Chemistry Review Data Sheet

VII. ESTABLISHMENT INSPECTION 13

**APPEARS THIS WAY
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CHEMISTRY REVIEW

Chemistry Review Data Sheet

Chemistry Review Data Sheet

1. NDA 21-112
2. REVIEW #: 2 (Addendum)
3. REVIEW DATE: 10-Dec-01
4. REVIEWER: Ernest G. Pappas
5. PREVIOUS DOCUMENTS:

<u>Previous Documents</u>	<u>Document Date</u>
Original	19-Mar-1999
Amendment (BC)	29-Apr-1999
Amendment (NC)	29-Apr-1999
Amendment (NC)	07-May-1999
Amendment (NC)	04-Jun-1999
Amendment (BC)	23-Jun-1999
Amendment (NC)	19-Aug-1999
Amendment (NC)	24-Sept-1999
Amendment (NC)	08-Nov-1999

6. SUBMISSION(S) BEING REVIEWED:

<u>Submission(s) Reviewed</u>	<u>Document Date</u>
Amendment (BC)	25-Oct-1999
Amendment (BC)	16-Dec-1999
Amendment (NC)	21-Feb-2000
Amendment (AZ)	20-Jul-2001
Amendment (BL)	16-Aug-2001
Amendment (BC)	26-Sept-2001
Amendment (BZ)	22-Nov-2001
Amendment (BC)	18-Dec-2001
Amendment (IN)	28-Dec-2001
Amendment (BC)	8-Jan-2002

CHEMISTRY REVIEW

Chemistry Review Data Sheet

7. NAME & ADDRESS OF APPLICANT:

Name: Hill Dermaceuticals, Inc.
Address: 2650 South Mellonville Avenue
Sanford, Florida 32773
Representative: Rosario G. Ramirez, MD
Telephone: (407)323-1887

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: Tri-Luma
- b) Non-Proprietary Name (USAN): fluocinolone acetonide; hydroquinone; tretinoin
- c) Code Name/# (ONDC only): None
- d) Chem. Type/Submission Priority (ONDC only):
 - Chem. Type: 4
 - Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: 505(b)(1)

10. PHARMACOL. CATEGORY: Cutaneous melanosis

11. DOSAGE FORM: Cream

12. STRENGTH/POTENCY: (0.01%) fluocinolone acetonide; (4.0%) hydroquinone;
(0.05%) tretinoin

13. ROUTE OF ADMINISTRATION: topical

14. Rx/OTC DISPENSED: Rx OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM)[Note27]:

SPOTS product – Form Completed

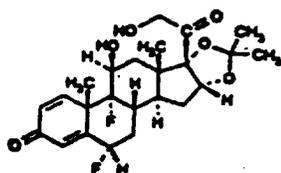
Not a SPOTS product

CHEMISTRY REVIEW

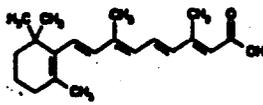
Chemistry Review Data Sheet

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

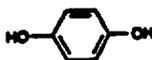
(1) Fluocinolone acetonide



(2) Tretinoin



(3) Hydroquinone



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CHEMISTRY REVIEW

Chemistry Review Data Sheet

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS
				3	Adequate	Aug. 1993	
				3	Adequate	2/22/01	
				3	Adequate	2/2/93	
				7	Adequate	12/18/01	
				3 7	Not reviewed	N/A	Item not used; see II.8

¹ Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 – Type 1 DMF

3 – Reviewed previously and no revision since last review

4 – Sufficient information in application

5 – Authority to reference not granted

6 – DMF not available

7 – Other (explain under "Comments")

² Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION

CHEMISTRY REVIEW

Chemistry Review Data Sheet

18. STATUS:

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
EES	Acceptable	29-Feb-2000	
Methods Validation	To be sent	4-Jan-2002	Pappas
OPDRA	Acceptable	11-Sept-2001	Mahmud
Microbiology	Acceptable	24-Sept-1999	Riley

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ON ORIGINAL

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Ernest G. Pappas
1/18/02 11:37:10 AM
CHEMIST

Tony: Per your request, I revised my chemistry review
#2, with an addendum to address the labeling
concerns.

Wilson H. DeCamp
1/18/02 11:52:39 AM
CHEMIST
concur with review

CHEMISTRY REVIEW

Executive Summary Section

The Chemistry Review for NDA 21-112

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

This NDA can be **approved** from a Chemistry standpoint.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if approvable

None

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

(1) Drug Product:

The drug product, Tri-Luma Cream, is packaged in _____ with a white _____, piercing screw cap. This product is a combination drug product, which contains Fluocinolone Acetonide, USP, Hydroquinone, USP, and Tretinoin, USP, as the active components.

A critical manufacturing parameter for Tri-Luma Cream occurs during the _____

_____, fluocinolone acetonide, tretinoin and hydroquinone, is added to _____ (see steps 9 – 13, Review #1, pg. 17). It is at these steps it is critical that fluocinolone acetonide, tretinoin and hydroquinone _____

_____ This is controlled by microscopic examination. However, particles were observed in the cream resulting from the insolubility of the inactive ingredient, magnesium aluminum silicate. These particles are controlled by a _____

The release specifications have been established following the principles of ICH Q6A, and give adequate assurance of identity, strength, quality and purity of the finished product. The validation of the assay methods adequately demonstrate that the methods are stability indicating. Each of the three active ingredients and their five known major degradation products can be assayed without interference from the other active ingredients and their related degradation products. In order to have this assurance, it was necessary to ask the applicant to carry out more extensive validation studies than are normally required.

CHEMISTRY REVIEW

Executive Summary Section

The applicant proposed a _____ for the product to be marketed in 30-g tubes. Acceptable stability data were submitted to support the proposed expiration date for storage at 20° - 25° C. _____ has been granted for this drug product.

The tradename, Tri-Luma, has been found acceptable by OPDRA. This labeling information, as well as the labels of the container and carton, is acceptable from a technical standpoint with exception of the use of the uninverted form of the systematic chemical name. This usage was not reflected in the submission of 20-Jul-2001.

Establishment Inspection: All facilities indicated in the NDA were found acceptable for CGMPs. An overall recommendation of approvable was received from the Office of Compliance on 29-Feb-2000.

Environmental Assessment: The applicant's claim of categorical exclusion under regulation 21 CFR 25.31 (b) is acceptable. The EIC projection was found to be at a level well below 1 ppb.

(2) Drug Substance:

The drug substances, fluocinolone acetonide, hydroquinone, and tretinoin, are controlled by USP monographs. These active ingredients must comply with the specifications as stipulated for these monographs. Tretinoin is light-sensitive, so the finished product should be protected from light. Hydroquinone is commonly used as a reducing agent in photographic developers, and has a depigmenting action on skin.

Impurity profiles were established for fluocinolone acetonide, hydroquinone, and tretinoin. These impurities have been found to be consistently found throughout their manufacture. Two related impurities have been identified for the manufacture of fluocinolone acetonide; they are _____ One related impurity _____, has been identified for the manufacture of hydroquinone. Two related impurities have been identified for the manufacture of tretinoin; they are _____

All degradation products have been qualified as required by ICH Q3A, and appropriate acceptance criteria established.

B. Description of How the Drug Product is Intended to be Used

The drug product is to be administered topically as an _____

CHEMISTRY REVIEW

Executive Summary Section

C. Basis for Approvability or Not-Approval Recommendation

The manufacturing and controls identified above are sufficient to assure the consistent identity, strength, quality and purity of the drug.

III. Administrative

A. Reviewer's Signature

B. Endorsement Block

ChemistName/Date: Same date as draft review
ChemistryTeamLeaderName/Date
ProjectManagerName/Date

C. CC Block

**APPEARS THIS WAY
ON ORIGINAL**

CHEMISTRY REVIEW

Chemistry Assessment Section

Chemistry Assessment

I. DRUG SUBSTANCE

No changes.

II. DRUG PRODUCT

No changes.

III. INVESTIGATIONAL FORMULATIONS: Acceptable per Chemist Review #1 dated 15-Dec-1999

IV. ENVIRONMENTAL ASSESSMENT: Acceptable per Chemist Review #1 dated 15-Dec-1999

V. METHODS VALIDATION: Pending

VI. LABELING: Acceptable with revision

Review #1 requested the applicant to use the uninverted form of the systematic chemical name. This usage was not reflected in the submission of 20-Jul-2001.

Amendment (BL) dated 16-Aug-2001 submitted mock-up color copies of the label for Tri-Luma carton and container. This labeling was reviewed and found to be acceptable from a technical standpoint.

The storage conditions for the drug product were found acceptable as follows:

- Store at controlled temperature 68⁰ – 77⁰ F (20⁰ – 25⁰ C)
- Protect from freezing

Comment: This addendum was written to address concerns by the chemists on the technical portion of the labeling which were conveyed to the applicant by telecon dated 1/18/02 as follows:

1. Regarding the mock-up color copies of the label for Tri-Luma carton and container, this labeling indicated the print of the proprietary name to be more than twice the size of the established names (fluocinolone acetonide, hydroquinone, tretinoin). In this regard, as required by Regulation 21 CFR 202.1 (b)(2), the established name should be printed in letters that are at least half as large as the proprietary name.

CHEMISTRY REVIEW

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2. Regarding the storage statement, this information should be printed as a separate paragraph instead of printing it with the ingredients paragraph so that that the consumer can clearly read it.
3. Regarding the package insert, the information describing Fluocinolone acetonide should be rewritten as described in the Derma-Smooth/FS labeling as follows:

(a) Fluocinolone acetonide is a synthetic fluorinated corticosteroid for topical dermatological use and is classified therapeutically as anti-inflammatory. The information regarding chemical/physical properties ("It is a white crystalline powder that is odorless and stable in light.") can remain in the labeling.

Note: The applicant agreed to make the above changes at the next printing and not to exceed 6 months of this labeling request.

VII. ESTABLISHMENT INSPECTION Acceptable per EES dated 29-Feb-2000

APPEARS THIS WAY
ON ORIGINAL