CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-835

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

Department of Health and Human Services
Food and Drug Administration

PATENT INFORMATION SUBMITTED WITH THE FILING OF AN NDA, AMENDMENT, OR SUPPLEMENT

For Each Patent That Claims a Drug Substance (Active Ingredient), Drug Product (Formulation and Composition) and/or Method of Use

Form Approved: OMB No. 0910-0513
Expiration Date: 07/31/06
See OMB Statement on Page 3.

NDA NUMBER
021835

NAME OF APPLICANT / NDA HOLDER
Dow Pharmaceutical Sciences

The following is provided in accordance with Section 505(b) and (c) of the Federal Food, Drug, and Cosmetic Act.

TRADE NAME (OR PROPOSED TRADE NAME)
CLOBEX (clobetasol propionate) Spray, 0.05%

ACTIVE INGREDIENT(S)	STRENGTH(S)
clobetasol propionate	0.05%

DOSAGE FORM
Topical Spray

This patent declaration form is required to be submitted to the Food and Drug Administration (FDA) with an NDA application, amendment, or supplement as required by 21 CFR 314.53 at the address provided in 21 CFR 314.53(d)(4).
Within thirty (30) days after approval of an NDA or supplement, or within thirty (30) days of issuance of a new patent, a new patent declaration must be submitted pursuant to 21 CFR 314.53(c)(2)(ii) with all of the required information based on the approved NDA or supplement. The information submitted in the declaration form submitted upon or after approval will be the only information relied upon by FDA for listing a patent in the Orange Book.

For hand-written or typewriter versions (only) of this report: If additional space is required for any narrative answer (i.e., one that does not require a "Yes" or "No" response), please attach an additional page referencing the question number.

FDA will not list patent information if you file an incomplete patent declaration or the patent declaration indicates the patent is not eligible for listing.

For each patent submitted for the pending NDA, amendment, or supplement referenced above, you must submit all the information described below. If you are not submitting any patents for this pending NDA, amendment, or supplement, complete above section and sections 5 and 6.

1. GENERAL

a. United States Patent Number	b. Issue Date of Patent	c. Expiration Date of Patent
5,990,100	11/23/1999	3/24/2018

d. Name of Patent Owner	Address *(of Patent Owner)*	
Panda Pharmaceuticals, LLC	1455 Union Avenue	
	City/State: Memphis/Tennessee	
	ZIP Code: 38104	FAX Number *(if available)*
	Telephone Number: 901-448-5795	E-Mail Address *(if available)*

e. Name of agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.52 and 314.95 (if patent owner or NDA applicant/holder does not reside or have a place of business within the United States)	Address *(of agent or representative named in 1.e.)*	
	City/State	
	ZIP Code	FAX Number *(if available)*
	Telephone Number	E-Mail Address *(if available)*

f. Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above? ☐ Yes ☒ No

g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date? ☐ Yes ☐ No

For the patent referenced above, provide the following information on the drug substance, drug product and/or method of use that is the subject of the pending NDA, amendment, or supplement.

2. Drug Substance (Active Ingredient)

2.1	Does the patent claim the drug substance that is the active ingredient in the drug product described in the pending NDA, amendment, or supplement?	☒ Yes	☐ No
2.2	Does the patent claim a drug substance that is a different polymorph of the active ingredient described in the pending NDA, amendment, or supplement?	☐ Yes	☒ No
2.3	If the answer to question 2.2 is "Yes," do you certify that, as of the date of this declaration, you have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA? The type of test data required is described at 21 CFR 314.53(b).	☐ Yes	☐ No
2.4	Specify the polymorphic form(s) claimed by the patent for which you have the test results described in 2.3.		
2.5	Does the patent claim only a metabolite of the active ingredient pending in the NDA or supplement? (Complete the information in section 4 below if the patent claims a pending method of using the pending drug product to administer the metabolite.)	☐ Yes	☒ No
2.6	Does the patent claim only an intermediate?	☐ Yes	☒ No
2.7	If the patent referenced in 2.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	☐ Yes	☐ No

3. Drug Product (Composition/Formulation)

3.1	Does the patent claim the drug product, as defined in 21 CFR 314.3, in the pending NDA, amendment, or supplement?	☒ Yes	☐ No
3.2	Does the patent claim only an intermediate?	☐ Yes	☒ No
3.3	If the patent referenced in 3.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	☐ Yes	☐ No

4. Method of Use

Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:

4.1	Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement?	☒ Yes	☐ No

4.2 Patent Claim Number *(as listed in the patent)*	Does the patent claim referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement?		
No. 7		☒ Yes	☐ No

4.2a If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.

Use: *(Submit indication or method of use information as identified specifically in the approved labeling.)*

Indication: Psoriasis

Directions: A method of treating psoriasis comprising topically administering to a human having psoriasis a pharmaceutical composition comprising (a) 0.0001 to 30 weight percent of an anti-psoriatic agent selected from the group consisting of corticosteroids, calcipotriol, retinoids, tar, and mixtures thereof and (b) 15 to 97 weight percent isopropyl myristate, said component (a) being present in an effective anti-psoriatic weight percent, said pharmaceutical composition being a liquid and being in a form suitable for topical administration to a human.

5. No Relevant Patents

For this pending NDA, amendment, or supplement, there are no relevant patents that claim the drug substance (active ingredient), drug product (formulation or composition) or method(s) of use, for which the applicant is seeking approval and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product.	☒ Yes	

6. Declaration Certification

6.1 ***The undersigned declares that this is an accurate and complete submission of patent information for the NDA, amendment, or supplement pending under section 505 of the Federal Food, Drug, and Cosmetic Act. This time-sensitive patent information is submitted pursuant to 21 CFR 314.53. I attest that I am familiar with 21 CFR 314.53 and this submission complies with the requirements of the regulation. I verify under penalty of perjury that the foregoing is true and correct.***

Warning: A willfully and knowingly false statement is a criminal offense under 18 U.S.C. 1001.

6.2 Authorized Signature of NDA Applicant/Holder or Patent Owner *(Attorney, Agent, Representative or other Authorized Official) (Provide Information below)*

Date Signed: 11/15/04

NOTE: Only an NDA applicant/holder may submit this declaration directly to the FDA. A patent owner who is not the NDA applicant/holder is authorized to sign the declaration but may not submit it directly to FDA. 21 CFR 314.53(c)(4) and (d)(4).

Check applicable box and provide information below.

☒ NDA Applicant/Holder	☐ NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official
☐ Patent Owner	☐ Patent Owner's Attorney, Agent (Representative) or Other Authorized Official

Name Dow Pharmaceutical Sciences	
Address 1330A Redwood Way	City/State Petaluma, California
ZIP Code 94954-1169	Telephone Number 707-793-2600
FAX Number *(if available)* 707-793-0145	E-Mail Address *(if available)* bchaudhuri@dowpharmsci.com

Department of Health and Human Services
Food and Drug Administration

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1. GENERAL

a. United States Patent Number	b. Issue Date of Patent	c. Expiration Date of Patent
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d. Name of Patent Owner
Panda Pharmaceuticals, LLC

Address *(of Patent Owner)*
1455 Union Avenue

City/State
Memphis/Tennessee

ZIP Code	FAX Number *(if available)*
38104	
Telephone Number	**E-Mail Address *(if available)***
901-448-5795	

e. Name of agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.52 and 314.95 (if patent owner or NDA applicant/holder does not reside or have a place of business within the United States)

Address *(of agent or representative named in 1.e.)*

City/State

ZIP Code	FAX Number *(if available)*
Telephone Number	**E-Mail Address *(if available)***

f. Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above? ☐ Yes ☒ No

g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date? ☐ Yes ☐ No

For the patent referenced above, provide the following information on the drug substance, drug product and/or method of use that is the subject of the pending NDA, amendment, or supplement.

2. Drug Substance (Active Ingredient)

2.1 Does the patent claim the drug substance that is the active ingredient in the drug product described in the pending NDA, amendment, or supplement?	☒ Yes	☐ No
2.2 Does the patent claim a drug substance that is a different polymorph of the active ingredient described in the pending NDA, amendment, or supplement?	☐ Yes	☒ No
2.3 If the answer to question **2.2** is "Yes," do you certify that, as of the date of this declaration, you have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA? The type of test data required is described at 21 CFR 314.53(b).	☐ Yes	☐ No
2.4 Specify the polymorphic form(s) claimed by the patent for which you have the test results described in **2.3**.		
2.5 Does the patent claim only a metabolite of the active ingredient pending in the NDA or supplement? (Complete the information in section 4 below if the patent claims a pending method of using the pending drug product to administer the metabolite.)	☐ Yes	☒ No
2.6 Does the patent claim only an intermediate?	☐ Yes	☒ No
2.7 If the patent referenced in **2.1** is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	☐ Yes	☐ No

3. Drug Product (Composition/Formulation)

3.1 Does the patent claim the drug product, as defined in 21 CFR 314.3, in the pending NDA, amendment, or supplement?	☒ Yes	☐ No
3.2 Does the patent claim only an intermediate?	☐ Yes	☒ No
3.3 If the patent referenced in **3.1** is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	☐ Yes	☐ No

4. Method of Use

Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:

4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement?	☒ Yes	☐ No
4.2 Patent Claim Number *(as listed in the patent)* No. 7	Does the patent claim referenced in **4.2** claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement? ☒ Yes	☐ No

4.2a If the answer to **4.2** is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.

Use: *(Submit indication or method of use information as identified specifically in the approved labeling.)*

Indication: Psoriasis

Directions: A method of treating psoriasis comprising topically administering to a human having psoriasis a pharmaceutical composition comprising (a) 0.0001 to 30 weight percent of an anti-psoriatic agent selected from the group consisting of corticosteroids, calcipotriol, retinoids, tar, and mixtures thereof and (b) 15 to 97 weight percent isopropyl myristate, said component (a) being present in an effective anti-psoriatic weight percent, said pharmaceutical composition being a liquid and being in a form suitable for topical administration to a human.

5. No Relevant Patents

For this pending NDA, amendment, or supplement, there are no relevant patents that claim the drug substance (active ingredient), drug product (formulation or composition) or method(s) of use, for which the applicant is seeking approval and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product.	☒ Yes

6. Declaration Certification

6.1 ***The undersigned declares that this is an accurate and complete submission of patent information for the NDA, amendment, or supplement pending under section 505 of the Federal Food, Drug, and Cosmetic Act. This time-sensitive patent information is submitted pursuant to 21 CFR 314.53. I attest that I am familiar with 21 CFR 314.53 and this submission complies with the requirements of the regulation. I verify under penalty of perjury that the foregoing is true and correct.***

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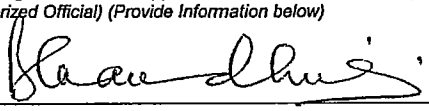
6.2 Authorized Signature of NDA Applicant/Holder or Patent Owner *(Attorney, Agent, Representative or other Authorized Official) (Provide Information below)*	Date Signed
	11/15/04

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Check applicable box and provide information below.

☒ NDA Applicant/Holder	☐ NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official
☐ Patent Owner	☐ Patent Owner's Attorney, Agent (Representative) or Other Authorized Official

Name Dow Pharmaceutical Sciences	
Address 1330A Redwood Way	City/State Petaluma, California
ZIP Code 94954-1169	Telephone Number 707-793-2600
FAX Number *(if available)* 707-793-0145	E-Mail Address *(if available)* bchaudhuri@dowpharmsci.com

EXCLUSIVITY SUMMARY

NDA # 21-835 SUPPL # HFD #

Trade Name CLOBEX

Generic Name clobetasol propionate

Applicant Name Dow Pharmaceuticals

Approval Date, If Known October 27, 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

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?

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# 21-535 Clobex Lotion

NDA#

NDA#

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:

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"):

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 # 62,543	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: Kalyani Bhatt
Title: Project Manager
Date:

Name of Office/Division Director signing form: Stanka Kukich, Acting Division Director
Title: Acting Divison Director

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

DEBARMENT CERTIFICATION

Dow Pharmaceutical Sciences herewith certifies that the services of any persons debarred under Section 306(a) or (b) were not and will not be used in any capacity in conjunction with this application.

Signed:  Date: November 23, 2004

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

PEDIATRIC PAGE

(Complete for all APPROVED original applications and efficacy supplements)

NDA/BLA #: 21-835 Supplement Type (e.g. SE5): N/A Supplement Number: N/A

Stamp Date: December 27, 2004 Action Date: October 27, 2005

HFD____ Trade and generic names/dosage form:

Applicant: Dow Pharmaceuticals Therapeutic Class: Anti - Inflammatory

Indication(s) previously approved: Moderate to severe psoriasis.

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

Number of indications for this application(s):_____

Indication #1: Moderate to severe psoriasis.

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
❑ Disease/condition does not exist in children
X Too few children with disease to study
❑ There are safety concerns
X Other: Clobex Spray does not represent a meaningful therapeutic benefit over existing treatments for pediatric patients and that Clobex Spray is not likely to be used in substantial number of patients.

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): _____

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

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

/s/

Jill Lindstrom
10/25/2005 03:18:36 PM

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_____ Deliberative Process

Withheld Track Number: Administrative- 1

********** -COMM. JOURNAL- ********** DATE OCT-26-2004 ***** TIME 17:06 ********

MODE = MEMORY TRANSMISSION START=OCT-26 17:02 END=OCT-26 17:06

FILE NO.=853

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-FDA/CDER/DDDDP/HFD540 -

********** -301 827 2075 - ***** - 301 827 2075- **********

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville, MD 20857

IND 62,543

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

Dear Mr. Calvarese:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for CLOBEX (clobetasol propionate) Spray, 0.05%.

We also refer to the meeting between representatives of your firm and the Agency on October 5, 2004. The purpose of the meeting was to obtain the Agency's guidance on the content and format regarding the planned NDA submission for CLOBEX (clobetasol propionate) Spray, 0.05% for the treatment of psoriasis.

The official minutes of that meeting are enclosed. You are responsible for notifying us of any significant differences in understanding regarding the meeting outcomes.

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

Sincerely,

{See appended electronic signature page}

Stanka Kukich, M.D.
Deputy Director
Division of Dermatologic and Dental Drug Products
Office of Drug Evaluation V
Center for Drug Evaluation and Research

Enclosure

MEMORANDUM OF MEETING MINUTES

Meeting Date: March 18, 2002 **Time:** 1:00pm **Location:** Rm. N225 **Mtg. ID #:** 8348

Meeting: End of Phase 2 Meeting

Application: IND 62,543, Clobetasol Propionate 0.05 % Spray

Sponsor: Dow Pharmaceutical Sciences

Meeting Chair: Jonathan Wilkin, M.D./Division Director

Meeting Recorder: Kalyani Bhatt/Regulatory Project Manager

FDA Attendees, titles, and Office/Division:

Jonca Bull, M.D., Acting Office Director, ODEV, HFD-105
Jonathan Wilkin, M.D., Division Director DDDDP, HFD-540
Wilson DeCamp, Ph.D., Chemistry Team Leader, DNDCIII, HFD-830
Saleh Turujman, Ph.D., Chemistry Reviewer, DNDCIII, HFD-830
Abigail Jacobs, Ph.D., Pharmacology/Toxicology Team Leader, DDDDP, HFD-540
Paul Brown, Ph.D., Pharmacology/Toxicology Reviewer, DDDDP, HFD-540
Veneeta Tandon, Ph.D., Acting Biopharmaceutics Team Leader, DPEIII, HFD-880
Susan Walker, M.D., Dermatology Team Leader, DDDDP, HFD-540
Denise Cook, M.D., Medical Reviewer, DDDDP, HFD-540
Kathleen Fritsch, Ph.D., Acting Biostatistics Team Leader, DOBIV, HFD-725
Chenxiong Le, Ph.D., Biostatistics Reviewer, DOBIV, HFD-725
Frank Cross, M.A., CDR, Senior Regulatory Management Officer, DDDDP HFD-540

External Constituent Attendees and titles:

Clawson Bowman, J.D., R.A.C., Vice President, Regulatory Affairs
Gordon Dow, Pharm.D., Founder and Chief Technical Officer
Elena Serbinova, Ph.D. R.A.C., Associate Director, Regulatory Affairs

Via Teleconference

Karen Yu, Ph.D., Project Manager
James Staszak, M.S., Statistician
Bhaskar Chaudhuri, Ph.D., President and CEO

Purpose:

To provide general guidance on the content and format for IND 62,543 and discuss plans for Phase 3 development of Clobetasol Propionate 0.05% spray for the treatment of psoriasis. The Sponsor's briefing jacket dated February 15, 2002, provides background and questions for discussion.

Chemistry, Manufacturing and Controls:

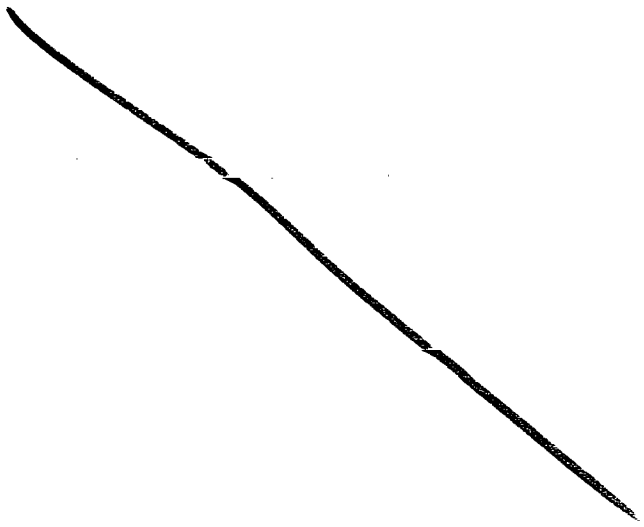
Agency:

The briefing package does not contain a CMC section nor does it contain CMC questions. While the CMC information provided was adequate for the Phase 2 study, the following remarks are provided to help guide the Sponsor to proceed to the Phase 3, and to prepare for the submission of an NDA acceptable for filing with the Agency.

1. Phase 3 Issues:

   a.

   b.



   c. A microbial limits test was performed as recommended in USP method <61> on a sample laboratory batch containing 0.01% clobetasol propionate (i.e. [redacted] of the to-be-marketed strength); the results met the general USP criteria for acceptance for the Microbial Limits Test.

      The Sponsor is requested to conduct a microbial limits test on the to-be-marketed drug product.

   d. The Sponsor states (in the IND submission) that a stability protocol will be initiated, that the results are not yet available and that [redacted] stability data will be available at the time the clinical trials are initiated.

i. Please be reminded that a stability protocol should be developed and available at the outset of the Phase 3 clinical study. Stability data (results) are not required at the beginning of a Phase 3 trial. Sufficient [redacted] stability data will be required, however, at the time of NDA submission.

ii. It is recommended that viscosity monitoring be incorporated into the stability protocol, in addition to monitoring the amount of spray per actuation.

iii. It is recommended that impurities be incorporated into the stability protocol.

e. Please note the following recommendations before start of Phase 3 clinical studies:

i. To include, in addition to the composition listing, both a definite weight and measure per unit dose.

ii. To provide updated information regarding the components, composition, and batch formula if different from that used in Phase 2.

iii. To provide a listing of all firms associated with the manufacturing and controls of the drug product, including the contractors for stability studies, packaging, labeling, and quality control release testing.

iv. To provide changes in the manufacturing method for the drug product, if any.

v. To include a full CMC section or references to appropriate Type III DMFs, including letters of authorization for all referenced DMFs for the container closure system. Please refer to the CDER Container Closure Guidance for Industry.

vi. To describe reprocessing procedures and pertinent controls, if applicable.

vii. To have the placebo provided for Phase 3 clinical study samples tested in order to demonstrate the absence of the active ingredient. The results should be filed in an annual report.

viii. To describe your plans for phasing in the child resistant closures/ packaging.

2. NDA Issues:

a. For planning purposes, the Sponsor is reminded that the NDA submission should contain stability data from both accelerated and long-term testing on three batches of the same formulation of the dosage form in the container closure that is proposed for marketing. Two of the three batches should be at least pilot scale.

The third batch may be smaller. Please refer to ICH Q1A Guidance. The Agency will evaluate submission of stability data that are less than recommended in ICH Q1A if adequate justification is provided. Please refer to the ICH Q1C Guideline.

b. The Sponsor is also reminded of the stability recommendations for the drug substance in Q1A. The Sponsor may want to inquire if the DMF holder has satisfied those recommendations.

c. The Sponsor is further reminded that for an NDA, the shelf life (expiration date) that will be granted will be based on a review of the (amount of) stability data provided under ICH conditions. It is recommended that the stability protocol be extended through the proposed expiration date.

d. To ensure appropriate stability data are generated for filing at the NDA stage, a stability protocol should be created which includes a description of the drug product, a description of the drug substance used to manufacture the drug product, a description of the packaging, a list of the tests, the analytical procedures, the acceptance criteria, the sampling time points for each of the tests, temperature and humidity conditions to be studied, expected duration of the stability program, and the proposed bracketing/matrixing protocol, if applicable.

e. The Sponsor should provide the planned production batch sizes, site.

f. ICH documents and FDA guidances, are available in hardcopy by request, and electronically from the CDER website"http:/www.fda.gov/cder/ guidance/index.htm".

Pharmacology/Toxicology:

Agency:

1. In general, the nonclinical information on clobetasol propionate appears adequate to support the proposed Phase 3 clinical studies.

2. The Sponsor should follow one of the following three mutually exclusive recommendations for nonclinical information recommended to support an NDA:

   a. The nonclinical information listed in the briefing package appears to be adequate to support a 505(b)(2) NDA for the clobetasol propionate spray if an adequate clinical bridge to an appropriate approved listed product was established.

   b. If a clinical bridge to an approved listed product was not established then additional nonclinical information would be needed to support the NDA.

The nonclinical information could be provided as study reports, right of reference to information submitted to the Agency by others, or literature information. The following nonclinical information should be included in the NDA in addition to the studies listed in the briefing package: information on general toxicity in a rodent species, effect on fertility and early embryonic development, effect on embryo-fetal development, effect on pre- and postnatal development and genotoxicity.

c. If the Sponsor submits an NDA under section 505(b)(1) of the FD&C Act then it would need to be supported by complete nonclinical pharmacology and toxicology information without referring to literature information or an approved drug product. Nonclinical information can be provided from the Sponsor's studies or from studies for which the Sponsor has obtained the right of reference.

Sponsor:

During the meeting the Sponsor stated that they intended to submit a 505(b)(1) application and that they would not be using information obtained through FOIA.

Agency:

3. The Division considers the treatment of psoriasis as a chronic indication. Consequently, it is recommended that the carcinogenicity and photoco- carcinogenicity of drugs used to treat psoriasis be evaluated even if the drug product is used in an intermittent manner. These studies could be conducted postapproval.

Sponsor:

During the meeting the Sponsor said that they would conduct a rodent dermal toxicity study and evaluate the results to determine feasibility and dose selection for a dermal carcinogenicity study. The Sponsor will also submit a proposal to evaluate the photcocarcinogenic potential of their drug product.

Agency:

Biopharmaceutics:

While an HPA axis suppression study is underway, the Agency would like to remind the Sponsor that in addition to this study they will be required to demonstrate the relative potency of their drug/ dosage form combination via the topical vasoconstrictor study. At the present time the Agency is willing to accept either the single or multi-point assessment methods provided that the test product is "bracketed" in the study by other corticosteroids of various potencies.

Clinical:

1. Sponsor's Question 2: "What are the FDA's comments and suggestions, if any, to the phase 3 protocol designed for 2 pivotal, identical phase 3 clinical trials?"

Agency:

a. At this point, the information provided in the briefing package does not allow the Division to completely concur with a primary efficacy time point of 4 weeks. The Division would suggest several alternatives described below. It is duly noted that the Sponsor plans to present the remainder of the HPA suppression study data at the meeting. However, we do not use meeting time to listen to new data but rather comment on the data presented in the briefing package (which we have had time to review). Further, the data presented for the interim analysis of the HPA axis suppression study is not clear. Clarification is needed regarding the data presented in section 4.4, page 20. It shows that patient -02 had a repeat cosyntropin stimulation test post study but was not suppressed at endpoint and patient -09, who was clearly suppressed at treatment endpoint, does not have a recorded post treatment cosyntropin stimulation test. Without those results, this patient would be regarded as having continuing suppression. The full study report should be submitted for review.

   All this is to say that the safety of the spray formulation of clobetasol propionate has not been clearly defined. Thus, if the Sponsor wants to submit only 4-week efficacy data in the Phase 3 trials, it would be running a risk. An alternative would be to use a nesting paradigm where primary efficacy is determined at 2 weeks and if efficacy is obtained, then the data from 4 weeks could be evaluated.

   Under this paradigm, although the efficacy endpoints should be the same (e.g., severity scales), the Division is aware that the degree of efficacy may not be the same at 2 weeks as it would be at 4 weeks and is willing to review a proposal for criteria for success at 2 weeks. Under this nested paradigm, the Sponsor must win at 2 weeks in order to get 4 weeks. Another alternative would be to split the alpha at 2 weeks and 4 weeks, if the Sponsor feels that the drug product is equally as good at 2 weeks as it is at 4 weeks (the Biostatistics reviewer will address this in more detail).

b. For HPA axis suppression evaluation, the following information is requested by the Agency:

   i. Identification of each patient by identifier number, age, height, and weight.

   ii. Specification of the dosage of cosyntropin used for each patient.

   iii. Baseline pre- and post-cosyntropin stimulation cortisol levels.

iv. Post-treatment or intra-treatment pre- and post-cosyntropin stimulation cortisol levels

v. Time intervals between cosyntropin stimulation and blood draw (alternatively, Cortrosyn stimulation time and blood draw time could be recorded).

vi. Demonstration of recovery of patients with abnormal HPA axis suppression data.

vii. Name and address of laboratory plus laboratory normal values for each measure of serum cortisol level.

viii. For topical corticosteroids, information is needed regarding the % body surface area applied and frequency of application. In general, topical corticosteroids for treatment of steroid-responsive dermatoses should be applied to diseased skin.

Cosyntropin administration and blood draws should generally be performed as labeled. Strict adherence to dosing and timing is suggested. Justification should be provided if any deviations in conduct of trial or interpretation of results are to be made in study design.

c. The Sponsor needs to more clearly define the "proposed" indication. The protocol, as it is currently, would support an indication of "the treatment o[redacted]plaque psoriasis covering up to 20% of the body surface area (BSA)". The Sponsor should give a rationale as to why the upper limit BSA should be 20%.

Sponsor:

During the meeting the Sponsor said that they will revisit the metrics.

Agency:

d. The Sponsor should provide a scientific rationale for women of childbearing potential to be required to use an effective form of birth control. The Phase 3 study should reflect the population of intended use in the manner in which the drug is to be prescribed.

e. The Sponsor should give a scientific rationale for not having a clinic visit at day 21 (week 3).

f. The Investigator's Global Assessment (Overall Disease Severity) scale and the scales for individual signs each should be a scale with no more than 5 levels without midpoints. These levels should have clearly defined morphological descriptors and should be *static* without reference to baseline. Mild, moderate, severe, and very severe are insufficient morphologic assessments

g. The Investigator's Global Assessment should incorporate all the signs and symptoms of psoriasis germane to the evaluation such that variability among investigators is a minimum. For a success, the Investigator's Global Assessment should be dichotomized to success vs. failure a priori in the protocol. The Division usually recognizes a 0-1 or clear/ almost clear as a success. Success should be clinically relevant, such that the patient, although not clear would not require further treatment. This is what would be expected at the end of 4 weeks proposal can be made for success at the end of 2 weeks, which would be reviewed.

h. Since skin atrophy can be a late occurring event, the Sponsor would be advised to follow-up patients for at least 2 weeks after end-of-treatment.

Addendum:

The Sponsor should submit an ethical and scientific rationale for excluding from their proposed Phase 3 protocols, patients less than 18 years of age.

2. Sponsor's Question 3: "Does the FDA concur that successful completion of the studies under the Phase 3 protocol supports NDA approval?"

Agency:

Two well-designed, placebo controlled, double-blind trials are adequate for seeking approval of a new drug product. Please see the Agency's response to Question 2 (above) for the deficiencies noted on this specific Phase 3 protocol.

3. Sponsor's Questions 4 and 5: (See page iii of the February 15, 2002, Meeting Briefing Package).

Agency:

The safety concerns of clobetasol propionate have been well established, both concerning its systemic effects (e.g., HPA axis suppression) and its cutaneous side effects (e.g., telangiectasias, cutaneous atrophy, etc). The numbers to establish efficacy for your drug product appear reasonable, but an adequate safety margin should be incorporated to insure adequate power given that dropouts will not be replaced. Safety, however, has to be discussed in the context of this particular drug product, which is a new formulation with a different delivery system. Adequate numbers for safety have to be discussed in the context of the results of the phase 2 HPA axis study, the complete data of which has not been submitted.

The Sponsor should also consult ICH E1 documents available at http://www.ifpma.org/ich5e.html The *Extent of Population Exposure to Assess Clinical Safety for Drugs Intended for Long-term Treatment of Non-Life-Threatening Conditions* was finalized *(Step 4)* in October 1994.

This gives recommendations on the numbers of patients and duration of exposure for the safety evaluation of drugs intended for the long-term treatment of non-life-threatening conditions.

Biostatistics:

1. The Sponsor plans to analyze efficacy at Week 4, however, as discussed in the clinical comments, the Sponsor could select primary endpoints at week 2 as alternatives. The primary efficacy endpoints could be defined at both Week 2 and Week 4. Two methods can be used for the efficacy analysis.

    a. Nested hypothesis test. In this analysis, the Sponsor has to 'win' at Week 2 and then the analysis at Week 4 can be carried out. No adjustment for Type I error is needed.

    b. Adjusted multiplicity hypothesis test. The Sponsor can win at either Week 2 or Week 4. In this case, the adjustment for Type I error need to be considered.

    It should be noted that the primary endpoint at Week 2 needs to be in agreement with the Division.

2. In Question 3, the Sponsor defines the primary endpoint as a dichotomized investigator evaluation of the Overall Disease Severity for psoriasis at Week 4, where success is defined as a 2-unit reduction from baseline of this 9-point static measure. This primary efficacy endpoint is not the same recommended by the Division. In the clinical comments of the Pre-IND meeting minutes dated December 19, 2000, the Division recommended that the primary efficacy endpoint should be the investigator's global assessment dichotomized to success or failure which is not a comparison to baseline.

3. Following the clinical comments (above), the primary efficacy endpoint should be based on a 4 or 5-point scale of the investigator's global assessment in stead of a 9-point scale. As a result, the inclusion and exclusion criteria should be based on the same 4 or 5-point scale.

4. The sample size calculation should be based on the primary endpoint recommended by the Division. The data from the bilateral Phase 2 trial should be used for sample size determination of the Phase 3 trials. The Sponsor carried out the sample size calculation based on 70% and 40% success rates on the active and vehicle treatment groups respectively, where success is defined as a 2-unit reduction on the 9-point scale. It is not clear whether the above response rates were obtained from the bilateral Phase 2 trial. In addition, dropouts should be considered in the sample size calculation.

5. The method to be used for the analysis of the primary efficacy endpoint should be pre-specified clearly. The Cochran Mantel-Haenszel test (controlling for investigators) is acceptable for the analysis of a dichotomized primary efficacy endpoint.

6. For secondary efficacy endpoints, the Sponsor proposes to use either Wilcoxon rank-sum test (controlling for investigator differences) or an analysis of covariance based on rank scores (with baseline as covariate) for some of the efficacy analyses. It should be clearly stated which method would be used under what conditions. In addition, if analysis of covariance is used, the model should be pre-specified and limited number of independent variables should be pre-specified as well.

7. The Sponsor stated that up to 144 patients will be enrolled for each study. A minimum number of patients should be specified and the number should be large enough for the study to have adequate power to detect the efficacy of the drug.

8. It is acceptable to use the ITT data set as the primary data set. However, the Division normally defines the ITT population as all subjects randomized into the study who are dispensed drug medication. The Sponsor should clarify how the missing values should be handled for those patients who do not have one on-treatment evaluation.

9. A randomization list, which shows patient treatment allocation, should be generated prior to study enrollment. The protocol should provide details about randomization such as block size, stratification if any.

Project Management:

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

   Per 21CFR 314.50(d)(7), NDA applications are required to contain "A section describing the investigation of the drug for use in pediatric populations, including an integrated summary of the information (the clinical pharmacology studies, controlled clinical studies, or uncontrolled clinical studies, or other data or information) that is relevant to the safety and effectiveness and benefits and risks of the drug in pediatric populations for the claimed indications, a reference to the full descriptions of such studies provided under paragraphs (d)(3) and (d)(5) of this section, and information required to be submitted under Section 314.55."

2. 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.

3. The Sponsor is encouraged to submit its revised protocols for the topical treatment of Psoriasis as Special Protocols through the 45-day Special Protocol Assessment (SPA) mechanism for Agency review, comment, and possible agreement, prior to study initiation.

4. The Sponsor should request a Pre-NDA Meeting at the appropriate time.

The meeting ended amicably.

Minutes Preparer:

Frank Cross, M.A., CDR
Senior Regulatory Management Officer
DDDDP, HFD-540

Chair Concurrence:

Jonathan Wilkin, M.D.
Division Director,
DDDDP, HFD-540

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

/s/

Jonathan Wilkin
9/5/02 06:19:34 PM

MEMORANDUM OF MEETING MINUTES

Meeting Date:	December 19, 2000 Time: 10:30 AM	**Location:** N225
Application:	Pre-IND Meeting	
Drug:	Clobetasol Propionate Spray, 0.05%	
Indication:	Psoriasis	
Sponsor:	Dow Pharmaceutical/Clementi	
Meeting Chair:	Jonathan Wilkin, M.D./Division Director	
Meeting Recorder:	Kalyani Bhatt/Project Manager	

FDA Attendees, titles, and Office/Division:

Jonathan Wilkin, M.D./Division Director DDDDP, HFD-540
Martin Okun, M.D., Ph.D./Medical Team Leader, DDDDP, HFD-540
Denise Cook, M.D./ Medical Officer DDDDP, HFD-540
Wilson Decamp, Ph.D./Chemistry Team Leader DDDDP, HFD-830
Paul Brown, Ph.D./Pharmacology Reviewer DDDDP, HFD-540
Mohamed Al-Osh, Ph.D./Team Leader, Biostatistics DDDDP, HFD-540
Don Hare/ Project Manager, DHHS, HFD-604
Kalyani Bhatt/Project Manager, DDDDP, HFD-540

External Constituent Attendees and titles:

Dow Pharmaceutical Sciences:
Dr. Gordon Dow, CEO
Clawson (Cal) Bowman, JD, VP of RA/QA
Dr. Karen Yu, Project Manager
Consultants
Dr. Dan Picquadio-Clinical
Dr. William Clementi-Regulatory Affairs

ORIGINAL
Received 2/12/01
CC

Purpose:

The purpose of the meeting is to provide general guidance on the content and format of the proposed new Investigational New Drug Application under 21 CFR 312. The sponsor submitted briefing package dated November 21, 2000.

Chemistry, Manufacturing and Controls:

This meeting is for a proposed pump spray formulation of clobetasol propionate, 5%. The following is the CMC response to question 3 in the briefing package:

Question # 3

Does this spray formulation ... require additional studies?

This question is primarily clinical in nature. Whether additional pharmaceutical development studies are needed will depend upon the exact phase for which the IND is submitted. We have additional comments, given below, on the assumption that the project is nearing Phase 3, and that product development is nearing completion.

1.0 Active ingredient
A letter authorizing reference to their DMF should be obtained from [redacted]

2.0 Drug Product

a) The solubility of clobetasol propionate should be determined in alcohol and in isopropyl myristate.

b) UV-visible spectra in the range of [redacted] should be submitted for all components of the drug product. This range includes both the analytical wavelengths and those of concern for potential photostability, phototoxicity, and photocarcinogenicity concerns. If possible, a UV-visible spectrum of the drug product should be submitted as well.

c) The drug product specifications should include analytical methods and acceptance criteria for known degradation products of clobetasol propionate.

d) Since the product will be delivered by a spray pump, and the amount delivered expressed by volume, we recommend that the addition of specifications for viscosity and product density be considered.

e) Unless data are submitted to show that clobetasol propionate is fully dissolved in the vehicle, the product should be monitored for particle size distribution in the stability studies.

ORIGINAL

Received 2/12/01 CC

f) The IND submission should include a stability protocol for the Phase 3 lots. This should be directed toward the submission of [redacted] of room-temperature stability data with the NDA.

g) A DMF reference authorization should be submitted for the supplier of both the bottles and the pump sprayer.

h) The acceptance criteria for the pump sprayer should include a study of the reproducibility of the delivery volume per actuation.

Pharmacology/Toxicology:

1) In general, the preexisting nonclinical information on clobetasol propionate together with the proposed nonclinical studies appears adequate to support the proposed clinical studies.

2) The proposed nonclinical dermal irritation and sensitization studies appear to be relatively insensitive as currently designed. The sponsor should consider using studies with greater sensitivity at detecting an effect. For example, the dermal irritation assay might be conducted with a longer exposure period. It is recommended that that the dermal sensitization study follow a standard protocol such as the guinea pig maximization test, Buehler assay or local lymph node assay.

3) If the evaluation of dermal irritation were positive then the Division would also consider the drug to be irritating to the eye and an eye irritation study would not be necessary.

4) Since the proposed concentration of isopropyl myristate has not been previously used in an approved drug product, the sponsor should submit literature or other information on the toxicity and safety of isopropyl myristate.

The following recommendations apply to later stages of drug development and eventual NDA submission.

5) Several corticosteroids have been shown to be genotoxic. The genotoxicity of clobetasol propionate has not been fully characterized. It is recommended that an *in vitro* test of genotoxicity in mammalian cells and an *in vivo* test of chromosomal damage be conducted. (See ICH Guidance's S2A, Specific Aspects of Regulatory Genotoxicity Tests for Pharmaceuticals and S2B, Genotoxicity: A Standard Battery for Genotoxicity Testing of Pharmaceuticals tests.)

6) If the drug product is considered safe enough to be used repeatedly for chronic recurring diseases, then it is recommended that the carcinogenic and photococarcinogenic potential of the drug product be evaluated. This is true even if the use is discontinuous. If safety concerns with the drug product limit its use so that it is not used repeatedly and the product is so labeled then an evaluation of its carcinogenicity and photococarcinogenicity may not be required.

7) Additional nonclinical studies may be recommended to support later stages of drug development based on the information submitted in the IND and on any safety concerns that arise during clinical trials.

FINAL
Received 2/12/01
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Biopharmaceutics:

In terms of the biopharmaceutic of the clobetasol propionate spray, the sponsor is proposing to do both the single point Stoughten-McKenzie (topical vasoconstriction assay) and a HPA axis suppression study. Both trials as outlined in the briefing document appear to be adequately designed, however, the Agency would like to be informed of the control formulations used in the topical vasoconstrictor studies and how the spray will be applied to the demarcated surface area in this trial. As for the HPA axis trial it again appears, on the basis of the material submitted, to be adequately designed, however, the material does not clarify the standards to be used in assessing HPA axis function (i.e. net increase over baseline ((7 units or more)) or an absolute value approach ((levels greater than some value)). Clarification of what constitutes a "win" should be done prior to study initiation.

Clinical:

Response to Question 1:

The Agency is willing to discuss the requirements for a 505(b)(2) application, but the decision as to whether this form of application would be the best approach should be decided by the sponsor.

If a 505(b)(2) application is submitted that relies in part upon the Agency's finding of safety and effectiveness for a previously approved drug, the sponsor must provide all the data necessary to support the finding that a dosage form different than that originally approved is safe and effective. In order to rely upon the finding of safety and effectiveness for the previously approved drug, the sponsor must provide a link to that product by providing comparative bioavailability data. A comparative pharmacodynamic study, a comparator HPA axis study, and a comparative clinical trial may be necessary. In addition, a 505(b)(2) applicant must provide certification to patents listed for the reference drug, and the timing for approval is governed by patents and exclusivity protecting the reference drug.

Response to Question 2:

As noted above, should the sponsor choose to submit a 505(b)(2) application, the sponsor needs to conduct a comparative bioavailability study to the reference listed drug product (RLD). The RLD must be an approved drug in which efficacy and safety have been established. In this regard, the establishment of a "bridge" to the reference listed drug product is essential for approval of an application submitted under a 505 (b)(2). This "bridge" may be established by conducting a comparative efficacy study and a comparative vasoconstrictor study. In this instance, an HPA axis suppression study will also need to be done to determine the effect of the new dosage formulation on the HPA axis. Phase I human skin irritation studies will be necessary. A vehicle arm should be added for the cumulative irritancy/sensitization study. Photoallergy and phototoxicity studies will be waived if the drug has no absorbance in the visible, UVA, or UVB light.

ORIGINAL
Received 2/12/01
CC

Response to Question 3:

Agency infers from this question that it is not the intention of the sponsor to pursue an indication for treatment of corticosteroid-responsive dermatosis, but rather only to pursue an indication for treatment of psoriasis. Is this inference correct?

The sponsor states that this is correct.

Commitments relating to the number of studies required to secure an indication are contingent upon results accrued in the Phase 2 studies. Agency could provide more definitive guidance on this topic at an End of Phase 2 meeting, which the sponsor is encouraged to request.

Response to Question 4:

The sponsor should be aware again, that the vehicle controlled trial must have a reference listed drug product. The formulation of the product should be as close as possible to the new drug product and should follow the conditions for use in the approved label. Neither the Phase 3 protocol nor the HPA axis suppression protocol included in this submission would be adequate for a 505 (b)(2) application. Both must have a comparator.

The sponsor should be aware that under the currently submitted Phase 3 protocol where 2 dosing frequencies are being investigated, when the comparator drug is added, this study will need to be a 6 arm study. Further, adjustments for multiple comparisons will have to be made.

The Agency would recommend that a dose ranging study be performed separately prior to the Phase 3 study. The dose ranging study does not have to be powered to demonstrate statistical significance but should show a trend toward efficacy regarding dosage and dosing frequency. Once a trend is established in the Phase 2 dose ranging study, then the Phase 3 pivotal comparator trial could begin.

It is strongly recommended that the sponsor conduct the HPA axis suppression study prior to the Phase 3 clinical trial as the findings in this trial will direct the duration of treatment in the Phase 3 clinical trial. If this is not done, the Agency would advise the sponsor that they are taking a risk, for it may be that the evaluation time point for efficacy in the pivotal trial (e.g. 3 weeks) may not be acceptable because of safety issues.

Response to Question 5:

The Agency advises the sponsor that unless they are prepared to conduct a full NDA under 505(b)(1), then a reference listed drug (comparator drug) must be used in the studies to be conducted.

Additional Comments regarding protocols

Proposed study #4: Assessment of HPA Axis Suppression

1) The HPA axis suppression study should use a cosyntropin stimulation test. The subjects should use an amount of spray per week equal to the weekly upper limit of

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total dosage permitted in the final package labeling. The area treated must be clinically involved skin. Applying medication to normal skin is to be avoided. The final package labeling will reflect the percentage of body surface area applied in the HPA axis suppression study. The Agency would recommend a total BSA of at least [redacted] The proposed duration of treatment in the final package labeling will reflect the duration and outcome of the HPA axis suppression test.

2) The study should incorporate a second arm in which another approved topical corticosteroid is applied to patients, in a manner, which is consistent with its labeling, for comparison. There should be a minimum of 30 evaluable patients, 15 in each arm. The RLD should be chosen should be at least as suppressive as the sponsor's drug product. Depending on the outcome of the HPA axis suppression study, the same RLD might be used in the pivotal Phase 3 trial.

3) The Cosyntropin stimulation test should be done at baseline and at one other timepoint (i.e. end of treatment) for a given patient. Once a patient has been stimulated after treatment at 2 weeks, performing the test at 4 weeks would not give any useful information. Thus, if the sponsor wants to look at two points, they should be performed in different patients.

4) [redacted]

5) The protocol should state clearly the quantity of medication to be applied at each application. The protocol should state clearly, how patients will be instructed to apply the medication, how much to use with each application (e.g., how many spray bursts), and at what distance to apply the spray.

6) The Agency recommends a washout period of 6 weeks for systemic anti-psoriasis medications. The sponsor should follow the pharmacologic profile of each drug to determine the washout period.

7) The Agency suggests that the assays be labeled in a blinded fashion.

Proposed Study #3: Vasoconstrictor Study

Comparisons in the Stoughton-McKenzie single point assay should be made with multiple drug products in adjacent classes in order to adequately establish the steroid class of the clobetasol spray product.

Proposed Study #2: Phase 3 pivotal trial

These are recommendations that are made at this point based on the information submitted in the submission jacket. However, these may be modified depending on data obtained from Phase 2 studies.

1) As stated under question 4, to qualify for a 505(b)(2), this study has to have a comparator arm (the reference listed drug product). As designed, with two different dosing frequencies, the study would need 6 arms. It should be noted here, that if once

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a day dosing is a dosing frequency to be explored, a separate vehicle arm would be necessary and those patients using active drug should not apply vehicle at all.

2) The primary efficacy endpoint should be the Investigator's Global Assessment. It assesses the overall severity of the disease. This should be a static morphological scale that refers to a point in time and not a comparison to baseline. The morphological scale should incorporate the clinical signs of erythema, plaque thickness, and lesional scaling.

3) The Investigator's Global Assessment should further be dichotomized to success and failure a prior in the protocol.

4) Assessments of a target lesion could be considered a secondary efficacy endpoint.

5) Given the probable potency of this steroid product, clobetasol propionate spray, a more appropriate indication might be for moderate to severe psoriasis. Thus, the inclusion criteria should reflect this population of patients.

6) For the same reason as number 5, the duration of the treatment should be 2 weeks in length, unless the HPA axis stimulation study directs otherwise.

7) [redacted]

8) The Agency agrees with the systemic safety evaluations in the protocol. The protocol should also state the specific cutaneous signs that will be monitored and might be expected with the use of a topical steroid.

9) The protocol, when submitted to the IND should have a full statistical analysis plan.

Biostatistics:

At this stage, it is early to provide detailed statistical comments. The following general comments are intended to provide guidance.

1) Drug development is a sequential process. The Sponsor is encouraged to carry out Phase 2 trials (dose-ranging finding) before proceeding to Phase 3 studies. Otherwise, an adjustment for multiplicity needs to be made for Sponsor's proposal of Phase 3 trial.

2) Results of Phase 2 trials such as appropriate dose ranging and treatment effect can be used for calculating the sample size for Phase 3 trial.

3) The Sponsor should submit detailed Phase 3 protocol for Agency's comments following their completion of Phase 2 trials.

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Regulatory Guidance:

505(b)(2) issue for the proposed Clobetasol Propionate Spray 0.05%.

1) Agree that Clobetasol Propionate 0.05% Spray could be eligible as a 505(b)(2) application.
A 505(b)(2) application can be used for a change in dosage form and/or a change in dosing regimen.

2) A 505(b)(2) applicant does not have to submit literature to support the underlying safety and efficacy data of the listed drug. The 505(b)(2) application is relying upon FDA's finding of safety and efficacy of the listed drug. Since a 505(b)(2) application is submitted under 505(b)(1) it must contain "Full Reports" and therefore the Division may request any additional data to insure that the application meets today's standards. This reliance upon FDA's finding of safety and efficacy for the listed drug is based upon an appropriate bridging study or comparable bioavailability study. This study does not necessarily have to demonstrate bioequivalence. A "Paper NDA" was for a duplicate post 1962 drug product and was required to support the safety and efficacy of their drug product with literature. However the "Paper NDA" policy was revoked by the agency because it was no longer needed after the passage of the 1984 Waxman-Hatch amendments.

However, literature may be used in a 505(b)(2) application to support the suggested change(s).

3) Unless a 505(b)(2) applicant is prepared to support a full NDA, it must cite a listed drug.

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Administrative Comments:

1) All comments are based upon the Pre-IND packet, which is an unofficial briefing document submitted as information. The final protocols should be submitted to the IND (21 CFR Part 312, Subpart B) for review.

2) The Food and Drug Administration Modernization Act [FDAMA] of 1997, Section 111, Pediatric Studies of Drugs, effective December 1998, requires the following:

3) Per 21 CFR 314.55(a), each NDA *application for a new ingredient, new indication, new dosage form, new dosing regimen, or new route of administration shall contain data that are adequate to assess the safety and effectiveness of the product for the claimed indications in all relevant pediatric subpopulations, and to support dosing and administration for each pediatric subpopulation for which the drug is safe and effective.* Under 21 CFR 314.55(d) *this section does not apply to any drug for an indication or indications for which orphan designation has been granted under part 316, subpart C, of this chapter.* A waiver can be requested in accordance with 21 CFR 314.55(c).

4) The Final Rule regarding Financial Disclosure was published on February 2, 1998, for applications submitted after February 2, 1999. The applicant is required either to certify to the absence of certain financial interests and arrangements of clinical investigators or to disclose those financial interests using Form 3454.

5) The Sponsor is encouraged to request an end-of Phase 2 meeting (21 CFR 312.47(b)) for each indication to be obtained for regulatory commitments for Phase 3 trials. Comments on Phase 1 and Phase 2 trials do not necessarily constitute commitments that can be extrapolated to Phase 3 trials.

Chair Concurrence:
Jonathan Wilkin, M.D./Division Director, DDDDP

Minutes Preparer: Kalyani Bhatt
Kalyani Bhatt/Project Manager, DDDDP

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

FACSIMILE TRANSMITTAL SHEET

DATE: October 25, 2005

To: Barry M. Calvarese, MS **Vice President Regulatory and Clinical Affairs**	**From: Kalyani Bhatt, Project Manager**
Company: Dow Pharmaceutical Sciences	**Division of Dermatologic and Dental Products**
Fax number: 707-793-0145	**Fax number: 301-796-9894**
Phone number: 707-665-4610	**Phone number: 301-796-0852**

Subject: NDA 21-835 CLOBEX (clobetasol propionate) Spray, 0.05%. Please see the Phase 4 commitment.

Total no. of pages including cover: 2

Comments:

Document to be mailed: ☐ **YES** **X NO**

Thank you.

We remind you of your postmarketing study commitments in your submission dated March 11, 2005 (SN0049 to IND 62,543). These commitments with a recommended timeline are listed below.

1. The applicant commits to conduct a dermal carcinogenicity study with clobetasol propionate and appropriate vehicles.

90-day dose range-finding study report:	December 16, 2005
Study protocol submission:	March 16, 2006
Study start date:	November 16, 2006
Final report submission:	November 16, 2009

2. The applicant commits to conducting a study to determine the photoco-carcinogenic potential of clobetasol propionate and appropriate vehicles.

90-day dose range-finding study report:	December 16, 2005
Study protocol submission:	March 16, 2006
Study start date:	November 16, 2006
Final report submission:	November 16, 2009

Bhatt, Kalyani

From: Paula Mueda [PMueda@dowpharmsci.com]
Sent: Monday, October 24, 2005 5:56 PM
To: kalyani.bhatt@fda.hhs.gov
Cc: Barry Calvarese
Subject: FW: Message to Kalyani Bhatt

Kalyani,

In response to your telephonic request at 12:30 pm today, attached is the color carton and container labeling for CLOBEX® Spray for NDA 21-835.

Also, in response to your request concerning the timeline for the Phase 4 commitment for Pharm/Tox for CLOBEX, the Sponsor commits to the following:

Carcinogenicity Study – Protocol to be submitted in November 2005 to the FDA for study on Clobex Lotion (0.0002%, 0.005%, 0.001%), Clobex Lotion vehicle and Clobex Shampoo vehicle. Study to start Q2 2006.

Photo-Carcinogenicty Study – Protocol to be submitted to FDA in November 2005 for study on Clobex Lotion 0.0002% and 0.001%. Study to start Q2 2006.

Paula Mueda
Sr. Regulatory Specialist
Dow Pharmaceutical Sciences
1330 Redwood Way
Petaluma, CA 94954-1169
707.285.1561 phone
707.285.2219 fax
pmueda@dowpharmsci.com

Bhatt, Kalyani

From: Paula Mueda [PMueda@dowpharmsci.com]
Sent: Tuesday, October 04, 2005 12:44 PM
To: Bhatt, Kalyani
Subject: RE: Clobex PATIENT INFORMATION draft 9.28.05

Good morning, Kalyani,

We have received your communication regarding the Patient Information draft for Clobex. As there was no message attached, I'm assuming you want us to review and approve this version and send back a clean copy to you, the same as you requested for the Package Insert labeling.

Please advise if my assumption is not correct.

Regards,

Paula

Paula Mueda

Sr. Regulatory Specialist

Dow Pharmaceutical Sciences

707.285.1561 phone

707.793.0145 fax

pmueda@dowpharmsci.com

-----Original Message-----
From: Bhatt, Kalyani [mailto:BHATTK@cder.fda.gov]
Sent: Tuesday, October 04, 2005 9:11 AM
To: Paula Mueda
Cc: Barry Calvarese
Subject: Clobex PATIENT INFORMATION draft 9.28.05

Bhatt, Kalyani

From: Paula Mueda [PMueda@dowpharmsci.com]
Sent: Tuesday, October 04, 2005 12:48 PM
To: Bhatt, Kalyani
Subject: RE: Clobex PATIENT INFORMATION draft 9.28.05

We will get working on it right away, Kalyani.

Thanks,

Paula

Paula Mueda

Sr. Regulatory Specialist

Dow Pharmaceutical Sciences

707.285.1561 phone

707.793.0145 fax

pmueda@dowpharmsci.com

-----Original Message-----
From: Bhatt, Kalyani [mailto:BHATTK@cder.fda.gov]
Sent: Tuesday, October 04, 2005 9:47 AM
To: Paula Mueda
Subject: RE: Clobex PATIENT INFORMATION draft 9.28.05

Yes that is correct. Try to send it ASAP since we are coming close to the PDUFA date.
Thanks,
Kalyani

-----Original Message-----
From: Paula Mueda [mailto:PMueda@dowpharmsci.com]
Sent: Tuesday, October 04, 2005 12:44 PM
To: Bhatt, Kalyani
Subject: RE: Clobex PATIENT INFORMATION draft 9.28.05

Good morning, Kalyani,

We have received your communication regarding the Patient Information draft for Clobex. As there was no message attached, I'm assuming you want us to review and approve this version and send back a clean copy to you, the same as you requested for the Package Insert labeling.

Please advise if my assumption is not correct.

Regards,

Paula

Paula Mueda

Sr. Regulatory Specialist

Dow Pharmaceutical Sciences

707.285.1561 phone

707.793.0145 fax

pmueda@dowpharmsci.com

-----Original Message-----
From: Bhatt, Kalyani [mailto:BHATTK@cder.fda.gov]
Sent: Tuesday, October 04, 2005 9:11 AM
To: Paula Mueda
Cc: Barry Calvarese
Subject: Clobex PATIENT INFORMATION draft 9.28.05

Bhatt, Kalyani

From: Paula Mueda [PMueda@dowpharmsci.com]
Sent: Thursday, October 06, 2005 8:44 PM
To: kalyani.bhatt@fda.hhs.gov
Cc: Barry Calvarese
Subject: FW: Draft Labeling - Clobex NDA 021835


Untitled Attachment


Clobex Spray Label draft 10.4....


Clobex Spray Label draft 10.4....

Bhatt, Kalyani

From: Katie Ditton [KDitton@dowpharmsci.com]

Sent: Monday, September 26, 2005 10:22 PM

To: BHATTK@cder.fda.gov; khorshidih@cder.fda.gov

Cc: Barry Calvarese; Nurjehan Jivani

Subject: Clobex Amendment 0008

Attached please find a response to the phone call from Hossein Khorshidi on 26 August 2005. Hard copies will be sent to the Agency in the morning. Please let me know if you have any questions.

Regards,

Katie Ditton
Associate Manager, Regulatory Affairs
Dow Pharmaceutical Sciences
1330 Redwood Way
Petaluma, CA 94954
707-285-1540

2 Page(s) Withheld

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_____ Draft Labeling

_____ Deliberative Process

Withheld Track Number: Administrative- 2

Dow Pharmaceutical Sciences
The D in Topicals R&D Since 1977

Via Federal Express

29 August 2005

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 # N 115
9201 Corporate Blvd. HFD-540
Rockville, Maryland 20850

N-000(BC)

ORIG AMENDMENT

RE: NDA 021835 - CLOBEX (clobetasol propionate) Spray, 0.05% for the Treatment of Psoriasis

Amendment No. 0006: Response to FDA Comments on DMFs

Dear Dr. Wilkin:

Dow Pharmaceutical Sciences, Inc. (DPSI) filed an eCTD New Drug Application (NDA 021835) for CLOBEX (clobetasol propionate) Spray, 0.05% for the treatment of psoriasis on December 22, 2004, which was received by the Agency on December 27, 2004.

This is in response to a request from the FDA dated August 2, 2005 (Comment 9). In lieu of updating the DMFs, DPSI has attached the requested information.

DPSI considers the material and data contained in this submission to be confidential. The legal protection of such confidential material is hereby claimed under the applicable provision of 18 USC, Section 331(j) and/or 21 CFR 312.130.

Should you require further information regarding this submission, please contact me by phone - 707.793.2600, by fax - 707.793.0145, or by e-mail - bcalvarese@dowpharmsci.com.

Sincerely,

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

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[redacted]

ORIGINAL

Dow Pharmaceutical Sciences
The D in Topicals R&D Since 1977

RECEIVED
AUG 16 2005
MEGA / CDER

Via Federal Express

N-000 CBC
ORIG AMENDMENT

15 August 2005

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 # N 115
9201 Corporate Blvd. HFD-540
Rockville, Maryland 20850

707-665-4610

RE: NDA 021835 - CLOBEX (clobetasol propionate) Spray, 0.05% for the Treatment of Psoriasis

Amendment No. 0005: Response to FDA Comments

650-373-7306

Dear Dr. Wilkin:

Dow Pharmaceutical Sciences, Inc. (DPSI) filed an eCTD New Drug Application (NDA 021835) for CLOBEX (clobetasol propionate) Spray, 0.05% for the treatment of psoriasis on December 22, 2004, which was received by the Agency on December 27, 2004.

This amendment is in response to the attached e-mail from Kalyani Bhatt dated August 2, 2005 regarding CMC comments.

DPSI considers the material and data contained in this submission to be confidential. The legal protection of such confidential material is hereby claimed under the applicable provision of 18 USC, Section 331(j) and/or 21 CFR 312.130.

Should you require further information regarding this submission, please contact me by phone - 707.793.2600, by fax - 707.793.0145, or by e-mail - bcalvarese@dowpharmsci.com.

Sincerely,

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

2 Page(s) Withheld

_____ Trade Secret / Confidential

_____ Draft Labeling

✓ Deliberative Process

Withheld Track Number: Administrative- 3

Bhatt, Kalyani

om: Bhatt, Kalyani
t: Monday, July 18, 2005 10:11 AM
'Paula Mueda'
Cc: Bhatt, Kalyani
Subject: NDA 21-835/Clobex Spray/ Dow Pharmaceuticals

Hi Paula,

Please provide information in a table listing total amount of dose applied, number of applications and % body surface area at the baseline for each subject for the HPA axis study, Study TI01-01009.
Thanks ,
Kalyani

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: July 15, 2005

TO: Kalyani Bhatt, Regulatory Project Manager
Denise Cook, 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 21-835

PROTOCOL(s): Protocol #T101-01010 entitled: "A Randomized, Double-Blind, Vehicle-Controlled, Parallel-Group Study of the Safety and Efficacy of Clobetasol Propionate 0.05% Spray versus Its Vehicle Spray in the Treatment of Plaque Psoriasis"

SPONSOR: Dow Pharmaceutical Sciences

DRUG: Clobex® (clobetasol propionate 0.05% spray)

INDICATION: Treatment of plaque psoriasis

CHEMICAL CLASSIFICATION: 3

THERAPEUTIC CLASSIFICATION: S

INSPECTION SUMMARY GOAL DATE: July 31, 2005

ACTION GOAL DATE: October 27, 2005

I. BACKGROUND:

In this NDA application, the sponsor included results of protocol T101-01010 to support the safe and efficacious use of clobetasol propionate in the treatment of plaque psoriasis.

A single inspection of the study site of Dr. Karl Beutner was requested by the Review Division as a result of the unusually high efficacy rate (100%) with treatment by the test article reported by this site.

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
Karl Beutner, M.D., Ph.D.	Vallejo,	CA	3 May 05	11 July 05	VAI/010902

Site # 6
Karl Beutner, M.D., Ph.D.
Solano Clinical Research
127 Hospital Drive, Suite 203A
Vallejo, California 94589
See **Overall Assessment and Recommendations**, below

a. 24 subjects were randomized to the study with 11 subjects failing screening. Four subjects did not complete the study. Signed consent forms were present for all randomized subjects. Source documents for five of the subjects were reviewed in depth, including, but not limited to target plaque assessments, test article accountability, safety assessments, adverse event reporting, and concomitant medications. In addition, subject records regarding the primary efficacy endpoint; i.e., investigator evaluation of Overall Disease Severity, were reviewed for all 24 subjects.

b. There were no limitations to the inspection.

c. A Form 483 was not issued. Based on the information provided in the EIR, no significant deviations from protocol or data discrepancies were noted; however, it was noted that one subject's complaint (#324) of burning and stinging after test article application at visit 2 was not noted in the respective CRF and thus not reported to the sponsor.

III. OVERALL ASSESSMENT OF FINDINGS AND GENERAL RECOMMENDATIONS

For Dr. Beutner's's site, there was sufficient documentation to assure that all audited subjects did exist, fulfilled the eligibility criteria, received the study medication, and had the primary efficacy endpoint data captured as specified in the protocol. The data submitted in support of this application by Dr. Beutner appear adequate in support of the relevant submission.

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 21-794
HFD-45/Program Management Staff (electronic copy)
HFD-46/RF
HFD-46/c/r/s
HFD-46/Blay

c:\mydocuments\data\royblay\clinical summaries\21835.doc
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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/

Roy Blay
7/15/05 03:05:44 PM
CSO

Ni Aye Khin
7/15/05 03:12:08 PM
MEDICAL OFFICER

CONSULTATION RESPONSE

DIVISION OF MEDICATION ERRORS AND TECHNICAL SUPPORT
OFFICE OF DRUG SAFETY
(DMETS; HFD-420)

DATE RECEIVED: July 11, 2005	**DUE DATE:** September 11, 2005 **PDUFA Date:** October 27, 2005	**ODS CONSULT #:** 05-0169

TO: Jonathan Wilkin, MD
Director, Division of Dermatology and Dental Products
HFD-540

THROUGH: Kalyani Bhatt
Project Manager
HFD-540

PRODUCT NAME: **Clobex Spray** (Clobetasol Propionate) Spray 0.05% **NDA#:** 21-835	**NDA SPONSOR:** Galderma Laboratories, L.P.

SAFETY EVALUATOR: Nora Roselle, PharmD

RECOMMENDATIONS:

1. DMETS has no objections to the use of the proprietary name, Clobex Spray. This is considered a final decision. However, if the approval of this application is delayed beyond 90 days from the signature date of this document, the name must be re-evaluated. A re-review of the name will rule out any objections based upon approval of other proprietary or established names from the signature date of this document.

2. DMETS recommends implementation of the label and labeling revisions outlined in section III of this review in order to minimize potential errors with the use of this product.

3. DDMAC finds the proprietary name, Clobex Spray, acceptable from a promotional perspective.

Denise Toyer, PharmD
Deputy Director
Division of Medication Errors and Technical Support
Office of Drug Safety

Carol Holquist, RPh
Director
Division of Medication Errors and Technical Support
Office of Drug Safety
Phone: (301) 827-3242 Fax: (301) 443-9664

Division of Medication Errors and Technical Support (DMETS)
Office of Drug Safety
HFD-420; PKLN Rm. 6-34
Center for Drug Evaluation and Research

PROPRIETARY NAME REVIEW

DATE OF REVIEW:	September 1, 2005
NDA NUMBER:	21-835
NAME OF DRUG:	Clobex Spray (Clobetasol Propionate) Spray 0.05%
NDA HOLDER:	Galderma Laboratories, L.P.

I. INTRODUCTION:

This consult was written in response to a request from the Division of Dermatology and Dental Products to review the proprietary name Clobex Spray, regarding potential name confusion with other proprietary and established names. The container labels, carton labeling and package insert labeling for Clobex Spray were submitted and reviewed for possible interventions in minimizing medication errors.

PRODUCT INFORMATION

Clobex Spray is the proposed proprietary name for clobetasol propionate spray, 0.05%, which is a synthetic fluorinated corticosteroid for topical dermatologic use. The proprietary names, Clobex Lotion and Clobex Shampoo, were reviewed by DMETS and found acceptable on June 6, 2003 and November 21, 2003, respectively. The new drug application (NDA# 21-535) for Clobex Lotion was approved on July 24, 2003. The new drug application (NDA# 21-644) for Clobex Shampoo was approved on February 5, 2004. Clobetasol propionate has anti-inflammatory, antipruritic, and vasoconstrictive properties. Clobex Spray is a super-high potent corticosteroid formulation indicated for the treatment of moderate to severe plaque psoriasis in patients 18 years of age or older. Clobex Spray should be applied to the affected skin areas twice daily and rubbed in gently and completely. The total dosage should not exceed 50 grams (50 mL or 1.75 fl. oz.) per week. Treatment should be limited to four consecutive weeks. This drug will be supplied in 50 gram bottles.

II. RISK ASSESSMENT:

A search was conducted of several standard published drug product reference texts[1,2] as well as several FDA databases[3] for existing drug names which sound-alike or look-alike to Clobex Spray to a degree where potential confusion between drug names could occur under the usual clinical practice settings. A search of the electronic online version of the U.S. Patent and Trademark

[1] MICROMEDEX Integrated Index, 2005, MICROMEDEX, Inc., 6200 South Syracuse Way, Suite 300, Englewood, Colorado 80111-4740, which includes all products/databases within ChemKnowledge, DrugKnowledge, and RegsKnowledge Systems.
[2] Facts and Comparisons, online version, Facts and Comparisons, St. Louis, MO.
[3] The Division of Medication Errors and Technical Support [DMETS] database of Proprietary name consultation requests, New Drug Approvals 98-05, and the electronic online version of the FDA Orange Book.
[4] WWW location http://www.uspto.gov/tmdb/index.html

Office's Text and Image Database[4] was also conducted. The Saegis[5] Pharma-In- Use database was searched for drug names with potential for confusion. The standard DMETS prescription analysis studies were not conducted because the proprietary name Clobex was approved on June 6, 2003. DMETS searched the FDA Adverse Event Reporting System (AERS) database in order to determine any post-marketing safety reports of medication errors associated with Clobex.

A. EXPERT PANEL DISCUSSION

An Expert Panel discussion was held by DMETS to gather professional opinions on the safety of the proprietary name "Clobex Spray". Potential concerns regarding drug marketing and promotion related to the proposed name were also discussed. This group is composed of DMETS Medication Errors Prevention Staff and representation from the Division of Drug Marketing, Advertising, and Communications (DDMAC). The group relies on their clinical and other professional experiences and a number of standard references when making a decision on the acceptability of a proprietary name.

1. The Panel had look-alike and sound-alike concerns with *Clorox, Lidex, Tobrex, Carbex, Capex, and Clob-X.* These products are listed in Table 1 (see below and page 4), along with the dosage forms available and usual dosage. These names are different than the names identified during the initial review of Clobex Lotion (ODS Consult 02-0213: June 6, 2003) and Clobex Shampoo (ODS Consult 03-0259: November 21, 2003) for, where DMETS evaluated Rubex, Klotrix, Clorpres, Cobex, Probax, and Klorvess as potential look-alike and or sound-alike names to Clobex.

2. DDMAC did not have concerns about the name "Clobex" with regard to promotional claims.

Table 1: Potential Sound-Alike/Look-Alike Names Identified by DMETS Expert Panel

Product Name	Dosage form(s), Generic name	Usual adult dose	Other
Clobex	Clobetasol Propionate Spray, 0.05%	Apply twice daily, once in the morning and once at night	
Clorox	Bleach	Bleach product used for sanitization and disinfection	LA
Lidex Lidex-E	Fluocinonide Cream, Gel, Ointment, Topical Solution: 0.05% Lidex-E Cream: 0.05%	Apply to the affected area as a thin film BID to QID	SA
Tobrex	Tobramycin Solution: 0.3% Ointment: 3 mg/g	1 to 2 drops 4 - 6 times a day or 1.25 cm ribbon of ointment bid to tid	SA
Carbex	Selegiline HCl Tablets: 5 mg	10 mg/day as divided dose of 5 mg each taken at breakfast and lunch	LA/SA
Capex	Fluocinolone Acetonide Shampoo: 0.01%	No more than approximately one (1) ounce of the medicated shampoo should be applied to the scalp area once daily, worked into a lather, and allowed to remain on the scalp for approximately five minutes. The hair	LA/SA

[5] Data provided by Thomson & Thomson's SAEGIS ™ Online Service, available at www.thomson-thomson.com

Product Name	Dosage form(s), Generic name	Usual adult dose*	Other**
Clobex	Clobetasol Propionate Spray 0.05%	Apply twice daily, once in the morning and once at night	
		and scalp should then be rinsed thoroughly with water.	
Clob-X *(foreign)*	Clobetasol Cream: 0.05% Ointment: 0.05% Topical Solution: 0.05%	Apply to affected skin areas twice daily.	LA/SA
*Frequently used, not all-inclusive. **SA (sound-alike), LA (look-alike)			

B. PHONETIC ORTHOGRAPHIC COMPUTER ANALYSIS (POCA)

As part of the name similarity assessment, proposed names are evaluated via a phonetic/orthographic algorithm. The proposed proprietary name is converted into its phonemic representation before it runs through the phonetic algorithm. Likewise, an orthographic algorithm exists which operates in a similar fashion. The POCA did not identify any additional names considered to have significant phonetic or orthographic similarities to Clobex.

C. AERS SEARCH

The Adverse Event Reporting System (AERS) was searched for all post-marketing safety reports of medication errors associated with Clobex. The MEDDRA Preferred Terms (PT) "Medication Error" and "Overdose" and the drug names of "Clobex" and "Clobe" were used as search criteria. The search did not identify any reports of name confusion or other medication errors in association with Clobex.

D. SAFETY EVALUATOR RISK ASSESSMENT

The root name, Clobex, was approved by the FDA on June 6, 2003. During the proprietary name reviews for Clobex Lotion and Clobex Shampoo, Rubex, Klotrix, Clorpres, Cobex, Probax, and Klorvess were evaluated and were found to have minimal potential for confusion. DMETS believes that the addition of the spray dosage form does not alter our decision with regard to the names mentioned above.

Six additional names were identified in this review to have potential for confusion with Clobex Spray. The six names are Clorox, Lidex, Tobrex, Carbex, Capex, and Clob-X. Upon consideration of these names, DMETS believes that the potential for name confusion between Clobex Spray and Clorox and Clob-X is minimal. Clorox was determined to have look-alike similarity with Clobex. Clorox is a household bleaching agent used in cleaning and laundry preparations. Due to its differing context of use compared to Clobex, we believe there is minimal risk of confusion and error between Clorox and Clobex. Clob-X, which sounds and looks like Clobex, is a foreign product name used by Galderma for the active ingredient clobetasol. Even if confused, the potential for harm is minimal due to the fact that it is the same active drug product, clobetasol. Furthermore, the AERS search did not identify any reports of name confusion between Clobex and other currently marketed products.

1. Look and Sound-alike Name Confusion

   a. The proposed proprietary name, Clobex Spray, is a different dosage form (spray vs. lotion and shampoo) than the currently marketed Clobex Lotion and Clobex Shampoo. Clobex Spray will share an overlapping dosing interval with Clobex Lotion (two times a day), while Clobex Shampoo is only applied once daily. While, these product characteristics may increase the potential for confusion, a prescription for Clobex will need to clearly identify the formulation being prescribed (lotion, shampoo, or spray) prior to dispensing. With additions to product lines, DMETS anticipates some confusion as the availability of three different dosage formulations may increase the potential of selection errors. Thus, the labels and labeling for Clobex Lotion, Clobex Shampoo, and Clobex Spray must be differentiated from each other.

   b. Lidex has a slight sound-alike similarity to Clobex. Lidex is indicated for relief of inflammatory and pruritic manifestations of corticosteroid responsive dermatoses. Lidex is available in a 0.05% cream, gel, ointment, and topical solution. Lidex is also available as Lidex-E in a 0.05% topical cream. Lidex is applied to the affected skin areas as a thin film two to four times daily. Lidex and Clobex have slight sound-alike characteristics in that the end of each name ("-dex" vs. "-bex") rhymes and each name has two syllables. However, the beginning of each name sounds completely different and helps distinguish one name from the other ("Li-" vs. "Clo-"). Lidex and Clobex are both applied topically twice daily, and have an overlapping product strength (0.05%). However, there are product characteristics which help differentiate one name from the other. The two products each have different dosage formulations. Lidex is available as a cream, gel, ointment, and topical solution. Clobex, on the other hand, will be available as a lotion, shampoo, and spray. When prescribing any of these products, a dosage form would need to be identified prior to product dispensing. Furthermore, the AERS search did not identify any reports of name confusion between Clobex and currently marketed Lidex products. While the two drugs have several overlapping product characteristics, the numerous dosage forms and lack of convincing sound-alike similarities decrease the risk for confusion and error between Lidex and Clobex.

   c. Tobrex has a sound-alike similarity to Clobex. Tobrex is indicated for the treatment of superficial ocular infections. Tobrex is available in a 0.3% ophthalmic solution and a 3 mg/g ophthalmic ointment. Tobrex is applied to the affected eye(s) as a 1.25 cm ribbon two to three times a day or as one or two drops four to six times per day. Tobrex and Clobex share some rhyming similarities; however, the letter "l" in Clobex in combination with the beginning "C" help to differentiate these two names. Tobrex and Clobex each have two syllables when spoken, but again are differentiated phonetically by the beginning letters ("To-" vs. "Clo-"). The ending of each name can also sound similar when spoken as "-brex" and "-bex" sound alike. Besides sound-alike similarities, Tobrex and Clobex can both be given twice daily. However, there are product characteristics which help differentiate one name from the other. The two products each have different dosage formulations. Tobrex is available as a solution and ointment. Clobex, on the other hand, will be available as a lotion, shampoo, and spray. In addition, the two products each have a different route of administration (ophthalmic vs. topical via skin), strength (0.3% and 3 mg/g vs.

0.5%), dose (1 or two drops or 1.25 cm ribbon vs. thin layer), and indication for use (antibiotic vs. corticosteroid). Furthermore, the AERS search did not identify any reports of name confusion between Clobex and currently marketed Tobrex products. DMETS believes that there is decreased risk for confusion and error between Tobrex and Clobex based on the sound-alike differences at the beginning of each name.

d. Carbex has a look and sound-alike similarity to Clobex. Carbex is indicated as an adjunct to levodopa/carbidopa in Parkinson's disease. Carbex is available in 5 mg oral tablets. The recommended dose of Carbex is 10 mg per day in divided doses with 5 mg taken at breakfast and lunch. Carbex and Clobex share similar orthographic and phonetic characteristics in that the names each begin with the letter "C" and end with the letters "bex". However, the second and third letters of each name differ as the "ar" in Carbex looks and sounds different than the "lo" in Clobex. Carbex and Clobex each have two syllables when spoken, but again are differentiated phonetically by the beginning letters ("Car-" vs. "Clo-"). Besides some look- and sound-alike similarities, Carbex and Clobex are both given twice daily. However, there are numerous product characteristics which help differentiate one name from the other. The two products each have a different dosage form (tablets vs. lotion, shampoo, spray), strength (5 mg vs. 0.05%), route of administration (oral vs. topical), dose (1 tablet or 5 mg vs. thin layer), and indication for use (Parkinson's disease vs. corticosteroid). Furthermore, the AERS search did not identify any reports of name confusion between Clobex and currently marketed Carbex. Thus, DMETS believes that the differences mentioned above will help minimize error between Carbex and Clobex.

Carbex Clobex

e. Capex has a look and sound-alike similarity to Clobex. Capex is indicated for the treatment of seborrheic dermatitis. Capex is available as a 0.01% topical shampoo. The recommended dose of Capex is approximately one ounce of the medicated shampoo applied to the scalp area once daily, worked into a lather, and allowed to remain on the scalp for approximately five minutes. The hair and scalp should then be rinsed thoroughly with water. Capex and Clobex share similar orthographic and phonetic characteristics in that the names each begin with the letter "C", end with the letters "ex", and have two syllables when spoken. However, the middle letters of each name differ as the "ap" in Capex looks and sounds different than the "lob" in Clobex. Capex and Clobex are both available in shampoo dosage forms, applied topically, and are corticosteroids. In addition, both products are available in single strengths and therefore a strength does not need to be designated prior to prescription filling and dispensing. While the drugs do share overlapping product characteristics, the AERS search did not identify any reports of name confusion between Clobex and the currently marketed Capex. Thus, given the lack of a strong look and sound similarity and the lack of AERS reports, we believe that there is decreased risk for confusion and error between Capex and Clobex.

Capex Clobex

1 Page(s) Withheld

_____ Trade Secret / Confidential

✓ Draft Labeling

_____ Deliberative Process

Withheld Track Number: Administrative- 4

IV. RECOMMENDATIONS:

A. DMETS has no objections to the use of the proprietary name, Clobex Spray. This is considered a final decision. However, if the approval of this application is delayed beyond 90 days from the signature date of this document, the name must be re-evaluated. A re-review of the name will rule out any objections based upon approvals of other proprietary and established names from the signature date of this document.

B. DMETS also recommends implementation of the labeling revisions outlined in Section III of this review in order to minimize potential errors with the use of this product. We would be willing to revisit these issues if the Division receives another draft of the labeling from the manufacturer.

C. DDMAC finds the proprietary name, Clobex Spray, acceptable from a promotional perspective.

DMETS would appreciate feedback of the final outcome of this consult. We would be willing to meet with the Division for further discussion, if needed. If you have further questions or need clarifications, please contact Diane Smith, project manager, at 301-796-2360.

Nora Roselle, PharmD
Safety Evaluator
Division of Medication Errors and Technical
Office of Drug Safety

Alina Mahmud, MS, RPh
Team Leader
Division of Medication Errors and Technical
Office of Drug Safety

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

/s/

Nora L. Roselle
9/30/2005 01:40:10 PM
DRUG SAFETY OFFICE REVIEWER

Denise Toyer
9/30/2005 03:02:40 PM
DRUG SAFETY OFFICE REVIEWER

Carol Holquist
9/30/2005 03:07:06 PM
DRUG SAFETY OFFICE REVIEWER

Dow Pharmaceutical Sciences
The D in Topicals R&D Since 1977

Via Federal Express

08 July 2005

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 # N 115
9201 Corporate Blvd. HFD-540
Rockville, Maryland 20850

RE: NDA 021835 - CLOBEX (clobetasol propionate) Spray, 0.05% for the Treatment of Psoriasis

Amendment No. 0004: Demographic Information

Dear Dr. Wilkin:

Dow Pharmaceutical Sciences, Inc. (DPSI) filed an eCTD New Drug Application (NDA 021835) for CLOBEX (clobetasol propionate) Spray, 0.05% for the treatment of psoriasis on December 22, 2004, which was received by the Agency on December 27, 2004.

This amendment is in response to an e-mail from Kalyani Bhatt dated June 24, 2005 requesting additional information of the demographics for Phase I of the dermal safety study and location of the protocols. Included in this response is the following:

- Location of the protocols which was e-mailed to Kalyani Bhatt on July 6, 2005
- Demographic data for the Phase I dermal safety study

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

Should you require further information regarding this submission, please contact me by phone - 707.793.2600, by fax - 707.793.0145, or by e-mail - bcalvarese@dowpharmsci.com.

Sincerely,

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

Dow Pharmaceutical Sciences
The D in Topicals R&D *Since 1977*

December 22, 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
5901-B Ammendale Road
Beltsville, MD 20705-1266

Subject: **New Drug Application No. 021835**
Product: CLOBEX (clobetasol propionate) Spray, 0.05%
Indication: Psoriasis
Sponsor: Dow Pharmaceutical Sciences

Dear Dr. Wilkin:

Pursuant to §505(b)(1) 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 CLOBEX (clobetasol propionate) Spray, 0.05%.

The new drug product contains the active drug substance, clobetasol propionate, USP, at a concentration of 0.05% in a clear, colorless alcoholic solution spray for the topical treatment of psoriasis. Previous information concerning this formulation has been submitted to the Agency under Investigational New Drug Application (IND) No. 62,543, filed on April 16, 2001.

This submission is being submitted entirely electronically on one (1) CD-ROM, with a total file size of approximately 650MB. In addition, hard copy versions and original signatures are provided for the following documents:

1330A Redwood Way • Petaluma, CA 94954-1169 • (707) 793-2600 • Fax (707) 793-0145 • www.dowpharmsci.com

- Cover letter
- Form FDA 356h, Application to Market a New Drug, Biologic, or an Antibiotic Drug for Human Use
- Form FDA 3397, User Fee Cover Sheet (the applicable User Fee of $672,000.00 was provided in United States currency in the form of Dow Pharmaceutical Sciences' check number 023949 on November 12, 2004)
- Debarment Certification
- Field Office Certification
- Financial Certification (FDA Form 3454): Financial Interests and Arrangements of Clinical Investigators
- Financial Disclosures (FDA Form 3455)
- Patent Information (FDA Form 3542a)
- Contents of the index-md5.txt file

The submission is virus free. All files have been scanned using Symantec's Antivirus Corporate Edition, Version 8.1.0.825.

- Summaries of safety and efficacy have been placed in Module 2 with links to the study reports in Module 5. ISS and ISE reports are provided in Module 2.7.3 and 2.7.4, respectively.

- As indicated in a correspondence with the electronic division on April 25, 2004, sections which were not applicable are not included in this submission.

- 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 CLOBEX (clobetasol propionate) Spray, 0.05% 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 cut-off date for clinical data inclusion and preparation of the summary of safety in this new drug application was August 5, 2004.

Reference is made to the Pre-IND meeting that occurred on December 19, 2000, and the Pre-NDA meeting held on October 5, 2004.

All facilities involved in the manufacture and release of the drug product will be ready for preapproval inspection (PAI) by November 23, 2004.

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.

If you have any questions regarding the content of the submission, please contact me at (707) 793-2600 x610 or by e-mail at bcalvarese@dowpharmsci.com.

Sincerely,

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

BMC/pm
Enclosures

3 Page(s) Withheld

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_____ Draft Labeling

_____ Deliberative Process

Withheld Track Number: Administrative- 5

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-835

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

Dear Mr. Calvarese:

Please refer to your November 23, 2004, new drug application (NDA) submitted under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act for CLOBEX (clobetasol propionate) Spray, 0.05%.

We are refusing to file this application under 21 CFR 314.101(d) for the following reason:

The electronic Common Technical Document NDA submission is unable to be opened and viewed. Therefore, it is not accessible for a preliminary review to evaluate the completeness for a substantive review.

We will refund 75% of the total user fee submitted with the application.

Within 30 days of the date of this letter, you may request in writing a meeting about our refusal to file the application. To file this application over FDA's protest, you must avail yourself of this informal conference.

If, after the informal conference, you still do not agree with our conclusions, you may request that the application be filed over protest. In that case, the filing date will be 60 days after the date you requested the informal conference. The application will be considered a new original application for user fee purposes, and you must remit the appropriate fee.

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

Sincerely,

{See appended electronic signature page}

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

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

/s/

Jonathan Wilkin
12/7/04 02:29:34 PM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Food and Drug Administration

Form Approved: OMB No. 0910-0396
Expiration Date: February 28, 2006

DISCLOSURE: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS

TO BE COMPLETED BY APPLICANT

The following information concerning [redacted] _____, who participated as a clinical investigator in the submitted study _____ [redacted] _____, is submitted in accordance with 21 CFR part 54. The named individual has participated in financial arrangements or holds financial interests that are required to be disclosed as follows:

Name of clinical investigator

Name of clinical study

Clobetasol Propionate 0.05% Spray

Please mark the applicable checkboxes.

☐ any financial arrangement entered into between the sponsor of the covered study and the clinical investigator involved in the conduct of the covered study, whereby the value of the compensation to the clinical investigator for conducting the study could be influenced by the outcome of the study;

☐ any significant payments of other sorts made on or after February 2, 1999 from the sponsor of the covered study such as a grant to fund ongoing research, compensation in the form of equipment, retainer for ongoing consultation, or honoraria;

☐ any proprietary interest in the product tested in the covered study held by the clinical investigator;

☒ any significant equity interest as defined in 21 CFR 54.2(b), held by the clinical investigator in the sponsor of the covered study.

Details of the individual's disclosable financial arrangements and interests are attached, along with a description of steps taken to minimize the potential bias of clinical study results by any of the disclosed arrangements or interests.

NAME [redacted]	TITLE [redacted]
FIRM / ORGANIZATION Dow Pharmaceutical Sciences	
SIGNATURE [redacted]	DATE 11/22/04

Paperwork Reduction Act Statement

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. Public reporting burden for this collection of information is estimated to average 4 hours per response, including time for reviewing instructions, searching existing data sources, gathering and maintaining the necessary data, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information to:

Department of Health and Human Services
Food and Drug Administration
5600 Fishers Lane, Room 14-72
Rockville, MD 20857

MEMORANDUM OF MEETING MINUTES

Meeting Date: October 5, 2004 Time: 9:30AM

Location: S 200 Meeting ID: 13753

Subject: Pre-NDA Meeting for IND 62,543

Drug: Clobex Spray

Indication: Psoriasis

Sponsor: Dow Pharmaceuticals, Inc.

Meeting Chair: Stanka Kukich, M.D./Deputy Director, DDDDP, HFD-540

Meeting Recorder: Kalyani Bhatt/Project Manager, DDDDP, HFD-540

AGENCY'S Attendees:

Stanka Kukich, M.D./Deputy Director, DDDDP, HFD-540
Jonca Bull, M.D./Director ODE V, HFD-105
Terri Rumble, R.N., B.S.N/Associate Director of Regulatory Affairs, ODE V, HFD-105
Saleh Turujman, Ph.D./Chemistry Reviewer, DNDCIII, HFD-830
David Lin, Ph.D./Team Leader, Chemistry, DNDCIII, HFD-830
Barbara Hill, Ph.D./Pharmacology Reviewer, DDDDP, HFD-540
Denise Cook, M.D./Medical Officer, DDDDP, HFD-540
Markham Luke, M.D., Ph.D./Team Leader, Clinical, Dermatology, DDDDP, HFD-540
Chandra Chaurasia, Ph.D./Clinical Pharmacology & Biopharmaceutics Reviewer, DPEIII, HFD-880
Raman Baweja Clinical Pharmacology & Biopharmaceutics Team Leader, DPEIII, HFD-880
Kathleen Fritsch, Ph.D./Biostatistics Reviewer, DBIII, HFD-725
Matt Soukup, Ph.D. / Biostatistics Reviewer, DBIII, HFD-725
Kalyani Bhatt, Regulatory Project Manager, DDDDP, HFD-540

Dow Attendees participating via teleconference:

Shawna Lemke, Ph.D., Associate Manager, Regulatory and Clinical Affairs
Harry Ingersol, Acting Director, Quality Assurance
Chuck Chavdarian, Senior Director, Analytical Services
Peggy Gromala, Project Coordinator I, Project Management
Karl Beutner, MD, PhD Vice President and Chief Medical Officer

Galderma Attendees:

Michael Graeber, MD, Head of Clinical Research, USA
Yin Liu, Ph.D., Head of Biometrics

Dow Attendees:

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

Chemistry, Manufacturing and Controls:

CMC Question 1.

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

AGENCY'S Response:

The outlined stability program is not acceptable. The following tests should be included in the stability program:

1. The spray rate (delivery volume per actuation; see also below)
2. Ethanol content
3. Isopropyl myristate content
4. Microbial limits test (see also below)

[There are data demonstrating the function of ethanol and isopropyl myristate as Therefore, the content of these two excipients might be critical to the performance of the drug product.]

It is noted in the meeting package (page 53) that the accelerated stability testing was terminated after

Other Deficiencies:

Regulatory Specification Deficiencies

1. The regulatory specification should include an Identification Test for clobetasol propionate.
2. A test for spray rate (delivery volume per actuation) should be included. The spray rate acceptance criterion for the pump sprayer should be supported by data from the study of the reproducibility of the delivery volume per actuation (as recommended in the pre-IND meeting of December 19, 2000 (see meeting minutes CMC item 2.0 (h)).
3. The regulatory specification should include an Identification Test/assay for ethanol.
4. The regulatory specification should include an Identification Test/assay for isopropyl myristate.
5. The acceptance criterion for unidentified impurities (individual unknowns) is above the identification threshold (Please refer to ICH Guidance Q3B(R), Attachment 1). Impurities above the threshold identification should be identified.
6. The acceptance criterion for related substances is high. The acceptance criterion for total impurities is also high. The sponsor was asked if these high levels of specified impurities and total impurities (Please refer to ICH Guidance Q3B(R), for definitions and for a decision tree) had been observed in the clinical batches, and if batches with this level of impurities had been qualified? The sponsor was informed that each acceptance criterion should be set no higher than the qualified level of the given degradation product. Furthermore, the acceptance criteria for specified impurities and for total impurities should be based on the results of stability studies of manufactured batches (clinical and registration).
7. The dosage form is "solution", to be followed by spray, to indicate the mode of delivery

Microbial Limits

A microbial limits test was performed as recommended in USP method <61> on a sample laboratory batch containing 0.01% clobetasol propionate (i.e. one fifth of the to-be-marketed strength); the results met the general USP criteria for acceptance for the Microbial Limits Test.

The sponsor was requested at the End-of-Phase 2 meeting on March 18, 2002, to conduct a microbial limits test on the to-be-marketed drug product. There is no reference as to whether the requested test was conducted.

- The sponsor was again requested to conduct a microbial limits test on the to-be-marketed drug product.

Unit Dose

The sponsor was requested at the End-of-Phase 2 meeting on March 18, 2002, to include, in addition to the composition listing, both a definite weight and measure per unit dose. The sponsor did not submit the requested information.

- It was again requested that the sponsor include, in addition to the composition listing, both a definite weight and measure per unit dose.

Viscosity

A recommendation was made to the sponsor at the End-of-Phase 2 meeting on March 18, 2002, that viscosity monitoring be incorporated into the stability protocol, in addition to monitoring the amount of spray per actuation. Although the sponsor states on page 54 of the briefing package that viscosity was included in the tests conducted during the stability program, there is no listing of viscosity values in the package.

- The sponsor was requested to provide the missing viscosity data in the NDA submission.

Solubility of Clobetasol Propionate in the vehicle

Unless data are submitted to show that clobetasol propionate is fully dissolved in the vehicle, the product should be monitored for particulate matter, e.g. by microscopic evaluation. It should be noted that the polymorphic form and the particle size of clobetasol propionate do not impact the bioavailability of the drug substance if clobetasol propionate is fully dissolved in vehicle.

- The sponsor was requested to provide data to show that clobetasol propionate is fully dissolved in the vehicle, or alternatively, to add a microscopic examination) to ascertain that clobetasol propionate remains in solution in the vehicle.

The sponsor should note the following reminders for their NDA submission.

- To include the establishment registration number, contact person name and phone number for all facilities and a statement that all the facilities are ready for inspection.
- To include the "Pharmaceutical Development", together with the investigational formulations.
- To identify critical points or critical steps in the manufacturing process.
- To describe reprocessing procedures and pertinent controls, if applicable.
- To include the exact location [in the DMF] of any packaging information referenced in the letters of authorization (LOA) for referenced Type 3 (packaging) DMFs in the NDA submission.

- To include plans for phasing in the child resistant closures/packaging.
- To include the following in the 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 Form

    Please refer to the 1987 Guideline: Guideline for Submitting Samples and Analytical Data for Methods Validation.

Pharmacology/Toxicology:

Sponsor's nonclinical question:
Does the Agency agree that the information provided in this package is sufficient to support the 505(b) (1) filing for CLOBEX (clobetasol propionate) Spray, 0.05%?

Division Pharmacology/Toxicology response:

1. In general, the nonclinical information listed appears adequate in principle to support the submission of a 505(b) (1) NDA for clobetasol propionate spray.

2. The Division considers the treatment of psoriasis a chronic indication. Consequently, it is recommended that a carcinogenicity study be conducted in which the drug product is applied to the skin of an animal model. It is also recommended that the photococarcinogenicity of this drug product be evaluated in a manner consistent with the CDER Guidance on Photosafety Testing. These studies could be conducted postapproval. It is recommended that the NDA include a commitment to conduct these studies and a timetable of when these studies will be conducted. It is recommended that the protocol for the dermal carcinogenicity study, final results of the dose range finding study and any other supporting information be submitted to the Agency for review by the Division and the Executive Carcinogenicity Assessment Committee prior to initiation of the dermal carcinogenicity study. (See the CDER guidance on Carcinogenicity Study Protocol Submissions.) As previously discussed with the sponsor, the carcinogenicity and photocarcinogenicity evaluations of the spray product may possibly be combined with the evaluations of other formulations of clobetasol propionate. The appropriateness of this strategy will depend on the final study designs.

3. It is noted that the briefing package makes reference to nonclinical findings in the labeling of the approved drug product. The labeling for the sponsor's clobetasol spray product should be derived from information obtained from studies conducted by or for the sponsor or for which the sponsor has the right to refer. Animal to human dose ratios should be based on AUC comparisons, if available, or on body surface area (mg/m^2).

Biopharmaceutics:

- From Clinical Pharmacology and Biopharmaceutics perspective, the Agency requests the sponsor to submit individual plasma cortisol levels along with the statistical data (i.e., mean, standard deviation and standard error of mean) at each sampling time points. In addition, the amount of Clobex Spray used and the body surface area treated in each individual patient should be provided in the NDA submission.

- The Agency recommended that the sponsor provides their plan for addressing bioavailability assessment in pediatric population per the Pediatric Research Equity Act (PREA) issued in Dec 2003.

- The Agency requested that the sponsor to make a good faith attempt to analyze the levels of clobetasol propionate in the plasma/serum samples collected during the HPA axis suppression study.

Clinical:

Question 1:

Does the Agency agree that the clinical data presented are adequate to support the filing of a 505 (b) (1) application for CLOBEX (clobetasol propionate) Spray, 0.05%?

Agency's Response:

Yes, from a clinical perspective (see pharm/tox comments).

Question 2:

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

Agency's Response:

- All of the secondary efficacy variables should be analyzed at weeks 2 and 4 for the pivotal trials in terms of success based on a dichotomized severity scale.

- Please submit tables for all adverse events ≥1% active vs. placebo with p values. Treatment related adverse events should be in the same format.

Question 3:

DPS plans to submit only the case report forms of patients who died, experienced a serious adverse event, discontinued the study due to an adverse event, or who dropped from the Phase 3 studies. Does the Agency find this acceptable?

Agency's Response:

Yes, however, the Agency may also request other CRFs during the review process.

Question 4: (see sponsor submission, page 38)

Agency's Response:

At the present time, the Agency cannot comment on studies that have not been fully reviewed. This is a review issue and will be addressed during the review cycle of the NDA.

Additional Comments:

- Please provide in a clear and concise manner line listings of all patients who participated in HPA axis suppression testing in all trials.

- Please provide protocols, amendments, summary reports for both HPA axis suppression studies to the NDA, both T101-01009 and D02-0204-03.

- Please provide analysis of HPA axis suppression using only post-stimulation serum cortisol of $\leq$ 18 µg/dL as evidence of suppression.
  In addition, if the Sponsor does not have any plans for pediatric development of Clobex Spray, please be advised that the appropriate sections of the label concerning pediatric patients will come from the Clobex Lotion label; unless new data is provided in the pediatric population.

- Under PREA, which went into effect on December 4, 2003, please provide your pediatric plans for this drug product.

- Please provide the proposed package insert in MSWord format.

- Please submit in the 120 day safety update a review of all available safety data from all Clobex products.

- With regard to the new Clinical Reviewer Template, please identify where in the eCTD submission specific items addressed in the Template may be found. Hot links to those items would be much appreciated, especially as there is not a detailed index to the eCTD submission to facilitate location of various items.

Biostatistics

Clinical Program

Questions 2:

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

Agency's Response:

No details regarding the line listings, draft tables, or statistical plan were included in the briefing package. The statistical analysis plan should follow the protocol.

Question 5:

DPS is planning to submit an electronic version of the data (SAS data set) contained in the report from only the Phase 3 clinical studies (1 and 2). Does the Agency find this acceptable?

Agency's Response:

The NDA submission should also include the electronic datasets for the HPA axis studies (TI01-1009 and D02-0204-03) in addition to the Phase 3 studies. The data sets should be submitted in SAS transport format. The database for the Phase 3 studies should include both raw variables (from the CRF) and derived variables suitable for conducting primary and secondary efficacy analyses (such as treatment success and indicators for ITT and Per Protocol status, etc.) Each dataset should include the treatment assignments. The submission should include adequate documentation for the datasets including definitions, formulas for derived variables, and decodes for any classification variables, so that all categories are well-defined in the documentation.

In addition, the NDA submission should include the following items:

a. study protocols, any protocol amendments, and statistical analysis plans
b. the randomization lists and the actual treatment allocations (with date of randomization) from the trials
c. subgroup analyses by race, age, gender, and baseline severity

Project Management:

1. For applications submitted after February 2, 1999, the sponsor is required either to certify to the absence of certain financial interests of clinical investigators or disclose those financial interests. For additional information, please refer to 21CFR 54 and 21CFR 314.50(k).

2. Please notify the Agency when the NDA will be submitted.

   The sponsor stated that they anticipate submitting the NDA in November.

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/s/

Stanka Kukich
10/26/04 04:24:50 PM

ORIGINAL

Dow Pharmaceutical Sciences
The D in Topicals R&D Since 1977

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Via Federal Express

April 22, 2005

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 # N 115
9201 Corporate Blvd. HFD-540
Rockville, Maryland 20850

N-000 (SU)
ORIG AMENDMENT

RE: NDA 021835 - CLOBEX (clobetasol propionate) Spray, 0.05% for the Treatment of Psoriasis

Amendment No. 0003: 120-Day Safety Update

Dear Dr. Wilkin:

Dow Pharmaceutical Sciences (DPS) filed an eCTD New Drug Application (NDA 021835) for CLOBEX (clobetasol propionate) Spray, 0.05% for the Treatment of Psoriasis on December 22, 2004, which was received by the Agency on December 27, 2004. Pursuant to 21 CFR 314.50(d)(5)(vi)(b) and 21 CFR 601.2, the purpose of this amendment is to provide information for the 120-Day Safety Update for NDA 021835.

In accordance with the request made by the Dermatological and Dental Drug Product Division during the Pre-NDA meeting for CLOBEX (clobetasol propionate) Spray, 0.05%, on October 5, 2004 and stated on page 7 of the October 26, 2004 minutes of that meeting, DPS is submitting a review of all available safety data from all CLOBEX products in the 120-Day Safety Update. Thus, safety data from the spray, lotion, and shampoo formulations of Clobex are included in this 120-Day Safety Update.

At the pre-NDA meeting for CLOBEX on October 5, 2004, the Biopharmaceutics reviewer requested that the Sponsor examine systemic levels of clobetasol propionate in subjects enrolled in the Phase 2 HPA Axis Suppression trial (Protocol No. D02-0204-03). As this endpoint was not part of the original trial protocol, sufficient blood sample was not available to examine every enrolled subject; however, the Sponsor utilized stored serum to complete this analysis wherever sample was available. The final study report for D02-0204-03 has now been amended to include this information and is provided in this update as **Attachment 1**. The final report for Protocol D02-0204-03, dated August 6, 2004; and Amendment 1 and

Annex VII, dated March 31, 2005, were submitted to IND 62,543 for CLOBEX (clobetasol propionate) Spray, 0.05%, in serial submission 0051 on April 14, 2005.

Enclosed is the following new safety information obtained since the filing of NDA 021835 on December 22, 2004, up to and including April 20, 2005, the cut-off date for the 120-Day Safety Update:

- Amendment to Final Clinical Study Report, Protocol D02-0204-03 [redacted] Final Report — **Attachment 1**
- 120-Day Safety Update Report (Summary of Adverse Events for Clobex® [Clobetasol Propionate] Lotion and Shampoo, 0.05%) — **Attachment 2**
  Please note: There were no adverse events for the Clobex® (Clobetasol Propionate) Spray, 0.05% during the 120-day safety update period.
- Periodic Adverse Drug Experience Submission, CLOBEX® Lotion, 0.05% - 5th Quarter — **Attachment 3**
- Periodic Adverse Drug Experience Submission, CLOBEX® Lotion, 0.05% - 6th Quarter — **Attachment 4**
- Periodic Adverse Drug Experience Submission, CLOBEX® Shampoo, 0.05% - 2nd Quarter — **Attachment 5**
- Periodic Adverse Drug Experience Submission, CLOBEX® Shampoo, 0.05% - 3rd Quarter — **Attachment 6**
- Periodic Adverse Drug Experience Submission, CLOBEX® Shampoo, 0.05% - 4th Quarter — **Attachment 7**
- Periodic Safety Update Report No. 1 for Clobetasol Propionate, 0.05% (cream, gel, lotion, scalp lotion, ointment and shampoo) — **Attachment 8**

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

Should you require further information regarding this submission, please contact me by phone - 707.793.2600, by fax - 707.793.0145, or by e-mail - bcalvarese@dowpharmsci.com.

Sincerely,

for

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

/pm
Enclosures

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

FILING COMMUNICATION

NDA 21-835

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 December 22, 2004 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for CLOBEX (clobetasol propionate) Spray, 0.05%.

We also refer to your submissions dated February 25, 2005 and March 8, 2005.

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 February 25, 2005 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

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
3/11/05 12:39:44 PM
sign off for Dr. Wilkin, Division Director

Bhatt, Kalyani

From: Paula Mueda [PMueda@dowpharmsci.com]
Sent: Thursday, March 10, 2005 12:14 PM
To: kalyani.bhatt@fda.hhs.gov
Subject: Your phone message

Kalyani,

I received the voicemail message you left for me today regarding sending in an official amendment to Clobetasol NDA 21-835 for the batch information we transmitted to you two days ago. I figured it made sense that it be sent as an amendment, so I prepared and submitted Amendment 0002 on March 8, 2005, same day I sent you the information by e-mail.

Take care,

Paula

Paula Mueda
Sr. Regulatory Specialist
Dow Pharmaceutical Sciences
707.285.1561 phone
707.793.0145 fax
pmueda@dowpharmsci.com

Dow Pharmaceutical Sciences
The D in Topicals R&D Since 1977

N-000(BM)

Via Federal Express

March 8, 2005

ORIG AMENDMEN

RECEIVED
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Jonathan Wilkin, MD, Director
Division of Dermatological & Dental Drug Products
Office of Drug Evaluation V
Center for Drug Evaluation & Research
Food & Drug Administration
9201 Corporate Boulevard, HFD-540
Rockville, MD 20850

Re: NDA 21-835 - CLOBEX™ (clobetasol propionate) Spray, 0.05% for the Treatment of Psoriasis

Amendment 0002: Batch Numbers and Batch Composition Used for CLOBEX™ Clinical Studies

Dear Dr. Wilkin:

Pursuant to 21 CFR 314.60, this Amendment 0002 is submitted to the Agency to provide information requested by Kalyani Bhatt, Regulatory Health Project Manager, of Barry Calvarese, Vice President of Regulatory and Clinical Affairs, DPS. Specifically, Ms. Bhatt requested that DPS provide a document listing the batch numbers used for all clinical studies conducted with CLOBEX™(clobetasol propionate) Spray, 0.05%.

Included in this amendment is Attachment 1, a table which lists study drug batch numbers for all CLOBEX™ clinical studies. Attachment 2 provides composition tables of the various batches used in the CLOBEX™ clinical studies. In addition, this Amendment is accompanied by a FDA Form 356h.

DPS considers the material and data contained in this submission 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.

If you have any questions or require additional information related to this submission, please contact me by telephone at 707.693.2600, by fax at 707.793.0145, or by e-mail at bcalvarese@dowpharmsci.com.

Sincerely,

DUPLICATE

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

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-835

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

Dear Mr. Calvarese:

We refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (the Act) for Clobex (clobetasol propionate) Spray, 0.05%.

Your December 16, 2004, request for formal dispute resolution, received on December 17, 2004, concerned a refund of the full user fee paid for NDA 21-835. Under the user fee provisions of the Act, 75 percent of the application fee is refunded for any application or supplement that is refused for filing.[1] Your letter to Ms. Kim Colangelo was sent to my attention as the Director, Office of Regulatory Policy, which oversees the User Fee Program in the Center for Drug Evaluation and Research (CDER).

We have reviewed your request and conclude that under the Act, we are unable to provide you with a refund of the user fee following the refuse to file action. [redacted] The statute is clear in stating that we will refund 75 percent of the fee for an application that has been refused for filing.

Further, the Office of Regulatory Policy is unable to modify a refuse to file action; authority for such actions resides in the Office of New Drugs. We have discussed the matter internally with representatives from the Office of New Drugs, the Office of Information Management, and the Center for Biologics Evaluation and Research. Our current guidance on electronic data submissions (Draft Guidance for Industry, Providing Regulatory Submissions in Electronic Format – Human Pharmaceutical Product Applications and Related Submissions) states that we may refuse to file an application under 21 CFR 314.101 that cannot be reviewed (e.g., one that is illegible, or uninterpretable). We were unable to open your electronic submission; in fact, we did not receive a submission which could be opened until December 27, 2004. Therefore, under current policy, the refuse to file action by the Division of Dermatologic and Dental Drug Products in the Office of New Drugs was permissible in this case.

If you wish to appeal this decision regarding your formal dispute resolution to the next level, your appeal should be directed to Dr. Steven Galson, Acting Director, CDER. The appeal should be sent

[1] Section 736(a)(1)(D) of the Act (21 U.S.C. 379h(a)(1)(D)).

again through the Center's Dispute Resolution Project Manager, Ms. Colangelo. Any questions concerning your appeal should be addressed via Ms. Colangelo at (301) 594-3937.

Sincerely,

{See appended electronic signature page}

Jane A. Axelrad, J.D.
Associate Director for Policy
Center for Drug Evaluation and Research

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/s/

Jane Axelrad
3/3/05 04:31:17 PM

Bhatt, Kalyani

From: Bhatt, Kalyani
Sent: Friday, February 25, 2005 1:43 PM
To: 'Paula Mueda'
Cc: Bhatt, Kalyani
Subject: RE: Response to FDA Fax dated February 14, 2005

Thanks Paula please also submit this as a formal submission to the archive,
Kalyani

-----Original Message-----
From: Paula Mueda [mailto:PMueda@dowpharmsci.com]
Sent: Friday, February 25, 2005 1:24 PM
To: kalyani.bhatt@fda.hhs.gov
Cc: Barry Calvarese; AJ Acker; Nurjehan Jivani
Subject: Response to FDA Fax dated February 14, 2005

<< Message: Untitled Attachment >> << File: Clobex spray - Non clinical response Feb 25 2005 - car_photocar timelines.doc >>

Bhatt, Kalyani

Kalyani,

In a fax to Dow Pharmaceutical Sciences (DPS) dated February 14, 2005, you requested the following:

"Please specify the timetable for the dermal carcinogenicity and photocarcinogenicity studies to be conducted as Phase 4 commitments."

The attached Word document details the timetable for the Non-Clinical Phase 4 Commitments for the combined Clobex Lotion/Shampoo/Spray program.

If you have questions or comments regarding this response, as always, please contact Barry M. Calvarese, Vice President of Regulatory and Clinical Affairs, DPS. Barry may be reached by phone at 707.665.4610, by fax at 707.793.0145, and by e-mail at bcalvarese@dowpharmsci.com.

Best regards,

Paula

Paula Mueda
Sr. Regulatory Specialist
Dow Pharmaceutical Sciences
707.285.1561 phone
707.793.0145 fax
pmueda@dowpharmsci.com

Bhatt, Kalyani

m: Paula Mueda [PMueda@dowpharmsci.com]
nt: Tuesday, February 08, 2005 3:32 PM
To: kalyani.bhatt@fda.hhs.gov
Subject: Request for Information: Clobetasol NDA 21-835


Untitled AttachmentResp to FDA req of 2-1-05.doc ...

Bhatt, Kalyani

From: Bhatt, Kalyani

Sent: Tuesday, February 08, 2005 2:08 PM

To: 'Paula Mueda'; Bhatt, Kalyani

Cc: Barry Calvarese; Baweja, Raman K; Zhang, Lei K

Subject: RE: NDA 21-835/Clobex Spray/ Clincial & Clinical Pharmacology and Biopharmaceutic

Hi Barry and Paula,
On Feb 1, 2005 there was a fax sent to Dow Pharmaceuticals/ Information Request. Please provide the following information request:

"Please confirm that all the Clinical studies were done with the to-be-marketed formulation. Please identify which module this can be located in the e-CTD in order to expedite the review process. Please clarify whether the "to be marketed" formulation was used in either or both of the HPA axis studies".

Thank-you

Kalyani

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

FACSIMILE TRANSMITTAL SHEET

DATE: February 1, 2005

To: Barry M. Calvarese, MS Vice President Regulatory and Clinical Affairs	**From:** Kalyani Bhatt, Project Manger
Company: Dow Pharmaceutical Sciences	Division of Dermatologic and Dental Drug Products
Fax number: 707-793-0145	**Fax number:** 301-827-2075
Phone number: 707-665-4610	**Phone number:** 301-827-2020

Subject: NDA 21-835 CLOBEX (clobetasol propionate) Spray, 0.05%. Clinical and Biopharmaceutics information request

Total no. of pages including cover: 1

Comments:

Please confirm that all the Clinical studies were done with the to-be-marketed formulation. Please identify which module this can be located in the e-CTD in order to expedite the review process.

Please clarify whether the "to be marketed" formulation was used in either or both of the HPA axis studies.

Document to be mailed: ☐ YES X NO

Thank you.

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/s/

Kalyani Bhatt
2/1/05 05:07:27 PM
CSO

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-835

Dow Pharmaceutical Sciences
Attention: Barry M. Calvarese, MS
Vice President, Regulatory and 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: CLOBEX (clobetasol propionate) Spray, 0.05%

Review Priority Classification: S

Date of Application: December 22, 2004

Date of Receipt: December 27, 2004

Our Reference Number: NDA 21-835

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 February 25, 2005, in accordance with 21 CFR 314.101(a). If the application is filed, the user fee goal date will be October 27, 2005.

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 not fulfilled the requirements. We acknowledge receipt of your request for a waiver of pediatric studies for this application. Once the application has been filed we will notify you whether we have waived the pediatric study requirement for this application.

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 Drug Products
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 Drug Products
HFD-540
9201 Corporate Boulevard
Rockville, Maryland 20850

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

Sincerely,

{See appended electronic signature page}

Mary Jean Kozma-Fornaro
Division of Dermatologic & Dental Drug Products
Office of Drug Evaluation V
Center for Drug Evaluation and Research

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/s/

Mary Jean Kozma Fornaro
1/7/05 05:09:18 PM

NDA/EFFICACY SUPPLEMENT ACTION PACKAGE CHECKLIST

Application Information			
NDA 21-835	Efficacy Supplement Type SE-	Supplement Number	
Drug:Clobetasol Propioinate		Applicant:	
RPM:Kalyani Bhatt		HFD-	Phone # 796-0852

Application Type: (X) 505(b)(1) ( ) 505(b)(2) (This can be determined by consulting page 1 of the NDA Regulatory Filing Review for this application or Appendix A to this Action Package Checklist.) **If this is a 505(b)(2) application, please review and confirm the information previously provided in Appendix B to the NDA Regulatory Filing Review. Please update any information (including patent certification information) that is no longer correct.** ( ) Confirmed and/or corrected	Listed drug(s) referred to in 505(b)(2) application (NDA #(s), Drug name(s)):

❖ Application Classifications:	
• Review priority	X) Standard ( ) Priority
• Chem class (NDAs only)	3s
• Other (e.g., orphan, OTC)	N/A
❖ User Fee Goal Dates	October 27, 2005
❖ Special programs (indicate all that apply)	( ) None Subpart H ( ) 21 CFR 314.510 (accelerated approval) ( ) 21 CFR 314.520 (restricted distribution) ( ) Fast Track ( ) Rolling Review ( ) CMA Pilot 1 ( ) CMA Pilot 2
❖ User Fee Information	
• User Fee	(X) Paid UF ID number 4906
• User Fee waiver	( ) Small business ( ) Public health ( ) Barrier-to-Innovation ( ) Other (specify) N/A
• User Fee exception	( ) Orphan designation ( ) No-fee 505(b)(2) (see NDA Regulatory Filing Review for instructions) ( ) Other (specify)
❖ Application Integrity Policy (AIP)	
• Applicant is on the AIP	( ) Yes (N) No

• This application is on the AIP	( ) Yes (x) No
• Exception for review (Center Director's memo)	
• OC clearance for approval	
❖ Debarment certification: verified that qualifying language (e.g., willingly, knowingly) was not used in certification & certifications from foreign applicants are cosigned by US agent.	(x) Verified
❖ Patent	
• Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought.	(x) Verified
• 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.	21 CFR 314.50(i)(1)(*i*)(A) ( ) Verified 21 CFR 314.50(i)(1) (x) (ii) ( ) (iii)
• [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).	**N/A**
• [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). *(If the application does not include any paragraph IV certifications, mark "N/A" and skip to the next box below (Exclusivity)).*	( ) N/A (no paragraph IV certification) ( ) Verified
• [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. Answer the following questions for each paragraph IV certification: (1) Have 45 days passed since the patent owner's receipt of the applicant's 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)? *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 box below (Exclusivity).* *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 ( ) Yes ( ) No ( ) Yes ( ) No

General Information	
❖ Actions	
• Proposed action	(X) AP ( ) TA ( ) AE ( ) NA
• Previous actions (specify type and date for each action taken)	
• Status of advertising (approvals only)	(X) Materials requested in AP letter ( ) Reviewed for Subpart H
❖ Public communications	
• Press Office notified of action (approval only)	( ) Yes (X) Not applicable
• Indicate what types (if any) of information dissemination are anticipated	(X) None ( ) Press Release ( ) Talk Paper ( ) Dear Health Care Professional Letter
❖ Labeling (package insert, patient package insert (if applicable), MedGuide (if applicable))	
• Division's proposed labeling (only if generated after latest applicant submission of labeling)	Yes
• Most recent applicant-proposed labeling	N/A
• Original applicant-proposed labeling	December 22, 2005
• Labeling reviews (including DDMAC, DMETS, DSRCS) and minutes of labeling meetings *(indicate dates of reviews and meetings)*	DDMAC 8-2-05 ,DMETS 9-30-05
• Other relevant labeling (e.g., most recent 3 in class, class labeling)	
❖ Labels (immediate container & carton labels)	
• Division proposed (only if generated after latest applicant submission)	
• Applicant proposed	
• Reviews	
❖ Post-marketing commitments	
• Agency request for post-marketing commitments	
• Documentation of discussions and/or agreements relating to post-marketing commitments	10-25-05
❖ Outgoing correspondence (i.e., letters, E-mails, faxes)	X
❖ Memoranda and Telecons	X
❖ Minutes of Meetings	
• EOP2 meeting (indicate date)	March 18, 2002
• Pre-NDA meeting (indicate date)	
• Pre-Approval Safety Conference (indicate date; approvals only)	
• Other	Regulatory Guiadnace 1-15-05
❖ Advisory Committee Meeting	N/A
• Date of Meeting	
• 48-hour alert	
❖ Federal Register Notices, DESI documents, NAS/NRC reports (if applicable)	

(Note: This can be determined by confirming whether the Division has received a written notice from the 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)? *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 box below (Exclusivity).* *If "**No**," continue with question (5).*	( ) Yes ( ) No
(5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification? (Note: This can be determined by confirming whether the Division has received a written notice from the 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 within the 45-day period). *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 box below (Exclusivity).* *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.*	( ) Yes ( ) No

❖ Exclusivity (approvals only)	
• Exclusivity summary • Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? (Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)	No
• Is there existing orphan drug exclusivity protection for the "same drug" for the proposed indication(s)? *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.*	( ) Yes, Application #_____ (X) No
❖ Administrative Reviews (Project Manager, ADRA) *(indicate date of each review)*	

Summary Application Review	
❖ Summary Reviews (e.g., Office Director, Division Director, Medical Team Leader) *(indicate date for each review)*	Medical Team Leader 10-25-05
Clinical Information	
❖ Clinical review(s) *(indicate date for each review)*	9-11-05
❖ Microbiology (efficacy) review(s) *(indicate date for each review)*	
❖ Safety Update review(s) *(indicate date or location if incorporated in another review)*	
❖ Risk Management Plan review(s) *(indicate date/location if incorporated in another rev)*	
❖ Pediatric Page(separate page for each indication addressing status of all age groups)	10-25-05
❖ Demographic Worksheet *(NME approvals only)*	
❖ Statistical review(s) *(indicate date for each review)*	9-14-05
❖ Biopharmaceutical review(s) *(indicate date for each review)*	9-28-05
❖ Controlled Substance Staff review(s) and recommendation for scheduling *(indicate date for each review)*	
❖ Clinical Inspection Review Summary (DSI)	
• Clinical studies	
• Bioequivalence studies	
CMC Information	
❖ CMC review(s) *(indicate date for each review)*	10-24-05
❖ Environmental Assessment	
• Categorical Exclusion *(indicate review date)*	
• Review & FONSI *(indicate date of review)*	
• Review & Environmental Impact Statement *(indicate date of each review)*	
❖ Microbiology (validation of sterilization & product sterility) review(s) *(indicate date for each review)*	
❖ Facilities inspection (provide EER report)	Date completed: ( ) Acceptable ( ) Withhold recommendation
❖ Methods validation	( ) Completed ( ) Requested ( ) Not yet requested
Nonclinical Pharm/Tox Information	
❖ Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)*	9-8-05
❖ Nonclinical inspection review summary	
❖ Statistical review(s) of carcinogenicity studies *(indicate date for each review)*	
❖ CAC/ECAC report	