CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-789

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

EXCLUSIVITY SUMMARY

NDA # 21-789 SUPPL # HFD # 540

Trade Name METROGEL, 1%

Generic Name metronidazole gel

Applicant Name Dow Pharmaceutical Sciences

Approval Date, If Known June 30, 2005

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES ☒ NO ☐

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3,SE4, SE5, SE6, SE7, SE8

505 (b)(2)

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES ☒ NO ☐

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

d) Did the applicant request exclusivity?

YES ☒ NO ☐

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

3 years

e) Has pediatric exclusivity been granted for this Active Moiety?

YES ☐ NO ☒

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES ☐ NO ☒

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES
(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES ☒ NO ☐

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# 20-743 Noritate Cream, 1%

NDA# 19-937 Metro Gel, 0.75%

NDA# 20-901 Metro Lotion, 0.75%

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES ☐ NO ☒

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.)
IF "YES," GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES ☒ NO ☐

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES ☒ NO ☐

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES ☒ NO ☐

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES ☐ NO ☒

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES ☐ NO ☒

If yes, explain:

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Investigation #1 : 0215R5.C-01-02

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1	YES ☐	NO ☒
Investigation #2	YES ☐	NO ☐

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1	YES ☐	NO ☒
Investigation #2	YES ☐	NO ☐

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

Investigation #1: 0215R5.C-01-02

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1		!
		!
IND # 64397	YES ☒	! NO ☐
		! Explain:

Investigation #2		!
		!
IND #	YES ☐	! NO ☐
		! Explain:

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1 !

YES ☐	! NO ☐
Explain:	! Explain:
	!
Investigation #2	!
	!
YES ☐	! NO ☐
Explain:	! Explain:

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES ☐ NO ☒

If yes, explain:

==========

Name of person completing form: Mary Jean Kozma Fornaro
Title: Chief, Project Management Staff
Date: 6/30/05

Name of Office/Division Director signing form: Stanka Kukich, M.D. Deputy Division Director
Title: Deputy Division Director

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05

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

/s/

Stanka Kukich
6/30/05 05:09:01 PM

PEDIATRIC PAGE

(Complete for all APPROVED original applications and efficacy supplements)

NDA/BLA # : 21-789 Supplement Type (e.g. SE5): _____ Supplement Number:

Stamp Date: August 30, 2004 Action Date: August 30, 2005

HFD 540 Trade and generic names/dosage form: METROGEL (metronidazole gel) 1 %

Applicant: Dow Pharmaceuticals Therapeutic Class: 3S

Indication(s) previously approved: NONE

Each approved indication must have pediatric studies: Completed, Deferred, and/or Waived.

Number of indications for this application(s): 1

Indication #1: Rosecea

Is there a full waiver for this indication (check one)?

X Yes: Please proceed to Section A.

❑ No: Please check all that apply: ____Partial Waiver ____Deferred ____Completed
NOTE: More than one may apply
Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

❑ Products in this class for this indication have been studied/labeled for pediatric population
X Disease/condition does not exist in children
❑ Too few children with disease to study
❑ There are safety concerns
❑ Other: Drug Product in not intended for Pediatric Use.

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived:

Min_____ kg_____ mo._____ yr._____ Tanner Stage_____
Max_____ kg_____ mo._____ yr._____ Tanner Stage_____

Reason(s) for partial waiver:

❑ Products in this class for this indication have been studied/labeled for pediatric population
❑ Disease/condition does not exist in children
❑ Too few children with disease to study
❑ There are safety concerns
❑ Adult studies ready for approval
❑ Formulation needed
❑ Other:_____

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section C: Deferred Studies

Age/weight range being deferred:

Min _____ kg_____ mo._____ yr._____ Tanner Stage_____
Max_____ kg_____ mo._____ yr._____ Tanner Stage_____

Reason(s) for deferral:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Adult studies ready for approval**
- ☐ **Formulation needed**

Other:_____

Date studies are due (mm/dd/yy): _____

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section D: Completed Studies

Age/weight range of completed studies:

Min _____ kg_____ mo._____ yr._____ Tanner Stage_____
Max_____ kg_____ mo._____ yr._____ Tanner Stage_____

Comments:

If there are additional indications, please proceed to Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

This page was completed by:

{See appended electronic signature page}

_____
Regulatory Project Manager

cc: NDA
HFD-950/ Terrie Crescenzi
HFD-960/Grace Carmouze
(revised 9-24-02)

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT, PEDIATRIC TEAM, HFD-960
301-594-7337

Attachment A

(This attachment is to be completed for those applications with multiple indications only.)

Indication #2: _____

Is there a full waiver for this indication (check one)?

- ☐ **Yes: Please proceed to Section A.**
- ☐ **No: Please check all that apply: ____Partial Waiver ____Deferred ____Completed**
  NOTE: More than one may apply
  Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Other:**_____

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived:

Min _____	**kg**_____	**mo.**_____	**yr.**_____	**Tanner Stage**_____
Max_____	**kg**_____	**mo.**_____	**yr.**_____	**Tanner Stage**_____

Reason(s) for partial waiver:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Adult studies ready for approval**
- ☐ **Formulation needed**
- ☐ **Other:**_____

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section C: Deferred Studies

Age/weight range being deferred:

Min _____ kg_____ mo._____ yr._____ Tanner Stage_____
Max_____ kg_____ mo._____ yr._____ Tanner Stage_____

Reason(s) for deferral:

- ❑ **Products in this class for this indication have been studied/labeled for pediatric population**
- ❑ **Disease/condition does not exist in children**
- ❑ **Too few children with disease to study**
- ❑ **There are safety concerns**
- ❑ **Adult studies ready for approval**
- ❑ **Formulation needed**
- ❑ **Other:_____**

Date studies are due (mm/dd/yy): _____

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section D: Completed Studies

Age/weight range of completed studies:

Min _____ kg_____ mo._____ yr._____ Tanner Stage_____
Max_____ kg_____ mo._____ yr._____ Tanner Stage_____

Comments:

If there are additional indications, please copy the fields above and complete pediatric information as directed. If there are no other indications, this Pediatric Page is complete and should be entered into DFS.

This page was completed by:

{See appended electronic signature page}

Regulatory Project Manager

cc: NDA
HFD-960/ Terrie Crescenzi
(revised 1-18-02)

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT, PEDIATRIC TEAM, HFD-960
301-594-7337

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/s/

Jill Lindstrom
6/24/05 08:58:42 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Division of Scientific Investigations
Office of Medical Policy
Center for Drug Evaluation and Research
Food and Drug Administration
Rockville MD 20857

CLINICAL INSPECTION SUMMARY

DATE: April 21, 2005

TO: Kalyani Bhatt, Regulatory Project Manager
Joseph Porres, Medical Officer
Division of Dermatologic and Dental Drug Products, HFD-540

THROUGH: Ni A. Khin, M.D.
Branch Chief
Good Clinical Practice Branch I, HFD-46
Division of Scientific Investigations

FROM: Roy Blay, Ph.D.
Good Clinical Practice Branch I, HFD-46

SUBJECT: Evaluation of Clinical Inspections

NDA: NDA 21-789

PROTOCOL(s): Protocol # 0215-R3.C-06-02

A Multi-Center, Investigator-Blind Clinical Trial to Assess the Safety and Efficacy of Metronidazole Gel, 1% as Compared to Metronidazole Gel Vehicle and Noritate Cream, 1% in the Treatment of Rosacea"

SPONSOR: Dow Pharmaceutical Sciences

DRUG: Metronidazole

INDICATION: Treatment of rosacea

CHEMICAL CLASSIFICATION: 3

THERAPEUTIC CLASSIFICATION: S

INSPECTION SUMMARY GOAL DATE: April 2005

ACTION GOAL DATE: June 30, 2005

I. BACKGROUND:

These inspections were requested by the reviewing division in response to a letter dated November 11, 2003, forwarded to the clinical sites by Karl Beutner, M.D., Ph.D. of [redacted]. Dr. Beutner's letter, in brief, requested that clinical sites review potentially discrepant data for specific subjects. If the clinical investigator felt that their initial assessments were in error, Dr. Beutner's letter invited them to correct the data prior to final data lock.

The review division requested that DSI conduct inspections to assess the manner in which this request to review and possibly revise data was implemented.

The objective of the study was to assess the safety and efficacy of metronidazole treatment of rosacea in comparison with its vehicle and another approved product.

The clinical sites of Drs. Wiltz and Lee were selected for inspection as two of the higher enrolling centers. In addition, to gain a better perspective on this request by the sponsor for clinical sites to review/revise potentially discrepant data, inspections were also done of the sponsor (Dow Pharmaceuticals) and monitor [redacted]. The goals of inspection included validation of submitted data and compliance of study activities with applicable statutes and Federal regulations. Among the study elements reviewed for compliance were subject record accuracy, appropriate informed consent, appropriate use of inclusion/exclusion criteria, adherence to protocol, randomization procedures, documentation of serious adverse events, and accuracy of drug disposition records.

II. RESULTS (by site):

NAME	CITY	STATE/ COUNTRY	ASSIGNED DATE	RECEIVED DATE	CLASSIFICATION/FILE NUMBER
Mark Lee, M.D.	San Antonio	Texas	11 Jan 05	18 Mar 05	VAI/011450
Hector Wiltz, M.D.	Miami	Florida	11 Jan 05	09 Mar 05	VAI/011443
Dow Pharmaceuticals	Petaluma	California	11 Jan 05	Pending*	VAI/*
[redacted]					

***Note that this classification is tentative pending review of the EIR for this site.**

Site #50
Mark Lee, M.D.
Progressive Research Clinic
4499 Medical Drive, Suite 145
San Antonio, TX 78229
See **Overall Assessment and Recommendations**, below

a. 44 subjects were screened for the study, 41 were randomized, and 3 dropped out. The relevant efficacy data was reviewed for all 44 subjects records prior to and after receipt of the November 18, 2003, letter from Dr. Beutner requesting that investigators re-evaluate potentially discrepant data for specific subjects. Review of this data indicated that it was not revised prior to or after receipt of this letter.

b. There were no limitations to the inspection.

c. A Form 483 was issued noting failure to obtain consent for all subjects, failure to follow the protocol, and inaccurate/inadequate records. Only the failure to obtain consent for three subjects using a revised consent form and failure to follow the protocol by using two investigators for lesion evaluation instead of only one were listed in the letter to the investigator.

d. Data appear acceptable

Site #60
Hector Wiltz, M.D.
11760 Bird Road, Suite 451
Miami, FL 33175
See **Overall Assessment and Recommendations**, below

a. Thirty-nine (39) subjects were enrolled in the study, seven subjects did not complete the study, and the records of 10 subjects were reviewed in-depth. Dr. Wiltz also received the follow-up letter from Dr. Beutner. Review of the data at Dr. Wiltz's site indicated that there were **no** revisions to the data after the receipt of this letter.

b. There were no limitations to the inspection.

c. A Form 483 was issued noting two instances of failure to report adverse events (flu and headache) and failure to sign a clinical assessment form for one subject. Inadequate record-keeping was noted in the untitled letter issued to Dr. Wiltz.

d. Data appear acceptable

Sponsor Site
Dow Pharmaceutical Sciences
1330A Redwood Way
Petaluma, CA 94954-1169
See **Overall Assessment and Recommendations**, below

a. Dr. Beutner of Solano Clinical Research (a subsidiary of Dow), the medical monitor for this study, sent letters in November of 2003 to 28 of 55 investigators requesting that they re-evaluate their findings for specific study subjects because of potential inconsistencies between lesion counts and global assessment scores. The study took place between May of 2003 and March of 2004 with 1299 subjects enrolled between the 55 clinical sites. Dr. Beutner noted that he used preliminary, unaudited data for his assessments of potential inconsistencies and worded the letters to investigators in such a way as to avoid introducing bias. Dr. Beutner said that he focused on study outcomes at Visit 5 as that would determine the efficacy of treatment.

As a result of re-evaluation of the data in response to Dr. Beutner's letter, data for three subjects at two sites were changed as follows:

Site No.	Subject No.	Prior IGA	Post IGA	Treatment
007	37 (visit 5)	mild	almost clear	Noritate
	48 (visit 5)	almost clear	clear	Vehicle
037	222 (visit 4)	mild	almost clear	Noritate

IGA= Investigator Global Assessment

Thus, across 28 sites, data was changed for only three subjects at two sites. In each case, the evaluation was one grade better than the original evaluation. None of these subjects were randomized to the study drug.

b. There were no limitations to the inspection.

c. A Form 483 was issued with a single observation that an amendment to the protocol was not submitted though new procedures for the validation of evaluators were implemented in a memo dated August 7, 2003, that was sent to all investigators.

d. The observation noted that [redacted] implemented a Documentation of Training form for those investigators who passed validation tests for the evaluation of the Global Severity Score and the Inflammatory Lesion Counts. This procedure does not significantly affect subject safety, the scope of the investigation, or the scientific quality of the study. Rather, the use of these training forms documented the qualifications of the investigators to conduct study assessments. As such, this observation will be omitted from the DSI letter to the sponsor.

Monitor Site

See **Assessment and Recommendations**, below

a. The inspection reviewed the selection process for clinical investigators and monitors; the review of subject records and transfer of data to the sponsor; the methods of quality assurance; the reporting of adverse events; methods of data collection and retention; and the disposition of the test article.

b. There were no limitations to the inspection.

c. A Form 483 was not issued. No objectionable conditions were noted.

d. Monitoring practices appeared acceptable.

III. OVERALL ASSESSMENT OF FINDINGS AND GENERAL RECOMMENDATIONS

The data submitted in support of this application by Drs. Wiltz and Lee appear adequate in support of the relevant submission. Inspection of the study monitor revealed no objectionable observations, and the inspection of the sponsor noted that they did not submit an amendment to the protocol as a result of the implementation of new validation procedures for evaluators.

In summary, in response to Dr. Beutner's letter issued to 28 sites, investigators at two sites revised their findings for three subjects. In each of these three cases, the evaluator revised their assessment by an increment of one; i.e., from "mild" to "almost clear" or from "almost clear" to "clear". These three subjects whose evaluations were changed were treated with the comparator agent or the vehicle, not the study drug. With a total study enrollment of 1299 subjects, the revised evaluations for these three subjects would not appear to have an impact on study outcome.

Overall, the data generated in support of this application appear acceptable.

Roy Blay, Ph.D.
Good Clinical Practice Branch I, HFD-46
Division of Scientific Investigations

CONCURRENCE:

Ni A. Khin, M.D.
Branch Chief
Good Clinical Practice Branch I, HFD-46
Division of Scientific Investigations

cc:
HFD-580/Doc. Rm. NDA 21-789
HFD-45/Program Management Staff (electronic copy)
HFD-46/RF
HFD-46/c/r/s
HFD-46/Blay

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O:\blay\21789.doc

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

/s/

Roy Blay
4/22/05 10:55:59 AM
CSO

Ready for your signature per discussion

Ni Aye Khin
4/22/05 11:59:57 AM
MEDICAL OFFICER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

APR 8 2005

Hector Wiltz, M.D.
11760 Bird Road, Suite 451
Miami, FL 33175

Dear Dr. Wiltz:

Between February 07 and 09, 2005, Ms. Jennifer M. Menendez representing the Food and Drug Administration (FDA), conducted an investigation to review your conduct of a clinical investigation (Protocol 0215-R5.C-01-02 entitled "A Multi-Center, Investigator-Blind, Clinical Trial to Assess the Safety and Efficacy of Metronidazole Gel, 1% as Compared to Metronidazole Gel Vehicle and Noritate™ Cream, 1% in the Treatment of Rosacea") of the investigational drug Metronidazole, performed for Dow Pharmaceutical Sciences. This inspection was conducted under the FDA's Bioresearch Monitoring Program, which includes inspections designed to review the conduct of clinical research involving investigational drugs and to ensure that the rights, safety, and welfare of the human subjects of the study have been protected.

From our review of the establishment inspection report and the documents submitted with that report, we conclude that you did not adhere to the applicable statutory requirements and FDA regulations governing the conduct of clinical investigations. We are aware that at the conclusion of the inspection, Ms. Menendez presented and discussed with you the items listed on Form FDA 483, Inspectional Observations. We acknowledge receipt of your letter dated February 10, 2005, in response to the 483. We wish to emphasize the following:

You did not prepare and maintain adequate and accurate case histories that record all observations and other data pertinent to the investigation [21 CFR 312.62(b)].

1. A source document for subject #1154 reports that the subject experienced influenza from November 12-16, 2003; however, this was not reported in the case report form.

2. The medical history for subject #0685 documents that the subject had a relevant medical condition/disease, headache. The case report form indicates that the headache started on 09/16/2003 and the date stop as "ongoing." A source document indicates that the headache started and stopped on 9/16/2003.

3. The Baseline Visit/Visit 1 Inflammatory Lesion Counts source document has a signature block for the evaluator. For subject #0673, this source document was not signed and dated by the evaluator who conducted the clinical assessment.

Please make appropriate corrections in your procedures to assure that the findings noted above are not repeated in any ongoing or future studies.

We appreciate the cooperation shown Investigator Menendez during the inspection. Should you have any questions or concerns regarding this letter or the inspection, please contact me by letter at the address given below.

Sincerely,

Ni A. Khin, M.D.
Branch Chief
Good Clinical Practice Branch I, HFD-46
Division of Scientific Investigations
Office of Medical Policy
Center for Drug Evaluation and Research
7520 Standish Place, Room 125
Rockville, MD 20855

FEI: 3004950729
Field Classification: VAI
Headquarters Classification:
____ 1) NAI
__X__ 2) VAI- no response required
_____ 3) VAI- response requested
_____ 4) OAI

If Headquarters classification is a different classification, explain why: N/A

Deficiencies noted: 6
06 Inadequate and inaccurate records....312.62

cc:
HFA-224
HFD-540 Kalyani Bhatt
HFD-540 Joseph Porres
HFD-46 J. Tavarez
HFD-46 Ni Khin
HFD-45 Reading File
HFR-SE250 Acting DIB, Ronnie Jackson
HFR-SE250 Bimo Monitor, Brunilda Torres
HFR-SE2560 Field Investigator, Jennifer Menendez

r/d: Tavarez: 3/30/05
reviewed:NK:4/6/05

c:\NDA 21-789\letters\Dr. Hector Wiltz untitled letter

Reviewer Note to Rev. Div. M.O.

This was a routine, data audit inspection of a clinical investigator, Hector Wiltz, M.D., to validate data submitted in support of NDA 21-789. This was the initial inspection of Dr. Wiltz. Thirty-nine (39) subjects were randomized to this trial, and 32 subjects completed the trial. The inspection encompassed an audit of all subjects' consent forms. Records for 10 subjects enrolled were reviewed during the inspection. All audited subjects who were enrolled met all inclusion criteria and did not meet any exclusion criteria. Data reported on the case report forms (CRF) were corroborated by the entries on the subject's clinic charts.

A Form FDA 483 (Inspectional Observations) was issued at the close of the inspection. Overall, data from this clinical site that had been inspected appear acceptable. The inspection was classified as VAI.

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/s/

Ni Aye Khin
4/12/05 05:58:08 PM

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: Kalyani Bhatt, Project Manager
Division of Dermatologic and Dental Drug Products
HFD-540

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
2-15-05	64, 397	21-789	Submission for Tradename	February 14, 2005

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
Metronidazole Gel, 1 %	10 month PDUFA	3S	March 15, 2005

NAME OF FIRM: Dow Pharmaceuticals

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE/ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE--NDA MEETING
- ☐ END OF PHASE II MEETING
- ☐ RESUBMISSION
- ☐ SAFETY/EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☒ OTHER *(SPECIFY BELOW)*: Trade name review

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
☐ TYPE A OR B NDA REVIEW ☐ END OF PHASE II MEETING ☐ CONTROLLED STUDIES ☐ PROTOCOL REVIEW ☐ OTHER (SPECIFY BELOW):	☐ CHEMISTRY REVIEW ☐ PHARMACOLOGY ☐ BIOPHARMACEUTICS ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE IV STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL-BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG EXPERIENCE

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

V. SCIENTIFIC INVESTIGATIONS

☐ CLINICAL	☐ PRECLINICAL

COMMENTS, CONCERNS, and/or SPECIAL INSTRUCTIONS:
Please review the Tradename MetroGel, 1%

PDUFA DATE: June 30, 2005
ATTACHMENTS: Draft Package Insert, Container and Carton Labels
CC:
Archival IND/NDA 21-789
HFD-540/Division File
HFD-540/Kalyani Bhatt RPM
HFD-540/Porres, J/Lindstrom, J

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SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

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/s/

Kalyani Bhatt
2/15/05 09:26:10 AM

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: Kalyani Bhatt, Project Manager
Division of Dermatologic and Dental Drug Products
HFD-540

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
2-15-05	64, 397	21-789	Submission for Tradename	February 14, 2005

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
Metronidazole Gel, 1 %	10 month PDUFA	3S	March 15, 2005

NAME OF FIRM: Dow Pharmaceuticals

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- ☐ FORMULATIVE REVIEW
- ☒ OTHER *(SPECIFY BELOW)*: Trade name review

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- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ PRECLINICAL

COMMENTS, CONCERNS, and/or SPECIAL INSTRUCTIONS:
Please review the Tradename MetroGel, 1%

PDUFA DATE: June 30, 2005
ATTACHMENTS: Draft Package Insert, Container and Carton Labels
CC:
Archival IND/NDA 21-789
HFD-540/Division File
HFD-540/Kalyani Bhatt RPM
HFD-540/Porres, J/Lindstrom, J

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SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

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/s/

Kalyani Bhatt
2/15/05 09:26:10 AM

DSI CONSULT: Request for Clinical Inspections

Date: December 9, 2004

To: Roy Blay, GCPB Reviewer/HFD-47

From: Kalyani Bhatt, Regulatory Project Manager/HFD-540

Subject: **Request for Clinical Inspections (Revised)**
NDA 21-789
Dow Pharmaceuticals
Tradename (Metronidazole) Gel 1%

Protocol/Site Identification:

As discussed with you, the following protocols/sites essential for approval have been identified for inspection. These sites are listed in order of priority.

Indication	Protocol #	Site (Name and Address)	Number of Subjects
Treatment of Rosacea	0215-R3.C-06-02	Site 50 Hector Wiltz MD 11760 Bird Rd Suite 451 Miami, FL 33175 305-220-5222	39
Treatment of Rosacea	0215-R3.C-06-02	Site 60 Mark S. Lee MD 4499 Medical Drive Suite 345 San Antonio TX 78229 210-614-5557	37

Rationale:

The purpose of the inspection is to verify the integrity of the data and the consistency between the data in original records and that in the CRFs.

Note: International inspection requests or requests for five or more inspections require sign-off by the ORM Division Director and forwarding through the Director, DSI.

Goal Date for Completion:

We request that the inspections be performed and the Inspection Summary Results be provided by (inspection summary goal date) **March 2005**. We intend to issue an action letter on this application by (action goal date) **June 30, 2005**.

Should you require any additional information, please contact Kalyani Bhatt.

Concurrence: (if necessary)

Markham Luke, M.D., Ph.D., Clinical Team Leader, Dermatology
Joe Porres, M.D., Clinical Reviewer
Mohamed Alosh, M.D., Biostatistics Team Leader
Steven Thomson, Ph.D., Biostatistics Reviewer

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/s/

Kalyani Bhatt
12/13/04 01:27:55 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

FILING COMMUNICATION

NDA 21-789

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

Dear Mr. Calvarese:

Please refer to your April 27, 2004 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for (metronidazole) gel, 1%.

We also refer to your submissions dated September 3 and 28, October 22, 2004.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, this application has been filed under section 505(b) of the Act on October 29, 2004 in accordance with 21 CFR 314.101(a).

At this time, we have not identified any potential filing review issues. Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review.

If you have any questions, please call Kalyani Bhatt, Regulatory Project Manager, at (301) 827-2020.

Sincerely,

{See appended electronic signature page}

Jonathan Wilkin, M.D.
Division Director
Division of Dermatologic and Dental Drug Products
Office of Drug Evaluation V
Center for Drug Evaluation and Research

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/s/

Jonathan Wilkin
11/10/04 04:51:17 PM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

TO *(Division/Office)*: **Quynh Nguyen, Project Manager**
Mail: ODS (Room 15B-08, PKLN Bldg.)

FROM: **Kalyani Bhatt, Project Manager, DDDDP, HFD-540**
301-827-2056

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
November 2, 2004	IND 64,397	21-789	Electronic Common Technical Document	August 27, 2004

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
Metronidazole Gel 1%		3S	March 27, 2004

NAME OF FIRM: **Dow Pharmaceuticals**

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE/ADDITION
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- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- **X OTHER *(SPECIFY BELOW)*:**
  Full e-CTD

II. BIOMETRICS

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- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS:

This is a full e-CTD. The reference listed drug is Noriatate NDA 20-743 (Dermik Labs). Filing meeting was 10-18-04. Filing Day is 10-29-04. The 74 day letter Is due November 12, 2004. Mid cycle review 1-27-05 and labeling day is April 25, 2004.

SIGNATURE OF REQUESTER	METHOD OF DELIVERY (Check one)
Kalyani Bhatt, Project Manager, DDDDP, HFD-540	X MAIL ☐ HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

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/s/

Kalyani Bhatt
11/3/04 11:59:02 AM

45 DAY MEETING CHECKLIST

FILEABILITY:

On initial overview of the NDA application: **YES**

CLINICAL:

1. On its face, is the clinical section of the NDA organized in a manner to allow substantive review to begin? **YES**

2. Is the clinical section of the NDA indexed and paginated in a manner to allow substantive review to begin? **There are some difficulties inherent to electronic-ONLY applications, such as accomplishing global searches and attach comments.**

3. On its face, is the clinical section of the NDA legible so that substantive review can begin? **YES**

4. 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)? **NO**

No specific study conducted. The Sponsor chose the drug concentration in the comparator. We do not know whether a higher strength could have a different efficacy and safety.

5. On its face, does the application include the requisite number of adequate and well-controlled studies? **YES**

Application Type: 505 (b) (2) (Y) Reference drug: Noritate 1% cream

Identification of pivotal trials: There was only one Phase 3 trial. Protocol Number: 0215-R5.C-01-02 Study Report: Page Location in NDA: Module 5, file: study-0215-r5-c-01-02

Is this an adequate multi-centered trial? **YES**

Center	**Patients Enrolled**			
(combined with)	Metronidazole gel 1%	Noritate	Vehicle	total
1	15	15	5	35
2 (2,3)	8	7	3	18
3	11	11	4	26
4 (4, 64)	10	11	3	24
5				
6 (6,41)	15	13	5	33
7 (7,33)	14	15	5	34
8	9	9	3	21
9 (9,20)	12	10	4	26
10				
11 (11, 54)	11	12	4	27
12	16	15	5	36
13 (13, 37)	10	9	3	22
14	4	6	2	12
15 (15, 26)	10	11	4	25
16	27	27	9	63
17				
18 (18,31)	12	10	4	26

19 (8,19)	9	9	3	21
20	8	7	2	17
21 (14, 21)	12	12	4	28
22				
23				
24	5	4	2	11
25	2	1	1	4
26	7	9	3	19
27 (25, 27)	14	15	4	33
28 (28, 46)	12	11	4	27
29	9	8	3	20
30	3	3	1	7
31	6	7	2	15
32	5	4	2	11
33	2	1	0	3
34	8	8	3	19
35	15	15	5	35
36 (24, 36)	12	14	4	30
37				
38				
39				
40 (34, 40)	10	11	3	24
41	1	2	1	4
42	5	4	2	11
43				
44	7	8	3	18
45	20	19	7	46
46	5	5	2	12
47 (47,49)	11	10	4	25
48				
49	8	7	3	18
50	16	18	5	39
51				
52	15	16	5	36
53 (42,53)	12	12	4	28
54	5	6	2	13
55 (55, 61)	15	14	5	34
56 (44,56)	12	10	3	25
57				
58 (32,58)	12	12	4	28
59	17	15	5	37
60	19	19	6	44
61	0	1	0	1
62 (29,62)	9	10	3	22
63	15	15	5	35
64	8	8	3	19
65 (30,65)	13	14	5	32

Study Title: "A Multi-Center Investigator-Blind Clinical Trial to Assess The Safety and Efficacy of Metronidazole Gel, 1% as Compared to Metronidazole Gel Vehicle and Noritate ™ Cream 1 % in the Treatment of Rosacea. " A total of 1299 subjects in 54 different study centers were randomized to receive one of the three study medications.
Study design: Randomized (Y, 3:3:1) Double Blind (Y, investigator blinded) Placebo controlled (Y) Multicentered (Y)

Indication: rosacea

Study arms (dosage, duration, treatment length for each arm): once daily for 10 weeks.

	Metronidazole gel 1%	Noritate cream 1%	Metronidazole gel vehicle
Enrolled (ITT) and Evaluable for safety	557	553	189
Withdrew	57	72	27
PP	480	479	158

Efficacy endpoints (Primary and secondary):
Primary endpoints:
Percent reduction in lesion (papules, pustules and nodules) counts at week 10
Proportion of patients rated at week 10 as success (clear or almost clear) in the 0-4 scale Investigator global assessment
Secondary endpoints:
- Raw inflammatory lesion counts at baseline and each post- baseline visit
- Reduction from baseline in inflammatory lesion counts at each post- baseline visit
- Percent reduction from baseline in inflammatory lesion counts at Weeks 2, 4, and 7
- Dichotomized Investigator's Global Severity Score at Weeks 2, 4, and 7
- Investigator's Global Severity Score at each post- baseline visit
- Raw combined (across 5 regions) Erythema Severity Scores at baseline and each post- baseline visit
- Change in raw combined Erythema Severity Scores at each post- baseline visit
- Worst (across 5 regions) Erythema Severity Scores at baseline and each post- baseline visit

The electronic submission, last updated 8/10/2004 states the final report of the phase 3 study is not finalized (page 12 of 36 in **0000\ Module 1\ individual- study- information. Pdf)**

How measured: The proposed drug product should show superiority to proposed drug vehicle and non-inferiority to comparator-listed drug product.

Summary: it seems the study has demonstrated these objectives.

6. Are the pivotal efficacy studies of appropriate design to meet basic requirements for approvability of this product based on proposed draft labeling? **Yes on the surface.**

Proposed indication from sponsor's draft labeling: **rosacea**

As designed, could endpoints in pivotal trial #1 support labeling? **yes**

7. Are all data sets for pivotal efficacy studies complete for the indication requested? (this is a stat question?)

8. 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? On the surface: **YES**

PreIND Mtg: (Y/N) **N**
IND number/s: 64,397

PreIND Mtg Date: n/a
EP2 Meeting Date: 2/16/01
Agency response to Phase 3 protocols: 11/6/02
An amended protocol was submitted on 6/05/02.
Another labeled 013 -but actually 014- has as protocol date May 6, 03, but is dated at the bottom of the page as July 30/03, received at the Agency on 8/3/04 (the study was already running for at least 3 months!) The study is reported as conducted from 5/03 to 1/04
PreNDA meeting date: 6/17/4

Do endpoints as described by sponsor in pivotal Study 1 conform to previous agency commitments? (**Y**)

9. Has the applicant submitted line listings in a format to allow reasonable review of the patient data? Has the applicant submitted line listings in the format agreed to previously by the Division?
This reviewer has not identified line listings within the submission.

10. Has the application submitted a rationale for assuming the applicability of foreign data (disease specific microbiologic specific) in the submission to the US population? **N/A**

11. Has the applicant submitted all additional required case record forms (beyond deaths and drop-outs) previously requested by the Division? **None requested yet.**

12. Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously agreed to by the Division?
The general investigative plan included evaluation of Metronidazole Gel, 1% in six clinical studies. Four of these studies were phase 1 studies:

- Protocol No. 0215-R3.C-05-02. a 21-day cumulative dermal irritation study
- Protocol No. 0215-R3.C-06-02, a contact sensitization (repeat insult patch test (RIPT)) study
- Protocol No. 0215-R3.C-02-02, a phototoxicity study
- Protocol No. 0215-R3.C-03-02, a photoallergy study.
- Protocol No. 0215-R3.C-04-02, a pk study

Additionally, the sponsor has presented safety data from the pivotal trial.

13. Has the applicant presented a safety assessment based on all current world-wide knowledge regarding this product? **The product is not marketed yet anywhere. Other topical products are marketed with the same drug ingredient: metronidazole**

14. Has the applicant submitted draft -labeling consistent with 21CFR 201.56 and 21CFR 201.57, current divisional policies, and the design of the development package? **YES**

15. Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions with the Sponsor? **YES**

16. Has the applicant complied with the requirements of the Pediatric Rule? **The Sponsor is requesting a waiver from pediatric studies in patients younger than 18 on the basis that rosacea is an adult disease and the product is not intended for pediatric use.**

a) Is this an indication that would be applicable to the pediatric population? **NO**
b) What pediatric ages are included in the protocol? n/a

c) Does the sponsor request pediatric labeling? What age groups? n/a

17. Financial disclosure of investigator. Does the NDA contain the appropriate form to comply with the filing requirement for Financial Disclosure for Investigators? **The NDA includes forms 3454 and 3455**

18. From a clinical perspective, is this NDA fileable? If "no", please state below why it is not. **YES**

If certain claims are not fileable please state which claims they are and why they are not fileable.

_____
Reviewing Medical Officer

_____
Medical Team Leader

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/s/

Joseph Porres
10/21/04 05:20:59 PM
MEDICAL OFFICER

Markham Luke
10/22/04 04:02:03 PM
MEDICAL OFFICER
Concur with fileable decision from Clinical.

Office of Clinical Pharmacology and Biopharmaceutics

New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA Number	21-789	**Brand Name**	Will be chosen at a later date
OCPB Division (I, II, III)	DPEIII	**Generic Name**	Metronidazole Gel 1%
Medical Division	HFD-540	**Drug Class**	Antiprotozoal and Antibacterial
OCPB Reviewer	Abi Adebowale	**Indication(s)**	Inflammatory lesions of Rosacea.
OCPB Team Leader	Ray Baweja	**Dosage Form**	Gel
		Dosing Regimen	Apply and rub in a thin film once daily to entire affected area(s)
Date of Submission, Filing Date	August 27th, 2004 October 27th, 2004	**Route of Administration**	Topical
Mid Cycle Review Date	January 27th, 2005		
Estimated Due Date of OCPB Review	April 15th, 2005	**Sponsor**	Dow Pharmaceutical Sciences
PDUFA Due Date	June 30th, 2005	**Priority Classification**	3S
Division Due Date	May 1st, 2005	**IND Number**	64,397

Clin. Pharm. and Biopharm. Information

Background and Introduction: **METRONIDAZOLE 1% GEL** contains metronidazole, USP. Chemically, metronidazole is 2-methyl-5-nitro-1 *H* -imidazole-1-ethanol. Metronidazole has a molecular weight of 171.16. It is a white to pale yellow crystalline powder. It is slightly soluble in alcohol and has a solubility in water of 10 mg/mL at 20°C. Metronidazole is a member of the imidazole class of anti-bacterial agents and is classified as an antiprotozoal and anti-bacterial agent. Metronidazole Gel 1% is an aqueous gel; each gram contains 10 mg of metronidazole in a base of purified water, betadex, niacinamide, edetate disodium, methylparaben, propylparaben, phenoxyethanol, propylene glycol, and hydroxyethyl cellulose

Metronidazole is an antimicrobial agent used in several approved prescription products indicated for the treatment of rosacea. These products are MetroGel® 0.75% (metronidazole 0.75%), MetroCream® 0.75% (metronidazole 0.75%), MetroLotion® 0.75% (metronidazole 0.75%), and Noritate® Cream, 1% (metronidazole 1%). The proposed product, Metronidazole Gel 1%, has been developed for the topical treatment of rosacea. This product will provide a non-alcoholic gel dosage form (often preferred by patients with rosacea) in a 1% metronidazole strength. In addition to topical products, oral and intravenous dosage forms of metronidazole are currently marketed for treatment of a variety of infectious diseases.

The product proposed in this 505(b)(2) application has been clinically evaluated in six clinical studies. Four of these studies were phase 1 studies; a 21-day cumulative dermal irritation study, a contact sensitization (RIPT) study, a phototoxicity study, and a photoallergy study. One of these studies was a phase 2 absorption study and one was a pivotal phase 3 controlled trial using Noritate® Cream, 1% as the reference drug. The applicant stated that the clinical program was agreed upon with the agency as outlined in Section 2.5.1 "Product Development Rationale".

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Study Numbers If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	X			
Tabular Listing of All Human Studies	X			
HPK Summary	X			
Labeling	X			
Reference Bioanalytical and Analytical Methods	X			Submitted to EDR on 10-22-04. Received access on 10-27-04

I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:				
multiple dose:	X	1		Study CR.U9429 (conducted to support Metrogel 0.75%) an approved product (supportive)
Patients-				
single dose:				
multiple dose:	X	1		Study No. 0215-R3.C-04-02 (pivotal) and supportive study MAR10124 (using Metrgel 0.75%)
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
PD (HEALTHY OR PATIENTS):				
Phase 1 or 2:				
Phase 3:				
PK/PD (HEALTHY OR PATIENTS):				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability:				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies:				
Dissolution:				
(IVIVC):				
Bio-wavier request based on BCS				
BCS class				
III. Other CPB Studies				
Genotype/phenotype studies:				
Other (in vitro percutaneous absorption study)				
Chronopharmacokinetics				
Pediatric development plan				
Literature References		**10**		To support ADME. information was not included in label
Total Number of Studies		**1**		

Fileability and QBR comments		
	"X" if yes	Comments Sent request through project manager for applicant to direct me to the location of the assay method for Study 0215-R3.C-04-02. Received on 10-22-04
Application filable?	**X**	Reasons if the application is not filable (or an attachment if applicable) For example, is clinical formulation the same as the to-be-marketed one?
Comments sent to firm?	**NA**	Comments have been sent to firm (or attachment included). FDA letter date if applicable.
QBR questions (key issues to be considered)	What is the maximal systemic exposure or bioavailability of metronidazole following application as a 1% gel to patients with rosacea? What is the exposure-response relationship for efficacy and safety? Do we need a PM consult? ***NO***	
Other comments or information not included above		
Primary reviewer Signature and Date	**Abi Adebowale**	
Secondary reviewer Signature and Date		

CC: NDA 21-789, HFD-850 (P.Lee), HFD-540 (K. Bhatt), HFD-880 (R.Baweja, A. Selen)

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

/s/

Abi Adebowale
10/28/04 01:20:15 PM
BIOPHARMACEUTICS

Raman Baweja
10/28/04 06:26:40 PM
BIOPHARMACEUTICS