

ATTACHMENT

MEMO OF FILING MEETING

DATE: March 31, 2004

BACKGROUND:

Clin-RA Gel (clindamycin 1%, tretinoin 0.025%) is a 505(b)(2) NDA application for the treatment of Acne Vulgaris.

ATTENDEES: Jonathan Wilkin, M.D., Markham Luke, M.D., Ph.D., Brenda Carr, M.D., Dennis Bashaw, Pharm. D., Abi Adebawale, Ph.D., Shiojjen Lee, Ph.D., Wilson DeCamp, Ph.D., Saleh Turujman, Ph.D., Jill Merrill, Ph.D., Paul Brown, Ph.D., Mary Jean Kozma-Fornaro, Leslie Vacari

ASSIGNED REVIEWERS:

| <u>Discipline</u> | <u>Reviewer</u> | <u>Review Date</u> |
|---|-----------------|--------------------|
| Medical: | Brenda Carr | October 15, 2004 |
| Secondary Medical: | N/A | |
| Statistical: | Shiojjen Lee | August 31, 2004 |
| Pharmacology: | Jill Merrill | August 9, 2004 |
| Statistical Pharmacology: | N/A | |
| Chemist: | Saleh Turujman | November 1, 2004 |
| Environmental Assessment (if needed): | N/A | |
| Biopharmaceutical: | Dennis Bashaw | October 9, 2004 |
| Microbiology, sterility: | | |
| Microbiology, clinical (for antimicrobial products only): | Fred Marsik | March 3, 2004 |
| DSI: | Roy Blay | |
| Regulatory Project Manager: | Jacquelyn Smith | |
| Other Consults: | | |

Per reviewers, are all parts in English or English translation? YES NO
If no, explain:

CLINICAL FILE REFUSE TO FILE _____

- Clinical site inspection needed: YES ___ NO not at this time(re-evaluate as review progresses)
- Advisory Committee Meeting needed? YES, date if known ___ NO
- If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance?

N/A YES NO

| | | |
|--|-------------------|----------------------|
| CLINICAL MICROBIOLOGY | FILE <u> X </u> | REFUSE TO FILE _____ |
| STATISTICS | FILE <u> X </u> | REFUSE TO FILE _____ |
| BIOPHARMACEUTICS | FILE <u> X </u> | REFUSE TO FILE _____ |
| • Biopharm. inspection needed: | | YES NO |
| PHARMACOLOGY | FILE <u> X </u> | REFUSE TO FILE _____ |
| • GLP inspection needed: | | YES NO |
| CHEMISTRY | FILE <u> X </u> | REFUSE TO FILE _____ |
| • Establishment(s) ready for inspection? | | YES <u> X </u> NO |
| • Microbiology | | YES NO |

ELECTRONIC SUBMISSION:
Any comments:

REGULATORY CONCLUSIONS/DEFICIENCIES:

_____ The application is unsuitable for filing. Explain why:

 X The application, on its face, appears to be well organized and indexed. The application appears to be suitable for filing.

_____ No filing issues have been identified.

 X Filing issues to be communicated by Day 74. List (optional):

Jacquelyn Smith
Regulatory Project Manager, HFD-540

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/s/

Jonathan Wilkin
4/14/04 12:03:00 PM

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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-739

Dow Pharmaceutical Sciences
Attention: Barry M. Calvarese, MS
Vice President, Regulatory & Clinical Affairs
1330A Redwood Way
Petaluma, CA 94954-1169

Dear Mr. Calvarese:

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

Name of Drug Product: ClinRa (clindamycin, 1% / tretinoin, 0.025%) Gel

Review Priority Classification: Standard (S)

Date of Application: February 6, 2004

Date of Receipt: February 9, 2004

Our Reference Number: NDA 21-739

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on April 9, 2004 in accordance with 21 CFR 314.101(a). If the application is filed, the user fee goal date will be December 9, 2004.

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We note that you have submitted pediatric studies with this application. Once the review of this application is complete we will notify you whether you have fulfilled the pediatric study requirement for this application.

NDA 21-739

Page 2

Please cite the NDA number listed above at the top of the first page of any communications concerning this application. Address all communications concerning this NDA as follows:

U.S. Postal Service:

Center for Drug Evaluation and Research
Division of Dermatologic & Dental Drugs
HFD-540
5600 Fishers Lane
Rockville, Maryland 20857

Courier/Overnight Mail:

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

If you have any questions, call Jacquelyn Smith, Regulatory Project Manager, at (301) 827-2020.

Sincerely,

{See appended electronic signature page}

Mary Jean Kozma-Fornaro
Supervisor, Project Management Staff
Division of Dermatologic & Dental Drugs
Office of Drug Evaluation V
Center for Drug Evaluation and Research

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/s/

Jacquelyn Smith
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Signed for Mary Jean Kozma-Fornaro

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NDA REGULATORY FILING REVIEW
(Including Memo of Filing Meeting)

NDA # 21-739 Supplement # N/A

SE1 SE2 SE3 SE4 SE5 SE6 SE7 SE8

Trade Name: Clin-RA Gel
Generic Name: clindamycin/tretinoin
Strengths: clindamycin, 1%, tretinoin, 0.025%

Applicant: Dow Pharmaceutical Sciences

Date of Application: February 6, 2004

Date of Receipt: February 9, 2004

Date clock started after UN: N/A

Date of Filing Meeting: March 31, 2004

Filing Date: April 9, 004

Action Goal Date (optional):

User Fee Goal Date: December 9, 2004

Indication(s) requested: Treatment of Acne Vulgaris

Type of Application: Original (b)(1) NDA _____ Original (b)(2) NDA X
(b)(1) Supplement _____ (b)(2) Supplement _____
[If the Original NDA was a (b)(2), all supplements are (b)(2)s; if the Original NDA was a (b)(1), the supplement can be either a (b)(1) or a (b)(2).]

NOTE: If the application is a 505(b)(2) application, complete the 505(b)(2) section at the end of this summary.

Therapeutic Classification: S X P _____
Resubmission after a withdrawal? NO Resubmission after a refuse to file? _____
Chemical Classification: (1,2,3 etc.) 3
Other (orphan, OTC, etc.) _____

User Fee Status: Paid X Waived (e.g., small business, public health) _____
Exempt (orphan, government) _____

Form 3397 (User Fee Cover Sheet) submitted: YES X NO

User Fee ID # 4688

Clinical data? YES X NO, Referenced to NDA # _____

Is there any 5-year or 3-year exclusivity on this active moiety in either a (b)(1) or a (b)(2) application?

YES NO X

If yes, explain:

Does another drug have orphan drug exclusivity for the same indication? YES NO X

If yes, is the drug considered to be the same drug according to the orphan drug definition of sameness [21 CFR 316.3(b)(13)]?

YES NO

Is the application affected by the Application Integrity Policy (AIP)? YES NO X
If yes, explain.

If yes, has OC/DMPQ been notified of the submission? YES NO

• Does the submission contain an accurate comprehensive index? YES X NO

• Was form 356h included with an authorized signature? YES X NO
If foreign applicant, both the applicant and the U.S. agent must sign.

• Submission complete as required under 21 CFR 314.50? YES X NO
If no, explain:

• If an electronic NDA, does it follow the Guidance? YES X NO
If an electronic NDA, all certifications must be in paper and require a signature.
Which parts of the application were submitted in electronic format?

All certifications are in paper with signatures. This is a complete electronic NDA.

Additional comments:

• If in Common Technical Document format, does it follow the guidance? YES NO

• Is it an electronic CTD? YES NO X
If an electronic CTD, all certifications must be in paper and require a signature.
Which parts of the application were submitted in electronic format?

Additional comments:

• Patent information included with authorized signature? YES X NO

• Exclusivity requested? YES, 3 years NO

Note: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.

• Correctly worded Debarment Certification included with authorized signature? YES X NO
If foreign applicant, both the applicant and the U.S. Agent must sign the certification.

NOTE: Debarment Certification must have correct wording, e.g.: "I, the undersigned, hereby certify that _____ Co. did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug and Cosmetic Act in connection with the studies listed in Appendix ____." Applicant may not use wording such as "To the best of my knowledge"

- Financial Disclosure information included with authorized signature? YES X NO
(Forms 3454 and/or 3455 must be used and must be signed by the APPLICANT.)
- Field Copy Certification (that it is a true copy of the CMC technical section)? YES X NO

Refer to 21 CFR 314.101(d) for Filing Requirements

- PDUFA and Action Goal dates correct in COMIS? YES X NO
If not, have the document room staff correct them immediately. These are the dates EES uses for calculating inspection dates.
- Drug name/Applicant name correct in COMIS? If not, have the Document Room make the corrections.
Yes
- List referenced IND numbers: 65,531
- End-of-Phase 2 Meeting(s)? Date(s) December 16, 2002
If yes, distribute minutes before filing meeting.
- Pre-NDA Meeting(s)? Date(s) October 1, 2003
If yes, distribute minutes before filing meeting.

Project Management

- Package insert consulted to DDMAC? YES NO X
will consult after filing
- Trade name (plus PI and all labels and labeling) consulted to ODS/Div. of Medication Errors and Technical Support? YES NO X
will consult after filing
- MedGuide and/or PPI (plus PI) consulted to ODS/Div. of Surveillance, Research and Communication Support? N/A YES NO X
- If a drug with abuse potential, was an Abuse Liability Assessment, including a proposal for scheduling, submitted? N/A YES NO

If Rx-to-OTC Switch application: N/A

- OTC label comprehension studies, all OTC labeling, and current approved PI consulted to ODS/ Div. of Surveillance, Research and Communication Support? YES NO
- Has DOTCDP been notified of the OTC switch application? YES NO

Clinical

- If a controlled substance, has a consult been sent to the Controlled Substance Staff? YES NO
N/A

Chemistry

- Did applicant request categorical exclusion for environmental assessment? YES X NO
If no, did applicant submit a complete environmental assessment? YES NO
If EA submitted, consulted to Nancy Sager (HFD-357)? YES NO
- Establishment Evaluation Request (EER) submitted to DMPQ? YES X NO
- If parenteral product, consulted to Microbiology Team (HFD-805)? YES NO

If 505(b)(2) application, complete the following section:

- Name of listed drug(s) and NDA/ANDA #:
Cleocin T Gel(NDA 50-537, 50-600, 50-615; Avita Cream(20-400, 20-404)
- Describe the change from the listed drug(s) provided for in this (b)(2) application (for example, "This application provides for a new indication, otitis media" or "This application provides for a change in dosage form, from capsules to solution").

This application provides for combination formula(clindamycin/tretinoia) .

- Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA? (Normally, FDA will refuse-to-file such NDAs.)
YES NO X
- Is the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action less than that of the reference listed drug (RLD)? (See 314.54(b)(1)). If yes, the application should be refused for filing under 314.101(d)(9).
YES NO X
- Is the rate at which the product's active ingredient(s) is absorbed or otherwise made available to the site of action unintentionally less than that of the RLD? (See 314.54(b)(2)). If yes, the application should be refused for filing under 314.101(d)(9).
YES NO X
- Which of the following patent certifications does the application contain? Note that a patent certification must contain an authorized signature.

___ 21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA.

___ 21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired.

X 21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire.

___ 21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted.

IF FILED, and if the applicant made a "Paragraph IV" certification [21 CFR 314.50(i)(1)(i)(A)(4)], the applicant must submit a signed certification that the patent holder

was notified the NDA was filed [21 CFR 314.52(b)]. Subsequently, the applicant must submit documentation that the patent holder(s) received the notification ([21 CFR 314.52(e)].

___ 21 CFR 314.50(i)(1)(ii): No relevant patents.

___ 21 CFR 314.50(i)(1)(iii): The patent on the listed drug is a method of use patent and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent. Applicant must provide a statement that the method of use patent does not claim any of the proposed indications.

___ 21 CFR 314.50(i)(3): Statement that applicant has a licensing agreement with the patent owner (must also submit certification under 21 CFR 314.50(i)(1)(i)(A)(4) above.)

___ Written statement from patent owner that it consents to an immediate effective date upon approval of the application.

• Did the applicant:

- Identify which parts of the application rely on information the applicant does not own or to which the applicant does not have a right of reference?

YES X NO

- Submit a statement as to whether the listed drug(s) identified has received a period of marketing exclusivity?

YES NO X

- Submit a bioavailability/bioequivalence (BA/BE) study comparing the proposed product to the listed drug?

YES X NO

- Certify that it is seeking approval only for a new indication and not for the indications approved for the listed drug if the listed drug has patent protection for the approved indications and the applicant is requesting only the new indication (21 CFR 314.54(a)(1)(iv).?)

YES NO N/A

- If the (b)(2) applicant is requesting exclusivity, did the applicant submit the following information required by 21 CFR 314.50(j)(4):

- Certification that each of the investigations included meets the definition of "new clinical investigation" as set forth at 314.108(a).

YES X NO

- A list of all published studies or publicly available reports that are relevant to the conditions for which the applicant is seeking approval.

YES NO X

- EITHER

The number of the applicant's IND under which the studies essential to approval were conducted.

YES NO

OR

A certification that it provided substantial support of the clinical investigation(s) essential to approval if it was not the sponsor of the IND under which those clinical studies were conducted?

YES NO

- Has the Director, Div. of Regulatory Policy II, HFD-007, been notified of the existence of the (b)(2) application?

YES NO will be notified after filing

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/s/

Jacquelyn Smith
4/12/04 03:05:16 PM
CSO

Mary Jean Kozma Fornaro
4/12/04 04:07:22 PM
CSO

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|--|------------------------|---|-------------------------------|--|
| DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION | | REQUEST FOR CONSULTATION | | |
| TO (Division/Office): Director, Division of Medication Errors and Technical Support (DMETS), HFD-420 PKLN Rm. 6-34 | | FROM: Jacquelyn Smith Project Manager Division of Dermatologic and Dental Drug Products | | |
| DATE: April 7, 2004 | IND NO. | NDA NO. 21-739 | TYPE OF DOCUMENT New NDA | DATE OF DOCUMENT: February 6, 2004 |
| NAME OF DRUG: ClinRA Gel (clindamycin, 1% - tretinoin, 0.025%) | PRIORITY CONSIDERATION | | CLASSIFICATION OF DRUG: 3S | DESIRED COMPLETION DATE: PDUFA Date: December 9, 2004 |
| NAME OF FIRM: Dow Pharmaceutical Sciences | | | | |
| REASON FOR REQUEST | | | | |
| I. GENERAL | | | | |
| <input type="checkbox"/> NEW PROTOCOL <input type="checkbox"/> PROGRESS REPORT <input type="checkbox"/> NEW CORRESPONDENCE <input type="checkbox"/> DRUG ADVERTISING <input type="checkbox"/> ADVERSE REACTION REPORT <input type="checkbox"/> MANUFACTURING CHANGE/ADDITION <input type="checkbox"/> MEETING PLANNED BY <input type="checkbox"/> PRE-NDA MEETING <input type="checkbox"/> END OF PHASE II MEETING <input type="checkbox"/> RESUBMISSION <input type="checkbox"/> SAFETY/EFFICACY <input type="checkbox"/> PAPER NDA <input type="checkbox"/> CONTROL SUPPLEMENT <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER <input type="checkbox"/> FINAL PRINTED LABELING <input type="checkbox"/> LABELING REVISION <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE <input type="checkbox"/> FORMULATIVE REVIEW <input checked="" type="checkbox"/> OTHER (SPECIFY BELOW): | | | | |
| II. BIOMETRICS | | | | |
| STATISTICAL EVALUATION BRANCH | | STATISTICAL APPLICATION BRANCH | | |
| <input type="checkbox"/> TYPE A OR B NDA REVIEW <input type="checkbox"/> END OF PHASE II MEETING <input type="checkbox"/> CONTROLLED STUDIES <input type="checkbox"/> PROTOCOL REVIEW <input type="checkbox"/> OTHER (SPECIFY BELOW): | | <input type="checkbox"/> CHEMISTRY REVIEW <input type="checkbox"/> PHARMACOLOGY <input type="checkbox"/> BIOPHARMACEUTICS <input type="checkbox"/> OTHER (SPECIFY BELOW): | | |
| III. BIOPHARMACEUTICS | | | | |
| <input type="checkbox"/> DISSOLUTION <input type="checkbox"/> BIOAVAILABILITY STUDIES <input type="checkbox"/> PHASE IV STUDIES | | <input type="checkbox"/> DEFICIENCY LETTER RESPONSE <input type="checkbox"/> PROTOCOL-BIOPHARMACEUTICS <input type="checkbox"/> IN-VIVO WAIVER REQUEST | | |
| IV. DRUG EXPERIENCE | | | | |
| <input type="checkbox"/> PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL <input type="checkbox"/> DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES <input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below) <input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP | | <input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY <input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE <input type="checkbox"/> POISON RISK ANALYSIS | | |
| V. SCIENTIFIC INVESTIGATIONS | | | | |
| <input type="checkbox"/> CLINICAL | | <input type="checkbox"/> PRECLINICAL | | |
| COMMENTS/SPECIAL INSTRUCTIONS: Please review the requested tradename, ClinRA Gel. The package insert is attached. I will also send a hard copy. PDUFA DATE: December 9, 2004 | | | | |
| SIGNATURE OF REQUESTER | | METHOD OF DELIVERY (Check one) <input checked="" type="checkbox"/> MAIL <input type="checkbox"/> HAND | | |
| SIGNATURE OF RECEIVER | | SIGNATURE OF DELIVERER | | |

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 Trade Secret / Confidential (b4)

✓ Draft Labeling (b4)

 Draft Labeling (b5)

 Deliberative Process (b5)

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/s/

Jacquelyn Smith
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|--|------------------------|---|--|---------------------------------------|
| DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION | | REQUEST FOR CONSULTATION | | |
| TO (Division/Office): Division of Drug Marketing, Advertising and Communications, HFD-42 PKLN Room 17B04 | | FROM: Jacquelyn Smith Project Manager Division of Dermatologic and Dental Drug Products | | |
| DATE: April 7, 2004 | IND NO. | NDA NO. 21-739 | TYPE OF DOCUMENT New NDA | DATE OF DOCUMENT: February 6, 2004 |
| NAME OF DRUG: ClinRA Gel (clindamycin, 1% - tretinoin, 0.025%) | PRIORITY CONSIDERATION | CLASSIFICATION OF DRUG: 3S | DESIRED COMPLETION DATE: PDUFA DATE: December 9, 2004 | |
| NAME OF FIRM: Dow Pharmaceutical Sciences | | | | |
| REASON FOR REQUEST | | | | |
| I. GENERAL | | | | |
| <input type="checkbox"/> NEW PROTOCOL <input type="checkbox"/> PROGRESS REPORT <input type="checkbox"/> NEW CORRESPONDENCE <input type="checkbox"/> DRUG ADVERTISING <input type="checkbox"/> ADVERSE REACTION REPORT <input type="checkbox"/> MANUFACTURING CHANGE/ADDITION <input type="checkbox"/> MEETING PLANNED BY <input type="checkbox"/> PRE-NDA MEETING <input type="checkbox"/> END OF PHASE II MEETING <input type="checkbox"/> RESUBMISSION <input type="checkbox"/> SAFETY/EFFICACY <input type="checkbox"/> PAPER NDA <input type="checkbox"/> CONTROL SUPPLEMENT <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER <input type="checkbox"/> FINAL PRINTED LABELING <input type="checkbox"/> LABELING REVISION <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE <input type="checkbox"/> FORMULATIVE REVIEW <input checked="" type="checkbox"/> OTHER (SPECIFY BELOW): | | | | |
| II. BIOMETRICS | | | | |
| STATISTICAL EVALUATION BRANCH | | STATISTICAL APPLICATION BRANCH | | |
| <input type="checkbox"/> TYPE A OR B NDA REVIEW <input type="checkbox"/> END OF PHASE II MEETING <input type="checkbox"/> CONTROLLED STUDIES <input type="checkbox"/> PROTOCOL REVIEW <input type="checkbox"/> OTHER (SPECIFY BELOW): | | <input type="checkbox"/> CHEMISTRY REVIEW <input type="checkbox"/> PHARMACOLOGY <input type="checkbox"/> BIOPHARMACEUTICS <input type="checkbox"/> OTHER (SPECIFY BELOW): | | |
| III. BIOPHARMACEUTICS | | | | |
| <input type="checkbox"/> DISSOLUTION <input type="checkbox"/> BIOAVAILABILITY STUDIES <input type="checkbox"/> PHASE IV STUDIES | | <input type="checkbox"/> DEFICIENCY LETTER RESPONSE <input type="checkbox"/> PROTOCOL-BIOPHARMACEUTICS <input type="checkbox"/> IN-VIVO WAIVER REQUEST | | |
| IV. DRUG EXPERIENCE | | | | |
| <input type="checkbox"/> PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL <input type="checkbox"/> DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES <input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below) <input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP | | <input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY <input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE <input type="checkbox"/> POISON RISK ANALYSIS | | |
| V. SCIENTIFIC INVESTIGATIONS | | | | |
| <input type="checkbox"/> CLINICAL | | <input type="checkbox"/> PRECLINICAL | | |
| COMMENTS/SPECIAL INSTRUCTIONS: The package insert is attached. I will also send a hard copy. PDUFA DATE: December 9, 2004 | | | | |
| SIGNATURE OF REQUESTER | | METHOD OF DELIVERY (Check one) <input checked="" type="checkbox"/> MAIL <input type="checkbox"/> HAND | | |
| SIGNATURE OF RECEIVER | | SIGNATURE OF DELIVERER | | |

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 Trade Secret / Confidential (b4)

✓ Draft Labeling (b4)

 Draft Labeling (b5)

 Deliberative Process (b5)

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Jacquelyn Smith
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Food and Drug Administration
 Center for Drug Evaluation and Research
 Office of Drug Evaluation ODE 5

FACSIMILE TRANSMITTAL SHEET

DATE: April 6, 2004

| | |
|---|---|
| To: Barry Calverese, MS, VP, Regulatory and Clinical Affairs | From: Jacquelyn Smith, Project Manager |
| Company: Dow Pharmaceutical Sciences | Division of Dermatologic and Dental Drug Products |
| Fax number: 707-793-0145 | Fax number: 301-827-2075 |
| Phone number: 707-793-2600 | Phone number: 301-827-2027 |
| Subject: NDA 21-739/ClinRA Gel | |

Total no. of pages including cover: 3

Document to be mailed: YES NO

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FDA Fax Memo

Date: April 6, 2004

Subject: NDA 21-739/ClinRA Gel

Dear Mr. Calvarese,

Please clarify the following:

According to the submitted clinical study report (for both pivotal trials), drug supplies were numbered sequentially in order and were dispensed sequentially to the subjects entering the study within an investigational site. Please explain any deviation about the treatment allocation.

Please contact me if you need further information.

Sincerely,

Jacquelyn Smith
Project Manager
DDDDP, HFD-540

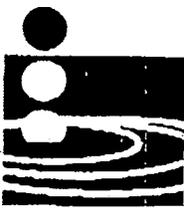
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Dow Pharmaceutical Sciences
 1330A Redwood Way
 Petaluma, CA 94954-1169
 Phone: 707.793.2600
 Fax: 707.793.0145

FAX TRANSMITTAL COVER

TO: JAQUELYN SMITH, PROJECT MANAGER, CDER

FAX NO. 301-827-2075 # of pages, including cover: 3

FROM: Paula Mueda, Sr. Regulatory Specialist

RE: ClinRA NDA 21-739 - Information on Manufacture of Tretinoin
 Drug Substance

Jacquelyn,

Per request from Barry Calvarese, Vice President, Regulatory and Clinical Affairs, attached is a copy of the fax sent to you on 2/13/04 which updated the Establishment Information for the ClinRA NDA submitted to the Agency on 2/6/04. Also attached is copy of the letter sent to Dr. Wilkin on the same day containing the corrected Establishment Information for ClinRA.

We are attempting to obtain the phone number for the _____ manufacturing facility in _____ As soon as we receive that number, I will fax it to you.

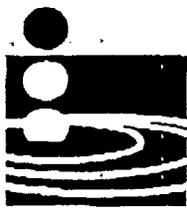
b(4)

Regards,

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Sent by: P. Mueda

Date: 3/29/2004



COPY

Dow Pharmaceutical Sciences
1330A Redwood Way
Petaluma, CA 94954-1169
Phone: 707.793.2600
Fax: 707.793.0145

FAX TRANSMITTAL COVER

TO: JACQUELYN SMITH – FDA/CDER, Div. of Derm. & Dental.

FAX NO. 301-827-2075 **# OF PAGES:** 4
(including cover sheet)

FROM: BARRY CALVARESE, MS

RE: Response to Your Fax of February 12, 2004

A hard copy of this response will be sent to you via Federal Express today for delivery on Tuesday, February 17, 2004 (since Monday, February 16, is a holiday).

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Sent by: P. Mueda

Date: February 13, 2004

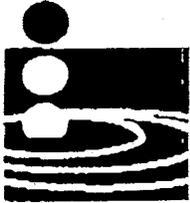
2 Page(s) Withheld

Trade Secret / Confidential (b4)

Draft Labeling (b4)

Draft Labeling (b5)

Deliberative Process (b5)



Dow Pharmaceutical Sciences
1330A Redwood Way
Petaluma, CA 94954-1169
Phone: 707.793.2600
Fax: 707.793.0145

FAX TRANSMITTAL COVER

TO: JAQUELYN SMITH, PROJECT MANAGER, CDER

FAX NO. 301-827-2075 # of pages, including cover: 3

FROM: Paula Mueda, Sr. Regulatory Specialist

RE: Pediatric Waiver Request for ClinRA NDA 21-739

Appears This Way
On Original

Sent by: P. Mueda

Date: 3/26/2004



Via Facsimile & Federal Express

March 25, 2004

Jonathan Wilkin, MD
Division of Dermatological and Dental Drug Products
Office of Drug Evaluation V
Center for Drug Evaluation and Research
Food and Drug Administration
Central Document Mail Room
12229 Wilkins Avenue
Rockville, MD 20852

Subject: **NDA 21-739 – ClinRA (clindamycin phosphate, 1%, tretinoin, 0.025%) Gel
for the Treatment of Acne Vulgaris**

Request for Pediatric Waiver

Dear Dr. Wilkin:

In accordance with a voicemail message received today from Jacquelyn Smith, FDA Project Manager, requesting submission of a Pediatric Waiver for the ClinRA Gel drug product, Dow Pharmaceutical Sciences (DPS) hereby requests a Pediatric Waiver for patients under the age of 11 years for NDA 21-739 for ClinRA Gel (clindamycin phosphate, 1%, tretinoin, 0.025%).

The youngest patient treated with ClinRA Gel in the Phase 3 clinical trials was 11 years old.

Per Ms. Smith's request, a copy of this letter is being transmitted to her via facsimile today. In addition, a duplicate hard copy will be sent to your attention via the FDA Central Document Mail Room.

DPS considers the information enclosed in this document to be confidential. The legal protection of such confidential material is hereby claimed under the applicable provision of 18 USC, §331 (j) and/or 21 CFR 312.130.

Jonathan Wilkin, MD
March 25, 2004
Page 2

If there are questions regarding this submission, please contact me or Elena Serbinova, PhD, at 707-793-2600, via fax at 707-793-0145, or by e-mail at:
bcalvarese@dowpharmsci.com eserbinova@dowpharmsci.com.

Sincerely,



Barry M. Calvarese, MS
Vice President Regulatory and Clinical Affairs

/pm
Enclosure

Facsimile copy: Jaquelyn Smith, FDA Project Manager

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4.2.6

Barry Calvarese
707-665-4610

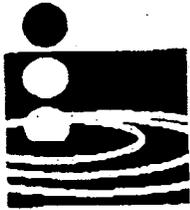
| | | | | | |
|--|---------|--|---|---|--|
| DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION | | REQUEST FOR CONSULTATION | | | |
| TO (<i>Division/Office</i>): Fran LeSane, SCSO/AL Sheldon, Micro TL HFD-520/9201 Corporate Blvd. | | | FROM: Jacquelyn Smith, PM/ Brenda Carr, MO HFD-540, Derm and Dental | | |
| DATE: February 13, 2004 | IND NO. | NDA NO 21-739 | TYPE OF DOCUMENT: New NDA | DATE OF DOCUMENT: February 6, 2004 | |
| NAME OF DRUG: Clin-RA (clindamycin 1%, tretinoin, 0.025%) GEL | | PRIORITY CONSIDERATION: | CLASSIFICATION OF DRUG: 3S | DESIRED COMPLETION DATE: Filing Date: April 9, 2004 | |
| NAME OF FIRM: Dow Pharmaceutical Sciences | | | | | |
| REASON FOR REQUEST | | | | | |
| I. GENERAL | | | | | |
| <input type="checkbox"/> NEW PROTOCOL <input type="checkbox"/> PROGRESS REPORT <input type="checkbox"/> NEW CORRESPONDENCE <input type="checkbox"/> DRUG ADVERTISING <input type="checkbox"/> ADVERSE REACTION REPORT <input type="checkbox"/> MANUFACTURING CHANGE/ADDITION <input type="checkbox"/> MEETING PLANNED BY | | <input type="checkbox"/> PRE-NDA MEETING <input type="checkbox"/> END OF PHASE II MEETING <input type="checkbox"/> RESUBMISSION <input type="checkbox"/> SAFETY/EFFICACY <input type="checkbox"/> PAPER NDA <input type="checkbox"/> CONTROL SUPPLEMENT | | <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER <input type="checkbox"/> FINAL PRINTED LABELING <input type="checkbox"/> LABELING REVISION <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE <input type="checkbox"/> FORMULATIVE REVIEW <input checked="" type="checkbox"/> OTHER (<i>SPECIFY BELOW</i>): | |
| II. BIOMETRICS | | | | | |
| STATISTICAL EVALUATION BRANCH | | | STATISTICAL APPLICATION BRANCH | | |
| <input type="checkbox"/> TYPE A OR B NDA REVIEW <input type="checkbox"/> END OF PHASE II MEETING <input type="checkbox"/> CONTROLLED STUDIES <input type="checkbox"/> PROTOCOL REVIEW <input type="checkbox"/> OTHER (<i>SPECIFY BELOW</i>): | | | <input type="checkbox"/> CHEMISTRY REVIEW <input type="checkbox"/> PHARMACOLOGY <input type="checkbox"/> BIOPHARMACEUTICS <input type="checkbox"/> OTHER (<i>SPECIFY BELOW</i>): | | |
| III. BIOPHARMACEUTICS | | | | | |
| <input type="checkbox"/> DISSOLUTION <input type="checkbox"/> BIOAVAILABILITY STUDIES <input type="checkbox"/> PHASE IV STUDIES | | | <input type="checkbox"/> DEFICIENCY LETTER RESPONSE <input type="checkbox"/> PROTOCOL-BIOPHARMACEUTICS <input type="checkbox"/> IN-VIVO WAIVER REQUEST | | |
| IV. DRUG EXPERIENCE | | | | | |
| <input type="checkbox"/> PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL <input type="checkbox"/> DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES <input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (<i>List below</i>) <input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP | | | <input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY <input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE <input type="checkbox"/> POISON RISK ANALYSIS | | |
| V. SCIENTIFIC INVESTIGATIONS | | | | | |
| <input type="checkbox"/> CLINICAL | | | <input type="checkbox"/> PRECLINICAL | | |
| <p>COMMENTS/SPECIAL INSTRUCTIONS: Please review NDA and give comments. The filing date is April 9, 2004. Please note that this NDA is completely electronic.</p> <p>The network path location for your NDA is listed below: <u>\\CDSESUB1\N21739\N_000\2004-02-06</u></p> | | | | | |
| SIGNATURE OF REQUESTER | | | METHOD OF DELIVERY (Check one) N/A <input type="checkbox"/> MAIL <input type="checkbox"/> HAND | | |
| SIGNATURE OF RECEIVER | | | SIGNATURE OF DELIVERER | | |

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

/s/

Frances LeSane
2/18/04 03:27:56 PM

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On Original



Dow Pharmaceutical Sciences
1330A Redwood Way
Petaluma, CA 94954-1169
Phone: 707.793.2600
Fax: 707.793.0145

FAX TRANSMITTAL COVER

TO: JACQUELYN SMITH – FDA/CDER, Div. of Derm. & Dental.

FAX NO. 301-827-2075 **# OF PAGES:** 4
(including cover sheet)

FROM: BARRY CALVARESE, MS

RE: Response to Your Fax of February 12, 2004

A hard copy of this response will be sent to you via Federal Express today for delivery on Tuesday, February 17, 2004 (since Monday, February 16, is a holiday).

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Sent by: P. Mueda *pm*

Date: February 13, 2004

2 Page(s) Withheld

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Draft Labeling (b4)

Draft Labeling (b5)

Deliberative Process (b5)



Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation ODE 5

FACSIMILE TRANSMITTAL SHEET

DATE: February 12, 2004

| | |
|---|---|
| To: Barry Calverese, MS, VP, Regulatory & Clinical Affairs | From: Jacquelyn Smith, Project Manager |
| Company: Dow Pharmaceutical Sciences | Division of Dermatologic and Dental Drug Products |
| Fax number: 707-793-0145 | Fax number: 301-827-2075 |
| Phone number: 707-793-2600 | Phone number: 301-827-2027 |
| Subject: NDA 21-739/Clin-RA Gel | |
| Total no. of pages including cover: 3 | |

Document to be mailed: YES NO

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW.

If you are not the addressee, or a person authorized to deliver this document to the addressee, you are hereby notified that any review, disclosure, dissemination, copying, or other action based on the content of this communication is not authorized. If you have received this document in error, please notify us immediately by telephone at 301-827-2020. Thank you.

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On Original

NDA 21-739

N-000

The chemistry team is reviewing NDA 21-739, Clin-RA (clindamycin, 1%, tretinoin, 0.025%) Gel for fileability, and has asked that the following be conveyed to you.

- The list of manufacturing sites does not include any sites for manufacture of either drug substance (clindamycin phosphate or tretinoin). Please submit a revised list of facilities.
- We urge you to ask each site to re-evaluate the date on which it will be ready for inspection. If the sites are not ready for inspection by the filing date, the application will be recommended for a refusal to file. Once the inspection has been requested, we cannot control when the inspection will be conducted. If the field tries to go on inspection and is told that the site is not ready, they might issue a withhold recommendation. Consequently, this would lead to an approvable recommendation from a CMC point of view. Due to the tight schedule of inspections, there might not be a chance that the site can be re-scheduled for another inspection within the 10 month PDUFA clock.

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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/

Jacquelyn Smith
2/12/04 10:14:32 AM
CSO

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Dow Pharmaceutical Sciences

The D in Topicals R&D

Since 1977

February 6, 2004

Jonathan Wilkin, MD
Division of Dermatological and Dental Drug Products
Office of Drug Evaluation V
Center for Drug Evaluation and Research
Food and Drug Administration
Central Document Mail Room
12229 Wilkins Avenue
Rockville, MD 20852

Subject: **New Drug Application No. 21,739**
Product: ClinRA (clindamycin 1%; tretinoin 0.025%) Gel
Indication: Acne Vulgaris
Sponsor: Dow Pharmaceutical Sciences

Dear Dr. Wilkin:

Pursuant to §505(b)(2) of the Federal Food, Drug and Cosmetic Act and in accordance with Title 21 of the Code of Federal Regulations, §314.50, Dow Pharmaceutical Sciences (DPS) herewith submits an original New Drug Application (NDA) for Clin-RA Gel (clindamycin 1%, tretinoin 0.025%).

The new drug product contains the active drug substance, clindamycin phosphate, USP, at a concentration of 1.2% and tretinoin at 0.025% concentration in a topical gel vehicle. Previous information concerning this formulation has been submitted to the Agency under Investigational New Drug Application (IND) No. 65,531.

DPS considers all the information contained in this application proprietary and confidential. Please be advised that the confidentiality of all enclosed information is provided for under 18 USC, §1905 and/or 21 USC, §331j.

RECEIVED

FEB 09 2004

CDR/CDER

RECEIVED

FEB 10 2004

MEGA/CDER

This submission is being submitted entirely electronically on 4 CD-ROMs, with a total file size of approximately 1.9 GB. In addition, original signatures are provided in hard copy for the cover letter, Form FDA 356h, and the Patent, Debarment, Field Office and Financial Certifications. The submission is virus free. All files have been scanned using Symantec's Antivirus Corporate Edition, Version 8.1. The complete NDA is submitted electronically on one set of compact discs. The order of the files on the CDs are not in chronological order in order to accommodate all files on a minimal number of CDs. The folder names and CD volume numbers of the files within this e-NDA are listed below.

| Section Number | Section | Folder Name | CD Volume Number |
|-----------------------|--|--------------------|-------------------------|
| 1 | Table of Contents Cover Letter 356h form | N21739 | 1 |
| 2 | Labeling | labeling | 1 |
| 3 | Application Summary | summary | 1 |
| 4 | Chemistry, Manufacturing and Controls | cmc | 1 |
| 5 | Nonclinical Pharmacology and Toxicology | pharmtox | 1 |
| 6 | Human Pharmacokinetics and Bioavailability | hpbio | 1 |
| 7 | Microbiology | micro | 1 |
| 8 | Clinical Data | clinstat | 1 and 2 |
| 9 | Safety Update | update | 2 |
| 11 | Case Report Tabulations | crt | 2 |
| 12 | Case Report Forms | crf | 3 and 4 |
| 13 | Patent Information | other | 4 |
| 14 | Patent Certification | other | 4 |
| 16 | Debarment Certification | other | 4 |
| 17 | Field Copy Certification | other | 4 |
| 18 | User Fee Cover Sheet | other | 4 |
| 19 | Financial Information | other | 4 |
| 20 | Other | other | 4 |

- SAS datasets for each of the two Phase 3 pivotal clinical studies are in SAS transport format and are located in the 'datasets' subfolder of the main 'crt' folder

- The tables and data listings for each of the two Phase 3 pivotal clinical studies are located in the '06-02' and '07-02' subfolders of the main 'clinstat' folder.
- All clinical trials submitted in this New Drug Application were conducted in accordance with 21 CFR, Part 56 for Institutional Review Boards or the Declaration of Helsinki provisions of the CFR.
- All pharmacology/toxicology studies conducted in support of Clin-RA Gel have been performed using acceptable, state-of-the-art protocols reflective of Agency animal welfare concern.
- The protocols are designed to support the safety of the drug and have been used for these types of studies to allow the data to be compared to that of other compounds.
- The studies complied with all applicable sections of the Final Rules of the Animal Welfare Act regulations (9 CFR) and the Public Health Service Policy on Humane Care and Use of Laboratory Animals (OPRR, NIH, 1986). Wherever possible, procedures used in the studies were designed to avoid or minimize discomfort, distress, and pain to the animals. All methods were described in the study protocols or in written laboratory standard operating procedures. All procedures were based on the most currently available technologies concerning proper laboratory animal use and management.
- All nonclinical toxicology studies were conducted in accordance with Part 58 of the CFR
- The integrated summary of safety for this new drug application includes all known safety data for the drug product from all domestic and foreign sources, to the greatest extent possible.
- The cut-off date for clinical data inclusion and preparation of the integrated summary of safety in this new drug application was December 20, 2003.
- Reference is made to the Pre-IND meeting that occurred on September 24, 2001 and the Pre-NDA meeting held on October 1, 2003 [meeting minutes dated October 17, 2003 (IND No. 65,531)].

✓

DPS and all facilities involved in the manufacture and release of the drug product will be ready for preapproval inspection (PAI) by June 7, 2004.

Please note that this application is accompanied by an appropriately completed and signed Form FDA 356h, Application to Market a New Drug, Biologic, or an Antibiotic Drug for Human Use; by Form FDA 3397, User Fee Cover Sheet and by the applicable User Fee of \$573,500.00, which was provided in United States currency in the form of Cashier's Check No. 20407 on December 18, 2003; by Form FDA 3454, Certification: Financial Interests and Arrangements of Clinical Investigators, and by Form FDA 3455, Disclosure: Financial Interests and Arrangements of Clinical Investigators.

Sincerely,



Barry M. Calvarese, MS
Vice President Regulatory and Clinical Affairs

BMC/pm
Enclosures

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FEB 09 2004

CDR/CDER

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

Form Approved: OMB No. 0910-0338
Expiration Date: August 31, 2005
See OMB Statement on page 2.

**APPLICATION TO MARKET A NEW DRUG, BIOLOGIC,
OR AN ANTIBIOTIC DRUG FOR HUMAN USE**
(Title 21, Code of Federal Regulations, Parts 314 & 601)

FOR FDA USE ONLY

APPLICATION NUMBER

APPLICANT INFORMATION

| | |
|---|--|
| NAME OF APPLICANT Dow Pharmaceutical Sciences | DATE OF SUBMISSION 2/6/04 |
| TELEPHONE NO. (Include Area Code) 707.793.2600 | FACSIMILE (FAX) Number (Include Area Code) 707.793.0145 |
| APPLICANT ADDRESS (Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued): 1330A Redwood Way Petaluma, CA | AUTHORIZED U.S. AGENT NAME & ADDRESS (Number, Street, City, State, ZIP Code, telephone & FAX number) IF APPLICABLE 94954-1169 |

PRODUCT DESCRIPTION

| | | |
|--|---|-------------------------------------|
| NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER (if previously issued) 21,739 | | |
| ESTABLISHED NAME (e.g., Proper name, USP/USAN name) Clindamycin and Tretinoin | PROPRIETARY NAME (trade name) IF ANY Clin-RA Gel | |
| CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME (if any) | CODE NAME (if any) | |
| DOSAGE FORM: Topical Gel | STRENGTHS: Clindamycin: 1%, Tretinoin: 0.025% | ROUTE OF ADMINISTRATION: Topical |
| (PROPOSED) INDICATION(S) FOR USE: Acne vulgaris | | |

APPLICATION DESCRIPTION

| | | |
|---|--|--|
| APPLICATION TYPE (check one) <input checked="" type="checkbox"/> NEW DRUG APPLICATION (CDA, 21 CFR 314.50) <input type="checkbox"/> ABBREVIATED NEW DRUG APPLICATION (ANDA, 21 CFR 314.94) <input type="checkbox"/> BIOLOGICS LICENSE APPLICATION (BLA, 21 CFR Part 601) | | |
| IF AN NDA, IDENTIFY THE APPROPRIATE TYPE <input type="checkbox"/> 505 (b)(1) <input checked="" type="checkbox"/> 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 <u>Clin-RA Gel</u> Holder of Approved Application <u>Dow Pharmaceutical Sciences</u> | | |
| TYPE OF SUBMISSION (check one) <input checked="" type="checkbox"/> ORIGINAL APPLICATION <input type="checkbox"/> AMENDMENT TO PENDING APPLICATION <input type="checkbox"/> RESUBMISSION <input type="checkbox"/> PRESUBMISSION <input type="checkbox"/> ANNUAL REPORT <input type="checkbox"/> ESTABLISHMENT DESCRIPTION SUPPLEMENT <input type="checkbox"/> EFFICACY SUPPLEMENT <input type="checkbox"/> LABELING SUPPLEMENT <input type="checkbox"/> CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT <input type="checkbox"/> OTHER | | |
| IF A SUBMISSION OF PARTIAL APPLICATION, PROVIDE LETTER DATE OF AGREEMENT TO PARTIAL SUBMISSION: _____ | | |
| IF A SUPPLEMENT, IDENTIFY THE APPROPRIATE CATEGORY <input type="checkbox"/> CBE <input type="checkbox"/> CBE-30 <input type="checkbox"/> Prior Approval (PA) | | |
| REASON FOR SUBMISSION | | |

| |
|--|
| PROPOSED MARKETING STATUS (check one) <input checked="" type="checkbox"/> PRESCRIPTION PRODUCT (Rx) <input type="checkbox"/> OVER THE COUNTER PRODUCT (OTC) |
| NUMBER OF VOLUMES SUBMITTED <u>4 CDs</u> THIS APPLICATION IS <input type="checkbox"/> PAPER <input type="checkbox"/> PAPER AND ELECTRONIC <input checked="" type="checkbox"/> ELECTRONIC |

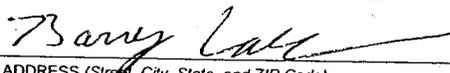
ESTABLISHMENT INFORMATION (Full establishment information should be provided in the body of the Application.)
Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone 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 attached

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

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FEB 10 2004

MEGA/CDER

| | | | |
|--|---|--|------------|
| This application contains the following items: (Check all that apply) | | | |
| <input checked="" type="checkbox"/> | 1. Index | | Electronic |
| <input checked="" type="checkbox"/> | 2. Labeling (check one) | <input checked="" type="checkbox"/> Draft Labeling <input type="checkbox"/> Final Printed Labeling | Electronic |
| <input checked="" type="checkbox"/> | 3. Summary (21 CFR 314.50 (c)) | | Electronic |
| <input checked="" type="checkbox"/> | 4. Chemistry section | | Electronic |
| <input checked="" type="checkbox"/> | A. Chemistry, manufacturing, and controls information (e.g., 21 CFR 314.50(d)(1); 21 CFR 601.2) | | Electronic |
| <input type="checkbox"/> | B. Samples (21 CFR 314.50 (e)(1); 21 CFR 601.2 (a)) (Submit only upon FDA's request) | | |
| <input checked="" type="checkbox"/> | C. Methods validation package (e.g., 21 CFR 314.50(e)(2)(i); 21 CFR 601.2) | | Electronic |
| <input checked="" type="checkbox"/> | 5. Nonclinical pharmacology and toxicology section (e.g., 21 CFR 314.50(d)(2); 21 CFR 601.2) | | Electronic |
| <input checked="" type="checkbox"/> | 6. Human pharmacokinetics and bioavailability section (e.g., 21 CFR 314.50(d)(3); 21 CFR 601.2) | | Electronic |
| <input type="checkbox"/> | 7. Clinical Microbiology (e.g., 21 CFR 314.50(d)(4)) | | |
| <input checked="" type="checkbox"/> | 8. Clinical data section (e.g., 21 CFR 314.50(d)(5); 21 CFR 601.2) | | Electronic |
| <input type="checkbox"/> | 9. Safety update report (e.g., 21 CFR 314.50(d)(5)(vi)(b); 21 CFR 601.2) | | |
| <input type="checkbox"/> | 10. Statistical section (e.g., 21 CFR 314.50(d)(6); 21 CFR 601.2) | (Information provided in Section 8) | Electronic |
| <input checked="" type="checkbox"/> | 11. Case report tabulations (e.g., 21 CFR 314.50(f)(1); 21 CFR 601.2) | | Electronic |
| <input checked="" type="checkbox"/> | 12. Case report forms (e.g., 21 CFR 314.50 (f)(2); 21 CFR 601.2) | | Electronic |
| <input checked="" type="checkbox"/> | 13. Patent information on any patent which claims the drug (21 U.S.C. 355(b) or (c)) | | Electronic |
| <input checked="" type="checkbox"/> | 14. A patent certification with respect to any patent which claims the drug (21 U.S.C. 355 (b)(2) or (j)(2)(A)) | | Electronic |
| <input type="checkbox"/> | 15. Establishment description (21 CFR Part 600, if applicable) | | |
| <input checked="" type="checkbox"/> | 16. Debarment certification (FD&C Act 306 (k)(1)) | | Electronic |
| <input checked="" type="checkbox"/> | 17. Field copy certification (21 CFR 314.50 (l)(3)) | | Electronic |
| <input checked="" type="checkbox"/> | 18. User Fee Cover Sheet (Form FDA 3397) | | Electronic |
| <input checked="" type="checkbox"/> | 19. Financial Information (21 CFR Part 54) | | Electronic |
| <input checked="" type="checkbox"/> | 20. OTHER (Specify) FDA Meeting Minutes | | Electronic |
| 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: | | | |
| <ol style="list-style-type: none"> 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: |
|  | | Barry M. Calvarese, MS, Vice President, Regulatory & Clinical | 2/6/04 |
| ADDRESS (Street, City, State, and ZIP Code) | | Telephone Number | |
| 1330A Redwood Way, Petaluma, CA 94954-1169 | | (707) 793-2600 | |
| 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 CDER, HFD-99 1401 Rockville Pike Rockville, MD 20852-1448 | | Food and Drug Administration CDER (HFD-94) 12229 Wilkins Avenue Rockville, MD 20852 | |
| 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. | | | |

2 Page(s) Withheld

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Draft Labeling (b4)

Draft Labeling (b5)

Deliberative Process (b5)

PRESCRIPTION DRUG USER FEE COVER SHEET

See Instructions on Reverse Side Before Completing This Form

A completed form must be signed and accompany each new drug or biologic product application and each new supplement. See exceptions on the reverse side. If payment is sent by U.S. mail or courier, please include a copy of this completed form with payment. Payment instructions and fee rates can be found on CDER's website: <http://www.fda.gov/cder/pdufa/default.htm>

| | |
|--|---|
| 1. APPLICANT'S NAME AND ADDRESS Dow Pharmaceutical Sciences 1330A Redwood Way Petaluma, CA 94954-1169 | 4. BLA SUBMISSION TRACKING NUMBER (STN) / NDA NUMBER 21,739 |
| 2. TELEPHONE NUMBER (Include Area Code) (707) 793-2600 | 5. DOES THIS APPLICATION REQUIRE CLINICAL DATA FOR APPROVAL? <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO IF YOUR RESPONSE IS "NO" AND THIS IS FOR A SUPPLEMENT, STOP HERE AND SIGN THIS FORM. IF RESPONSE IS "YES", CHECK THE APPROPRIATE RESPONSE BELOW: <input checked="" type="checkbox"/> THE REQUIRED CLINICAL DATA ARE CONTAINED IN THE APPLICATION. <input type="checkbox"/> THE REQUIRED CLINICAL DATA ARE SUBMITTED BY REFERENCE TO: _____ (APPLICATION NO. CONTAINING THE DATA). |
| 3. PRODUCT NAME ClinRA | 6. USER FEE I.D. NUMBER 4688 |

7. IS THIS APPLICATION COVERED BY ANY OF THE FOLLOWING USER FEE EXCLUSIONS? IF SO, CHECK THE APPLICABLE EXCLUSION.

| | |
|--|---|
| <input type="checkbox"/> A LARGE VOLUME PARENTERAL DRUG PRODUCT APPROVED UNDER SECTION 505 OF THE FEDERAL FOOD, DRUG, AND COSMETIC ACT BEFORE 9/1/92 (Self Explanatory) | <input type="checkbox"/> A 505(b)(2) APPLICATION THAT DOES NOT REQUIRE A FEE (See item 7, reverse side before checking box.) |
| <input type="checkbox"/> THE APPLICATION QUALIFIES FOR THE ORPHAN EXCEPTION UNDER SECTION 736(a)(1)(E) of the Federal Food, Drug, and Cosmetic Act (See item 7, reverse side before checking box.) | <input type="checkbox"/> THE APPLICATION IS SUBMITTED BY A STATE OR FEDERAL GOVERNMENT ENTITY FOR A DRUG THAT IS NOT DISTRIBUTED COMMERCIALY (Self Explanatory) |

8. HAS A WAIVER OF AN APPLICATION FEE BEEN GRANTED FOR THIS APPLICATION? YES NO
(See Item 8, reverse side if answered YES)

Public reporting burden for this collection of information is estimated to average 30 minutes per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

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

Food and Drug Administration
CDER, HFD-94
and 12420 Parklawn Drive, Room 3046
Rockville, MD 20852

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|--|--|--------------------|
| SIGNATURE OF AUTHORIZED COMPANY REPRESENTATIVE | TITLE Vice President, Regulatory and Clinical Affairs | DATE 12/18/2003 |
|--|--|--------------------|

MEMORANDUM OF TELECON

DATE: September 26, 2003 TIME: 2:00 PM

APPLICATION NUMBER: IND 65,531

DRUG PRODUCT: Clin-RA Gel

BETWEEN:

Name: Barry Calvarese, VP, Regulatory & Clinical Affairs

Phone: (707) 793-2600

Representing: Dow Pharmaceutical Sciences

AND

Name: Division of Dermatologic and Dental Drug Products, HFD-540

Stanka Kukich, Division Deputy Director

Markham Luke, M.D., Ph.D., Clinical Team Leader

Brenda Carr, M.D., Clinical Reviewer

Leonthena Carrington, Regulatory Project Manager

Jacquelyn Smith, Regulatory Project Manager

SUBJECT: IND 65,531

The teleconference was requested by the Division to discuss the above referenced IND. A Pre-NDA meeting is scheduled with the Sponsor on October 1, 2003. During this teleconference, the Division conveyed to the Sponsor that it was unusual to have a Pre-NDA meeting while clinical trials are ongoing and with no safety and efficacy data included in a briefing package. The Division told the Sponsor that a summary of safety and efficacy data was needed for a more productive meeting. With this being noted, the Division suggested postponing or reclassifying the Pre-NDA meeting to a teleconference or a face-to-face Guidance meeting.

The Agency also stated that the Sponsor's briefing document included no long term safety data and inquired if the Sponsor had any such data, per the ICH E1A Guideline for Industry. The Sponsor replied that there were no long term safety data and that long term safety was not addressed in the Pre-IND or EOP2 meetings. The sponsor acknowledged being familiar with the ICH E1A Guideline for Industry. The Agency wanted to know how the Sponsor planned to meet the requirement for long-term safety data. The Sponsor expressed that the issue of long-term safety had not been raised in the development of any of their other acne products. The Sponsor was advised to submit a proposal for addressing long-term safety. The Sponsor was also advised that long term safety data might be considered as a Phase 4 commitment; however, their proposal for addressing long-term safety should be submitted for review.

The Sponsor was also asked to submit the proposed label before the Sponsor meeting, as it was not submitted in the briefing document. The Sponsor stated that they would fax the proposed label.

The Sponsor stated that they plan to have the SAS program results around the first week in December. This timeframe will be discussed with Medicis.

The Sponsor stated that they were looking at submitting the NDA at the end of this year. The Sponsor also stated that the suggestion to postpone the Pre-NDA meeting or reclassify as a Guidance meeting would be discussed with their their partner, Medicis Pharmaceutical Sciences. This would mean rescheduling the meeting for the first week in December, preferably December 8, 2003. The Sponsor wanted a commitment to accommodate the date, so that NDA can still be filed by the end of this year.

Action Item: Project Manger will check on available dates in early December to reschedule Pre-NDA meeting.

Addendum: The proposed label was faxed on September 26, 2003. The Sponsor responded by fax on September 26, 2003 that they decided to keep their original Pre-NDA meeting date of October 1, 2003.

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/s/

Stanka Kukich
10/27/03 08:45:16 AM

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MEMORANDUM OF MEETING MINUTES



Meeting Date: October 1, 2003 **Time:** 1:00 PM
Location: 9201 Corporate, N225 **Meeting ID:** 11326
Topic: IND 65, 531, Clin-RA Gel
Subject: Pre-NDA Meeting
Sponsor: Dow Pharmaceutical Sciences
Meeting Chair: Stanka Kukich, M.D., Deputy Division Director, DDDDP, HFD-540
acting for Jonathan Wilkin, M.D., Division Director, DDDDP, HFD-540

Meeting Recorder: Jacquelyn Smith., Project Manager, DDDDP, HFD-540

FDA Attendees:

Stanka Kukich, M.D., Deputy Division Director, DDDDP, HFD-540
Markham C. Luke, M.D., Ph.D./Team Leader, Clinical, DDDDP, HFD-540
Wilson DeCamp, Ph.D., Team Leader, Chemistry, DNDCIII, HFD-830
Saleh Turujman, Ph.D., Chemistry Reviewer, DNDCIII, HFD-830
Paul Brown, Ph.D., Pharmacology-Toxicology Reviewer, DDDDP, HFD-540
Brenda Carr, M.D., Clinical Reviewer, DDDDP, HFD-540
Shiowjen Lee, Ph.D., Biostatistian, DBIII, HFD-725
Terri Rumble, R.N., B.S.N, Associate Director of Regulatory Affairs, ODE V, HFD-105
Jacquelyn Smith, Regulatory Project Manager, DDDDP HFD-540

Sponsor Attendees:

Dow

Gordon J. Dow, PharmD, Founder, Chief Technical Officer
Karl Beunter, M.D., Ph.D., Chief Medical Officer
Barry M. Calvarese, MS, Vice President Regulatory and Clinical Affairs
Charles G. Chavdarian, Ph.D., Senior Director of Analytical Services
Elena Serbinova, Ph.D., Associate Director of Regulatory Affairs

Medicis

Todd Plott, M.D., Vice President, Clinical Research and Regulatory Affairs
Michelle Wells, Regulatory Manager
Debra Marti, Senior Project Team Leader

Consultants:

b(4)

Purpose:

To provide general guidance on the content and format of the Investigational New Drug Application under 21CFR 312. The pre-NDA meeting briefing document provides background and questions for discussion. To discuss the information that will be submitted in the NDA for Clin-RA Gel.

Electronic Submission:

This NDA will be submitted in electronic CDER format and will comply with the current guidance document entitled "Providing Regulatory Submissions in Electronic Format NDAs", January 1999. The electronic submission will be a stand alone document with a PDF table of contents with hyper links, table of contents formatted to 356h and hyperlink capability in the text. An archival copy will be provided in electronic format.

Sponsor's Question #1:

How many review copies of the electronic NDA do you require?

Agency Response:

The Agency does not require any review copies of the electronic NDA.

Sponsor's Question #2:

Are there any issues related to the Derm Divisions's preferences for electronic NDA submissions that need to be discussed? For example, do any of the potential reviewers require particular cross-references, bookmarks, or review aids?

Agency Response:

It is often helpful to prepare a small sample demonstrating of the level of bookmarking and hyperlinking you were planning. The only review aid that should be submitted is an MS Word copy of your draft labeling in addition to the PDF version you submit.

Sponsor's Question #3:

Can the Field Copy be provided in electronic format or must it be a paper copy?

Agency Response:

Contact your field office to determine if the electronic materials you have submitted to CDER are sufficient.

Other Comments:

Please refer to the guidance, Providing Regulatory Submissions in Electronic Format-NDAs, <http://www.fda.gov/cder/guidance/2353fml.pdf>. The electronic submissions contact persons are Gary Gensinger (Gensinger@cder.fda.gov) and Randy Levin (Levinr@cder.fda.gov).

The Sponsor was advised that Gary Gensinger is the contact person regarding submission of an electronic NDA. The Sponsor was also referred to the website, esub@cder.fda.gov, for guidance in submitting an electronic NDA.

Chemistry, Manufacturing and Controls:

Sponsor's Question #1:

Does the information provided comply with the general requirements for filing the NDA?

FDA Response:

Yes, but please note the following reminders.

- To include the establishment registration number for all facilities. No facility description is needed for the NDA. The facility description can be located on-site for the FDA investigator. [FDA no longer accepts Type 1 DMFs, which contain essentially the same kind of information (facility description)].
- (Under "I. Drug Substance, D. Tests, Specifications and Analytical Methods of the Drug Substance") To report, identify and qualify the impurities at the thresholds indicated in the revised ICH Q3A Guidance. For a drug product with a maximum daily dose of ≤ 2 g, the thresholds are 0.05, 0.10, and 0.15%, respectively.
- To include the "Pharmaceutical Development", together with the investigational formulations.
-
-
-
-
-
-
- To include the following in their Method Validation package:
 - A Tabular Listing of All Samples To Be Submitted
 - A Listing of All Proposed Regulatory Specifications
 - Information Supporting the Integrity of the Reference Standard
 - A Detailed Description of Each Method of Analysis
 - Information Supporting the Suitability of the Methodology for the New Drug Substance
 - Information Supporting the Suitability Methodology for the Dosage FormPlease refer to the 1987 Guideline: Guideline for Submitting Samples and Analytical Data for Methods Validation.

b(4)

Sponsor's Question #2:

Does the outlined stability program meet with the Agency's approval?

FDA Response:

The outlined stability program is deficient in the following areas:

- (a) Please identify the source of the drug substance used in, and the manufacturing site of, each of the primary stability batches of the drug product. These stability batches should be designed in such a manner that ~~the~~ proposed clindamycin phosphate sources and ~~the~~ proposed drug product manufacturing sites are represented.

b(4)

(b) According to the recommendation in Q1A(R), there should be at least 12 months of long-term stability data on a minimum of ~~one~~ primary batches of the drug product. Please include in the NDA 12 months of long-term data on a ~~one~~ primary batch, in addition to the ~~one~~ batches shown in Table 1.8, p. 18. Alternatively, please justify why a reduced amount of stability data is acceptable in this case.

b(4)

(c) It is recommended that updated stability data be submitted in an amendment during the NDA review period, but no later than seven months after the NDA submission. Please indicate in the NDA your plan for such a stability data update.

(d) Although homogeneity test is mentioned at the top of p. 20, it is not included in the stability test attributes for either primary batches (p. 19) or commitment (commercial) batches (p. 21). Please revise the test attributes to include a homogeneity test.

(e) Please be advised that the commitment (commercial) batches of the drug product should be placed on accelerated as well as long-term stability studies, according to Q1A(R).

Pharmacology and Toxicology:

Sponsor's Question #1:

Does the Agency agree that the information provided in this package is sufficient enough to support the 505(b)(1) NDA filing for Clin-RA Gel?

Agency Response:

The proposed content of the nonclinical pharmacology and toxicology section of the NDA appears acceptable to support an NDA for the clindamycin phosphate/tretinoin gel product. This NDA should be submitted under section 505(b)(2) of the FD&C Act since the sponsor is relying on information (literature) derived from underlying data for which they do not have right of reference.

During the meeting the Sponsor acknowledged that they did not have right of reference to some of the underlying pharm/tox data and would therefore be submitting the application as a 505(b)2. The Sponsor raised the question of whether there is any difference in the user fee depending on whether it is a 505(b)(1) or 505(b)(2) application. The Agency will be getting clarification on the Sponsor's user fee question..

Addendum:

Please contact Michael Jones (Jonesm@cder.fda.gov) for user fee clarification.

Microbiology:

Sponsor's Question #1:

The sponsor does not plan on providing information in the Microbiology section of the NDA in addition to what is available in the literature.

Is this acceptable?

Agency Response:

Please see Clinical.

Biopharmaceutics:

Sponsor's Question #1:

Does the Agency require an electronic version of the data (SAS data set) contained in the report from the Phase 2 clinical study "Absorption Evaluation of Clindamycin and Tretinoin Following Maximal Topical Exposure to Clin-RA Gel in Subjects with Moderate to Severe Acne Vulgaris"

Agency Response:

No, given the relatively small size of the data set, an electronic version would not be required.

Clinical:

Sponsor's Question #1:

The proposed new drug formulation, Clin-RA Gel (Clindamycin 1%, Tretinoin 0.025%), is a combination formulation of 1% clindamycin (1.2% clindamycin phosphate) and 0.025% tretinoin. This formulation has been evaluated clinically in four phase 1 studies; a 21-day cumulative dermal irritation study, a contact sensitization (RIPT) study, a phototoxicity study, and a photoallergy study. In addition, the sponsor has performed in a Phase 2 dermal absorption study. All of these studies show this formulation to be safe in healthy subjects. The sponsor believes that this data supports the safety usage of the proposed new product, Clin-RA.

Does the Agency agree that the data are adequate to support NDA approval?

Agency Response:

The appropriate dermal safety studies appear to have been conducted. However, review of the data will determine the extent to which they might be supportive of NDA approval. Further, the Sponsor has not proposed to submit sufficient information regarding long-term safety (see response to Question #3 below). No data or summary of data has been included in the briefing packet; thus, it would be difficult to comment on further safety or efficacy studies needed.

Sponsor's Question #2:

Enrollment for the two Phase 3 studies was completed on July 20, 2003, with a total of 2,524 subjects randomized to receive one of the four study medications. Six hundred ninety seven (697) patients have completed the study and 1,721 patients are currently active. Based on the 12 week treatment period, the last subject is scheduled to complete the study on October 12, 2003. These documents contain summaries of the line listings, draft tables, and statistical plan for these two Phase 3 studies.

Does the Agency agree that the proposed formats for line listings, draft tables, and statistical plan for the two Phase 3 studies are adequate to support NDA approval?

Agency Response:

The proposed formats appear to be acceptable. However, approvability is a review issue. Also, it was previously suggested that the sponsor's statistical plan consider both the change and mean percent change in lesion counts at Week 12. Please see the comments of the statistical reviewer.

Sponsor's Question #3:

A total of approximately 800 acne subjects and 300 healthy subjects will have been exposed to Clin-RA during the clinical development program.

Additional comments:

1. The following reviewer aids are requested as desk copies: the proposed package insert, correspondence with the Agency, discussion of risk/benefit, Integrated Summary of Efficacy and Integrated Summary of Safety.
2. Please include in the submission an index that would enable the reviewer to make the association between investigator's verbatim terminology used to describe an adverse event and the preferred term used for coding the adverse event in the submission's adverse event tables.
3. Please include a graphic presentation of mean scores of each sign and symptom (e.g., erythema, scaling) over time.
4. If the NDA does not contain a Clinical Microbiology section, the wording below would likely be considered acceptable for the Microbiology section of the label: ~~_____~~

b(4)

Biostatistics:

Comments:

(Clinical Program) Question #2:

Enrollment for the two Phase 3 studies was completed on July 20, 2003, with a total of 2,524 subjects randomized to receive one of the four study medications. Six hundred ninety seven (697) patients have completed the studies and 1,721 patients are currently active. Based on the 12-week treatment period, the last subject is scheduled to complete the study on October 13, 2003. This document contains summaries of the line listing, draft tables, and statistical plan for the two Phase 3 studies.

Does the Agency agree that the proposed formats for line listings, draft tables, and statistical plan for the two Phase 3 studies are adequate to support NDA approval?

Agency's Response:

The proposed formats for line listings draft tables and statistical plan generally seem acceptable. However,

- a. The numbers of patients who completed the studies (697) and not yet complete the studies (1,721) do not constitute a total of 2,524 randomized patients, as indicated by the sponsor. According to the ICH E9 guidance, the primary analysis for superiority comparisons should be based on the Intent-to-treat (ITT) population. The Division recommends that the ITT population include all randomized patients who are dispensed drug medication. The sponsor should clarify such a difference.

The sponsor had clarified that approximately 2,400 patients were randomized, not 2,524 patients.

- b. The sponsor's draft tables included analyses of percent change from baseline in inflammatory, non-inflammatory and total lesion counts. Following the Division's comment made at the EOP-2 Meeting (dated 12/16/02), the change in lesion counts from baseline to week 12 should be presented as well.
- c. The sponsor indicated that the analysis of dichotomized Evaluator's Global Severity score would be based on Cochran-Mantel-Haenszel (CMH) test stratified by investigational group (page 8, Section 6.0) and SAS PROC CATMOD procedure (which fits a linear model to functions of response frequencies, page 9, Section 6.0). It is not clear which is the primary analysis. The

sponsor should note that the primary analysis for establishing efficacy should be based on the method pre-specified in the protocols. Others could be supportive.

- d. The Division recommended previously that the last observation carried forward (LOCF) method should be used for imputing missing data for the Global Severity score for the consistency in handling missing data across the various endpoints. Please submit the analysis based on LOCF method for imputing missing data in the NDA in addition to that treating them as failures as proposed.
- e. For the analysis of percent lesion count, the sponsor indicated (page 8, Section 6.0) that the interaction of treatment and investigational group would be removed under the condition explained in Section 3.14. However, no Section 3.14 is identified.
- f. The sponsor listed several secondary efficacy endpoints each to be assessed at different time points (page 5, Section 6.0). The Agency reiterates the comment made previously that if efficacy results for these endpoints are intended for labeling, then these endpoints need to be clinically relevant and multiplicity adjustment would be needed.
Based on the discussion at the meeting, the Division requests that analyses of all secondary efficacy endpoints should be submitted and adjusts for multiplicity.
- g. The formats for line listings draft tables and statistical plan are required for an NDA submission. The approvability of the NDA is a review issue.

(Statistical Analysis) Question #1:

Is the summary information presented in the investigational group analysis sufficient to permit the Agency's review? In other words, is there any other information that the Agency finds necessary to complete the review process at the investigational group level?

Agency's Response:

The summary information presented seems acceptable. However, the sponsor indicated that each pivotal trial was intended to be conducted in a manner such that a minimum of 10 patients would be enrolled per arm for any investigator (page 9, Section 6.0). This would imply that 20 centers should have been included. Approximately 60 study centers participated in each study (page 63, Section 5.0). Please clarify.

The sponsor had clarified that approximately 30 centers were in each study, not 60 centers. Consequently, the enrollment of patients at some centers reached the recommendation, but some centers did not.

(Statistical Analysis) Question #2:

A test for skewness of the distribution (H_0 : skewness = 0) of percent change from baseline in the lesion counts (inflammatory, non-inflammatory, and total) will be conducted for treatment groups. The test will be based on the methods presented in J.H. Zar (2nd Edition 1984. Biostatistical Analysis, Prentice-Hall, Inc. NJ. Section 8.13, page 118-119) and will be applied to the residuals resulting from an ANOVA with factors of treatment and investigational group.

If the two-sided p-value for the skewness test is significant at 0.01, then would the Agency be willing to permit the sponsor to perform a rank transformation of the percent change in lesion counts prior to inferential analysis of the data?

Agency's Response:

The primary analyses for establishing efficacy should be based on the methodology pre-specified in the protocols. However, the sponsor might present other analyses along with their justification. The utility of these analyses in establishing efficacy is a review issue.

Please include the following items in the NDA submission for each study:

- a. Hard copies of Integrated Summary of Efficacy and Integrated Summary of Safety.
- b. Copies of the original study protocols, amendments and randomization lists with documentation.
- c. Electronic data sets in SAS transport file format.

Administrative Comments:

1. 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.
2. Comments shared today with the Sponsor are based upon the contents of the briefing document, which is considered to be an informational aid to facilitate today's discussion. Review of the information submitted to the NDA might identify additional comments or informational requests.

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Stanka Kukich
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MEMORANDUM OF MEETING MINUTES



Meeting Date: December 16, 2002 **Time:** 2:30 PM
Location: 9201 Corporate, S400
Application: IND 65, 531, Clin-RA Gel
Meeting ID: 9579, End-of-Phase 2 Meeting
Sponsor: Dow Pharmaceutical Sciences
Meeting Chair: Jonathan Wilkin, M.D./Division Director
Meeting Recorder: Jacquelyn Smith/Project Manager

FDA Attendees, Titles, and Office/Division:

Jonathan Wilkin, M.D./Division Director, DDDDP, HFD-540
Wilson DeCamp, Ph.D./Team Leader, Chemistry, DNDCIII, HFD-830
Saleh Turujman, Ph.D./Chemistry Reviewer, DNDCIII, HFD-830
Paul Brown, Ph.D./Pharmacology-Toxicology Reviewer, DDDDP, HFD-540
Dennis Bashaw, Pharm.D./Team Leader, Pharmacokinetics, DPEIII, HFD-880
Markham C. Luke, M.D., Ph.D./Team Leader, Clinical, DDDDP, HFD-540
Brenda Carr, M.D./ Clinical Reviewer, DDDDP, HFD-540
Mohamed Al-Osh, Ph.D./Team Leader, Biostatistics, DBIII, HFD-725
Jonca Bull, M.D./Director ODE V, HFD-105
Jacquelyn Smith/ Regulatory Project Manager, DDDDP HFD-540

External Constituent Attendees and Titles:

Dow:

Clawson Bowman, JD, RAC, VP Regulatory Affairs
Gordon Dow, Pharm D, Founder and CTO
Elena Serbinova, PhD, RAC, Associate Director Regulatory Affairs
Karen Yu, PhD, Project Manager
Shawna Lemke, M.D., Clinical Project Manager (Teleconference)

CRO representatives and consultants:

Todd Plott, MD, Executive Director, Clinical Research
Debey Marti, Senior Project Manager
Bhiku G. Patel, PhD, Director Product Development
Mitchell Wortzman, Executive Vice President, Research and Development

b(4)

Purpose:

To provide general guidance on content and format of the investigational New Drug Application under 21 CFR 312. The briefing document submitted November 15, 2002 provides background and questions for discussion.

Chemistry, Manufacturing and Controls:

There were no CMC questions identified in the briefing document. The Agency has the following comments:

Specifications

- ◆ The sponsor states that the impurity profiles for the two drug substances are being defined, and that the impurities will be evaluated as required by the Phase 3 stability protocol. The sponsor was reminded that according to the ICH Q6A, a specification is defined as a list of tests, references to analytical procedures and appropriate acceptance criteria that are numerical limits, ranges or other criteria for the tests described. It was recommended that in the Table of specifications, the column heading [should] read "acceptance criteria", instead of the current "specifications", and that [tentative] acceptance criteria be set for the impurities, as it has been [set] for the drug substances
- ◆ The sponsor was also reminded that specifications for both the drug substance and drug product should be provided. Any subsequent changes to the specifications or to the acceptance criteria should be reported in an information amendment.
- ◆ As was indicated at the pre-IND meeting, the sponsor was reminded that ~~_____~~ and ~~_____~~ are likely impurities ~~_____~~, for which acceptance criteria should be set. Specifically, the sponsor was referred to the recommendation in ICH Q3B (Attachment 1) whereby the analytical methods developed should be capable of detecting and quantifying the main ~~_____~~ at ~~_____~~ in the drug product. Chromatograms obtained under the same HPLC conditions as those used to assay ~~_____~~, using reference standards for these impurities should be provided. b(4)
- ◆ ~~_____~~, NF. ~~_____~~ residue test is required, or a COA from the supplier/manufacturer.

Manufacturing, Process and Process Controls

- ◆ The sponsor is reminded that a general step-by-step description of the manufacturing process should be provided, including key equipment employed. The description should indicate how the material is being processed and can be general enough to allow for flexibility in development in an information amendment. In planning the clinical batch size, the sponsor should consider the production scale of the to-be-marketed-batches (refer to SUPAC-SS Guidance for clinical batch size). A brief description of the packaging and labeling process for clinical supplies should be provided in an Annual Report. Reprocessing procedures and pertinent controls should be described, if applicable.

b(4)

Container Closure System

- ◆ The sponsor is reminded that any changes in the container closure system (also referred to as the packaging system) should be reported.
- ◆ If the liner of the _____ is not food grade, it could adulterate the drug product due to extractants leaching into the vehicle. If the lining is not food grade, it is the sponsor's responsibility to ascertain that their vehicle does not cause extractables to leach into the drug product by including qualitative and quantitative extraction profiles of the container closure using the vehicle or an appropriate solvent. Please refer to Attachment C of the CDER Guidance for Industry "*Container Closure Systems for Packaging Human Drugs and Biologics*", which is available on the CDER website. b(4)

Stability

- ◆ The sponsor states that a stability protocol sufficient to support an NDA has been developed and will be initiated with the manufacturing of the clinical supplies.

The sponsor is reminded of the following:

- ◆ The stability protocol should include an information amendment and include a description of the drug product under investigation in the stability program, a description of the packaging, a list of the tests, sampling time points for each of the tests, expected duration of the stability program.
- ◆ A data table that includes the lot number, manufacturing site, the date of manufacture of the drug product, and the drug substance used to manufacture the lot should be provided in an annual report. Specifically, proposed acceptance criteria for _____ and _____ should be included. Representative chromatograms should be provided, if applicable. b(4)
- ◆ A short description should be provided for each of the test attributes being investigated in the stability program (i.e., stress, long-term, and accelerated) demonstrating that the appropriate controls and storage conditions are in place to ensure the quality of the product used in clinical trials. Tests unique to the stability program should be adequately defined.
- ◆ It is recommended that the NDA submission contain the ICH Q1A(R) recommended stability data package from accelerated and long-term testing on _____ batches of the same formulation of the dosage form in the container closure proposed for marketing. b(4)

Pharmacology/Toxicology:

Sponsor's Question 6:

Nonclinical Program for NDA

Dow Pharmaceutical Sciences ("Dow") agrees with the Agency's requirements and suggestions as defined in the Pre-IND meeting minutes for the nonclinical program and is in the process of implementing them. For the NDA submission Dow will complete a 3-mo dermal toxicity study in minipigs with 1-mo recovery period and a development segment II study with extended pretreatment period. Both study protocols were reviewed and accepted by the Pharm/Tox reviewer.

Dow does not plan to perform any additional nonclinical studies not mentioned in the IND for the NDA.

Does the Agency agree?

Agency Response:

The 3 month dermal toxicity study in minipigs and segment II study reproductive toxicity study are acceptable to support an NDA for Clin-RA Gel. Additional nonclinical studies are not recommended at this time.

Sponsor's Question 7:

Carcinogenicity/Photocarcinogenicity Strategy:

Clindamycin Carcinogenicity

Previously Dow submitted a dermal carcinogenicity study for a product containing Clindamycin 1% in a similar vehicle to the one prepared for Clin-RA Gel. To support the safety of the Clin-RA Gel formulation Dow would like to cross-reference the previously submitted data on Clindamycin 1% Gel (IND ~~XXXXXX~~, SS# 008, June 11, 1999) and is planning to have a separate submission to the IND and Carcinogenicity Advisory Committee (CAC) asking for a waiver of any additional nonclinical carcinogenicity studies with the to-be-marketed formulation, Clin-RA Gel. b(4)

The carcinogenicity study referenced above was reviewed and accepted by the CAC and used to support NDA 50-782 for Clindagel™ (Clindamycin 1% Gel) approved November 7, 2000. Clindagel™ is currently marketed and has no label warnings with respect to carcinogenesis.

Results from the dermal carcinogenicity study performed indicate that under the defined experimental conditions, Clindamycin 1% Gel did not induce dermal carcinogenicity response in mice. In this study, 4 groups of 60 male and 60 female CD-1 mice were treated by dermal application for 2 years. Animals received clindamycin at doses of 27 and 150 mg/kg/day (2.7 mL and 15 mL of Clindamycin 1% Gel respectively). There were no notable neoplastic findings in either sex, which could be attributed to the application of Clindamycin 1% Gel.

Does the Agency agree?

Agency Response:

It is acceptable to address the photocarcinogenicity and carcinogenicity of tretinoin in the NDA based on published literature. It is acceptable to refer to the carcinogenicity study conducted with Clindamycin 1% Gel that was previously submitted by the sponsor to the FDA if the sponsor still has the right to refer to this information. A request for a waiver from the Carcinogenicity Assessment Committee (CAC) for conducting additional carcinogenicity studies would not be necessary. The CAC does not provide waivers for carcinogenicity studies.

Biopharmaceutics:

There were no biopharmaceutics questions identified in the briefing document. The Agency has the following comments:

At the pre-meeting on 9/24/01 the sponsor was advised to address the systemic availability of their active ingredients. In this package the sponsor has indicated that a maximal use study in patients with acne was initiated in Nov. 2002 and that preliminary results are due shortly. At this time we have no further comments for the sponsor but that we look forward to reviewing the data when it becomes available.

Clinical:

Sponsor's Question 2:

In acne vulgaris trials, the usual standard for a 'win' in lesion counting is to be successful in two of three counts, that is inflammatory, non-inflammatory and total lesions counts. In addition to lesion counting, Dow will use the Evaluator's Global Severity Score that was developed as a result of the discussions at the FDA's Advisory Committee Meeting on Acne vulgaris November 4-5, 2002. A "win" based on the Evaluator's Global Severity Score will be either a "clear" or "almost clear" evaluation, or a 2 grade improvement from baseline.

- a) Clin-RA Gel superior to Clindamycin phosphate 1.2% Gel in reducing two of the three following lesion counts: inflammatory lesions (papules and pustules), non-inflammatory lesions (open and closed comedones) and total lesions, as indicated by mean change from baseline at week 12; the percent of subjects who clear or almost clear, or show a 2 grade improvement at Week 12 as judged by the Evaluator's Global Severity Scale.
- b) Clin-RA Gel superior to Tretinoin 0.025% Gel in reducing two of the three following lesion counts: inflammatory lesions, non-inflammatory lesions and total lesions, as indicated by mean change from baseline at week 12; the percent of subjects who clear or almost clear, or show a 2 grade improvement at Week 12 as judged by the Evaluator's Global Severity Scale.
- c) Clin-RA Gel superior to Clin-RA vehicle in reducing two of three following lesion counts: inflammatory lesions, non-inflammatory lesions and total lesions, as indicated by mean change from baseline at week 12, the percent of subjects who clear or almost clear, or show a 2 grade improvement at Week 12 as judged by the Evaluator's Global Severity Scale.

Does the Agency concur with this criteria?

Agency Response:

The sponsor is requested to present the change and mean percent change in lesion counts from baseline to week 12. Pertaining to the global severity score, the recommended primary variable is the proportion of subjects who are clear or almost clear at Week 12.

In question #7 ("Carcinogenicity/Photocarcinogenicity Strategy"), the sponsor indicates that they propose to develop their product for "mild to moderate acne." This should be clearly specified in the

protocol, including in the Inclusion Criteria (i.e., study subjects should have mild to moderate acne at enrollment). It is noted that according to the sponsor's proposed scale, with a two-grade improvement, subjects with mild or moderate acne would achieve the clear or almost clear states, respectively: subjects with mild acne would "clear" (Grade 2 to Grade 0); subjects with moderate acne would "almost clear" (Grade 3 to Grade 1).

Discussion during meeting: The sponsor stated that their intent is to seek a general indication of "acne vulgaris" and that "mild to moderate" was inadvertently left in the text of question #7. The sponsor considers that their proposed lesion counts (particularly as pertains to the minimum of 20 inflammatory lesions) will weight enrollment towards subjects of a "severe" grade and that a two-grade improvement from "severe" to "mild" would be clinically meaningful. The sponsor was advised that while two-grade improvement data could be submitted as supportive, the division would measure efficacy by the proportion of subjects who are "clear" or "almost clear" (Grade 0 and 1, respectively) at efficacy evaluation. The representativeness in the "severe" category would be important to the meaningfulness of the two-grade improvement data.

The sponsor was advised that for a general indication of "acne vulgaris," they could demonstrate efficacy by demonstrating that

- their combination product is superior to vehicle in inflammatory and non-inflammatory lesion counts and the global severity score **and**
- their combination product is superior to both monads in two of three lesion counts (inflammatory, non-inflammatory and total) and the global severity score.

Sponsor's Question 3:

Dow has developed an Evaluator's Global Severity Score Scale based on guidance from the literature and the FDA's Advisory Committee Meeting on Acne vulgaris (November 4-5, 2002). (See abbreviated protocol (Attachment 1-1) for Scale.)

Dow would like the FDA to confirm that they accept the Scale and definitions presented at the Advisory Committee meeting.

Agency Response:

The scale appears to be acceptable; however, the sponsor is requested to clarify the definition of the "mild" category.

Sponsor's Question 4:

The safety of the two active ingredients in Clin-RA Gel, clindamycin phosphate and tretinoin, is well characterized and the drugs are approved for use in a number of products. Therefore, Dow does not intend to conduct any laboratory analysis as part of the Phase 3 studies.

Does the FDA agree?

Agency Response:

Laboratory evaluations should be obtained as clinically indicated.

Sponsor's Question 5:

Dow has excluded non-inflammatory lesion counts from the nose due to the difficulty in distinguishing comedones from large pores on the nose.

Does the FDA find this acceptable?

Agency Response:

It is felt that a distinction can be made between comedones and pores on the nose, and the sponsor is encouraged to attempt to make this distinction in their trials. However, nose lesions can be counted separately from the other areas on the face.

Additional Comments:

1. The rationale for having subjects apply the first dose of study drug under observation of study personnel is unclear. This would not be encouraged in phase 3 trials, unless there is some unique property of the study drugs which would require initial application under observation (and this would be reflected in labeling).
2. It is suggested that subjects be advised to use sunscreen daily and not only when sun exposure is anticipated.
3. It is noted that the sponsor intends to provide a list of acceptable moisturizers/sunscreens and cleansers and study use, rather than specifying a particular product.
4. The sponsor was requested to include burning, stinging and itching in the assessment of local tolerance of their product.

Biostatistics:

The sponsor submitted an abbreviated protocol for 2 identical Phase 3 clinical studies. The sponsor raised several questions related to the abbreviated protocol. The following is response to the questions related to biostatistics based on the information submitted. Additional statistical comments might be added when full text protocols are submitted.

Sponsor's Question 1:

In the current study design, we propose to have a treatment ratio of 2:2:1:1 for Clin-RA Gel:Tretinoin 0.025%:Clindamycin phosphate 1.2%: Clin-RA Gel vehicle, respectively, based on the power calculations of our statistical consultant.

We plan to enroll a total of 1200 subjects in each of the two pivotal trials, with a target range of approximately 40 subjects per site. We do not plan to restrict site enrollment, so some sites may enroll more than 40 subjects.

Does the Agency concur with the enrollment strategy?

Agency Response:

Adequacy of the sample size depends on having reliable estimates for the various treatment arms in the trial. For the sample size determination the sponsor used in Section 9.10 information from Velac to get estimates for differences in percent change from baseline for the combination and tretinoin and clindamycin for inflammatory, non-inflammatory and total lesions. However, the sample size calculation was not powered for the co-primary endpoint, the dichotomized Evaluator's Global Evaluation (EGE). It is recommended that the sponsor power their Phase 3 trials for this co-primary endpoint along with allowance for drop-out to ensure that Phase 3 trials are not under-powered.

Sponsor's Question 2:

In acne vulgaris trials, the usual standard for a 'win' in lesion counting is to be successful in two of three counts, that is inflammatory, non-inflammatory and total lesions counts. In addition to lesion counting, Dow will use the Evaluator's Global Severity Score that was developed as a result of the discussions at the FDA's Advisory Committee Meeting on Acne vulgaris November 4-5, 2002. A "win" based on the Evaluator's Global Severity Score will be either a "clear" or "almost clear" evaluation, or a 2 grade improvement from baseline.

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- b) Clin-RA Gel superior to Tretinoin 0.025% Gel in reducing two of the three following lesion counts: inflammatory lesions, non-inflammatory lesions and total lesions, as indicated by mean change from baseline at week 12; the percent of subjects who clear or almost clear, or show a 2 grade improvement at Week 12 as judged by the Evaluator's Global Severity Scale.
- c) Clin-RA Gel superior to Clin-RA vehicle in reducing two of three following lesion counts: inflammatory lesions, non-inflammatory lesions and total lesions, as indicated by mean change from baseline at week 12, the percent of subjects who clear or almost clear, or show a 2 grade improvement at Week 12 as judged by the Evaluator's Global Severity Scale.

Does the Agency concur with this criteria?

Agency Response:

Sponsor's statement related to question 2. The sponsor proposed to define win based on the Evaluator's Global Severity Score to be either a 'clear' or 'almost clear' evaluation or a 2 grade improvement from baseline. For planning Phase 3 trials, the Division recommends using a 'clear' or 'almost clear' evaluation to define success. The sponsor might carry out a supportive analysis with success defined as a 'clear' or 'almost clear' evaluation or a 2 grade improvement from baseline. The utility of such analysis for establishing efficacy in case such efficacy is not established under 'clear' or 'almost clear' dichotomization will be a review issue.

Sponsor's questions 2.a-2.c are related to criteria for success in terms of lesion counts.

For establishing efficacy of Clin-RA Gel the combination products needs to be:

- (i) Superior to vehicle with respect to inflammatory, non-inflammatory lesion counts in addition to being superior to the vehicle with respect to the dichotomized success rate for the Evaluator Global Evaluation, and
- (ii) Superior to both Clindamycin and Tretinoin 0.025% Gel for two out of the following three lesion types (inflammatory, non-inflammatory and total lesion) in addition to the superiority for the dichotomized success rate for Evaluator Global Evaluation success.

Additional Statistical comments on the statistical methods planned (pp.-32-36 of the sponsor's submission)

- a) The use of what is denoted as 'blocking factor' in Section 9.5 page 32 while is a novel approach it is not recommended as it might introduce bias in the efficacy assessment.
- b) Enrollment should be planned for 10 subjects per treatment arm, as recommended originally. The protocol however might pre-specify a criteria for pooling small center (based on geographic location or center size, or any other reasonable criteria agreed upon with division) in case the actual enrollment turns out to be not meeting this recommendation.
- c) The sponsor's proposed analyses in Section 9.7 under Pooling Analyses is not recommended as efficacy results should be robust and not dependent on certain pooling as a result of post-hoc analyses.

The sponsor is encouraged to submit full text protocols for Phase 3 trials for the Division comments and concurrence.

Administrative Comments:

- 1. 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.
- 2. The Sponsor is encouraged to submit the full text protocol to the IND as Special Protocol through the 45-day Special Protocol Assessment (SPA) mechanism for Agency review, comment and agreement, prior to study initiation.
- 3. Comments shared today with the Sponsor are based upon the contents of the briefing document, which is considered to be an informational aid to facilitate today's discussion. Review of the information submitted to the IND might identify additional comments or informational requests.

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/s/

John Kelsey
3/21/03 02:50:26 PM
for Dr. Wilkin

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/s/

Shalini Jain

9/6/2006 04:04:52 PM

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NDA 50-802

INFORMATION REQUEST LETTER

Dow Pharmaceutical Sciences
1330A Redwood Way
Petaluma, CA 94954-1169
Attention: Barry Calvarese
Vice President, Regulatory and Clinical Affairs

Dear Dr. Calvarese:

Please refer to your February 9, 2004, new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Clin RA Gel (clindamycin, 1%; tretinoin, 0.025%).

We also refer to your submission dated May 5, August 8 and August 11, 2006.

We are reviewing the Chemistry, Manufacturing and Controls section of your submission and have the following comments and requests for additional information. We request a prompt written response by September 1, 2006, in order to continue our evaluation of your NDA.

1. Please include homogeneity test, particle size and weight change in Table 4.26 "Testing to be performed" for all time points. In addition, the microbial limit test (Table 4.27) should be performed at the last time point for long term, intermediate, and accelerated conditions.
2. The August 11, 2006 Amendment provided only labeling text, please provide mock-up container and carton labels. These labels should be presented in the sizes and colors proposed for marketing.
3. Revise the package insert information listed below:
 - a. Replace the proprietary name and established name, as shown below, in the HIGHLIGHTS OF PRESCRIBING INFORMATION and FULL PRESCRIPTION INFORMATION: Bullets 11 (DESCRIPTION) and 16 (HOW SUPPLIED/STORAGE AND HANDLING).
Replace
~~_____~~
with
~~_____~~
 - b. Revise the storage condition to "Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature]"
 - c. Add name and address of the manufacturer or distributor per 21 CFR 201.1.

b(4)

4. Revise all cartons and immediate containers labels:
 - a. Revise the proprietary name and established name following the recommendation in Item 3 above.
 - b. Revise the storage condition to “Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature]”. Where space on the immediate container is limited, either of the following statements are acceptable:
Store at 25°C (77°F); excursions to 15-30 °C (59-86°F) or
Store at 25°C (77°F) (see insert)
5. Revise the proprietary name and established name on the “patient instructions” following the recommendation in Item 3 above.

If you have any questions, call Linda Mullins Athey, Regulatory Health Project Manager for Quality, at 301-796-2096.

Sincerely,

{See appended electronic signature page}

Moo-Jhong Rhee, Ph.D.
Chief, Branch III
Pre-Marketing Assessment Division II
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

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/s/

Moo-Jhong Rhee
8/24/2006 02:47:43 PM

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NDA 50-802

INFORMATION REQUEST LETTER

Dow Pharmaceutical Sciences
1330A Redwood Way
Petaluma, CA 94954-1169
Attention: Barry Calvarese
Vice President, Regulatory and Clinical Affairs

Dear Dr. Calvarese:

Please refer to your February 9, 2004, new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Clin RA Gel (clindamycin, 1%; tretinoin, 0.025%).

We also refer to your submission dated May 5 and August 8, 2006.

We are reviewing the Chemistry, Manufacturing and Controls section of your submission and have the following comments and requests for additional information. We request a prompt written response by August 28, 2006, in order to continue our evaluation of your NDA.

1. Please tighten the acceptance criteria for free Clindamycin ~~_____~~ and total degradation products to NMT ~~_____~~ NMT ~~_____~~ and NMT ~~_____~~, respectively, for the drug product specification. The recommended limits are derived from "mean + 3σ" based on 24 months long term stability data. b(4)

~~_____~~
~~_____~~ Therefore, b(4)
accelerated conditions for 6 months are not indicative for the drug product stability under long term storage conditions for 24 months.

2. The first ~~_____~~ commercial batches should be placed on long term stability studies throughout the proposed shelf life, on intermediate studies, and on accelerated studies per ICH Q1A (R2).

If you have any questions, call Linda Mullins Athey, Regulatory Health Project Manager for Quality, at 301-796-2096.

Sincerely,

{See appended electronic signature page}

Moo-Jhong Rhee, Ph.D.
Chief, Branch III
Pre-Marketing Assessment Division II
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

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/s/

Moo-Jhong Rhee
8/22/2006 11:43:45 AM

REQUEST FOR CONSULTATION

TO (Division/Office):
Fran LeSane/Maureen Dillon Parker/Fred Marsik/Harold Silver
Division of Anti Infective Drug Products

FROM: Shalini Jain
Division of Dermatology and Dental Products

DATE
8/11/06

IND NO.

NDA NO.
50-802

TYPE OF DOCUMENT
RS of NDA

DATE OF DOCUMENT
May 5, 2006

NAME OF DRUG

Clindamycin/tretinoin

PRIORITY CONSIDERATION

This is a 6 month RS review time frame

CLASSIFICATION OF DRUG

Combination antibiotic/retinoid

DESIRED COMPLETION DATE

Prior to labeling review date as determined by team

NAME OF FIRM: Dow

REASON FOR REQUEST

I. GENERAL

- | | | |
|--|--|--|
| <input type="checkbox"/> NEW PROTOCOL | <input type="checkbox"/> PRE-NDA MEETING | <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER |
| <input type="checkbox"/> PROGRESS REPORT | <input type="checkbox"/> END OF PHASE II MEETING | <input type="checkbox"/> FINAL PRINTED LABELING |
| <input type="checkbox"/> NEW CORRESPONDENCE | <input type="checkbox"/> RESUBMISSION | <input type="checkbox"/> LABELING REVISION |
| <input type="checkbox"/> DRUG ADVERTISING | <input type="checkbox"/> SAFETY/EFFICACY | <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE |
| <input type="checkbox"/> ADVERSE REACTION REPORT | <input type="checkbox"/> PAPER NDA | <input type="checkbox"/> FORMULATIVE REVIEW |
| <input type="checkbox"/> MANUFACTURING CHANGE/ADDITION | <input type="checkbox"/> CONTROL SUPPLEMENT | <input type="checkbox"/> OTHER (SPECIFY BELOW): |
| <input type="checkbox"/> MEETING PLANNED BY | | |

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH

STATISTICAL APPLICATION BRANCH

- | | |
|--|---|
| <input type="checkbox"/> TYPE A OR B NDA REVIEW | <input type="checkbox"/> CHEMISTRY REVIEW |
| <input type="checkbox"/> END OF PHASE II MEETING | <input type="checkbox"/> PHARMACOLOGY |
| <input type="checkbox"/> CONTROLLED STUDIES | <input type="checkbox"/> BIOPHARMACEUTICS |
| <input type="checkbox"/> PROTOCOL REVIEW | <input type="checkbox"/> OTHER (SPECIFY BELOW): |
| <input type="checkbox"/> OTHER (SPECIFY BELOW): | |

III. BIOPHARMACEUTICS

- | | |
|--|---|
| <input type="checkbox"/> DISSOLUTION | <input type="checkbox"/> DEFICIENCY LETTER RESPONSE |
| <input type="checkbox"/> BIOAVAILABILITY STUDIES | <input type="checkbox"/> PROTOCOL-BIOPHARMACEUTICS |
| <input type="checkbox"/> PHASE IV STUDIES | <input type="checkbox"/> IN-VIVO WAIVER REQUEST |

IV. DRUG EXPERIENCE

- | | |
|--|--|
| <input type="checkbox"/> PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL | <input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY |
| <input type="checkbox"/> DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES | <input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE |
| <input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below) | <input type="checkbox"/> POISON RISK ANALYSIS |
| <input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP | |

V. SCIENTIFIC INVESTIGATIONS

CLINICAL

PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS:

This NDA previously received a NA and the sponsor conducted additional studies. The PDUFA due date is 11/8/06. Mid Cycle meeting already scheduled as well as labeling review dates.

PM Shalini Jain

Thank you.

SIGNATURE OF REQUESTER

METHOD OF DELIVERY (Check one)

MAIL

HAND

SIGNATURE OF RECEIVER

SIGNATURE OF DELIVERER

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/s/

Frances LeSane
8/15/2006 10:02:03 AM

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ACTION PACKAGE CHECKLIST

| Application Information | | |
|---|----------------------------------|---|
| BLA # NDA # 50-802 | BLA STN# NDA Supplement # N/A | If NDA, Efficacy Supplement Type |
| Proprietary Name: ZIANA Gel Established Name: clindamycin phosphate 1.2% and tretinoin 0.025% Dosage Form: Topical Gel | | Applicant: Medicis, The Dermatology Company |
| RPM: Shalini Jain | | Division: DDDP Phone # 301-796-0692 |
| <p>NDA Application Type: <input type="checkbox"/> 505(b)(1) <input checked="" type="checkbox"/> 505(b)(2)</p> <p>Efficacy Supplement: <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)</p> <p>(A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). Consult page 1 of the NDA Regulatory Filing Review for this application or Appendix A to this Action Package Checklist.)</p> | | <p>505(b)(2) NDAs and 505(b)(2) NDA supplements: Listed drug(s) referred to in 505(b)(2) application (NDA #(s), Drug name(s)):</p> <p>Retin A Gel and clindamycin</p> <p>Provide a brief explanation of how this product is different from the listed drug. combination product with clindamycin phosphate 1.2% and tretinoin 0.025% gel</p> <p><input type="checkbox"/> If no listed drug, check here and explain:</p> <p>Review and confirm the information previously provided in Appendix B to the Regulatory Filing Review. Use this Checklist to update any information (including patent certification information) that is no longer correct.</p> <p><input checked="" type="checkbox"/> Confirmed <input type="checkbox"/> Corrected Date: 11/3/06</p> |
| ❖ User Fee Goal Date | | 12/09/04 |
| ❖ Action Goal Date (if different) | | 11/08/06 |
| ❖ Actions | | |
| • Proposed action | | <input checked="" type="checkbox"/> AP <input type="checkbox"/> TA <input type="checkbox"/> AE <input type="checkbox"/> NA <input type="checkbox"/> CR |
| • Previous actions (specify type and date for each action taken) | | <input type="checkbox"/> None NA, 12/07/04 |
| ❖ Advertising (approvals only) Note: If accelerated approval (21 CFR 314.510/601.41), advertising must have been submitted and reviewed (indicate dates of reviews) | | <input checked="" type="checkbox"/> Requested in AP letter <input type="checkbox"/> Received and reviewed |

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| | |
|--|---|
| ❖ Application Characteristics | |
| Review priority: <input type="checkbox"/> Standard <input checked="" type="checkbox"/> Priority Chemical classification (new NDAs only): 3S NDAs, BLAs and Supplements: <input type="checkbox"/> Fast Track <input type="checkbox"/> Rolling Review <input type="checkbox"/> CMA Pilot 1 <input type="checkbox"/> CMA Pilot 2 <input type="checkbox"/> Orphan drug designation NDAs: Subpart H <input type="checkbox"/> Accelerated approval (21 CFR 314.510) <input type="checkbox"/> Restricted distribution (21 CFR 314.520) Subpart I <input type="checkbox"/> Approval based on animal studies BLAs: Subpart E <input type="checkbox"/> Accelerated approval (21 CFR 601.41) <input type="checkbox"/> Restricted distribution (21 CFR 601.42) Subpart H <input type="checkbox"/> Approval based on animal studies NDAs and NDA Supplements: <input type="checkbox"/> OTC drug Other: resubmission after NA requiring 6 month review clock for resubmission Other comments: | |
| ❖ Application Integrity Policy (AIP) | |
| <ul style="list-style-type: none"> Applicant is on the AIP | <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No |
| <ul style="list-style-type: none"> This application is on the AIP <ul style="list-style-type: none"> Exception for review (<i>file Center Director's memo in Administrative Documents section</i>) OC clearance for approval (<i>file communication in Administrative Documents section</i>) | <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No <input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Yes <input type="checkbox"/> Not an AP action |
| ❖ Public communications (approvals only) | |
| <ul style="list-style-type: none"> Office of Executive Programs (OEP) liaison has been notified of action | <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No |
| <ul style="list-style-type: none"> Press Office notified of action | <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No |
| <ul style="list-style-type: none"> Indicate what types (if any) of information dissemination are anticipated | <input checked="" type="checkbox"/> None <input type="checkbox"/> FDA Press Release <input type="checkbox"/> FDA Talk Paper <input type="checkbox"/> CDER Q&As <input type="checkbox"/> Other |

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| ❖ Exclusivity | |
|---|---|
| <ul style="list-style-type: none"> • NDAs: Exclusivity Summary (approvals only) (<i>file Summary in Administrative Documents section</i>) | <input checked="" type="checkbox"/> Included |
| <ul style="list-style-type: none"> • Is approval of this application blocked by any type of exclusivity? <ul style="list-style-type: none"> • NDAs/BLAs: Is there existing orphan drug exclusivity for the “same” drug or biologic for the proposed indication(s)? <i>Refer to 21 CFR 316.3(b)(13) for the definition of “same drug” for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification.</i> • NDAS: Is there remaining 5-year exclusivity that would bar effective approval of a 505(b)(2) application? (<i>Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.</i>) • NDAs: Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? (<i>Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.</i>) • NDAs: Is there remaining 6-month pediatric exclusivity that would bar effective approval of a 505(b)(2) application? (<i>Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.</i>) | <input checked="" type="checkbox"/> No <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If, yes, NDA/BLA # and date exclusivity expires: <input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If, yes, NDA # and date exclusivity expires: <input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If, yes, NDA # and date exclusivity expires: |
| ❖ Patent Information (NDAs and NDA supplements only) | |
| <ul style="list-style-type: none"> • Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought. If the drug is an old antibiotic, skip the Patent Certification questions. | <input checked="" type="checkbox"/> Verified <input type="checkbox"/> Not applicable because drug is an old antibiotic. |
| <ul style="list-style-type: none"> • Patent Certification [505(b)(2) applications]: Verify that a certification was submitted for each patent for the listed drug(s) in the Orange Book and identify the type of certification submitted for each patent. • [505(b)(2) applications] If the application includes a paragraph III certification, it cannot be approved until the date that the patent to which the certification pertains expires (but may be tentatively approved if it is otherwise ready for approval). | 21 CFR 314.50(i)(1)(i)(A) <input checked="" type="checkbox"/> Verified 21 CFR 314.50(i)(1) <input checked="" type="checkbox"/> (ii) <input type="checkbox"/> (iii) <input checked="" type="checkbox"/> No paragraph III certification Date patent will expire |
| <ul style="list-style-type: none"> • [505(b)(2) applications] For each paragraph IV certification, verify that the applicant notified the NDA holder and patent owner(s) of its certification that the patent(s) is invalid, unenforceable, or will not be infringed (review documentation of notification by applicant and documentation of receipt of notice by patent owner and NDA holder). (<i>If the application does not include any paragraph IV certifications, mark “N/A” and skip to the next section below (Summary Reviews).</i>) • [505(b)(2) applications] For each paragraph IV certification, based on the questions below, determine whether a 30-month stay of approval is in effect due to patent infringement litigation. <p>Answer the following questions for each paragraph IV certification:</p> <p>(1) Have 45 days passed since the patent owner’s receipt of the applicant’s</p> | <input checked="" type="checkbox"/> N/A (no paragraph IV certification) <input type="checkbox"/> Verified <input type="checkbox"/> Yes <input type="checkbox"/> No |

notice of certification?

(Note: The date that the patent owner received the applicant's notice of certification can be determined by checking the application. The applicant is required to amend its 505(b)(2) application to include documentation of this date (e.g., copy of return receipt or letter from recipient acknowledging its receipt of the notice) (see 21 CFR 314.52(e)).

If "Yes," skip to question (4) below. If "No," continue with question (2).

- (2) Has the patent owner (or NDA holder, if it is an exclusive patent licensee) submitted a written waiver of its right to file a legal action for patent infringement after receiving the applicant's notice of certification, as provided for by 21 CFR 314.107(f)(3)?

Yes No

If "Yes," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (Summary Reviews).

If "No," continue with question (3).

- (3) Has the patent owner, its representative, or the exclusive patent licensee filed a lawsuit for patent infringement against the applicant?

Yes No

(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)).

If "No," the patent owner (or NDA holder, if it is an exclusive patent licensee) has until the expiration of the 45-day period described in question (1) to waive its right to bring a patent infringement action or to bring such an action. After the 45-day period expires, continue with question (4) below.

- (4) Did the patent owner (or NDA holder, if it is an exclusive patent licensee) submit a written waiver of its right to file a legal action for patent infringement within the 45-day period described in question (1), as provided for by 21 CFR 314.107(f)(3)?

Yes No

If "Yes," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (Summary Reviews).

If "No," continue with question (5).

- (5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the (b)(2) applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification?

Yes No

(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced

| | |
|---|---|
| <p>within the 45-day period).</p> <p>If "No," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (Summary Reviews).</p> <p>If "Yes," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007) and attach a summary of the response.</p> | |
| <p>Summary Reviews</p> | |
| <p>❖ Summary Reviews (e.g., Office Director, Division Director) (indicate date for each review)</p> | <p>10/23/06</p> |
| <p>❖ BLA approvals only: Licensing Action Recommendation Memo (LARM) (indicate date)</p> | <p>N/A</p> |
| <p>Labeling</p> | |
| <p>❖ Package Insert</p> | |
| <ul style="list-style-type: none"> • Most recent division-proposed labeling (only if generated after latest applicant submission of labeling) | <p>11/06/06</p> |
| <ul style="list-style-type: none"> • Most recent applicant-proposed labeling (only if subsequent division labeling does not show applicant version) | <p>11/06/06</p> |
| <ul style="list-style-type: none"> • Original applicant-proposed labeling • Other relevant labeling (e.g., most recent 3 in class, class labeling), if applicable | <p>09/06/06</p> |
| <p>❖ Patient Package Insert</p> | |
| <ul style="list-style-type: none"> • Most-recent division-proposed labeling (only if generated after latest applicant submission of labeling) | <p>11/06/06</p> |
| <ul style="list-style-type: none"> • Most recent applicant-proposed labeling (only if subsequent division labeling does not show applicant version) | <p>11/06/06</p> |
| <ul style="list-style-type: none"> • Original applicant-proposed labeling • Other relevant labeling (e.g., most recent 3 in class, class labeling), if applicable | <p>09/06/06</p> |
| <p>❖ Medication Guide</p> | |
| <ul style="list-style-type: none"> • Most recent division-proposed labeling (only if generated after latest applicant submission of labeling) | |
| <ul style="list-style-type: none"> • Most recent applicant-proposed labeling (only if subsequent division labeling does not show applicant version) | |
| <ul style="list-style-type: none"> • Original applicant-proposed labeling • Other relevant labeling (e.g., most recent 3 in class, class labeling) | |
| <p>❖ Labels (full color carton and immediate-container labels)</p> | |
| <ul style="list-style-type: none"> • Most-recent division-proposed labels (only if generated after latest applicant submission) | <p>11/06/06</p> |
| <ul style="list-style-type: none"> • Most recent applicant-proposed labeling | <p>11/06/06</p> |
| <p>❖ Labeling reviews and minutes of any labeling meetings (indicate dates of reviews and meetings)</p> | <p><input checked="" type="checkbox"/> DMETS 10/23/06 <input checked="" type="checkbox"/> DSRCS 10/18/06 <input checked="" type="checkbox"/> DDMAC 10/04/06 <input checked="" type="checkbox"/> SEALD 10/11/06 <input type="checkbox"/> Other reviews <input type="checkbox"/> Memos of Mtgs</p> |

Administrative Documents

| | |
|---|---|
| ❖ Administrative Reviews (RPM Filing Review/Memo of Filing Meeting; ADRA) (<i>indicate date of each review</i>) | 04/12/04 (original) and 10/18/06 (resubmission w/corrections) |
| ❖ NDA and NDA supplement approvals only: Exclusivity Summary (<i>signed by Division Director</i>) | <input type="checkbox"/> Included |
| ❖ AIP-related documents <ul style="list-style-type: none"> Center Director's Exception for Review memo If AP: OC clearance for approval | |
| ❖ Pediatric Page (all actions) | <input checked="" type="checkbox"/> Included |
| ❖ Debarment certification (original applications only): verified that qualifying language was not used in certification and that certifications from foreign applicants are cosigned by U.S. agent. (<i>Include certification.</i>) | <input checked="" type="checkbox"/> Verified, statement is acceptable |
| ❖ Postmarketing Commitment Studies <ul style="list-style-type: none"> Outgoing Agency request for post-marketing commitments (<i>if located elsewhere in package, state where located</i>) Incoming submission documenting commitment | <input checked="" type="checkbox"/> None |
| ❖ Outgoing correspondence (letters including previous action letters, emails, faxes, telecons) | included |
| ❖ Internal memoranda, telecons, email, etc. | included |
| ❖ Minutes of Meetings | |
| • Pre-Approval Safety Conference (<i>indicate date; approvals only</i>) | N/A |
| • Pre-NDA/BLA meeting (<i>indicate date</i>) | <input type="checkbox"/> No mtg 10/01/03 |
| • EOP2 meeting (<i>indicate date</i>) | <input type="checkbox"/> No mtg 12/12/02 |
| • Other (e.g., EOP2a, CMC pilot programs) | N/A |
| ❖ Advisory Committee Meeting | <input checked="" type="checkbox"/> No AC meeting |
| • Date of Meeting | |
| • 48-hour alert or minutes, if available | |
| ❖ Federal Register Notices, DESI documents, NAS/NRC reports (if applicable) | |

CMC/Product Quality Information

| | |
|--|--|
| ❖ CMC/Product review(s) (<i>indicate date for each review</i>) | 12/07/04 & 9/22/06 & 10/18/06 |
| ❖ Reviews by other disciplines/divisions/Centers requested by CMC/product reviewer (<i>indicate date for each review</i>) | <input checked="" type="checkbox"/> None |
| ❖ BLAs: Product subject to lot release (APs only) | <input type="checkbox"/> Yes <input type="checkbox"/> No |
| ❖ Environmental Assessment (check one) (original and supplemental applications) | |
| • <input type="checkbox"/> Categorical Exclusion (<i>indicate review date</i>)(<i>all original applications and all efficacy supplements that could increase the patient population</i>) | 12/07/04 |
| • <input type="checkbox"/> Review & FONSI (<i>indicate date of review</i>) | N/A |
| • <input type="checkbox"/> Review & Environmental Impact Statement (<i>indicate date of each review</i>) | N/A |
| ❖ NDAs: Microbiology reviews (sterility & apyrogenicity) (<i>indicate date of each review</i>) | N/A |
| ❖ Facilities Review/Inspection | <input checked="" type="checkbox"/> Not a parenteral product |
| ❖ NDAs: Facilities inspections (include EER printout) | Date completed: 04/16/04 <input checked="" type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation |

| | |
|--|--|
| ❖ BLAs: Facility-Related Documents <ul style="list-style-type: none"> • Facility review (<i>indicate date(s)</i>) • Compliance Status Check (approvals only, both original and supplemental applications) (<i>indicate date completed, must be within 60 days prior to AP</i>) | <input type="checkbox"/> Requested <input type="checkbox"/> Accepted <input type="checkbox"/> Hold |
| ❖ NDAs: Methods Validation | <input type="checkbox"/> Completed <input checked="" type="checkbox"/> Requested <input type="checkbox"/> Not yet requested <input type="checkbox"/> Not needed |
| Nonclinical Information | |
| ❖ Pharm/tox review(s), including referenced IND reviews (<i>indicate date for each review</i>) | 11/23/04 & 10/19/04 |
| ❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer (<i>indicate date for each review</i>) | <input checked="" type="checkbox"/> None |
| ❖ Statistical review(s) of carcinogenicity studies (<i>indicate date for each review</i>) | <input checked="" type="checkbox"/> No carc |
| ❖ ECAC/CAC report/memo of meeting | N/A |
| ❖ Nonclinical inspection review Summary (DSI) | <input checked="" type="checkbox"/> None requested |
| Clinical Information | |
| ❖ Clinical review(s) (<i>indicate date for each review</i>) | 12/07/04 & 10/31/06 |
| ❖ Financial Disclosure reviews(s) or location/date if addressed in another review | 10/31/06 |
| ❖ Clinical consult reviews from other review disciplines/divisions/Centers (<i>indicate date of each review</i>) | <input type="checkbox"/> None micro only see below |
| ❖ Microbiology (efficacy) reviews(s) (<i>indicate date of each review</i>) | <input type="checkbox"/> Not needed 09/13/06 |
| ❖ Safety Update review(s) (<i>indicate location/date if incorporated into another review</i>) | 12/07/04 |
| ❖ Risk Management Plan review(s) (including those by OSE) (<i>indicate location/date if incorporated into another review</i>) | N/A |
| ❖ Controlled Substance Staff review(s) and recommendation for scheduling (<i>indicate date of each review</i>) | <input checked="" type="checkbox"/> Not needed |
| ❖ DSI Inspection Review Summary(ies) (<i>include copies of DSI letters to investigators</i>) | <input checked="" type="checkbox"/> None requested |
| • Clinical Studies(II) | |
| • Bioequivalence Studies | |
| • Clin Pharm Studies | |
| ❖ Statistical Review(s) (<i>indicate date for each review</i>) | <input type="checkbox"/> None 10/15/04 & 10/11/06 |
| ❖ Clinical Pharmacology review(s) (<i>indicate date for each review</i>) | <input type="checkbox"/> None 11/04/04 & 08/22/06 |

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**Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation III**

FACSIMILE TRANSMITTAL SHEET

DATE: 7/6/06

For Shalini Jain

To: Barry Calvarese

From: Mary Jean Kozma-Fornaro
Supervisor, Project Management Staff

Company: Dow Pharmaceutical Sciences

Division of Dermatology & Dental Products

Fax number: 707 793-0145

Fax number: (301) 796-9894/9895

Phone number: 707 793-2600

Phone number: (301) 796-2110

Subject: NDA 50802

Total no. of pages including cover:

Please see attached Statistical Information Needs which are critical for application review. Need information as soon as possible.

Document to be mailed:

YES

NO

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW.

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Comments to be Conveyed to the Sponsor: NDA 50-802

1. Based upon the primary analysis data set (AD_OPV.XPT) submitted, the reviewer was not able to reproduce the sponsor's results as reported in the study report for Study 1501-02.
 2. Per the SPA, analysis of the percent change in lesion counts was planned to use ANOVA with terms for treatment and pooled center. In addition a sensitivity analysis was planned to ensure efficacy results were not driven by extreme centers. However, the current submission states analysis of the percent change in lesion counts will be based on the Cochran-Mantel-Haenszel Mean Score statistic. Further, the study report does not appear to include a sensitivity analysis to examine the effect of influential center(s).
 3. The SPA defined the primary analysis of the multiple endpoints to be based on the ITT population imputing missing data by the LOCF approach which the Agency concurred. However, the study reports define the primary analysis of dichotomized EGSS to be based upon treating all subjects with no week 12 data as EGSS failures.
 4. The protocol submitted to the SPA provided an algorithm to pool small centers, defined as centers that fail to recruit at least 8 subjects per treatment arm. However, the data sets do not appear to provide a variable corresponding to pooled sites.
 5. A proposed label was not found in the electronic submission.
- To address the above information request and facilitate the review, the Agency requests the following information.
1. The Agency requests the sponsor submit the data in the following format which is similar to that of AD_OPV.XPT.
 - For each subject the following variables should always be recorded and never be recorded as missing:
 - PTID: please use the nomenclature used in the EFFICACY.XPT and DEMO.XPT data sets.
 - site: investigator site number
 - visit: 1 through 6 corresponding to screening through wk 12
 - Note that if the screening visit (visit 1) and the baseline visit (visit 2) are the same, all data values for visit 1 and visit 2 should be the same (i.e. no missing should be recorded).
 - trtxt: Treatment assigned—same as included in AD_OPV.XPT
 - itt: 1 = ITT evaluable, 0 = not ITT evaluable
 - pp: 1 = PP evaluable, 0 = not PP evaluable
 - visitflag: 1 = visit was on time \pm protocol defined window, 0 = visit was not on time.
 - The following variables should be recorded based on observed data and in the case a subject did not attend the visit or the variable was not recorded, the data should be recorded as missing. Note that the nomenclature is much the same as used in AD_OPV.XPT.
 - inf_bsl: inflammatory lesion count at baseline
 - inf_obs: observed inflammatory lesion count
 - inf_cbsl: change in inflammatory lesion counts from baseline
 - inf_pbsl: percent change in inflammatory lesion counts from baseline.
 - non_bsl: non-inflammatory lesion count at baseline
 - non_obs: observed non-inflammatory lesion count
 - non_cbsl: change in non-inflammatory lesion counts from baseline
 - non_pbsl: percent change in non-inflammatory lesion counts from baseline.
 - tot_bsl: total lesion count at baseline
 - tot_obs: observed total lesion count

- tot_cbsl: change in total lesion counts from baseline
 - tot_pbsl: percent change in total lesion counts from baseline.
 - egss_bsl: EGSS at baseline
 - egss_obs: observed EGSS
 - egss_cbsl: change in EGSS from baseline
 - visitdt: date of visit
 - trtdur: treatment duration= current visit – baseline visit + 1
- When imputing missing values, new variables may be recorded similarly to those used in AD_OPV.XPT. Please provide adequate documentation for how the imputation was carried out.
 - For LOCF: locf_inf, locf_non, locf_tot, and locf_egss
 - Sensitivity analysis 1: sens1_inf, sens1_non, sens1_tot, sens1_egss.
 - Sensitivity analysis 2: sens2_inf, sens2_non, sens2_tot, sens2_egss.
 - Note that results can also incorporate missing data for changes from baseline.
 - For example: locf_egss_cbsl
2. The sponsor should provide results of the percent change in lesion counts using ANOVA as agreed upon in the SPA along with the sensitivity analysis for examining the effect of influential sites as provided in the protocol submitted to the SPA.
 3. Per the SPA and prior Agency concurrence, the primary efficacy analysis of dichotomized EGSS will be based upon the ITT population imputing missing data with the LOCF approach. Please submit such information to the NDA.
 4. In addition to the variables requested above, the data set should also include a variable for pooled sites which follows the algorithm provided in the SPA. Analysis of the primary endpoints should be conducted which includes a term for pooled site.
 5. Please provide a copy of the proposed label.

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

/s/

Mary Jean Kozma Fornaro
7/6/2006 01:28:53 PM
CSO

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45 DAY MEETING CHECKLIST

FILEABILITY:

On initial overview of the NDA application:

YES

Note: This is submitted as a complete response to a Not Approvable action (letter date: December 7, 2004)

CLINICAL:

1. Identify the general format that has been used for this application. Electronic
2. On its face is the clinical section of the NDA organized in a manner to allow substantive review to begin? **YES**
3. Is the clinical section of the NDA indexed and paginated in a manner to allow substantive review to begin? **YES**
4. On its face, is the clinical section of the NDA legible so that substantive review can begin? **YES**
5. If needed, has the sponsor made an appropriate attempt to determine the most appropriate dosage and schedule for this product (i.e., appropriately designed dose- ranging studies)? **Dose-ranging studies were not conducted**
6. On its face, do there appear to be the requisite number of adequate and well-controlled studies in the application? **YES**

Application Type: 505 (b)(2)

7. Identification of pivotal trials:

Pivotal Study #1: Protocol Number: MP-1501-02

Study Title: "A Multi-Center, Phase 3 Randomized, Double-Blind, Clinical Trial to Compare the Safety and Efficacy of Clin RA Gel vs. Clindamycin Phosphate 1.2% Gel in the Treatment of Acne Vulgaris"

Study design: multicenter, randomized, double-blind, active-controlled, parallel group

Indication: acne vulgaris

Study arms: Clin RA Gel (clindamycin phosphate 1.2% and tretinoin 0.025%) vs. Clindamycin Phosphate 1.2% once daily for 12 weeks

A total of 2010 subjects were enrolled: 1008 subjects were randomized to Clin RA Gel and 1002 subjects to clindamycin phosphate 1.2% gel.

Study #2: Protocol Number: MP-1501-01

Study Title: "A Multi-Center, Open-Label, Long-Term Safety Trial of Clin RA Gel in the Treatment of Acne Vulgaris"

Study design: Open-label, Single-Arm, Multi-centered

Indication: Acne Vulgaris

Study arms: Clin RA Gel once daily for up to 12 months

A total of 442 subjects were enrolled: 352 completed 6 months of treatment, and 213 of these subjects continued treatment into the 6-12 month phase of the study; 195 completed 12 months of treatment

8. Are the pivotal efficacy studies of appropriate design to meet basic requirements for approvability of this product based on proposed draft labeling? draft labeling not found

Proposed indication from sponsor's draft labeling: not found

Endpoint in pivotal trial #1:

Primary efficacy variables:

- Percent change from Baseline to Week 12 in inflammatory lesion counts;
- Percent change from Baseline to Week 12 in noninflammatory lesion counts;
- Percent change from Baseline to Week 12 in total lesion counts;
- Percentage of subjects who were clear or almost clear at Week 12 or achieved at least 2 grades of improvement in the EGSS (treatment success) from Baseline to Week 12.

Endpoint in trial #2: safety

9. Are all data sets for pivotal efficacy studies complete for all indications (indications) requested? (this is a stat question?)

10. Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling? draft labeling not found

IND number/s: 65,531

PreIND Mtg Date: September 24, 2001

EP2 Meeting Date: December 16, 2002

PreNDA meeting date: October 1, 2003

Original Submission Date: February 6, 2004

Not-Approvable Letter: December 7, 2004

Post- Not-Approvable meeting: February 16, 2005

Formal Dispute Resolution: February 25, 2005

Do endpoints in pivotal Study 1 conform to previous agency commitments? Yes

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

/s/

Brenda Carr
6/6/2006 01:51:33 PM
MEDICAL OFFICER

Markham Luke
6/6/2006 02:30:15 PM
MEDICAL OFFICER
For 74 day letter items, please see Biostat and
CMC filing notes.

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