This application contains the following items: *(Check all that apply)*

☐	1. Index
☐	2. Labeling *(check one)* ☐ Draft Labeling ☐ Final Printed Labeling
☐	3. Summary (21 CFR 314.50 (c))
☐	4. Chemistry section
☐	A. Chemistry, manufacturing, and controls information (e.g., 21 CFR 314.50(d)(1); 21 CFR 601.2)
☐	B. Samples (21 CFR 314.50 (e)(1); 21 CFR 601.2 (a)) (Submit only upon FDA's request)
☐	C. Methods validation package (e.g., 21 CFR 314.50(e)(2)(i); 21 CFR 601.2)
☐	5. Nonclinical pharmacology and toxicology section (e.g., 21 CFR 314.50(d)(2); 21 CFR 601.2)
☐	6. Human pharmacokinetics and bioavailability section (e.g., 21 CFR 314.50(d)(3); 21 CFR 601.2)
☐	7. Clinical Microbiology (e.g., 21 CFR 314.50(d)(4))
☐	8. Clinical data section (e.g., 21 CFR 314.50(d)(5); 21 CFR 601.2)
☐	9. Safety update report (e.g., 21 CFR 314.50(d)(5)(vi)(b); 21 CFR 601.2)
☐	10. Statistical section (e.g., 21 CFR 314.50(d)(6); 21 CFR 601.2)
☐	11. Case report tabulations (e.g., 21 CFR 314.50(f)(1); 21 CFR 601.2)
☐	12. Case report forms (e.g., 21 CFR 314.50 (f)(2); 21 CFR 601.2)
☐	13. Patent information on any patent which claims the drug (21 U.S.C. 355(b) or (c))
☐	14. A patent certification with respect to any patent which claims the drug (21 U.S.C. 355 (b)(2) or (j)(2)(A))
☐	15. Establishment description (21 CFR Part 600, if applicable)
☐	16. Debarment certification (FD&C Act 306 (k)(1))
☐	17. Field copy certification (21 CFR 314.50 (l)(3))
☐	18. User Fee Cover Sheet (Form FDA 3397)
☐	19. Financial Information (21 CFR Part 54)
☐	20. OTHER *(Specify)*

CERTIFICATION

I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including, but not limited to the following:

1. Good manufacturing practice regulations in 21 CFR Parts 210, 211 or applicable regulations, Parts 606, and/or 820.
2. Biological establishment standards in 21 CFR Part 600.
3. Labeling regulations in 21 CFR Parts 201, 606, 610, 660, and/or 809.
4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR Part 202.
5. Regulations on making changes in application in FD&C Act section 506A, 21 CFR 314.71, 314.72, 314.97, 314.99, and 601.12.
6. Regulations on Reports in 21 CFR 314.80, 314.81, 600.80, and 600.81.
7. Local, state and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act, I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.

The data and information in this submission have been reviewed and, to the best of my knowledge are certified to be true and accurate.

Warning: A willfully false statement is a criminal offense, U.S. Code, title 18, section 1001.

SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT	TYPED NAME AND TITLE	DATE
Susan Pickrel	Susan Pickrel Regulatory Affairs Associate	19-SEP-2003

ADDRESS *(Street, City, State, and ZIP Code)*	Telephone Number
14501 North Freeway Fort Worth, Texas 76177	(817) 961.5335

GALDERMA
USA

ORIGINAL

September 25, 2003

RECEIVED
SEP 2 6 2003
MEGA/CDER

Food and Drug Administration
Division of Dermatological and Dental Drug Products (HFD-540)
Center for Drug Evaluation and Research
ATTENTION: Document Control Room
9201 Corporate Blvd.
Rockville, Maryland 20850

Su
ORIG AMENDMENT

RE: NDA 21-644
CLOBEX™ (clobetasol propionate shampoo) shampoo, 0.05%
4-Month Safety Update

Dear Sir or Madam:

Reference is made to the New Drug Application 21-644 for Clobetasol Propionate Shampoo, 0.05%. This submission amends the application with the 4-month safety update required by 21 CFR 314.50 (d)(5)(vi)(*b*). I apologize for the delay in the submission of this amendment.

If additional information is needed, please feel free to contact me.

Regards,

Susan Pickrel

Susan Pickrel
Regulatory Affairs Associate
Telephone: 817-961-5335
Fax: 817-961-0020

APPEARS THIS WAY
ON ORIGINAL

c: FDA Archival Original
FDA Desk Copy
Galderma Laboratories, L.P. Active File Copy
Galderma Laboratories, L.P. Archival File Copy
Fax of Cover Letter to Jacquelyn Smith, FDA Project Manager

NDA REGULATORY FILING REVIEW
(Including Memo of Filing Meeting)

NDA # 21-644 Supplement # N/A SE1 SE2 SE3 SE4 SE5 SE6 SE7 SE8

Trade Name: Clobex Shampoo
Generic Name: Clobetasol Propionate
Strengths: 0.05%

Applicant: Galderma Laboratories, L.P.

Date of Application: May 2, 2003
Date of Receipt: May 6, 2003
Date clock started after UN:
Date of Filing Meeting: June 18, 2003
Filing Date: July 3, 2003
Action Goal Date (optional): User Fee Goal Date: March 6, 2004

Indication(s) requested: Treatment of Moderate to Severe forms of _____ Scalp Psoriasis.

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

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

Therapeutic Classification: S __X_____ P _____
Resubmission after a withdrawal? ___NO_____ Resubmission after a refuse to file? _____
Chemical Classification: (1,2,3 etc.) __3_____
Other (orphan, OTC, etc.) _____

User Fee Status: Paid _X_____ Waived (e.g., small business, public health) _____
Exempt (orphan, government) _____
Form 3397 (User Fee Cover Sheet) submitted: YES X NO
User Fee ID # 4530
Clinical data? YES ___X_____ NO, Referenced to NDA # _____

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

YES NO X

If yes, explain:

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

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

YES NO

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

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

- Does the submission contain an accurate comprehensive index? YES X NO
- Was form 356h included with an authorized signature? YES X NO
  If foreign applicant, both the applicant and the U.S. agent must sign.
- Submission complete as required under 21 CFR 314.50? YES X NO
  If no, explain:

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

  Additional comments:

- If in Common Technical Document format, does it follow the guidance? N/A X YES NO

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

  Additional comments:

- Patent information included with authorized signature? YES X NO
- Exclusivity requested? YES, ___3___years NO

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

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

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

- Financial Disclosure information included with authorized signature? YES X NO
  (Forms 3454 and/or 3455 must be used and must be signed by the APPLICANT.)

- Field Copy Certification (that it is a true copy of the CMC technical section)? YES X NO

Refer to 21 CFR 314.101(d) for Filing Requirements

- PDUFA and Action Goal dates correct in COMIS? YES X NO
  If not, have the document room staff correct them immediately. These are the dates EES uses for calculating inspection dates.

- Drug name/Applicant name correct in COMIS? If not, have the Document Room make the corrections.
  Yes
- List referenced IND numbers: IND 60, 934

- End-of-Phase 2 Meeting(s)? Date(s) January 13, 2000 NO
  If yes, distribute minutes before filing meeting.

- Pre-NDA Meeting(s)? Date(s) March 8, 2002 NO
  If yes, distribute minutes before filing meeting.

Project Management

- Package insert consulted to DDMAC? YES NO X

- Trade name (plus PI and all labels and labeling) consulted to ODS/Div. of Medication Errors and Technical Support? YES NO X

- MedGuide and/or PPI (plus PI) consulted to ODS/Div. of Surveillance, Research and Communication Support? N/A YES NO X

- If a drug with abuse potential, was an Abuse Liability Assessment, including a proposal for scheduling, submitted?
  N/A YES NO X

If Rx-to-OTC Switch application:

- OTC label comprehension studies, all OTC labeling, and current approved PI consulted to ODS/ Div. of Surveillance, Research and Communication Support?

  N/A X YES NO

- Has DOTCDP been notified of the OTC switch application? YES NO

Clinical

- If a controlled substance, has a consult been sent to the Controlled Substance Staff?

  YES NO X

Chemistry

- Did applicant request categorical exclusion for environmental assessment? YES X NO
  If no, did applicant submit a complete environmental assessment? YES NO
  If EA submitted, consulted to Nancy Sager (HFD-357)? YES NO

- Establishment Evaluation Request (EER) submitted to DMPQ? YES NO X

- If parenteral product, consulted to Microbiology Team (HFD-805)? N/A YES NO

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

- Name of listed drug(s) and NDA/ANDA #:

Temovate (NDA 19-966), Temovate E (NDA 20-340) and Olux Foam (NDA 21-142)

- Describe the change from the listed drug(s) provided for in this (b)(2) application (for example, "This application provides for a new indication, otitis media" or "This application provides for a change in dosage form, from capsules to solution").

  This application provides for a new topical dosage form.

- Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA? (Normally, FDA will refuse-to-file such NDAs.)

  YES NO X

- Is the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action less than that of the reference listed drug (RLD)? (See 314.54(b)(1)). If yes, the application should be refused for filing under 314.101(d)(9).

  YES NO X

- Is the rate at which the product's active ingredient(s) is absorbed or otherwise made available to the site of action unintentionally less than that of the RLD? (See 314.54(b)(2)). If yes, the application should be refused for filing under 314.101(d)(9).

  YES NO X

- Which of the following patent certifications does the application contain? Note that a patent certification must contain an authorized signature.

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

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

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

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

  IF FILED, and if the applicant made a "Paragraph IV" certification [21 CFR 314.50(i)(1)(i)(A)(4)], the applicant must submit a signed certification that the patent holder was notified the NDA was filed [21 CFR 314.52(b)]. Subsequently, the applicant must submit documentation that the patent holder(s) received the notification ([21 CFR 314.52(e)].

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

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

  ____ 21 CFR 314.50(i)(3): Statement that applicant has a licensing agreement with the patent owner (must also submit certification under 21 CFR 314.50(i)(1)(i)(A)(4) above.)
  ____ Written statement from patent owner that it consents to an immediate effective date upon approval of the application.

- Did the applicant:

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

    YES X NO

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

    YES NO X

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

    YES X NO

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

    N/A YES NO

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

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

      YES X NO

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

      YES NO X

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

      YES, IND # 60, 934 NO

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

      N/A X YES NO

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

**Will be notified after filing YES NO X

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

/s/

Jacquelyn Smith
7/30/03 02:51:59 PM
CSO

Mary Jean Kozma Fornaro
8/4/03 12:38:49 PM
CSO
PI, PPI and tradename sent to appropriate consults ODS/DDMAC after filing .

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

FACSIMILE TRANSMITTAL SHEET

DATE: July 18, 2003

To: Bobbi Woodward, Manager, Regulatory Affairs	**From:** Jacquelyn Smith, Project Manager
Company: Galderma Laboratories, LP	Division of Dermatologic and Dental Drug Products
Fax number: 817-961-0020	**Fax number:** 301-827-2075
Phone number: 817-961-5347	**Phone number:** 301-827-2027

Subject: NDA 21-644/Clobex Shampoo/ Filing Review Letter

Total no. of pages including cover: 6

Comments: Please see following page(s).

Document to be mailed: ☐ YES X NO

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

FILING REVIEW LETTER

NDA 21-644

Galderma Laboratories, L.P.
Attention: Bobbi Woodward, M.S., RAC
14501 North Freeway
Fort Worth, Texas 76177

Dear Ms. Woodward:

Please refer to your May 2, 2003, new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Clobex (clobetasol propionate) Shampoo, 0.05%.

We also refer to your submissions dated June 13, 2003 and June 26, 2003.

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 July 3, 2003 in accordance with 21 CFR 314.101(a).

In our filing review, we have identified the following potential review issues:

Chemistry, Manufacturing and Controls:

1. DMF — held by your ——— has been found to be deficient. The DMF holder has not responded to the deficiency letter issued by the Agency.

Pharmacology/Toxicology:

1. Reference to the (Physicians' Desk reference) PDR for nonclinical information.

2. [redacted]

3. Plans to evaluate carcinogenicity and photococarcinogenicity, including a timeline for fulfilling these phase 4 commitments have not been submitted.

4. The noncompendial excipients have not been fully qualified.

Clinical:

1. In the adult adrenal suppression study, the subjects were stimulated weekly for four weeks, and sampled 60 minutes post-stimulation. In the adolescent study, the subjects were stimulated at week four, but sampled 60 minutes post-stimulation.

We are providing comments to give you preliminary notice of potential 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. Issues may be added, deleted, expanded upon, or modified as we review the application.

Biostatistics:

1. Data sets for the primary studies giving subject ID, date of screening, date of randomization, treatment, and final disposition was not submitted in the NDA.

We request that you submit the following information to address the potential review issues described above:

Chemistry, Manufacturing and Controls:

1. An NDA cannot be approved if a Type II DMF is deficient. We recommend one of the following choices:

   (a) Contact the DMF holder to correct deficiencies.

   (b) [redacted]

Pharmacology/Toxicology:

1. Please do not refer to the PDR for nonclinical information. References to information found in the PDR should be removed from the label.

2. If the review of the NDA finds that there is no measurable systemic absorption and no systemic effects, then a fertility study will not be required. However, if the review of the NDA finds systemic absorption or systemic effects, then a Phase 4 commitment to conduct a fertility study will be required.

3. According to the Pre-NDA meeting minutes dated March 8, 2002, you were advised that the Division considers the treatment of psoriasis as a chronic indication. Please evaluate carcinogenicity and photococarcinogenicity. These studies may be conducted postapproval. Please agree to these Phase 4 commitments and a timeline for completion.

4. Including the excipients in a dermal carcinogenicity study is sufficient to qualify them. Please agree to this as a Phase 4 commitment.

Clinical:

1. Please provide the submitted protocols and amendments for the pivotal studies and all other studies.

Biostatistics:

1. Please submit data sets for the primary studies giving subject ID, date of screening, date of randomization, treatment, and final disposition.

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

Sincerely,

{See appended electronic signature page}

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

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this page is the manifestation of the electronic signature.

/s/

Jonathan Wilkin
7/18/03 08:19:35 AM

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

/s/

Jacquelyn Smith
7/18/03 11:07:42 AM
CSO

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-644

Galderma Laboratories, Inc.
Attention: Ms. Bobbi Woodward
Manager, Regulatory Affairs
14501 North Freeway
Fort Worth, TX 76177

Dear Ms. Woodward:

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) Shampoo, 0.05%

Review Priority Classification: Standard (S)

Date of Application: May 2, 2003

Date of Receipt: May 6, 2003

Our Reference Number: NDA 21-644

The application was filed on July 3, 2003, in accordance with 21 CFR 314.101. The user fee goal date will be March 6, 2004.

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 Jacquelyn Smith, Regulatory Project Manager, at (301) 827-2020.

Sincerely,

{See appended electronic signature page}

MARY JEAN KOZMA-FORNARO
SUPERVISOR, PROJECT MANAGEMENT
Division of Dermatologic & Dental Drugs
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/

Jacquelyn Smith
7/15/03 10:38:11 AM
Signed for Mary Jean Kozma-Fornaro

Office of Clinical Pharmacology and Biopharmaceutics *New Drug Application Filing and Review Form*			
General Information About the Submission			
	Information		Information
NDA Number	21-535	Brand Name	Clobex™
OCPB Division (I, II, III)	DPE III	Generic Name	Clobetasol Propionate, 0.05%
Medical Division		Drug Class	Topical Steroid
OCPB Reviewer	Chandra S. Chaurasia, Ph. D.	Indication(s)	[redacted]
OCPB Team Leader	E. Dennis Bashaw, Pharm. D.	Dosage Form	Lotion
		Dosing Regimen	Twice daily limited to 2 or 4 consecutive weeks
Date of Submission	SEP 25, 2002	Route of Administration	Topical
Estimated Due Date of OCPB Review	March 01, 2003	Sponsor	Galderma Laboratories, L. P. Fortworth, TX 76177
PDUFA Due Date	Jul 27, 2003	Priority Classification	
Division Due Date			

Clin. Pharm. and Biopharm. Information				
	"X" if included at filing	**Number of studies submitted**	**Number of studies reviewed**	**Critical Comments If any**
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables data, etc.	X			
Tabular Listing of All Human Studies	X			
HPK Summary	X			
Labeling	X			
Reference Bioanalytical and Analytical Methods	X			
I. Clinical Pharmacology				
Mass balance:	X			In Vitro, CG.03.SRE.4637
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:	X	2		Vasoconstriction Assays: CG.03.SRE.2117 and CG.03.SRE.2570
multiple dose:				
Patients-				
single dose:				
multiple dose:		3		HPA Suppression Studies: GUS.04.SRE.18009, RD.06.SRE.1806 and CR.U9708
Dose proportionality -				
fasting / non-fasting single dose:				

fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:	X			Pooled Data
pediatrics:	X			In Adolescents Age Group 12-17-yr only for HPA Suppression study
geriatrics:				
renal impairment:				
hepatic impairment:				
PD:				
Phase 2:	X	3		HPA axes suppression in patient with atopic dermatitis (GUS.04.SRE.18009 and RD.06,SRE.18061) psoriasis (CR.U9708)
Phase 3:	X	2		Vasoconstriction Atopic Dermatitis: GUS.04.SRE.180001, and Psoriasis: CR.U9707.R02
PK/PD:				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability:				
Alternate formulation as reference:	X	1		[redacted]
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies:				
Dissolution:				
(IVIVC):				
Bio-wavier request based on BCS				
BCS class				
III. Other CPB Studies				
Genotype/phenotype studies:				

Chronopharmacokinetics				
Pediatric development plan				
Literature References	X	3		PD articles on skin blanching
Total Number of Studies		6		Five in vivo and one in vitro studies

Filability and QBR comments		
	"X" if yes	**Comments**
Application filable?	X	Reasons if the application is not filable (or an attachment if applicable) For example, is clinical formulation the same as the to-be-marketed one?
Comments sent to firm		Comments have been sent to firm (or attachment included). FDA letter date if applicable.
QBR questions (key issues to be considered)	• What are the highlights of the physicochemical properties of clobetasol propionate? • What are the properties of the formulation of the drug product? What are the differences between clinical and to-be-marked formulations? • What are the proposed therapeutic indication, dosage, route of administration, and mechanism of action of clobetasol propionate? • Are the active moieties in the plasma or other biological fluid appropriately identified and measured to assess pharmacokinetic parameters? • What are the basic pharmacokinetic parameters of clobetasol propionate (ADME)? • Is the vasoconstriction assay appropriate to classify the potency class of clobetasol propionate lotion? • Is the vasoconstriction assay methodology validated? • Is the study to evaluate clobetasol propionate lotion potential to suppress the hypothalamus-pituitary-adrenal (HPA) axis appropriately designed with respect to a) the study populations relevant to the proposed indication, b) dose and dosing regimen appropriate for the treatment of the proposed indication, and c) bioanalytical methods used to assess the amount of cortisol level in study specimens. • Is the liberation-penetration Diffusion Cell Study appropriately designed to obtain comparative in vitro evaluation of clobetasol propionate lotion? • Are analytical methods sensitive enough to determine the extent of clobetasol in the in vitro study?	
Other comments or information not included above		
Primary reviewer Signature and Date	**Chandra S. Chaurasia, Ph. D.**	
Secondary reviewer Signature and Date	**E. Dennis Bashaw, Pharm. D.**	

CC: NDA 21-535, HFD-850 (P. Lee), HFD-540 (M. Harris), HFD-880 (D. Bashaw, J. Lazor, A. Selen)

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

/s/

Chandra S. Chaurasia
7/15/03 02:08:43 PM
BIOPHARMACEUTICS

Dennis Bashaw
7/15/03 03:30:30 PM
BIOPHARMACEUTICS

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

REQUEST FOR CONSULTATION

TO *(Division/Office)*:
Division of Drug Risk Evaluation (DDRE), HFD-430
(Room 15B-08, PKLN Bldg.)

FROM: Jacquelyn Smith
Project Manger, HFD-540
Division of Dermatologic and Dental Drug Products

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
July 15, 2003		21-644	New NDA	May 2, 2003

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
Clobex (clobetasol Propionate) Shampoo, 0.05%		3S	Labeling Day is scheduled for December3, 2003

NAME OF FIRM: Galderma Laboratories, L.P.

REASON FOR REQUEST

I. GENERAL

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

II. BIOMETRICS

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

III. BIOPHARMACEUTICS

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

IV. DRUG EXPERIENCE

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

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS:

Labeling is attached. A hard copy is being sent via courier. Labeling Day is December 3, 2003. Please provide comments.

SIGNATURE OF REQUESTER	METHOD OF DELIVERY (Check one)
Jacquelyn Smith	X☐ MAIL ☐ HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

17 page(s) of draft labeling has been removed from this portion of the review.

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

/s/

Jacquelyn Smith
7/15/03 02:27:18 PM

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

REQUEST FOR CONSULTATION

TO *(Division/Office)*:
Director, Division of Medication Errors and Technical Support (DMETS), HFD-420
PKLN Rm. 6-34

FROM:
Jacquelyn Smith
Project Manager
Division of Dermatologic and Dental Drug Products

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
July 15, 2003		21-644	New NDA	May 2, 2003

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
Clobex (clobetasol propionate) Shampoo, 0.05%		3S	PDUFA date March 6, 2004

NAME OF FIRM: Galderma Laboratories, L.P.

REASON FOR REQUEST

I. GENERAL

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

II. BIOMETRICS

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

III. BIOPHARMACEUTICS

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

IV. DRUG EXPERIENCE

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

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ PRECLINICAL

COMMENTS, CONCERNS, and/or SPECIAL INSTRUCTIONS:

Please review the requested tradename "Clobex." The labeling is attached. I will also send a hard copy. Labeling Day is scheduled for December 3, 2003.

PDUFA DATE: March 6, 2004

SIGNATURE OF REQUESTER	METHOD OF DELIVERY (Check one)
Jacquelyn Smith	X☐ MAIL ☐ HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

14 page(s) of draft labeling has been removed from this portion of the review.

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/s/

Jacquelyn Smith
7/15/03 02:52:45 PM

45 DAY MEETING CHECKLIST

FILEABILITY:

On initial overview of the NDA application:

CLINICAL:

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

2. Is the clinical section of the NDA indexed and paginated in a manner to allow substantive review to begin? Yes

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

4. If needed, has the sponsor made an appropriate attempt to determine the most appropriate dosage and schedule for this product (i.e., appropriately designed dose- ranging studies)?

   Study Number: 1.CG.03.SPR.2577
   Study Title: Evaluation of Efficacy and Tolerance in Subjects with Scalp Psoriasis after Three Different Application Times

   Sample Size: 60 Arms: 5
   NDA Volume: 1.28 Pages: 02710

   Study Number: 1.CG.03.SPR.2578
   Study Title: Evaluation of Efficacy and Tolerance in Subjects with Scalp Seborrrheic Dermatitis after Three Different Application Times

   Sample Size: 55 Arms: 5
   NDA Volume: 1.30 Pages: 03357

   Study Number: 1.CG.03.SPR.2591
   Study Title: Parallel Group Comparison of a 3-week Treatment with Clobetasol Proprionate 0.05% Shampoo Different Application Patterns – A Pilot Study in Patients with Scalp Psoriasis

   Sample Size: 59 Arms: 4
   NDA Volume: 1.31 Pages: 03711

5. On its face, do there appear to be the requisite number of adequate and well-controlled studies in the application?

   Application Type: 505(b)(2) YES No Reference listed drug:

   Identification of pivotal trials: Study reports, but not protocols, were included in the NDA. These were requested and will need to be supplied.

Pivotal Study #1: Protocol Number: RD.06.SRE.18075
Page Location in NDA: Protocol: p.4406, vol. 1.33 Study Report: p. 4387, vol. 1.33

Is this an adequate multi-centered trial?

Analysis Center	Center	Patients Enrolled Active/Vehicle/Total
01		14/7/21
02		12/6/18
03		12/6/18
04		10/5/15
05		10/4/14
06		9/4/13
07		7/4/11
08		6/3/9
09		6/3/9
10		2/1/3
11		4/2/6
12	2128/Mark Lebwohl, MD	7/4/11

Study Title: A Randomized, Double-Blind, Parallel Group Evaluation of Clobetasol Proprionate Shampoo, 0.05% Versus Its Vehicle – An Efficacy and Safety Study in Subjects with Scalp Psoriasis

Study design: Randomized (Y) Double Blind (Y) Placebo controlled (Y) Multicentered (Y)

Indication: moderate to severe scalp psoriasis, defined as Global Severity of at least 3 on a scale of 0 to 5 points, in males or females 12 years of age or older.

Study arms (dosage, duration, treatment length for each arm): The study was comprised of two arms, active (clobetasol propionate shampoo, 0.05%) and vehicle, with the study agent applied once daily to the affected areas of dry scalp and left in place for 15 minutes before lathering and rinsing, repeated daily for 4 weeks followed by a 2-week treatment-free follow-up period.

Efficacy endpoints (Primary and secondary): The primary efficacy parameter was the success rate at Week 4 endpoint for the ITT population; success rate for each treatment was defined as the proportion of subjects with a global severity score of clear or minimal. The secondary efficacy parameters were global severity score (full scale); total severity score (TSS), which is the sum of erythema, plaque thickening, and scaling scores; individual disease scores of erythema, plaque thickening, scaling, pruritus, and scalp surface area of involvement; global assessment of improvement by the investigator; and global assessment of improvement by the subject.

How measured:

Global Severity Scale

Score	Category	Category Description
0	Clear	Plaque thickening = none (no elevation or thickening over normal skin) Scaling = none (no evidence of scaling) Erythema = ± (hyperpigmentation or residual red coloration)
1	Minimal	Plaque thickening = ± (possible but difficult to ascertain whether there is a slight elevation above normal skin level) Scaling = ± (residual surface dryness and scaling) Erythema = up to moderate (up to definite red coloration)
2	Mild	Plaque thickening = slight (slight but definite elevation) Scaling = fine (fine scales partially or mostly covering lesions) Erythema = up to moderate (up to definite red coloration)
3	Moderate	Plaque thickening = moderate (moderate elevation with rounded or sloped edges) Scaling = coarser (most lesions at least partially covered) Erythema = moderate (definite red coloration)
4	Severe	Plaque thickening = marked (marked elevation typically with hard or sharp edges) Scaling = coarse (non-tenacious scale predominates, covering most or all of the lesions) Erythema = very severe (very bright red coloration)
5	Very Severe	Plaque thickening = very marked (very marked elevation typically with hard or sharp edges) Scaling = very coarse (thick tenacious scale covers most or all of the lesions) Erythema = very severe (extreme red coloration; deep red coloration)

Total Severity Score: the sum of the individual scores for erythema, scaling, and plaque thickening. Each individual parameter was scored on a 4-point scale from 0 to 3 on the whole scalp.

Erythema (abnormal redness of the skin)

0	None	No erythema
1	Mild	Slight pinkness present
2	Moderate	Definite redness; easily recognized
3	Severe	Intense redness

Scaling (scales attached to the scalp)

0	None	No scale visible on the scalp
1	Mild	Some scales, which may often be fine, on the scalp
2	Moderate	Numerous flakes of scaling present on the scalp
3	Severe	Presence of very numerous flakes of scaling, usually large, on the scalp

Plaque Thickening (a thickening or elevation of a circumscribed lesion or plaque)

0	None	No plaque thickening
1	Mild	Slight thickening
2	Moderate	Definite but not solid thickening
3	Severe	Marked, solid thickening

Pruritus (an itching sensation)

0	None	No itching
1	Mild	Slight itching, not really bothersome
2	Moderate	Definite itching, somewhat bothersome, without loss of sleep
3	Severe	Intense itching that has caused pronounced discomfort; night rest interrupted. Excoriation of the skin from scratching may be present.

Global Assessment of Improvement (As Per Investigator)

Score	Category	Category Description
5	Clear	All signs and symptoms of disease have resolved (100% improvement from Baseline)
4	Almost clear	Nearly all signs and symptoms of disease have cleared (about 90% improvement from Baseline); only minimal residual signs and symptoms remain
3	Marked improvement	Majority of the signs and symptoms have resolved (about 75% improvement from Baseline)
2	Moderate improvement	Significant improvement, but many signs and symptoms remain (about 50% improvement from Baseline)
1	Minimal improvement	Slight overall improvement, but not clinically significant (about 25% improvement from Baseline)
0	No change	Overall severity similar to baseline
-1	Worse	Worse than Baseline

Global Assessment of Improvement (as per subject): Global improvement from Baseline as per the Subject was scored on a –1 (worse) to 5 (clear) scale for the whole scalp.

Pivotal Study #2: Protocol Number: RD.06.SPR.18076
Location in NDA: Protocol: p. 6677, vol. 1.39 Study Report: p. 6660, vol. 1.39

Has the sponsor stated that this protocol is identical in design to Study #1? Unknown

Is this an adequate multi-centered trial?

Analysis Center	Investigator Number/Name	Patients Enrolled Active/Vehicle/Total
01	[redacted]	12/6/18
02	0439/Michael Jarratt, MD	10/5/15
03	[redacted]	10/5/15
04		9/5/14
05		9/4/13
06		7/3/10
07		6/3/9
08		6/3/9
09		6/3/9
10		5/3/8
11		4/3/7
12		6/2/8
13		5/2/7

Study Title: A Randomized, Double-Blind, Parallel Group Evaluation of Clobetasol Propionate Shampoo, 0.05% Versus Its Vehicle – An Efficacy and Safety Study In Subjects With Scalp Psoriasis.

Study design: Randomized – yes Double Blind – yes Placebo controlled - yes Multicentered yes

Indication: moderate to severe scalp psoriasis, defined as Global Severity of at least 3 on a scale of 0 to 5 points, in males or females 12 years of age or older.

Study arms (dosage, duration, treatment length for each arm): The study was comprised of two arms, active (clobetasol propionate shampoo, 0.05%) and vehicle, with the study agent applied once daily to the affected areas of dry scalp and left in place for 15 minutes before lathering and rinsing, repeated daily for 4 weeks followed by a 2-week treatment-free follow-up period.

Efficacy endpoints (Primary and secondary): The primary efficacy parameter was the success rate at Week 4 endpoint for the ITT population; success rate for each treatment was defined as the proportion of subjects with a global severity score of clear or minimal. The secondary efficacy parameters were global severity score (full scale); total severity score (TSS), which is the sum of erythema, plaque thickening, and scaling scores; individual disease scores of erythema, plaque thickening, scaling, pruritus, and scalp surface area of involvement; global assessment of improvement by the investigator; and global assessment of improvement by the subject.

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3	Severe	Marked, solid thickening

Pruritus (an itching sensation)

0	None	No itching
1	Mild	Slight itching, not really bothersome
2	Moderate	Definite itching, somewhat bothersome, without loss of sleep
3	Severe	Intense itching that has caused pronounced discomfort; night rest interrupted. Excoriation of the skin from scratching may be present.

Global Assessment of Improvement (As Per Investigator)

Score	Category	Category Description
5	Clear	All signs and symptoms of disease have resolved (100% improvement from Baseline)
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1	Minimal improvement	Slight overall improvement, but not clinically significant (about 25% improvement from Baseline)
0	No change	Overall severity similar to baseline
-1	Worse	Worse than Baseline

Global Assessment of Improvement (as per subject): Global improvement from Baseline as per the Subject was scored on a –1 (worse) to 5 (clear) scale for the whole scalp.

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

Proposed indication from sponsor's draft labeling: "indicated [redacted] moderate to severe forms of scalp psoriasis"

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

As designed, could endpoints in pivotal trial #2 support labeling? Yes

7. Are all data sets for pivotal efficacy studies complete for all indications requested? It appears that the data sets are complete, but Stats need to verify availability of data sets in SAS Transport format.

8. Do all pivotal efficacy studies appear to be adequate and well controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?

   PreIND/EoP2 Mtg: Yes
   IND number: 60,934
   PreIND/EoP2 Mtg Date: January 13, 2000
   Agency response to Phase 3 protocols: October 26, 2000
   PreNDA meeting date: March 8, 2002

   Do endpoints as described by sponsor in pivotal Study 1 conform to previous agency commitments? Yes
   Do endpoints as described by sponsor in pivotal Study 2 conform to previous agency commitments? Yes
   Are the pivotal trials multi-centered? Yes
   Are there adequate numbers of patients enrolled? Yes. However, the numbers enrolled in the individual centers are low.

9. Has the applicant submitted line listings in a format to allow reasonable review of the patient data? Has the applicant submitted line listings in the format agreed to previously by the Division? Yes

10. Has the application submitted a rationale for assuming the applicability of foreign data (disease specific microbiologic specific) in the submission to the US population? The two pivotal studies were both conducted in the United States.

11. Has the applicant submitted all additional required case record forms (beyond deaths and dropouts) previously requested by the Division? Yes

12. Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously agreed to by the Division? Yes. However, in the adult adrenal suppression study, the subjects were stimulated weekly for four weeks, and sampled 60 minutes post-timulation. In the adolescent study, the subjects were stimulated at week four, but sampled 60 minutes post-stimulation.

13. Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product? Yes

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

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

16. Has the applicant complied with the requirements of the Pediatric Rule? Yes

    a) Is this an indication that would be applicable to the pediatric population? Yes
    b) What pediatric ages are included in the protocol? 12 to 18 years
    c) Does the sponsor request pediatric labeling? What age groups? ———

17. Financial disclosure of investigator

    a) Does the NDA contain the appropriate form to comply with the filing requirement for Financial Disclosure for Investigators? The disclosure information is insufficient based on initial review; the Sponsor should submit a clear statement as to whether any of the Investigators had a financial stake in the outcome of this study.

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

_____
Reviewing Medical Officer

_____
Medical Team Leader

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/s/

Jill Lindstrom
6/20/03 01:41:54 PM
MEDICAL OFFICER

Markham Luke
6/23/03 03:49:06 PM
MEDICAL OFFICER
Additional information needed for review (e.g. protocols and statistical plans) have been requested from the Sponsor. It should be emphasized to the Sponsor that these should be sent in sooner rather than later.

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

FACSIMILE TRANSMITTAL SHEET

DATE: June 19, 2003

To: Bobbi Woodward, Manager, Regulatory Affairs	**From:** Jacquelyn Smith, Project Manager
Company: Galderma Laboratories	Division of Dermatologic and Dental Drug Products
Fax number: 817-961-0020	**Fax number:** 301-827-2075
Phone number: 817-961-5347	**Phone number:** 301-827-2027

Subject: NDA 21-644/Clobex Shampoo/ Request for Information

Total no. of pages including cover: 3

Comments: Please see following page(s).

Document to be mailed: ☐ YES X NO

NDA 21-644

FDA Fax Memo

Date: June 19, 2003

Subject: NDA 21-644/Clobex Shampoo

RE: Statiscal Analysis and Design Information

Dear Ms. Woodward,

To facilitate the review process, the following information is being requested:

1. Hard copy of each of the pivotal studies protocol along with any amendments to the protocol and/or the statistical analysis plan including the dates of such amendments if any. Also, it is helpful to submit this information for each of the supportive studies.

2. Hard copy of the treatment allocation list for each pivotal which shows treatment assignment to patients prior to enrollment in the trial.

3. Another hard copy of the volumes of the Clinical Section of the submission for the Biostatistics review, as the Statistical Section of the submission should include, apart from the copy of the Case Report Forms, the same information as the Clinical Section.

Please submit the above information to my attention.

Thank You,

Jacquelyn Smith
Project Manager
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/

Jacquelyn Smith
6/19/03 10:01:44 AM
CSO

Division of Dermatologic and Dental Drug Products (HFD-540)

Pharmacology/Toxicology Checklist for NDA Filing Meeting

Date: 6/18/03
Reviewer: Paul C. Brown
NDA Number: 21-644
Sponsor: Galderma
Product Name: Clobetasol Propionate Shampoo, 0.05%
Drug Substance(s): clobetasol propionate
Indication: [redacted] moderate to severe forms of scalp psoriasis
Route of Administration: topical
Date CDER Received: 5/6/03
User Fee Due Date (if filed): 3/5/04
Expected Date of Draft Review (if filed): 8/30/03

(1) Does the pharmacology/toxicology section of the NDA appear to be organized in a manner that would allow a substantive review to be completed?
Yes.

(2) Is the pharmacology/toxicology section of the NDA indexed and paginated in a manner to enable a timely and substantive review?
Yes.

(3) Is the pharmacology/toxicology section of the NDA sufficiently legible to permit a substantive review to be completed?
Yes.

(4) Based upon a cursory review, does the presentation of data appear to be appropriate (consider tables, graphs, completeness of study reports, inclusion of individual animal data, appropriateness of data analysis, etc.)?
Yes.

(5) Are all necessary nonclinical studies completed and submitted in this NDA?

Yes for filing, but additional studies will be required as phase 4 commitments (see below).

(6) Please itemize the pivotal nonclinical studies included in the NDA and indicate any important nonclinical studies that were omitted.

Note: This NDA was submitted under 505(b)(2) of the FD&C Act. It refers to published literature for much of the nonclinical information normally required to support an NDA. The following list includes the literature references and the sponsor-conducted studies as indicated.

Pivotal studies included:

A. Single-dose rodent:
   1. Rat, oral (literature)
   2. Mouse, oral (literature)
   3. Rat, subcutaneous (literature)
   4. Mouse, subcutaneous (literature)
   5. Rat, intraperitoneal (literature)
   6. Mouse, intraperitoneal (literature)

B. Single-dose non-rodent: none

B. Multiple-dose rodent:
   1. Rat, subcutaneous, 3 month (literature)
   2. Rat, subcutaneous, 6 month (literature)
   3. Rat, topical (ointment and cream), 1 month (literature)
   4. Rat, topical (ointment and cream), 3 month (literature)

C. Multiple-dose non-rodent:
   1. Minipig, topical range-finding, 4 week (sponsor)
   2. Minipig, topical, 13 week (sponsor)

D. Biodistribution and elimination:
   1. *In vitro*, human skin (sponsor)
   2. *In vivo*, rat, topical (sponsor)

E. Reproductive and developmental toxicity:
   1. Fertility and early embryonic development: No information on the effect of clobetasol propionate on fertility is provided. The NDA refers to information in the labels of approved drug products found in the Physician's Desk Reference. This is not acceptable since the sponsor has not established a clinical bridge to a listed drug.
   2. Embryo-fetal development:
      a. Rat, topical range-finding (lotion), (sponsor)
      b. Rat, topical (lotion), (sponsor)
   3. Pre- and postnatal development
      a. Rat, subcutaneous (literature)

F. Genotoxicity:
   1. *In vitro* chromosomal aberration in CHO cells (sponsor by right of reference)

2. *In vivo* mouse micronucleus assay (sponsor by right of reference)

G. Special toxicity studies:

1. Rabbit, topical, skin irritation (sponsor)
2. Rabbit, ocular irritation (sponsor)
3. Guinea pig, skin sensitization (sponsor)

Pivotal studies omitted:
At the pre-NDA meeting the following recommendation was provided to the sponsor.

If a clinical bridge to the reference 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 and literature information listed in the briefing package: effect on fertility and early embryonic development, effect on pre- and postnatal development and genotoxicity.

This NDA does not establish a clinical bridge to a listed product. The sponsor has not provided information on the effect of clobetasol propionate on fertility and early embryonic development. The sponsor notes that plasma concentrations obtained in patients under normal clinical conditions for up to 4 weeks did not exceed the limit of detection of . The sponsor has also concluded that the shampoo caused no suppression of the HPA axis. If these findings are confirmed by the clinical and biopharmaceutics reviewers, then information on the effect of clobetasol propionate on fertility may not be needed. If the clinical and biopharmaceutics reviewers find that the shampoo produced measurable systemic levels of clobetasol propionate or systemic effects, then a study on the effect of clobetasol propionate on fertility should be provided as a phase 4 commitment.

(7) Based upon a cursory review, do the pivotal nonclinical studies appear to have been adequately designed (e.g., appropriate numbers of animals, adequate monitoring consistent with the proposed clinical use, state-of-the art protocols, etc.)?
Yes.

(8) As appropriate, were the test materials utilized in the

pivotal nonclinical studies identical to the drug product or drug substance proposed for commercial use (including impurity profiles)? If not, or if this matter is unclear, please comment.
Many of the studies are published reports and as such are unlikely to be identical to the drug product and drug substance proposed for commercial use. The studies conducted by the sponsor with the shampoo appear to use the same formulation as the proposed commercial formulation.

(9) Based upon a cursory review, do the excipients appear to have been adequately qualified?
No. Polyquaternium-10, cocobetaine and sodium laureth sulfate are noncompendial and do not appear to have been used in an approved prescription drug product previously. The NDA contains reviews of the safety information available for each of these compounds. All appear to be widely used in cosmetic products. These three compounds do not appear to have been assessed for reproductive and developmental toxicity. Cocobetaine and sodium laureth sulfate have not been fully assessed for genotoxicity. Polyquaternium-10 and cocobetaine do not appear to have been tested for carcinogenicity. In spite of the lack of nonclinical studies of these compounds it may be reasonably safe to permit filing and approval of the NDA, since these compounds are widely used and have been used in the 3 month minipig study and the clinical studies. The CDER guidance on nonclinical evaluation of excipients says that existing human data for some excipients can substitute for nonclinical safety data and an excipient with documented prior human exposure under circumstances relevant to the proposed use may not require evaluation in the full battery of toxicology studies. The cocobetaine and sodium laureth sulfate are surfactants and probably would not be very amenable to in vitro genotoxicity studies. Therefore, qualification of these excipients would be sufficient if they are included in a dermal carcinogenicity study.

(10) Was the route of administration used in the nonclinical studies the same as the intended clinical route of administration?
Some of the studies were conducted by routes other than topical but this is acceptable.

(11) Has proposed draft labeling been submitted?
Yes. It is noted that some of the nonclinical information in the

label appears to have been taken from labels of approved drug products. The sponsor does not have right to refer to this information and consequently this information should probably not be included in the label.

(12) From a pharmacology/toxicology perspective, should this NDA be filed? If not, or if you have additional concerns, please indicate your recommendations in the form of draft comments that may be transmitted to the sponsor.
Yes.

Information to sponsor:
The sponsor can not refer to the PDR for nonclinical information. References to information found in the PDR should be removed from the label.

The NDA does not contain any information on the effect of clobetasol propionate on fertility as was requested at the pre-NDA meeting. If the review of the NDA finds that there is no measurable systemic absorption and no systemic effects, then a fertility study will not be required. However, if the review of the NDA finds systemic absorption or systemic effects then a phase 4 commitment to conduct a fertility study will be required.

In addition, the sponsor was told at the Pre-NDA meeting that the Division considers the treatment of psoriasis as a chronic indication. The Division recommended that carcinogenicity and photococarcinogenicity be evaluated. The Division stated that these studies could be conducted postapproval.

The sponsor was advised to submit in the NDA their plans to evaluate carcinogenicity and photococarcinogenicity, including a timeline for fulfilling these phase 4 commitments. The sponsor has not submitted these plans. The sponsor will need to agree to these phase 4 commitments and a timeline for their completion.

The noncompendial excipients have not been fully qualified. Including the excipients in a dermal carcinogenicity study would be sufficient to qualify them. The sponsor will need to agree to this as a phase 4 commitment.

Reviewing Pharmacologist Date Signed

Pharmacology Supervisor Date Signed

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

/s/

Paul Brown
6/18/03 03:13:07 PM
PHARMACOLOGIST

Barbara Hill
6/18/03 03:33:15 PM
PHARMACOLOGIST
Acting Pharmacology/Toxicology supervisor for Abby Jacobs

ATTACHMENT

MEMO OF FILING MEETING

DATE: June 18, 2003

BACKGROUND:
Clobex is a 505(b)(2) NDA application for the treatment of Moderate to Severe forms of ——— ——— Scalp Psoriasis. The NDA reference drugs are Temovate (NDA, 19-966), Temovate E (NDA 20, 340) and Olux Foam (NDA 21-142).

ATTENDEES: Jonathan Wilkin, M.D., Mohamed Alosh, Ph.D., Markham Luke, M.D., Jill Lindstrom, M.D.,Wilson DeCamp, Ph.D., Paul Brown, Ph.D., Chandra Chaurasia, Pharm. D., Roy Blay, Ph.D., Mary Jean Kozma-Fornaro

ASSIGNED REVIEWERS:

Discipline	**Reviewer**	**Review Date**
Medical:	Jill Lindstrom	November 30
Secondary Medical:	N/A	
Statistical:	Steve Thomson	December 15
Pharmacology:	Paul Brown	August 30
Statistical Pharmacology:	N/A	
Chemist:	Saleh Turujman	November 15
Environmental Assessment (if needed):	N/A	
Biopharmaceutical:	Chandra Chaurasia	October 15
Microbiology, sterility:	N/A	
Microbiology, clinical (for antimicrobial products only):		
DSI:	Roy Blay	
Regulatory Project Manager:	Jacquelyn Smith	
Other Consults:		

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

CLINICAL FILE __X___ REFUSE TO FILE _____

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

N/A YES NO

CLINICAL MICROBIOLOGY	FILE _____	REFUSE TO FILE _____	N/A
STATISTICS	FILE ___X__	REFUSE TO FILE _____	
BIOPHARMACEUTICS	FILE _X____	REFUSE TO FILE _____	
• Biopharm. inspection needed:		YES XNO not at this time	
PHARMACOLOGY	FILE __X___	REFUSE TO FILE _____	
• GLP inspection needed:		YES NO	
CHEMISTRY	FILE __X__	REFUSE TO FILE _____	
• Establishment(s) ready for inspection?		_X YES NO	
• Microbiology		YES NO	

ELECTRONIC SUBMISSION:
Any comments:

REGULATORY CONCLUSIONS/DEFICIENCIES:

_____ The application is unsuitable for filing. Explain why:

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

_____ No filing issues have been identified.

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

_____
Jacquelyn Smith
Regulatory Project Manager, HFD-540

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/s/

Jonathan Wilkin
8/19/03 05:45:50 PM

NDA FILEABILITY CHECKLIST

NDA Number: 21-644 **Drug Name:** CLOBEX™ (clobetasol propionate) Shampoo, 0.05%

Applicant: GALDERMA Laboratories, L.P.

IS THE CMC SECTION OF THIS APPLICATION FILEABLE? (Yes or No) _Yes___

Table 1 Fileability Checklist

The following parameters are necessary for initiating a full review, e.g. complete enough for review but may have deficiencies.

	PARAMETER	YES	NO	COMMENT
1	Is the NDA organized adequately for its CMC content?	X		
2	Are the CMC sections adequately indexed & paginated?	X		
3	Are the CMC sections legible?	X		
4	Are all facilities identified with full street addresses, contact names & CFN #s?	X		
5	Is there a statement that all facilities are prepared for GMP inspections?	X		**EER for DS pending; for DP acceptable**
6	Has an environmental assessment or categorical exclusion been provided?	X		
7	Does the drug substance section contain controls?	X		**refers to DMF**
8	Does the drug product section contain controls?	X		
9	Has stability data been submitted to justify the requested expiry date?	X		
10	Has the applicant provided all requested data by the division during the IND & pre-NDA phases?			**Most**
11	Have draft container labels been provided?	X		
12	Has a draft package insert been provided?	X		
13	Has an Investigational Formulations section been included?	X		
14	Are there three Methods Validation documents?		X	**Only 2 docs**
15	Is a statistical consult required?		X	
16	Is there a separate microbiological section? Is a micro consult required?		X X	

EER REPORT ATTACHED

Table 2 STABILITY DATA REQUIRED FOR FILEABILITY

	STABILITY DATA REQUESTED	YES	NO
1	Does the NDA include 12 or more months of stability data?	X	
2	Does the stability data cover the expiry date?	X	
3	Does the stability data include **only** the largest & smallest container sizes?		X*
4	Does the stability data include all packages sizes?	X	
5	Are there tabular data for each size and batch?	X	
6	Are there graphical data for each size and batch?		
7	Is a statistical consult required?		X
8	Is a stability protocol included?	X	
9	Are the stability-indicating assays described?	X	
10	Is there the three-point stability commitment?	X	

* Stability data submitted includes all package sizes. See next item

Table 3 DMF INFORMATION

DMF #	DMF HOLDER	TYPE	LOA DATE	DATE OF LAST REVIEW
		II	March 9, 2001	May 15, 2003
		II	July 5, 2001	February 14, 2003*
		III	December 5, 2000	June 29, 2000**
		III	April 11, 2002	
		III	November 7, 2001	May 3, 2002
		III	May 31, 2001	March 14, 2002**
		III	October 2, 2001	
		III	April 15, 2002	
			April 20, 2002	
		III	August 28, 2000	
		III	August 12, 2002	
		III	August 3, 2001	

* Inadequate. Deficiency letter issued

Completion Date: June 16, 2002

Saleh A. Turujman, Ph.D.
Review Chemist

Wilson H. DeCamp, Ph.D.
Chemistry Team Leader

Attachment

Cc: NDA 21-644
HFD-540/Division File
HFD-540/Chm/SATurujman
HFD-540/ChmTL/WHDeCamp
HFD-540/ProjMgr/JSmith
HFD-830/DivDir/CChen

C:\Data\My Documents\turujman\reviews\NDA\NDAs 2003\NDA 21-644 Clobex Shampoo 0.05%\NDA 21-644 FILEABILITY CHECKLIST.doc

ESTABLISHMENT EVALUATION REQUEST

SUMMARY REPORT

Application : NDA 21644/000
Org Code : 540
Priority : 3S

Sponsor: GALDERMA LABORATORIES INC
14501 NORTH FREEWAY
FORT WORTH, TX 76177

Stamp Date : 06-MAY-2003
PDUFA Date : 06-MAR-2004
Action Goal :
District Goal: 06-JAN-2004

Brand Name : CLOBEX(CLOBETASOL PROPIONATE)
0.05%
Estab. Name:
Generic Name: CLOBETASOL PROPIONATE SHAMPOO
0.05%
Dosage Form: (SHAMPOO)
Strength : 0.05%

FDA Contacts:			
J. SMITH	Project Manager	(HFD-540)	301-827-2020
S. TURUJMAN	Review Chemist	(HFD-540)	301-827-2085
W. DECAMP II	Team Leader	(HFD-540)	301-827-2041

--Overall Recommendation:

Establishment : CFN : [redacted] FEI :
DPT LABORATORIES INC
307 EAST JOSEPHINE STREET
SAN ANTONIO, TX 78215

DMF No: AADA:

Responsibilities: FINISHED DOSAGE MANUFACTURER
FINISHED DOSAGE PACKAGER
FINISHED DOSAGE RELEASE TESTER

Profile : LIQ OAI Status: NONE
Last Milestone: OC RECOMMENDATION

Milestone Date: 04-JUN-03

Decision : ACCEPTABLE

Reason : DISTRICT RECOMMENDATION

Establishment : [redacted]

DMF No: [redacted]

Responsibilities: [redacted]

Profile : CSN OAI Status: NONE

Last Milestone: SUBMITTED TO DO

Milestone Date: 03-JUN-03

:

:

Establishment : [redacted]

DMF No:

ESTABLISHMENT EVALUATION REQUEST

SUMMARY REPORT

Responsibilities: [redacted]

Profile : CSN OAI Status: NONE

Last Milestone: SUBMITTED TO DO

Milestone Date: 03-JUN-03

:

:

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/s/

Saleh Turujman
6/17/03 12:49:26 PM
CHEMIST

For your concurrence

Wilson H. DeCamp
6/17/03 01:05:09 PM
CHEMIST
concur with fileability recommendation

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

Form Approved: OMB No. 0910-0297
Expiration Date: February 29, 2004.

USER FEE COVER SHEET

See Instructions on Reverse Side Before Completing This Form

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

1. APPLICANT'S NAME AND ADDRESS

Galderma Laboratories, L.P.
14501 North Freeway
Fort Worth, TX 76177

2. TELEPHONE NUMBER *(Include Area Code)*

(817) 961-5347

3. PRODUCT NAME

Clobetasol Propionate Shampoo, 0.05%

4. BLA SUBMISSION TRACKING NUMBER (STN) / NDA NUMBER

N021644

5. DOES THIS APPLICATION REQUIRE CLINICAL DATA FOR APPROVAL?

☒ YES ☐ NO

IF YOUR RESPONSE IS "NO" AND THIS IS FOR A SUPPLEMENT, STOP HERE AND SIGN THIS FORM.

IF RESPONSE IS 'YES', CHECK THE APPROPRIATE RESPONSE BELOW:

☒ THE REQUIRED CLINICAL DATA ARE CONTAINED IN THE APPLICATION.

☐ THE REQUIRED CLINICAL DATA ARE SUBMITTED BY REFERENCE TO:

_____
(APPLICATION NO. CONTAINING THE DATA).

6. USER FEE I.D. NUMBER

4530

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

☐ A LARGE VOLUME PARENTERAL DRUG PRODUCT APPROVED UNDER SECTION 505 OF THE FEDERAL FOOD, DRUG, AND COSMETIC ACT BEFORE 9/1/92 *(Self Explanatory)*

☐ A 505(b)(2) APPLICATION THAT DOES NOT REQUIRE A FEE *(See item 7, reverse side before checking box.)*

☐ THE APPLICATION QUALIFIES FOR THE ORPHAN EXCEPTION UNDER SECTION 736(a)(1)(E) of the Federal Food, Drug, and Cosmetic Act *(See item 7, reverse side before checking box.)*

☐ THE APPLICATION IS A PEDIATRIC SUPPLEMENT THAT QUALIFIES FOR THE EXCEPTION UNDER SECTION 736(a)(1)(F) of the Federal Food, Drug, and Cosmetic Act *(See item 7, reverse side before checking box.)*

☐ THE APPLICATION IS SUBMITTED BY A STATE OR FEDERAL GOVERNMENT ENTITY FOR A DRUG THAT IS NOT DISTRIBUTED COMMERCIALLY *(Self Explanatory)*

8. HAS A WAIVER OF AN APPLICATION FEE BEEN GRANTED FOR THIS APPLICATION?

☐ YES ☒ NO

(See Item 8, reverse side if answered YES)

SIGNATURE OF AUTHORIZED COMPANY REPRESENTATIVE	TITLE	DATE
Bobbi Woodward Bobbi Woodward	Manager, Regulatory Affairs	April 18, 2003

NDA/EFFICACY SUPPLEMENT ACTION PACKAGE CHECKLIST

Application Information			
NDA 21-644	Efficacy Supplement Type SE- N/A	Supplement Number : N/A	
Drug: Clobex Shampoo, 0.05% (clobetasol propionate)		Applicant: Galderma Laboratories, LP	
RPM: Jacquelyn Smith		HFD-540	Phone # 301-827-2020
Application Type: ( ) 505(b)(1) (x) 505(b)(2)		Reference Listed Drug (NDA #. Drug name):	

❖ Application Classifications:	
• Review priority	(x) Standard ( ) Priority
• Chem class (NDAs only)	3S
• Other (e.g., orphan, OTC)	N/A
❖ User Fee Goal Dates	March 6, 2004
❖ Special programs (indicate all that apply)	(x) None Subpart H ( ) 21 CFR 314.510 (accelerated approval) ( ) 21 CFR 314.520 (restricted distribution) ( ) Fast Track ( ) Rolling Review
❖ User Fee Information	
• User Fee	(x) Paid
• User Fee waiver	( ) Small business ( ) Public health ( ) Barrier-to-Innovation ( ) Other
• User Fee exception	( ) Orphan designation ( ) No-fee 505(b)(2) ( ) Other
❖ Application Integrity Policy (AIP)	
• Applicant is on the AIP	( ) Yes (x) 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 and certifications from foreign applicants are co-signed by U.S. agent.	(x) Verified
❖ Patent	
• Information: Verify that patent information was submitted	(x) Verified
• Patent certification [505(b)(2) applications]: Verify type of certifications submitted	21 CFR 314.50(i)(1)(*i*)(A) ( ) I ( ) II ( ) III ( ) IV 21 CFR 314.50(i)(1) ( ) (ii) ( ) (iii)
• For paragraph IV certification, verify that the applicant notified the patent holder(s) of their certification that the patent(s) is invalid, unenforceable, or will not be infringed (certification of notification and documentation of receipt of notice).	( ) Verified
❖ Exclusivity Summary (approvals only)	x
❖ Administrative Reviews (Project Manager, ADRA) *(indicate date of each review)*	N/A

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	( ) 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)	N/A
• Most recent applicant-proposed labeling	Dec. 30, 2003
• Original applicant-proposed labeling	May 2, 2003
• Labeling reviews (including DDMAC, Office of Drug Safety trade name review, nomenclature reviews) and minutes of labeling meetings *(indicate dates of reviews and meetings)*	DDMAC(Oct.14, 2003); DDRE(Oct. 30, 2003); DMETS (Nov. 21, 2003)
• Other relevant labeling (e.g., most recent 3 in class, class labeling)	N/A
❖ Labels (immediate container & carton labels)	
• Division proposed (only if generated after latest applicant submission)	N/A
• Applicant proposed	May 2, 2003
• Reviews	
❖ Post-marketing commitments	
• Agency request for post-marketing commitments	Dec. 23, 2003
• Documentation of discussions and/or agreements relating to post-marketing commitments	Dec. 23, 2003, Jan.15, 2004
❖ Outgoing correspondence (i.e., letters, E-mails, faxes)	x
❖ Memoranda and Telecons	x
❖ Minutes of Meetings	
• EOP2 meeting (indicate date) Pre-IND/EOP2	January 13, 2000
• Pre-NDA meeting (indicate date)	March 7, 2002
• Pre-Approval Safety Conference (indicate date; approvals only)	N/A
• Other	
❖ Advisory Committee Meeting	
• Date of Meeting	N/A
• 48-hour alert	N/A
❖ Federal Register Notices, DESI documents, NAS, NRC (if any are applicable)	N/A

Clinical and Summary Information	
❖ Summary Reviews (e.g., Office Director, Division Director, Medical Team Leader) *(indicate date for each review)*	
❖ Clinical review(s) *(indicate date for each review)*	Jan. 15, 2004
❖ Microbiology (efficacy) review(s) *(indicate date for each review)*	N/A
❖ Safety Update review(s) *(indicate date or location if incorporated in another review)*	Jan. 15, 2004
❖ Pediatric Page(separate page for each indication addressing status of all age groups)	x
❖ Statistical review(s) *(indicate date for each review)*	Jan. 12, 2004
❖ Biopharmaceutical review(s) *(indicate date for each review)*	Jan. 7, 2004
❖ Controlled Substance Staff review(s) and recommendation for scheduling *(indicate date for each review)*	N/A
❖ Clinical Inspection Review Summary (DSI)	
• Clinical studies	Nov. 25, 2003
• Bioequivalence studies	N/A
CMC Information	
❖ CMC review(s) *(indicate date for each review)*	Dec. 19, 2003
❖ Environmental Assessment	
• Categorical Exclusion *(indicate review date)*	Dec. 19, 20030
• Review & FONSI *(indicate date of review)*	N/A
• Review & Environmental Impact Statement *(indicate date of each review)*	N/A
❖ Micro (validation of sterilization & product sterility) review(s) *(indicate date for each review)*	N/A
❖ Facilities inspection (provide EER report)	Date completed: June 3, 2003 (x) Acceptable ( ) Withhold recommendation
❖ Methods validation	( ) Completed ( ) Requested ( ) Not yet requested (X) Pending
Nonclinical Pharm/Tox Information	
❖ Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)*	Aug. 29, 2003
❖ Nonclinical inspection review summary	N/A
❖ Statistical review(s) of carcinogenicity studies *(indicate date for each review)*	N/A
❖ CAC/ECAC report	N/A