



**DEPARTMENT OF HEALTH & HUMAN SERVICES**

Public Health Service

Food and Drug Administration  
Rockville, MD 20857

NDA 22-087

**INFORMATION REQUEST LETTER**

Galderma Laboratories, LLC  
Attention: Paul Clark  
Director, Regulatory Affairs  
14501 N. Freeway  
Fort Worth, TX 76177

Dear Mr. Clark:

Please refer to your December 21, 2007, new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for TRADENAME (calcitriol) Ointment, 3mcg/g.

We have reviewed your request for proposed trade name "Silkis" and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

We object to your proposed trade name "Silkis" because it overstates the efficacy of the product. "Silkis" easily evokes the word "silky," which can be defined as "of or like silk; smooth, lustrous, soft, or delicate" (<http://dictionary.reference.com/browse/silkysoft>; accessed 3/10/08) and "smooth, like silk" (<http://dictionary.cambridge.org/define.asp?key=73689&dict=CALD>; accessed 3/10/08). Given that the proposed indication of "Silkis" is for the topical treatment of plaque-type psoriasis, it misleadingly implies that diseased skin will become "silky, smooth, lustrous, or soft" after the use of this product. Without substantial evidence to support that treatment with "Silkis" will provide clear, "silky" skin, the proposed trade name is misleading.

Please note that the Federal Food Drug and Cosmetic Act provides that labeling or advertising can misbrand a product if misleading representations are made, whether through a proposed trade name or otherwise; this includes suggestions that a drug is better, more effective, useful in a broader range of conditions or patients, safer, has fewer, or lower incidence of, or less serious side effects or contraindications than has been demonstrated by substantial evidence or substantial clinical experience. [21 U.S.C 321(n); see also 21 U.S.C. 352(a) & (n); 21 CFR 202.1(e)(5)(i);(e)(6)(i)].

Submit two new trade names as soon as possible. Your request should indicate which name is your first choice.

If you have any questions, call Bronwyn Collier, Acting Chief, Project Management Staff, at (301) 796-2110.

Sincerely,

*(See appended electronic signature page)*

Susan J. Walker, M.D., F.A.A.D.  
Director  
Division of Dermatology and Dental Products  
Office of Drug Evaluation III  
Center for Drug Evaluation and Research

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/s/

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Bronwyn Collier  
6/23/2008 12:23:19 PM  
Signed for Susan Walker, M.D., F.A.A.D.

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Executive CAC

Date of Meeting: May 27, 2008

Committee: David Jacobson-Kram, Ph.D., OND IO, Chair  
Abby Jacobs, Ph.D., OND IO, Member  
Paul Brown, Ph.D., OND IO, Member  
Dan Mellon, Ph.D., DAARP, Alternate Member  
Barbara Hill, Ph.D., DDDP, Team Leader  
Norman A. See, Ph.D., DDDP, Presenting Reviewer

Author of Draft: Norman A. See, Ph.D.

The following information reflects a brief summary of the Committee discussion and its recommendations. Detailed information may be found in the associated Pharmacology and Biostatistics reviews.

NDA # 22-087

Drug Name: Calcitriol

Sponsor: Galderma Laboratories, L.P.

The committee discussed the results of two carcinogenicity studies that were conducted with calcitriol, including a study in which rats were dosed orally and a study in which mice were treated topically.

#### Rat Carcinogenicity Study

Background: A two-year topical carcinogenicity study was conducted in which calcitriol solution was orally administered (via gavage) daily to rats. Dosages of approximately 0.005, 0.03, and 0.1 µg/kg/day were investigated. The vehicle for the test material was Neobee oil M5. Neobee oil M5 is a medium chain triglyceride.

respectively. The study included both a vehicle-treated control group and a second control group which received water. The protocol for the study, including the dosages used, was discussed by the executive CAC on April 8, 2003; dosage selection was based upon the MTD. Survival rates did not differ significantly between groups; terminal sacrifice of all groups occurred following 104 weeks of treatment. The incidence of benign pheochromocytomas was significantly increased in female rats (pairwise p-value of 0.0001; trend value of 0.0036). These data are summarized below:

Rat Females	W	V	L	M	H	Pair	Trend
ADRENAL GLANDS							
Benign pheochromocytoma,	0	0	0	2	7	0.0001	0.0036

No other tumor incidence data differed according to the Haseman-Lin-Rahman criteria.

#### Mouse Carcinogenicity Study

**Background:** A two-year topical carcinogenicity study was conducted in which calcitriol ointment was applied to the skin of mice. Materials that contained calcitriol at concentrations of 0 (vehicle), 0.3, 0.6, and 1.0 ppm were evaluated. The vehicle for the test material was identical to the vehicle of Silkis ointment (NDA 22-087). The protocol for the study, including the test materials to be used, was discussed by the executive CAC on April 8, 2003. Dosage selection was based upon the estimated MTD. The MTD was exceeded in the study. Because of reduced mean weight gain and treatment-related deaths, treatment was suspended for several weeks beginning week 23 and week 29 for groups receiving 0.6 ppm and 1.0 ppm materials, respectively. Treatment of all groups (including those receiving vehicle and 0.3 ppm calcitriol) subsequently was changed to a frequency of three applications per week. Due to reduced survival, and upon recommendation from the executive CAC, males receiving 1.0 ppm calcitriol were sacrificed during week 97 and all groups of females were sacrificed during study week 101. No statistically significant differences in tumor incidence were observed in this study.

**Executive CAC Recommendations and Conclusions:**

- 1. The Committee found both the study in rats and the study in mice to be valid in all respects, including the dosages that were evaluated.**
- 2. The Committee found that oral administration of calcitriol for a lifetime resulted in an increased incidence of benign pheochromocytomas in female rats; no evidence of carcinogenesis was observed in male rats. No evidence of potential to induce carcinogenesis was obtained in a study in which calcitriol was applied to the skin of male and female mice over a lifetime.**

**David Jacobson-Kram, Ph.D.**  
**Chair, Executive CAC**

cc:\n  
**/Division File, DDDP**  
**/B Hill/Team leader, DDDP**  
**/N See/Reviewer, DDDP**  
**/M Owens/PM, DDDP**  
**/B Collier/PM, ODE III**  
**/A Seifried, OND IO**

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/s/

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David Jacobson-Kram  
5/29/2008 11:56:06 AM

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**FOOD AND DRUG ADMINISTRATION**

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**Meeting Date:** November 20, 2006  
**Time:** 1:00 PM – 1:20 PM  
**Meeting Type:** CMC Type C Teleconference  
**Meeting Location:** Food and Drug Administration, White Oak Campus  
**Application Number:** NDA 22-087  
**Product Name:** Silkis (calcitriol) Ointment, 3mcg/g  
**Sponsor Name:** Galderma Laboratories  
**Meeting Requestor:** Paul Clark, Director Regulatory Affairs  
**Meeting Chair:** Shulin Ding, Ph.D., Pharmaceutical Assessment Lead  
**Meeting Recorder:** Linda Athey, Regulatory Health Project Manager for Quality  
**Meeting Attendees:** Paul Clark, Director Regulatory Affairs, Galderma Laboratories

**FDA Attendees**

**CENTER OF DRUG EVALUATION AND RESEARCH**

Office of New Drug Quality Assessment:

Shulin Ding, Ph.D., Pharmaceutical Assessment Lead, DPMA II

Jane Chang, Ph.D., Chemist, DPMA II

Linda Athey, Regulatory Health Project Manager for Quality, DPMA II

**1.0 BACKGROUND**

The teleconference was requested by FDA to discuss CMC and quality issues concerning the submitted NDA for Silkis (calcitriol) ointment, 3mcg/g. This is a follow-up to the Teleconference held on November 14, 2006 and a response to the proposal sent by Galderma through e-mail on November 20, 2006 (see Attachment 1).

2.0 DISCUSSION

2.1 EVALUATION OF EXISTING BATCHES

A) Galderma proposes to compare Batch 056\*03 manufactured in November 2003, at Industrial Development in France with Batch 036835 ID 102518 manufactured in May 2004, at GPCI. Batch 056\*03 was used in a nonclinical study RDS.03.SRE.12394, a 9-month Dermal Toxicity Study in Minipigs. Batch 0368365 was a validation batch which was also used as a primary stability batch.

FDA asked for clarification about the packaging size of Batch 036835 ID 102518. Galderma acknowledged that an error was made in the size identification for Batch 036835. The correct ID should be 102519, which is a 100g tube size, rather than 102518, which is a 5g size. Galderma stated that it was their intention to compare 100g tube size with 100g tube size.

B) Galderma proposes that the physical and chemical characteristics of these two lots be evaluated. The evaluation would include full testing and rheology studies. If these two lots have similar characteristics, the IVRT would be done using these two lots.

FDA agrees with the evaluation of the physical and chemical characteristics. FDA asked whether the manufacturing process for Batch 056\*03 was the same as that for phase 3 clinical batches. Galderma replied that they were not sure, and would check and get back with FDA.

C) Galderma states in the proposal that if the lots do not have similar characteristics, new lots will be manufactured and filled into 100g tubes supplied by \_\_\_\_\_ Galderma plans to compare only 100g tubes made at both sites. Galderma objects to a comparison of the in-vitro release rate among different fill sizes because all tube sizes are manufactured and filled in the same manner.

b(4)

FDA explained that th \_\_\_\_\_

b(4)

\_\_\_\_\_ The filling and cooling operations are part of manufacturing process. The cooling rate experienced in each tube size was likely to be different due to different ratio of ointment amount to surface area. Therefore, the in-vitro release rates for the 5g \_\_\_\_\_ tubes will need to be compared with the 100g tubes to show that the drug release rate is not impacted by different cooling rates.

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FDA asked Galderma whether the 5p \_\_\_\_\_ tube sizes were used in the clinical studies. Galderma stated that only 100g tubes were used in the clinical studies.

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D) Galderma objects to a comparison of the drug product for the in-vitro release throughout the proposed shelf-life.

FDA agreed to consider their reasoning but stated that it was necessary to do in-depth review regarding the structure of the formulation and potential changes upon storage. In the teleconference held on Nov. 14, 2006, FDA had requested Galderma to provide more information regarding the observed \_\_\_\_\_ structure.

## **2.2 CORRECTION TO THE EMAIL SENT NOVEMBER 20, 2006.**

FDA requested a correction in the name from Dr. Ding to Dr. Chang in their proposal (Attachment 1), with the exception of the first sentence. This was done and sent through e-mail (Attachment 2).

Additionally FDA commented that the comparisons conveyed to Galderma in Nov. 14, 2006, teleconference were Batches D to E (Study 3) and Batches D to F (Study 4).

However, the comparisons of Batches C to E and Batches C to F as proposed in Attachment 1 would be acceptable.

## **3.0 ISSUES REQUIRING FURTHER DISCUSSION**

The sponsor would like a teleconference with the Branch Chief to further discuss testing of the different fill sizes.

## **4.0 ACTION ITEMS**

The sponsor will verify that the manufacturing process for Batch 056\*03 is the same as that for phase 3 clinical Batches. The sponsor will try to respond to FDA for this information by November 22, noon EST.

## **5.0 ATTACHMENTS AND HANDOUTS**

Attachment 1 – email sent to the Project Manager containing Galderman's response and requests for clarification to the November 14, 2006 teleconference.

Attachment 2 – Corrected email sent to the Project Manager containing Galderman's response.

**ATTACHMENT 1**

**From:** CLARK, Paul [mailto:paul.clark@galderma.com]  
**Sent:** Monday, November 20, 2006 10:05 AM  
**To:** Owens, Margo  
**Subject:** NDA 22-087 CALCITRIOL OINTMENT - GALDERMA'S RESPONSE TO REQUEST FOR IVRT DATA

Dear Margo:

This is Galderma's response to the Division's request to provide IVRT data. I will only be in the office during the morning. If you need to reach me after that, please call my cell at \_\_\_\_\_

b(6)

Paul

Paul Clark  
Director, Regulatory Affairs  
Galderma Laboratories, L.P.  
817 961 5336 Phone  
817 961 0020 Fax

**SUMMARY OF TELECONFERENCE OF NOVEMBER 14, 2006**

During the teleconference Dr. Ding inquired if Galderma had performed IVRT on products manufactured at the two locations. Galderma stated that this type of comparison had not been done. Dr. Ding then inquired if there were samples of product of similar age available for IVRT. Galderma replied that it was uncertain about the availability of lots of comparable age.

Dr. Ding proposed that if no lots of comparable age were available, one batch of the drug product be made at each location, filled and tested according to the table below.

Industrial Development	Galderma Production
------------------------	---------------------

Alby sur Cheran, France	Canada Inc.
Bulk Product (A)	Bulk Product (B)
100 g tube _____ (C)	100g tube _____ (D)
	_____ (E)
	5g _____ (F)

b(4)

**IVRT studies**

Study 1	Compare A to B
Study 2	Compare C to D
Study 3	Compare C to E
Study 4	Compare C to F

Dr. Ding requested that these lots be placed on long term stability according to the protocol described in table 3.2.P.8.3 and that IVRT testing be done at T0, T18 and end of shelf-life with the T0 IVRT data submitted to FDA on or before April 30, 2007.

**GALDERMA'S AGREEMENT**

Galderma agrees to provide IVRT information comparing one lot manufactured at each site filled into 100 g tubes according the following proposal on or before April 30, 2007. We have some concerns regarding the technical aspects of the test due to the low concentration of active ingredient, 3 mcg/g, and the composition of the vehicle, \_\_\_\_\_

\_\_\_\_\_ If we encounter difficulties in performing the test, we will contact the Division immediately.

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**GALDERMA'S PROPOSAL**

**EVALUATION OF EXISTING BATCHES**

A review of the batches manufactured at the two sites identified two batches that were manufactured 5 months apart; batch 056\*03 manufactured in November 2003 at Industrial Development in France and batch 036835 ID 102518 manufactured in May 2004 at GPCI. Batch 056\*03 was used in a nonclinical study RDS.03.SRE.12394, a 9-month Dermal Toxicity Study in Minipigs (Report may be found in 4.2.3.2.11); 0368365 was used a primary stability batch (the executed MBR may be found at 3.2.R.1.P.1.03, EMBR lot 036835 ID 102518).

Galderma proposes that the physical and chemical characteristics of these two lots be evaluated. The evaluation would include full testing and rheology studies. If these two lots have similar characteristics, the IVRT would be done using these two lots.

If the lots do not have similar characteristics, new lots will be manufactured and filled into 100 g tubes supplied by \_\_\_\_\_

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#### **GALDERMA'S OBJECTION TO THE REQUEST TO COMPARE THE DRUG PRODUCT THROUGHOUT THE PROPOSED SHELF-LIFE**

ONDQA is requesting information not prescribed by regulation, guidance or previous discussion with the Applicant. Specifically, there is no mention in stability guidance *Q1A Stability Testing of New Drug Substances and Products* nor SUPAC-SS concerning the application of IVRT as a stability parameter. The guidance also states that "The development and validation of an in vitro release test are not required for approval of an NDA, ANDA, or AADA nor is the in vitro release test required as a routine batch-to-batch quality control test." The request for a commitment to conduct IVRT throughout the product's proposed shelf life is contradictory to this statement.

Galderma therefore requests that this requirement be withdrawn.

#### **GALDERMA'S OBJECTION TO THE REQUEST TO USE IVRT TO COMPARE DIFFERENT PACKAGING SIZES**

SUPAC-SS states that the role of in vitro release testing is to evaluate the release characteristics of the drug product. The drug product is manufactured, stored, and filled in the same manner regardless of package size. The request to manufacture and compare the characteristics of the drug product in different package sizes is not supported by any scientific rationale.

Galderma therefore requests that this requirement be withdrawn.

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**ATTACHMENT 2**

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**From:** CLARK, Paul [mailto:paul.clark@galderma.com]  
**Sent:** Monday, November 20, 2006 2:49 PM  
**To:** Owens, Margo; Athey, Linda  
**Subject:** GALDERMA'S RESPONSE TO FDA'S REQUEST FOR IVRT

Dear Margo, Linda:

Thanks for the teleconference this morning. I've corrected our response to specify that the tubes to be tested will be the same, 100 g, and corrected the names of ONDQA personnel.

Margo, I had already e-mailed our response prior to this teleconference. I attempted to recall the message, but doubt if I was successful. Please disregard the previous e-mail.

I am concerned about this request. During the teleconference, meeting PDUFA goals was mentioned. Is this being considered a fileability issue or a review issue? I really want to have a teleconference with the Branch Chief or even the Division Director, Elaine Morefield, to discuss the need for IVRT on different package sizes and as a stability parameter.

I've sent an e-mail to my colleagues in France requesting confirmation that the batches were all made with the same process. I hope to have this confirmation in the morning.

Let me know if you have any other questions.

Paul

Paul Clark  
Director, Regulatory Affairs  
Galderma Laboratories, L.P.  
817 961 5336 Phone  
817 961 0020 Fax

<b>DEPARTMENT OF HEALTH AND HUMAN SERVICES</b> <b>FOOD AND DRUG ADMINISTRATION</b> <b>APPLICATION TO MARKET A NEW DRUG, BIOLOGIC,</b> <b>OR AN ANTIBIOTIC DRUG FOR HUMAN USE</b> <i>(Title 21, Code of Federal Regulations, Parts 314 &amp; 601)</i>		Form Approved OMB No. 0910-0128 Expiration Date: April 30, 2009 See OMB Statement on page 6.
		FOR FDA USE ONLY
		APPLICATION NUMBER
<b>APPLICANT INFORMATION</b>		
NAME OF APPLICANT Galderma Laboratories, L.P.		DATE OF SUBMISSION 11/28/2006
TELEPHONE NO. (Include Area Code) 917 991 3000		FACSIMILE (FAX) NUMBER (Include Area Code) 917 991 0830
APPLICANT ADDRESS (Number, Street City, State, County, ZIP Code or Mail Code, and U.S. License number if previously issued): 14891 North Fwy Fort Worth, TX 76177		AUTHORIZED U.S. AGENT NAME & ADDRESS (Number, Street City, State, ZIP Code, telephone & FAX number if APPLICABLE)
<b>PRECEDENT DESCRIPTION</b>		
NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGIC LICENSE APPLICATION NUMBER (if previously issued) 22-087		
TRADENAME NAME (e.g., Proprietary name, USFDA name) Calcitol Ointment, 3 microgram/cm <sup>2</sup>		PROPRIETARY NAME (trade name) if any Siba Ointment
CHEMICAL/BIOCHEMICAL/BIOLOGIC PRODUCT NAME (if any)		CODE NAME (if any)
DOSAGE FORM Ointment	STRENGTH 3 microgram/cm <sup>2</sup>	ROUTE OF ADMINISTRATION Topical to the skin
(PREVIOUS) INDICATION(S) FOR USE: For the treatment of plaque-type psoriasis		
<b>APPLICATION INFORMATION</b>		
APPLICATION TYPE (check one) <input checked="" type="checkbox"/> NEW DRUG APPLICATION (NDA, 21 CFR 314.6) <input type="checkbox"/> ABBREVIATED NEW DRUG APPLICATION (ANDA, 21 CFR 314.64) <input type="checkbox"/> BULK/GENERIC LICENSE APPLICATION (BLA, 21 CFR Part 601)		
IF ANDA, IDENTIFY THE APPROPRIATE TYPE <input type="checkbox"/> ANDA (21) <input type="checkbox"/> ANDA (202)		
IF ANDA, OR ANDA, IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION Name of Drug: _____ Holder of Approved Application: _____		
TYPE OF SUBMISSION (check one) <input type="checkbox"/> ORIGINAL APPLICATION <input type="checkbox"/> AMENDMENT TO A PENDING APPLICATION <input type="checkbox"/> REVISION <input type="checkbox"/> PREVIOUSLY APPROVED <input type="checkbox"/> ANNUAL REPORT <input type="checkbox"/> CORRECTION/RECALL SUPPLEMENT <input type="checkbox"/> EFFICACY SUPPLEMENT <input type="checkbox"/> LABELING SUPPLEMENT <input type="checkbox"/> CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT <input type="checkbox"/> OTHER		
IF A SUPPLEMENT OF PARTIAL APPLICATION, PROVIDE LETTER SURVEY OR AGREEMENT TO PARTIAL SUBMISSION: _____		
IF A SUPPLEMENT, IDENTIFY THE APPROPRIATE CATEGORY <input type="checkbox"/> CBE <input type="checkbox"/> CBE-01 <input type="checkbox"/> Pre-Approved (PA)		
REASON FOR SUBMISSION: Response to Agency's request for NME comparison testing		
PREVIOUS MARKETING STATUS (check one) <input checked="" type="checkbox"/> PREVIOUSLY MARKETED (P) <input type="checkbox"/> OVER THE COUNTER PRODUCT (OTC)		
NUMBER OF VOLUMES SUBMITTED: 1 THE APPLICATION IS <input checked="" type="checkbox"/> PAPER <input type="checkbox"/> PAPER AND ELECTRONIC <input type="checkbox"/> ELECTRONIC		
SUPPLEMENTARY INFORMATION (Full establishment information should be provided in the body of the application.) Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (indicate sites that may be used if necessary). Include name, address, contact information, telephone number, registered number (FDA), GMP number, and manufacturing steps and/or type of testing (e.g. Final dosage form, stability testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.		
Cross Reference (list related License Applications, NDAs, ANDAs, FDAs, OTCs, BLAs, ANDAs, ANDAs, and OTCs referenced in the current application)		

This application contains the following items: (Check all that apply)		
<input type="checkbox"/>	1. Index	
<input type="checkbox"/>	2. Labeling (check one) <input type="checkbox"/> Draft Labeling <input type="checkbox"/> Final Printed Labeling	
<input type="checkbox"/>	3. Summary (21 CFR 314.50 (c))	
<input type="checkbox"/>	4. Chemistry section	
	A. Chemistry, manufacturing, and controls information (e.g., 21 CFR 314.50(a)(1); 21 CFR 601.2)	
	B. Samples (21 CFR 314.50 (a)(1); 21 CFR 601.2 (a)) (Submit only upon FDA's request)	
	C. Methods validation package (e.g., 21 CFR 314.50(a)(2); 21 CFR 601.2)	
<input type="checkbox"/>	5. Nonclinical pharmacology and toxicology section (e.g., 21 CFR 314.50(a)(3); 21 CFR 601.2)	
<input type="checkbox"/>	6. Human pharmacokinetics and bioavailability section (e.g., 21 CFR 314.50(a)(4); 21 CFR 601.2)	
<input type="checkbox"/>	7. Clinical Microbiology (e.g., 21 CFR 314.50(a)(5))	
<input type="checkbox"/>	8. Clinical data section (e.g., 21 CFR 314.50(a)(6); 21 CFR 601.2)	
<input type="checkbox"/>	9. Safety update report (e.g., 21 CFR 314.50(a)(7)-(8); 21 CFR 601.2)	
<input type="checkbox"/>	10. Statistical section (e.g., 21 CFR 314.50(a)(9); 21 CFR 601.2)	
<input type="checkbox"/>	11. Case report information (e.g., 21 CFR 314.50(a)(10); 21 CFR 601.2)	
<input type="checkbox"/>	12. Case report forms (e.g., 21 CFR 314.50 (a)(11); 21 CFR 601.2)	
<input type="checkbox"/>	13. Patent information on any patent which claims the drug (21 U.S.C. 355(a) or (c))	
<input type="checkbox"/>	14. A patent certification with respect to any patent which claims the drug (21 U.S.C. 355 (a)(2) or (b)(1)(A))	
<input type="checkbox"/>	15. Establishment description (21 CFR Part 606, if applicable)	
<input type="checkbox"/>	16. Debarment certification (FDCA Act 355 (c)(1))	
<input type="checkbox"/>	17. Field copy certification (21 CFR 314.50 (c)(2))	
<input type="checkbox"/>	18. User Fee Cover Sheet (Form FDA 355f)	
<input type="checkbox"/>	19. Financial information (21 CFR Part 34)	
<input checked="" type="checkbox"/>	20. OTHER (Specify) Correspondence	
<b>CERTIFICATION</b>		
I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including, but not limited to the following:		
<ol style="list-style-type: none"> <li>1. Good manufacturing practice regulations in 21 CFR Parts 210, 211 or applicable regulations, Parts 606, and/or 608.</li> <li>2. Biological establishment standards in 21 CFR Part 608.</li> <li>3. Labeling regulations in 21 CFR Parts 201, 605, 610, 606, and/or 608.</li> <li>4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR Part 302.</li> <li>5. Regulations on making changes in application in FDCA Act section 302A, 21 CFR 314.71, 314.72, 314.97, 314.98, and 601.12.</li> <li>6. Regulations on Reports in 21 CFR 314.50, 314.61, 608.08, and 608.01.</li> <li>7. Local, state and Federal environmental impact laws.</li> </ol>		
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 safety false statement is a criminal offense, U.S. Code, title 18, section 1081.		
SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT 	TYPE NAME AND TITLE Paul Clark, Director	DATE 12/1/06
ADDRESS (Street, City, State, and ZIP Code) 14891 North Freeway, Fort Worth, TX 76177	Telephone Number/ 817 561 8336	
Public reporting burden for this collection of information is estimated to average 26 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:		
Department of Health and Human Services Food and Drug Administration Center for Drug Evaluation and Research (CDER-145) Center for Biologics Evaluation and Research 2091-G Annapolis Road Bethesda, MD 20892-1458	Department of Health and Human Services Food and Drug Administration Center for Drug Evaluation and Research (CDER-08) 1400 Rockville Pike Rockville, MD 20850-1408	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.



November 20, 2006

Margo Owens
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Dermatological and Dental Drug Products
Central Document Room
5901-B Amundale Road
Beltsville MD 20705-1266

RE: NDA 22-087
Calcitriol Ointment 3 mcg/g
Applicant's Response to Agency's Request for IVRT Testing

Dear Ms. Owens:

A teleconference was held on November 14, 2006 between representatives of ONDQA, DDDP, and Galderma regarding the availability of comparative IVRT data for the clinical batches and batches manufactured at the proposed commercial manufacturing site.

SUMMARY OF TELECONFERENCE OF NOVEMBER 14, 2006

During the teleconference Dr. Ding, Pharmaceutical Assessment Lead, ONDQA, inquired if Galderma had performed IVRT on products manufactured at the two locations. Galderma stated that this type of comparison had not been done. Dr. Jane Chang, Ph.D., Chemistry Reviewer, ONDQA, then inquired if there were samples of product of similar age available for IVRT. Galderma replied that it was uncertain about the availability of lots of comparable age.

Dr. Chang proposed that if no lots of comparable age were available, one batch of the drug product be made at each location, filled and tested according to the table below.

Table with 2 columns: Industrial Development, Alby sur Cheran, France; Galderma Production, Canada Inc. Rows include Bulk Product (A), 100 g tube (C), Bulk Product (B), 100g tub (D), (E), and 5g (F).

b(4)

Page 2  
 NDA 22-087  
 Galderma Laboratories, L.P.  
 Silkis (calcitriol) Ointment, 3 mcg/g

#### IVRT studies

Study 1	Compare A to B
Study 2	Compare C to D
Study 3	Compare D to E
Study 4	Compare D to F

Dr. Cheng requested that these lots be placed on long term stability according to the protocol described in table 3.2.P.3.3 and that IVRT testing be done at T0, T18 and end of shelf-life with the T0 IVRT data submitted to FDA on or before April 30, 2007.

#### GALDERMA'S AGREEMENT

Galderma agrees to provide IVRT information comparing one lot manufactured at each site filled into 100g tubes according the following proposal on or before April 30, 2007. We have some concerns regarding the technical aspects of the test due to the low concentration of active ingredient, 3 mcg/g, and the composition of the vehicle. \_\_\_\_\_ if we encounter difficulties in performing the test, we will consult the Division immediately.

b(4)

#### GALDERMA'S PROPOSAL

##### EVALUATION OF EXISTING BATCHES

A review of the batches manufactured at the two sites identified two batches that were manufactured 5 months apart; batch 056\*03 filled into 100g tubes manufactured in November 2003 at Industrial Development in France and batch 036835 ID 102519 filled into 100g tubes manufactured in May 2004 at GFCL. Batch 056\*03 was used in a nonclinical study RDS.03.SRE.12394, a 9-month Dermal Toxicity Study in Minipigs (Report may be found in 4.2.3.2.11); 036835 was used a primary stability batch (the executed MBR may be found at 3.2.R.1.P.1.03, EMBR lot 036835 ID 102519).

Galderma proposes that the physical and chemical characteristics of these two lots be evaluated. The evaluation would include full testing and rheology studies. If these two lots have similar characteristics, the IVRT would be done using these two lots.

If the lots do not have similar characteristics, new lots will be manufactured and filled into 100 g tubes supplied by: \_\_\_\_\_

Page 3  
NDA 22-087  
Galderma Laboratories, L.P.  
Silkis (calcitriol) Ointment, 3 mcg/g

**GALDERMA'S OBJECTION TO THE REQUEST TO COMPARE THE DRUG PRODUCT THROUGHOUT THE PROPOSED SHELF-LIFE**

ONDQA is requesting information not prescribed by regulation, guidance or previous discussion with the Applicant. Specifically, there is no mention in stability guidance *Q1A Stability Testing of New Drug Substances and Products* nor SUPAC-SS concerning the application of IVRT as a stability parameter. The guidance also states that "The development and validation of an in vitro release test are not required for approval of an NDA, ANDA, or AADA nor is the in vitro release test required as a routine batch-to-batch quality control test." The request for a commitment to conduct IVRT throughout the product's proposed shelf life is contradictory to this statement.

Galderma therefore requests that this requirement be withdrawn.

**GALDERMA'S OBJECTION TO THE REQUEST TO USE IVRT TO COMPARE DIFFERENT PACKAGING SIZES**

SUPAC-SS states that the role of in vitro release testing is to evaluate the release characteristics of the drug product. The drug product is manufactured, stored, and filled in the same manner regardless of package size. The request to manufacture and compare the characteristics of the drug product in different package sizes is not supported by any scientific rationale.

Galderma therefore requests that this requirement be withdrawn.

If I can be of assistance with any questions or concerns, please contact me.

Sincere regards,



Paul M. Clark  
Director, Regulatory Affairs  
Telephone: 817-961-5336  
Fax: 817-961-0020

c: Archive  
CMC  
Desk Copy - M. Owens

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/s/

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Linda D Mullins-Athey  
12/1/2006 02:35:55 PM

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## MEMORANDUM OF TELECON

DATE: 11/14/06, 9:40 A.M.

APPLICATION NUMBER: NDA 22-087

DRUG PRODUCT: Silkis (calcitriol) Ointment, 3mcg/g

**BETWEEN:**

**Name:** Jean-Pierre Etchegaray, Manager, Pharmaceutical Development,  
Galderma R&D Sophia Antipolis, France  
Isabelle Preuilh, Project Team Representative, Galderma R&D  
Sophia Antipolis, France  
Catherine Franc, Scientific Writer, Galderma R&D  
Sophia Antipolis, France  
Michael Graeber, Head, US Clinical Development, Galderma R&D,  
Cranbury, New Jersey  
Paul Clark, Director Regulatory Affairs, Galderma Laboratories, Fort  
Worth, Texas

**Phone:** (866) 377-3416

**Representing:** Galderma Laboratories, L.P.

**AND**

**Name:** Division of Dermatologic and Dental Products  
Shulin Ding, Ph.D., Pharmaceutical Assessment Lead, ONDQA  
Jane Chang, Ph.D., CMC Reviewer, ONDQA  
Jill Lindstrom, M.D., Clinical Team Leader  
Abimbola Adebawale, Ph.D., Clinical Pharmacology/Biopharmaceutics  
Reviewer, DBEIII  
Margo Owens, Regulatory Project Manager

**SUBJECT:** NDA 22-087 CMC Issues

The teleconference was requested by FDA to discuss CMC and quality issues concerning the submitted NDA for Silkis (calcitriol) ointment, 3mcg/g.

The following concerns were conveyed to the applicant:

**1. In-vitro Release Testing (IVRT)**

The phase 3 pivotal clinical batches were prepared at Galderma Industrial Development France. Drug product produced at the proposed commercial site, Galderma Production Canada Inc., has never been used for clinical studies. The site change is a Level 3 change per "SUPAC-SS:

Nonsterile Semisolid Dosage Forms; Scale-Up and Post-Approval Changes: Chemistry, Manufacturing and Controls; In Vitro Release Testing and In Vivo Bioequivalence Documentation". In-vitro release testing to establish "sameness" for the drug products manufactured at both sites is required per this guidance.

The Agency asked whether the applicant has drug product batches of comparable age prepared from these two sites. The applicant stated "no". The clinical batches are from 2001 and the validation batches are from 2003. The applicant further stated that they have not generated any in vitro release data.

FDA recommended the following:

- 1) Prepare drug product batches from both the French and Canadian sites:
  - a. 100 g tubes by Galderma Industrial Development France using the pilot-scale process in Figure 1 in Section 3.2.P.2.3. Use \_\_\_\_\_ container closure system.
  - b. 5 g \_\_\_\_\_ and 100 g tubes by Galderma Production Canada Inc. using the process described in Figure 4 in Section 3.2.P.2.3. Use \_\_\_\_\_ container closure system for the 100 g tubes. Use \_\_\_\_\_ container closure system for at least one of the 5 g \_\_\_\_\_ tubes if you are seeking approval of the container closure systems from both suppliers. b(4)
  - c. The two batches should be prepared in a reasonable time frame such that they are comparable in age.
  
- 2) Perform in-vitro release testing to establish "sameness" for the drug product manufactured at both sites by comparing:
  - a. the bulk drug products produced at the two sites
  - b. the 100 g tubes produced at the two sites
  - c. the 100 g \_\_\_\_\_ tubes produced at Galderma Production Canada Inc. b(4)
  - d. the 100 g and 5 g tubes produced at Galderma Production Canada Inc.
  
- 3) Perform stability study for the four batches of drug product from Item 1. In addition to the stability testing described in Table 8 of Section 3.2.P.8.3 (specified microorganisms, i.e. \_\_\_\_\_ should also be tested), in-vitro release testing described in Item 2 should be performed at 18 months and 36 months (or the proposed expiry date). b(4)

The Agency proposed a submission date for information and data in response to Items 1 and 2 of no later than April 30, 2007. The stability data in Item 3 can be submitted when the data becomes available.

The applicant stated that they cannot make a commitment to submit the information and data by April 30, 2007 on this teleconference as all decision makers were not in attendance. The applicant agreed to do their best to provide their commitment no later than November 20, 2006.

2. \_\_\_\_\_ Aspect of the Drug Product  
Please clarify the \_\_\_\_\_ aspect of the drug product (Section 3.2.P.2.2, pages 7-9): b(4)

- What is the crystalline material?
- Does the drug substance, calcitriol, remain in the liquid phase or the crystalline phase?
- When do the crystals form during the manufacture?

3. Container/Closure System for Drug Product

The qualification information for the container/closure system of the proposed drug product can not be found in the NDA. Please provide the information or indicate where it is located.

The applicant stated they would provide a response next week.

The conversation ended amicably.

**ADDENDUM:** An email (see attachment) was sent to the Project Manager containing Galderma's response and requests for clarification to our Nov. 14, 2006 teleconference.

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**ATTACHMENT**

**From:** CLARK, Paul [mailto:paul.clark@galderma.com]  
**Sent:** Monday, November 20, 2006 10:05 AM  
**To:** Owens, Margo  
**Subject:** NDA 22-087 CALCITRIOL OINTMENT - GALDERMA'S RESPONSE TO REQUEST FOR IVRT DATA

Dear Margo:

This is Galderma's response to the Division's request to provide IVRT data. I will only be in the office during the morning. If you need to reach me after that, please call my cell at \_\_\_\_\_

b(6)

Paul

Paul Clark  
Director, Regulatory Affairs  
Galderma Laboratories, L.P.  
817 961 5336 Phone  
817 961 0020 Fax

**SUMMARY OF TELECONFERENCE OF NOVEMBER 14, 2006**

During the teleconference Dr. Ding inquired if Galderma had performed IVRT on products manufactured at the two locations. Galderma stated that this type of comparison had not been done. Dr. Ding then inquired if there were samples of product of similar age available for IVRT. Galderma replied that it was uncertain about the availability of lots of comparable age.

Dr. Ding proposed that if no lots of comparable age were available, one batch of the drug product be made at each location, filled and tested according to the table below.

Industrial Development, Alby sur Cheran, France	Galderma Production, Canada Inc.
Bulk Product (A)	Bulk Product (B)
100 g tub (C)	100g tub (D)
	(E)
	5g (F)

b(4)

**IVRT studies**

Study 1	Compare A to B
Study 2	Compare C to D
Study 3	Compare C to E
Study 4	Compare C to F

Dr. Ding requested that these lots be placed on long term stability according to the protocol described in table 3.2.P.8.3 and that IVRT testing be done at T0, T18 and end of shelf-life with the T0 IVRT data submitted to FDA on or before April 30, 2007.

**GALDERMA'S AGREEMENT**

Galderma agrees to provide IVRT information comparing one lot manufactured at each site filled into 100 g tubes according the following proposal on or before April 30, 2007. We have some concerns regarding the technical aspects of the test due to the low concentration of active ingredient, 3 mcg/g, and the composition of the vehicle, \_\_\_\_\_

\_\_\_\_\_ If we encounter difficulties in performing the test, we will contact the Division immediately.

b(4)

**GALDERMA'S PROPOSAL**

**EVALUATION OF EXISTING BATCHES**

A review of the batches manufactured at the two sites identified two batches that were manufactured 5 months apart; batch 056\*03 manufactured in November 2003 at Industrial Development in France and batch 036835 ID 102518 manufactured in May 2004 at GPCI. Batch 056\*03 was used in a nonclinical study RDS.03.SRE.12394, a 9-month Dermal Toxicity Study in Minipigs (Report may be found in 4.2.3.2.11); 0368365 was used a primary stability batch (the executed MBR may be found at 3.2.R.1.P.1.03, EMBR lot 036835 ID 102518).

Galderma proposes that the physical and chemical characteristics of these two lots be evaluated. The evaluation would include full testing and rheology studies. If these two lots have similar characteristics, the IVRT would be done using these two lots.

If the lots do not have similar characteristics, new lots will be manufactured and filled into 100 g tubes supplied by \_\_\_\_\_

**GALDERMA'S OBJECTION TO THE REQUEST TO COMPARE THE DRUG PRODUCT THROUGHOUT THE PROPOSED SHELF-LIFE**

ONDQA is requesting information not prescribed by regulation, guidance or previous discussion with the Applicant. Specifically, there is no mention in stability guidance *Q1A Stability Testing of New Drug Substances and Products* nor SUPAC-SS concerning the application of IVRT as a stability parameter. The guidance also states that "The development and validation of an in vitro release test are not required for approval of an NDA, ANDA, or AADA nor is the in vitro release test required as a routine batch-to-batch quality control test." The request for a commitment to conduct IVRT throughout the product's proposed shelf life is contradictory to this statement.

Galderma therefore requests that this requirement be withdrawn.

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**SUPAC-SS states that the role of in vitro release testing is to evaluate the release characteristics of the drug product. The drug product is manufactured, stored, and filled in the same manner regardless of package size. The request to manufacture and compare the characteristics of the drug product in different package sizes is not supported by any scientific rationale.**

**Galderma therefore requests that this requirement be withdrawn.**

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/s/

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Margo Owens  
11/29/2006 09:48:33 AM  
CSO

Shulin Ding  
11/29/2006 02:32:45 PM  
CHEMIST

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**DEPARTMENT OF HEALTH & HUMAN SERVICES**

Public Health Service

Food and Drug Administration  
Rockville, MD 20857

NDA 22-087

Galderma Laboratories, L.P.  
Attention: Paul Clark  
Director, Regulatory Affairs  
14501 N. Freeway  
Fort Worth, TX 76177

Dear Mr. Clark:

Please refer to your September 25, 2006 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Silkis (calcitriol) Ointment, 3 mcg/g.

After a preliminary review, we find your application is not sufficiently complete to permit a substantive review. Therefore, we are refusing to file this application under 21 CFR 314.101(d) for the following reasons:

The application is incomplete because it does not contain CMC data supporting the manufacturing process at the designated commercial manufacturing site which is a filing requirement (21CFR 314.101 (d)(3)).

The designated commercial manufacturing site and process are different from those of Phase 3 clinical supplies. Bridging data to support these changes are missing. 21CFR 314.50 (d)(1) (ii)(a) requires dissolution data to ensure quality and bioavailability of the product.

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 Margo Owens, Regulatory Health Project Manager, at 301-796-2110.

Sincerely,

*{See appended electronic signature page}*

Susan Walker, M.D.  
Director  
Division of Dermatology and Dental Products  
Office of Drug Evaluation III  
Center for Drug Evaluation and Research

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/s/

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Susan Walker

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**MEMORANDUM**

DEPARTMENT OF HEALTH AND HUMAN SERVICES  
PUBLIC HEALTH SERVICE  
FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH

**DATE:** November 21, 2006

**TO:** Jill Lindstrom, Clinical Team Leader (HFD-540)

**CC:** J. Beitz, S. Walker, M. Nasr, M. Rhee, M. Owens

**FROM:** Shulin Ding, Pharmaceutical Assessment Lead (ONDQA)

**CONCURRENCE:** Elaine Morefield, Division II Director (ONDQA)

**SUBJECT:** **ONDQA Refusal-to-File Recommendation for NDA 22-087**

The application is not fileable from the CMC and quality perspective. The submission of data supporting the manufacturing process at the designated commercial manufacturing site is a filing requirement (21CFR 314.101 (d)(3)).

The designated commercial manufacturing site and process are different from those of Phase 3 clinical supplies. Bridging data to support these changes are missing. Specifically, there are no in-vitro drug release results in the NDA. 21CFR 314.50 (d)(1) (ii)(a) requires dissolution data to ensure quality and bioavailability of the product.

This issue has been discussed in teleconferences with the NDA applicant. It is apparent that they do not have this piece of data available, and the in vitro drug release method has not been developed. In addition, it is unclear whether suitable batches exist for use in this testing or new batches will need to be made. The drug, calcitriol, is known to be light sensitive and easily oxidizable by air. This will complicate their attempt to develop a method for the in vitro drug release study. There are significant technical hurdles in generating this type of data for this drug in this dosage form. Their ability to generate the required data within an adequate time frame to allow timely review in the review cycle is in doubt.

Therefore, ONDQA recommends a refusal to file.

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Shulin Ding  
11/21/2006 05:15:49 PM  
CHEMIST

Elaine Morefield  
11/21/2006 05:41:58 PM  
CHEMIST

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Susan Walker

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

## **FACSIMILE TRANSMITTAL SHEET**

**Date:** October 24, 2006

**To:** Paul Clark  
Director, Regulatory Affairs  
Galderma Laboratories, L.P.  
Phone: (817) 961-5336  
Fax: (817) 961-0020

**From:** Margo Owens, Project Manager  
Phone: (301) 796-2110  
Fax: (301) 796-9894 or 9895

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---

## FDA Facsimile Memorandum

**Date:** October 24, 2006  
**To:** Paul Clark  
Director, Regulatory Affairs  
**From:** Margo Owens, Project Manager  
**Subject:** NDA 22-087/ Silkis (calcitriol) Ointment, 3mcg/g

Mr. Clark,

The CMC reviewer has the following information request regarding your NDA 22-087 Silkis (calcitriol) Ointment, 3 mcg/g.

**Pharmacology/Toxicology Information Request:**

The establishment information submitted in the continuation sheet of Form 356h is not complete. Please provide the CF number, address, contact person, and phone number of all sites performing:

- manufacturing, release testing, and stability testing of the drug substance
- manufacturing, release testing, stability testing, packaging, and sample storage (if different from the testing site) of the drug product

Additionally, a statement regarding the readiness of the facilities for a GMP inspection is necessary.

Please call if you have questions.

Margo Owens  
Project Manager

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/s/

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Margo Owens

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

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Director, Regulatory Affairs  
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- manufacturing, release testing, stability testing, packaging, and sample storage (if different from the testing site) of the drug product

Additionally, a statement regarding the readiness of the facilities for a GMP inspection is necessary.

Please call if you have questions.

Margo Owens  
Project Manager

## **Office of Biostatistics Information Sheet for Submission of Data and for Methods of Data Analysis of Carcinogenicity Studies**

**(The electronic data format is for two-year studies as well as transgenic mouse studies using all except the TgAC mouse models)**

The statistical reviewer responsible for this carcinogenicity-study review requests that the sponsor recreate the tumor data in conformance to the electronic format specified in the Agency's guidance document of January 1999.

To streamline the reviewing process and improve the review quality, the Agency published *Guidance for Industry, Providing Regulatory Submissions in Electronic Format-NDAs* in January 1999. In Appendix 1 of this document the Agency details the data-format specifications for the pharmacology and toxicology datasets. The sponsor needs to familiarize itself with the data-format requirements in detail. We are only requesting the tumor dataset at this time (see page 61 of the guidance).

The above guidance document can be found at <http://www.fda.gov/cder/guidance/2353fnl.pdf> (or, one can go to the Guidances index page (<http://www.fda.gov/cder/guidance/index.htm>) then find the Electronic Submissions section, then access Regulatory Submissions in Electronic Format: New Drug Application (Issued 1/1999, Posted 1/27/1999). To assist the sponsor to correctly construct the tumor data, the Agency provides a downloadable example. Please visit Example of an Electronic New Drug Application Submission (posted 2/17/1999) at [http://www.fda.gov/cder/guidance/NDA\\_Example.htm](http://www.fda.gov/cder/guidance/NDA_Example.htm). The data for submission should have exactly the same format as the data in the example (named tumor.xpt), including designated variable names.

Please contact the Agency to provide a time line regarding providing the tumor data. The sponsor needs to carefully meet the data-format specifications in order to comply with the above guidance. Any data without 100% conformity will have to be returned for resubmission.

Full cooperation in providing data sets in the required format will facilitate a prompt review of the submission. In addition to a copy for the statistical reviewer, NDA submissions require an archival copy of all data sets for the Electronic Document Room - see Guidance for Industry: Providing Regulatory Submission in Electronic Format - General Considerations at <http://www.fda.gov/cder/guidance/2867fnl.pdf> for instructions.

Note that the current draft guidance for the statistical analysis of chronic rodent carcinogenicity studies is available on the FDA web site at <http://www.fda.gov/cder/guidance/815dft.pdf>. Sponsors are urged to use the statistical methods recommended in the guidance to analyze the carcinogenicity study data in their IND or NDA submissions. The cover page of the document is attached to the end of this information sheet.

NDA 22-087

For questions related to the data format and the methods of statistical analysis, please contact Karl K. Lin, Ph.D., Room 5238, Building 22, Office of Biostatistics, Center for Drug Evaluation and Research, U.S. Food and Drug Administration, 10903 New Hampshire Avenue, Silver Spring, MD 20993-0002, 301-796-0943, [karl.lin@fda.hhs.gov](mailto:karl.lin@fda.hhs.gov).

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**Office of Biostatistics Information Sheet for Submission of Data and for  
Methods of Data Analysis of Carcinogenicity Studies Using Tg.AC  
Transgenic Mice**

The statistical reviewer responsible for this carcinogenicity-study review requests that the sponsor recreate the weekly count data of skin papillomas of individual animals as a SAS dataset in the format presented in Table 1. Numbers of skin papillomas developed on the site of application (SOA) and other sites of the body (Non-sites of application, NSOA) should be listed separately. Examples of non-sites of applications used in some previous studies are given in the table. A period (.) should be used for count of each of the weeks after death if an animal died before the end of the study.

The agency recommends that the sponsor conduct a statistical analysis of the skin papillomas weekly count data using the method proposed by Dunson et al. (2000). The paper is available on website

<http://toxsci.oxfordjournals.org/cgi/content/full/55/2/293>.

For questions related to the data format and the methods of statistical analysis, please contact Karl K. Lin, Ph.D., Room 5238, Building 22, Office of Biostatistics, Center for Drug Evaluation and Research, U.S. Food and Drug Administration, 10903 New Hampshire Avenue, Silver Spring, MD 20993-0002, 301-796-0943, [karl.lin@fda.hhs.gov](mailto:karl.lin@fda.hhs.gov) or [link@cdcr.fda.gov](mailto:link@cdcr.fda.gov).



(Courtesy of Dr. David Jacobson-Kram)

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**Table 1**

**Sample Tg.AC Mouse Bioassay Data  
Number of Papillomas, by Study Weeks**

Group	Gender	Animal No.	Tumor Site	1	2	3	...	26	27
			NSOA	0	0	0	...	0	0
			a	0	0	0	...	0	0
			b	0	0	0	...	0	0
			c	0	0	0	...	0	0
			d	0	0	0	...	0	0
			e	0	0	0	...	0	0
			f	0	0	0	...	0	0
			NSOA	0	0	0	...	0	0
			a	0	0	0	...	0	0
			b	0	0	0	...	0	0
			c	0	0	0	...	0	0
			d	0	0	0	...	0	0
			e	0	0	0	...	0	0
			f	0	0	0	...	0	0
			NSOA	0	0	0	...	0	0
			a	0	0	0	...	0	0
			b	0	0	0	...	0	0
			c	0	0	0	...	0	0
			d	0	0	0	...	0	0
			e	0	0	0	...	0	0
			f	0	0	0	...	0	0

Note: SOA=Site of application, NSOA=Non-site of application  
a=mouth, b=genital area, c=scrotal, d=vaginal, e=anal, f=abdominal

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

## **FACSIMILE TRANSMITTAL SHEET**

**Date:** October 23, 2006

**To:** Paul Clark  
Director, Regulatory Affairs  
Galderma Laboratories, L.P.  
Phone: (817) 961-5336  
Fax: (817) 961-0020

**From:** Margo Owens, Project Manager  
Phone: (301) 796-2110  
Fax: (301) 796-9894 or 9895

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## FDA Facsimile Memorandum

**Date:** October 23, 2006  
**To:** Paul Clark  
Director, Regulatory Affairs  
School of Medicine, Dermatology  
**From:** Margo Owens, Project Manager  
**Subject:** NDA 22-087/ Silkis (calcitriol) Ointment, 3mcg/g

Mr. Clark,  
The Pharmacology/Toxicology reviewer has the following information request regarding your NDA 22-087 Silkis (calcitriol) Ointment, 3 mcg/g.

**Pharmacology/Toxicology Information Request:**

Please submit electronic sets of the tumor incidence data from the two carcinogenicity studies:

1. Calcitriol ointment - 104 week dermal carcinogenicity study in the mouse, study No. 913/118 (alternative study No. RDS.03.SRE.12299), submitted in SN 000 to NDA 22-087, letter date 25-SEP-2006.
2. Calcitriol - 104 week oral (gavage) carcinogenicity study in the rat, study No. 913/119 (alternative study No. RDS.03.SRE.12318), submitted in SN 000 to NDA 22-087, letter date 25-SEP-2006.

Also, please submit .pdf files of the reports of the two 104-week carcinogenicity studies that are listed above.

You are directed to submit tumor datasets following the recommended formats in the attached information sheets and the Guidance documents referenced below:

FDA, Center for Drug Evaluation and Research, *Providing Regulatory Submissions in Electronic Format – General Considerations* (Revision 1), guidance for Industry, available on the Internet at <http://www.fda.gov/cder/guidance>.

• FDA, Center for Drug Evaluation and Research, *Regulatory Submissions in Electronic Format – NDAs*, guidance for industry, available on the Internet at <http://www.fda.gov/cder/guidance>.

• FDA, Center for Drug Evaluation and Research, *Statistical Aspects of Design, Analysis, and Interpretation of Chronic Rodent Carcinogenicity Studies of Pharmaceuticals*, guidance for industry, available on the Internet at <http://www.fda.gov/cder/guidance>

Please call if you have questions.

Margo Owens, Project Manager

## **Office of Biostatistics Information Sheet for Submission of Data and for Methods of Data Analysis of Carcinogenicity Studies**

**(The electronic data format is for two-year studies as well as transgenic mouse studies using all except the TgAC mouse models)**

The statistical reviewer responsible for this carcinogenicity-study review requests that the sponsor recreate the tumor data in conformance to the electronic format specified in the Agency's guidance document of January 1999.

To streamline the reviewing process and improve the review quality, the Agency published *Guidance for Industry, Providing Regulatory Submissions in Electronic Format-NDA's* in January 1999. In Appendix 1 of this document the Agency details the data-format specifications for the pharmacology and toxicology datasets. The sponsor needs to familiarize itself with the data-format requirements in detail. We are only requesting the tumor dataset at this time (see page 61 of the guidance).

The above guidance document can be found at <http://www.fda.gov/cder/guidance/2353fml.pdf> (or, one can go to the Guidances index page (<http://www.fda.gov/cder/guidance/index.htm>) then find the Electronic Submissions section, then access Regulatory Submissions in Electronic Format: New Drug Application (Issued 1/1999, Posted 1/27/1999). To assist the sponsor to correctly construct the tumor data, the Agency provides a downloadable example. Please visit Example of an Electronic New Drug Application Submission (posted 2/17/1999) at [http://www.fda.gov/cder/guidance/NDA\\_Example.htm](http://www.fda.gov/cder/guidance/NDA_Example.htm). The data for submission should have exactly the same format as the data in the example (named tumor.xpt), including designated variable names.

Please contact the Agency to provide a time line regarding providing the tumor data. The sponsor needs to carefully meet the data-format specifications in order to comply with the above guidance. Any data without 100% conformity will have to be returned for resubmission.

Full cooperation in providing data sets in the required format will facilitate a prompt review of the submission. In addition to a copy for the statistical reviewer, NDA submissions require an archival copy of all data sets for the Electronic Document Room - see Guidance for Industry: Providing Regulatory Submission in Electronic Format - General Considerations at <http://www.fda.gov/cder/guidance/2867fml.pdf> for instructions.

Note that the current draft guidance for the statistical analysis of chronic rodent carcinogenicity studies is available on the FDA web site at <http://www.fda.gov/cder/guidance/815dft.pdf>. Sponsors are urged to use the statistical methods recommended in the guidance to analyze the carcinogenicity study data in their IND or NDA submissions. The cover page of the document is attached to the end of this information sheet.

NDA 22-087

**For questions related to the data format and the methods of statistical analysis, please contact Karl K. Lin, Ph.D., Room 5238, Building 22, Office of Biostatistics, Center for Drug Evaluation and Research, U.S. Food and Drug Administration, 10903 New Hampshire Avenue, Silver Spring, MD 20993-0002, 301-796-0943, [karl.lin@fda.hhs.gov](mailto:karl.lin@fda.hhs.gov).**

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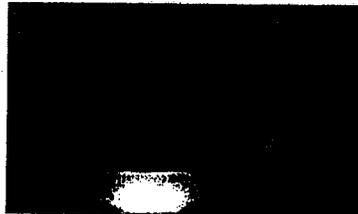
**Office of Biostatistics Information Sheet for Submission of Data and for  
Methods of Data Analysis of Carcinogenicity Studies Using Tg.AC  
Transgenic Mice**

The statistical reviewer responsible for this carcinogenicity-study review requests that the sponsor recreate the weekly count data of skin papillomas of individual animals as a SAS dataset in the format presented in Table 1. Numbers of skin papillomas developed on the site of application (SOA) and other sites of the body (Non-sites of application, NSOA) should be listed separately. Examples of non-sites of applications used in some previous studies are given in the table. A period (.) should be used for count of each of the weeks after death if an animal died before the end of the study.

The agency recommends that the sponsor conduct a statistical analysis of the skin papillomas weekly count data using the method proposed by Dunson et al. (2000). The paper is available on website

<http://toxsci.oxfordjournals.org/cgi/content/full/55/2/293>.

For questions related to the data format and the methods of statistical analysis, please contact Karl K. Lin, Ph.D., Room 5238, Building 22, Office of Biostatistics, Center for Drug Evaluation and Research, U.S. Food and Drug Administration, 10903 New Hampshire Avenue, Silver Spring, MD 20993-0002, 301-796-0943, [karl.lin@fda.hhs.gov](mailto:karl.lin@fda.hhs.gov) or [link@cder.fda.gov](mailto:link@cder.fda.gov).



(Courtesy of Dr. David Jacobson-Kram)

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Table 1

Sample Tg.AC Mouse Bioassay Data  
 Number of Papillomas, by Study Weeks

Group	Gender	Animal No.	Tumor Site	1	2	3	...	26	27
2	M	16	SOA	0	0	1	...	19	19
			NSOA	0	0	0	...	0	0
			a	0	0	0	...	0	0
			b	0	0	0	...	0	0
			c	0	0	0	...	0	0
			d	0	0	0	...	0	0
			e	0	0	0	...	0	0
			f	0	0	0	...	0	0
17			SOA	0	0	0	...	0	0
			NSOA	0	0	0	...	0	0
			a	0	0	0	...	0	0
			b	0	0	0	...	0	0
			c	0	0	0	...	0	0
			d	0	0	0	...	0	0
			e	0	0	0	...	0	0
			f	0	0	0	...	0	0
18			SOA	0	0	1	...	4	5
			NSOA	0	0	0	...	0	0
			a	0	0	0	...	0	0
			b	0	0	0	...	0	0
			c	0	0	0	...	0	0
			d	0	0	0	...	0	0
			e	0	0	0	...	0	0
			f	0	0	0	...	0	0

Note: SOA=Site of application, NSOA=Non-site of application  
 a=mouth, b=genital area, c=scrotal, d=vaginal, e=anal, f=abdominal

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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration  
Rockville, MD 20857

NDA 22-087

Galderma Laboratories, LP  
Attention: Paul Clark  
Director, Regulatory Affairs  
14501 North Freeway  
Forth Worth, TX 76177

Dear Mr. Clark:

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:           Silkis (calcitriol) Ointment, 3mcg/g

Review Priority Classification: S

Date of Application:             September 25, 2006

Date of Receipt:                 September 27, 2006

Our Reference Number:         NDA 22-087

The application will be filed on November 26, 2006, in accordance with 21 CFR 314.101(a).  
The user fee goal date will be July 27, 2007.

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

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:

NDA 22-087

Page 2

**Center for Drug Evaluation and Research  
Division of Dermatology & Dental Products  
Central Document Room  
5901-B Ammendale Road  
Beltsville, MD 20705-1266**

**If you have any questions, call Margo Owens, Regulatory Project Manager, at (301) 796-2110.**

**Sincerely,**

*{See appended electronic signature page}*

**Mary Jean Kozma-Fomaro  
Supervisor, Project Management  
Division of Dermatology & Dental Products  
Office of Drug Evaluation III  
Center for Drug Evaluation and Research**

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Signed for Mary Jan Kozam-Fornaro

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**DEPARTMENT OF HEALTH & HUMAN SERVICES**

Public Health Service

Food and Drug Administration  
Rockville, MD 20857

IND 62,151

Galderma Laboratories, L.P.  
Attention: Paul M. Clark  
Director, Regulatory Affairs  
14501 N. Freeway  
Tort Worth, TX 76177

Dear Dr. Clark:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Silkis (calcitriol) Ointment, 3 $\mu$ g/g.

We also refer to the meeting between representatives of your firm and the FDA on May 17, 2006. The purpose of the meeting was to obtain the Agency's concurrence that the quality, nonclinical, and clinical development of Silkis (calcitriol) Ointment, 3 $\mu$ g/g to date are adequate to support the filing of a New Drug Application.

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, call Margo Owens, Regulatory Project Manager, at (301) 796-2110.

Sincerely,

*{See appended electronic signature page}*

Jill Lindstrom, M.D.  
Lead Medical Officer  
Division of Dermatologic and Dental  
Products  
Office of Drug Evaluation III  
Center for Drug Evaluation and Research

Enclosure

**MEMORANDUM OF MEETING MINUTES**



**Meeting Date:** May 17, 2006      **Time:** 9:00 A.M.  
**Location:** WO 1311      **Meeting ID:** 18645  
**Topic:** IND 62,151 Silkis (calcitriol) Ointment, 3µg/g  
for the treatment of plaque type psoriasis  
**Subject:** Pre-NDA Meeting  
**Sponsor:** Galderma Laboratories, L.P.  
**Meeting Chair:** Jill Lindstrom, M.D./Deputy Division Director (acting), DDDP  
**Meeting Recorder:** Margo Owens/Regulatory Project Manager, DDDP

**FDA Attendees:**

Stanka Kukich, M.D./Division Director (acting), DDDP  
Jill Lindstrom, M.D./Deputy Division Director (acting), DDDP, HFD-540  
Shulin Ding, Ph.D./Pharmaceutical Assessment Lead, ONDQA  
Maria Ysern, Ph.D./Chemistry Reviewer, ONDQA  
Paul Brown, Ph.D./Supervisor, Pharmacology, DDDP, HFD-540  
Norman See, Ph.D./Pharmacology Reviewer, DDDP, HFD-540  
John Hunt, Pharm.D./Acting Director, Pharmacokinetics, DPEIII, HFD-880  
Brenda Carr, M.D./Clinical Reviewer, DDDP, HFD-540  
David Kettl, M.D./Clinical Reviewer, DDDP, HFD-540  
Kenneth Katz, M.D./Clinical Reviewer, DDDP, HFD-540  
Mohamed Al-Osh, Ph.D./Team Leader, Biostatistics, DBIII, HFD-725  
Kathleen Fritsch, Ph.D./Biostatistician, DBIII, HFD-725  
Margo Owens/Regulatory Project Manager, DDDDP, HFD-540

**Sponsor Attendees:**

**Galderma Laboratories, L.P.**

Michael Graeber, M.D./U.S., Clinical  
Zana Leitz, M.D./CPM  
Yin Liu, Ph.D./Biostatistics  
Phillippe Briantais, BSc/Biostatistics  
Isabelle Preuith, PharmD/Pharmaceutics  
Guy Bouvier, Ph.D./Nonclinical  
Phillippe Andres, M.D./Project Leader  
Phillippe Bouissou, Ph.D./ Research and Development  
Oliver Watts, Ph.D./Research and Development  
Paul Clark, BSc/Regulatory Affairs

**Purpose:**

The pre-meeting briefing document (April 13, 2006) provides background and questions (pgs. 6-10) for discussion. The sponsor requests concurrence from the Agency that the quality, nonclinical, and clinical development of Silkis (calcitriol) Ointment, 3µg/g to date are adequate to support the filing of a New Drug Application.

**Chemistry, Manufacturing and Controls:**

**Sponsor's Question:**

Concurrence is sought that stability data from Galderma Industrial Development and Galderma Production Canada Inc. is adequate to support the submission of a 505(b) (1) application.

**Agency's Comment:**

Stability data is available on three clinical batches (36 months data at 25°C/60% RH and 9 month data at 40°C/75%RH) and on three validation batches (12 month data at 25°C/60% RH and 6 month data at 40°C/75%RH). The validation batches are identical to the to-be-marketed formulation.

The sponsor indicates that at the time of submission there will be 18 months at 25°C/60% RH for the first two validation batches and 12 months for the third validation batch, in addition to 6 months at 40°C/75%RH. We consider this adequate to support the submission. The actual expiry dating that will be granted is a review issue.

**Sponsor's Question:**

Concurrence is sought that the limits set for impurities when using the proposed method are adequate to ensure the quality of the drug product throughout shelf life.

**Agency's Response:**

Unless there is a safety concern, then the proposed limits set for impurities are acceptable.

**Additional CMC Comments from FDA:**

Specifications for mold and yeast should be included.

*In response to Agency inquiry, the sponsor stated that they do not plan to make any claims regarding the vitamin E in their product. The sponsor was advised that this would be reflected in labeling.*

*The Agency understands that the proposed limit of \_\_\_\_\_ for the concentration of \_\_\_\_\_ present in white petrolatum is in compliance with European Pharmacopeia. However, the acceptance criterion has not been officially endorsed in the U.S. In view of the fact that \_\_\_\_\_ are known carcinogens, you need to provide adequate justification to support this limit of \_\_\_\_\_*

b(4)

*We would like to bring your attention to 21CFR 172.880. A specification which uses a spectrophotometric method is described there for petrolatum. We accept this CFR specification as a way to control \_\_\_\_\_ in petrolatum.*

b(4)

*In case that the petrolatum used in your product fails to meet the CFR specification, please inform the Agency as soon as possible.*

**Pharmacology/Toxicology:**

**Sponsor's Nonclinical Question 1:**

The sponsor is seeking concurrence that the...Nonclinical...development of Silkis (calcitriol ointment 3 µg/g) to date are adequate to support the filing of a New Drug Application.

**Agency's Response:**

The adequacy of the database will be a review issue under the NDA. As the sponsor has previously been cautioned, it is important to document that the systemic exposures achieved in pivotal nonclinical studies were adequate to qualify the exposures observed clinically under conditions of maximum exposure (as defined by the Biopharmaceutics reviewer). In the NDA, please include a section in which the systemic exposure to the drug substance and metabolites thereof that were observed in each pivotal in vivo toxicology study is directly compared to the clinical level of exposure observed in patients under conditions of maximum exposure. In instances where the AUC values are below the limit of quantitation, it may be acceptable to discuss surrogate endpoints as evidence of systemic exposure (e.g., altered levels of calcium in the serum or urine). It may also be appropriate to discuss data from studies conducted with radiolabeled materials.

**Sponsor's Nonclinical Question 2:**

Concurrence is sought that the method used to calculate the safety margin is appropriate.

**Agency's Response:**

The proposed method of comparing systemic exposures (comparing amounts of drug substance topically applied per unit of surface area in nonclinical and clinical studies) is less than ideal, since it assumes that penetration of the drug substance through lesioned (psoriatic) skin and intact skin (in nonclinical studies) would be the same. The sponsor apparently documented that systemic exposure to the drug substance occurred in psoriasis patients in clinical studies ("calcitriol mean AUC and mean C<sub>max</sub> levels increased by approximately 40% from baseline to Day 21 [in clinical study RD.03.SRE.40005]", but did not achieve measurably increased plasma levels of the drug substance in topical nonclinical studies. While the limitations of chemical analytical methods are understood, the sponsor was cautioned that it was important to achieve sufficient levels of systemic exposure in nonclinical studies to qualify the levels observed clinically. For example, the Division's FAX dated May 5, 2003, stated in part: "The division reserves the right to request data from a study or studies that fully qualify the systemic exposure to the drug substance and any metabolites thereof observed clinically under conditions of maximum exposure. It may be necessary to administer the drug substance orally or parenterally in nonclinical studies to achieve a level of systemic exposure adequately high to qualify the clinical systemic exposure". Possibly the toxicokinetic data from the pivotal nonclinical studies can be supplemented with data from studies conducted with materials that contained radiolabeled drug substance. These issues will be considered under the NDA (if the NDA is filed).

**Additional Nonclinical Comments from FDA:**

The NDA should include data which adequately qualify the proposed exposures to all impurities, including documentation that any proposed specifications are adequately supported by nonclinical and/or clinical data. Such documentation should include data which concern the levels of impurities in all lots of materials that were used in the nonclinical and clinical studies that the sponsor may cite in support of the proposed specifications. The NDA should include an analysis of the exposure to each specified impurity that was achieved in those studies, with a comparison to the exposure of a patient under worst-case conditions.

**Clinical Pharmacology/BioPharmaceutics:**

**Agency:**

The sponsor's study (SRE.40005) in adult patients had been conducted under maximal usage condition. The report will be reviewed during NDA submission. It is expected that the sponsor will report plasma levels of calcium along with calcitriol levels in the final report. All the data should be submitted in SAS transport format.

In terms of pediatric study (SPR.18102) design, the sponsor should sub-divide the age group (12 - 17 years) into two sub-groups (12-<15) and (15-17) and recruit equal number of patients in each group.

*The sponsor affirmed that they plan to start this study in June 2006*

**Clinical:**

The briefing package did not include any specific questions; however, the following questions were included in the meeting request:

**Sponsor's Question:**

Concurrence is sought that the four clinical studies developed after consultation with the FDA (Pivotal studies RD.06.SRE.18053 and RD.06.SRE.18054, the long term safety study RD.06.SRE.2663, and the adult PK study RD.03.SRE.40005) are appropriate to support the submission of a 505(b)(1) application. The sponsor considers the 41 additional studies included in the NDA supportive.

**Agency's Response:**

While the four studies cited would appear to support submission of a marketing application, dermal safety studies (each conducted with an adequate number of subjects) are also required to support the application. The sponsor was advised at the Pre-IND/End-of-Phase 2 meeting (November 15, 1999), that such studies are "necessary" for filing of the NDA. From review of Appendix 9.1, it appears that the sponsor has conducted dermal safety studies (combined contact sensitization and cumulative irritancy, phototoxicity and photoallergic contact sensitization); however, it is unclear whether the formulation used in those studies was the to-be-marketed formulation. Also, the numbers of subjects in each study were not provided.

*The sponsor indicated that the dermal safety studies were all conducted with the to-be-marketed formulation.*

**Regulatory:**

**Sponsor's Question:**

Concurrence is sought that the application will be submitted on paper in CTD format.

**Agency's Response:**

This is acceptable.

**Sponsor's Question:**

Concurrence is sought that a \_\_\_\_\_

b(4)

**Agency's Response:**

The Division would agree \_\_\_\_\_

b(4)

*The sponsor indicated that they will submit a Proposed Pediatric Study Request.*

**Additional Clinical Comments from FDA:**

1. Please provide a comprehensive index which identifies the specific location (volume and page numbers) for each data listing. Also please provide an index for where items in the Clinical Reviewer Template can be found in the NDA. It is requested that this index identify the location of the template items by volume and page numbers and by sections of the CTD.
2. Please include reference ranges for all laboratory values in the data listings where those laboratory values are presented.
3. Please provide a table that indicates what formulation was used in each clinical trial.
4. Please include a copy of the proposed label in Microsoft WORD.
5. Please include copies of all foreign labeling translated into English.
6. Please submit case report forms (CRFs) for all patients who are excluded from the per protocol analysis, who are lost to follow-up, or who are early discontinuations. Additional CRFs may be requested during the review process.
7. Please include the primary efficacy analysis broken down by investigator.
8. Please include an index that would enable the reviewer to make the association between investigator's verbatim terminology used to describe an adverse event and the preferred term used for coding the adverse event in the submission's adverse event tables.
9. Please include a safety report from worldwide use of the product.
10. Please generate a table showing laboratory values for all subjects whose values for parameters of calcium homeostasis are outside of the reference range (the table should also include baseline values).

11. In the presentation of laboratory data, please "flag" all laboratory values and vital signs that are outside of the reference ranges.

*The sponsor will submit a PSUR in the NDA, and they will submit a Safety Update during the course of the review.*

*The sponsor stated that they plan to submit the NDA in September 2006.*

#### **Biostatistics:**

##### **Sponsor's Biostatistics Question 1:**

Concurrence is sought that the analysis plan and format of statistical tables to be presented ISS and ISE are appropriate to support the submission of the application.

##### **Agency's Response:**

The brief description of the ISS and ISE plans and the sample tables appear to be generally acceptable from a statistics perspective.

##### **Sponsor's Biostatistics Question 2:**

It is planned to submit SAS data sets for the two well-controlled phase 3 studies (RD.06.SRE.18053, RD.06.SRE.18054), the long-term safety study (RD.03.SRE.2663), as well as the package insert in electronic format. At the time of NDA submission, will other data sets be required?

##### **Agency's Response:**

The dataset for the PK study (RD.03.SRE.40005) should be submitted along with the datasets for the Phase 3 studies and the long-term safety study. The datasets should be submitted in SAS transport format and the package insert should be submitted in WORD format. The database for the Phase 3 studies should include both raw variables (from the CRF, without imputation) and derived variables (with imputation for missing data) suitable for conducting primary and secondary efficacy analyses (such as success rate on the global severity score). The database should also include indicators for ITT and Per Protocol status. 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, 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

#### **Administrative Comments**

1. For applications submitted after February 2, 1999, the applicant 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. The sponsor is reminded of the Pediatric Research Equity Act of 2003 which requires all applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred.
3. Comments shared today with the sponsor are based upon the contents of the briefing document, which is considered to be an informational aid to facilitate today's discussion. Review of the information submitted to the IND and/or NDA might identify additional comments or information requests.
4. The sponsor is reminded that all new NDAs/BLAs and efficacy supplements submitted on or after June 30, 2006 must include content and format of prescribing information based on the new Physicians Labeling Rule at the time of submission (see attached website <http://www.fda.gov/cder/regulatory/physLabel/default.htm> for additional details).

*The sponsor acknowledged their labeling will comply with the new labeling rule. They proposed early dialogue in the labeling discussions. The Agency agreed to work with the sponsor toward this end.*

Minutes Preparer: \_\_\_\_\_  
Margo Owens/Regulatory Project Manager DDDP

Chair Concurrence: \_\_\_\_\_  
Jill Lindstrom, M.D./Lead Medical Officer, DDDP

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**Executive CAC**

**Date of Meeting: April 8, 2003**

**Committee:**

Jim Farrelly, Ph.D., HFD-530, Acting Chair  
Joseph Contrera, Ph.D., HFD-901, Alternate Member  
Tim McGovern, Ph.D., HFD-170, Alternate Member  
Abby Jacobs, Ph.D., HFD-540, Team Leader  
Norman See, Ph.D., HFD-540, Presenting Reviewer

**Author of Draft: Norman See, Ph.D.**

The following information reflects a brief summary of the Committee discussion and its recommendations. Detailed study information can be found in the individual review.

The committee did not address the sponsor's proposed statistical evaluation, as this does not affect the sponsor's ability to initiate the assay. The sponsor may seek guidance on the statistical evaluation of assay results from agency staff separately. Data files should be submitted electronically following section E of the 'Guidance for Industry, Providing Regulatory Submission in Electronic Format, New Drug Application.'

If the sponsor plans histological evaluation of tissues from only control and high dose treatment groups, they will also need to conduct histopathologic examination of other dose groups under any of the following circumstances:

- (a) for any macroscopic findings in the low and mid dose groups for a given tissue, they will need to look at that tissue for all of the dose groups
- (b) for an increase in the incidence of tumors (rare or common) in the high dose group for a tissue, even if not statistically significant, they will also need to look at the next lower dose group
- (c) for an increase in tumors in an organ for a tumor type that should be analyzed across tissue sites as well as by tissue site (e.g., hemangiosarcoma, lymphoma etc.; see McConnell et al, JNCI 76:283, 1986) they should look at all relevant tissues for that dose level and the next lower dose level,
- (d) for an excessive decrease in body weight or survival in the examined dose group, they should examine lower dose groups.

**IND # 62,151**

**Drug Name: Calcitriol ointment**

**Sponsor: Galderma Laboratories**

**104 week oral rat and topical mouse Carcinogenicity Study Protocols and Dose Selection**

**Background:** The sponsor has proposed to conduct two 104-week bioassays to partially support marketing of a topical psoriasis product that contains calcitriol. One proposed study would involve oral (gavage) administration of calcitriol to the rat at exposure levels of 0 (water control), 0 (vehicle control), 0.005, 0.025, and 0.1 µg/kg/day. Neobee oil M5 would be used as a vehicle. Neobee M5 is a medium chain triglyceride, primarily with 8 and 10 carbon side chains (caprylic and capric acid) in proportions of approximately 68% and 32%, respectively. The study would not include toxicokinetic analysis, since plasma levels of calcitriol were below the limit of quantitation (200 pg/mL) in a 90 day study, even at three times the maximum exposure proposed for use in the bioassay.

The second proposed study would involve topical application of several concentrations of calcitriol in ointment base to the skin of mice; the sponsor has proposed exposure levels of 0 (vehicle control), 0.3 ppm, 0.6 ppm, and 1 ppm. Treatment would involve application of 25  $\mu\text{L}/\text{day}$ ; these exposures equate to approximately 0.3, 0.6, and 1  $\mu\text{g}/\text{kg}/\text{day}$  if a body weight of 25 g is assumed.

**Executive CAC Recommendations and Conclusions concerning the proposed 104 week oral bioassay in rats:**

1. The committee recommended that the number of animals of each gender in each treatment or control group be increased to 60.
2. The committee recommended exposure levels of 0.005, 0.03, and 0.1  $\mu\text{g}/\text{kg}/\text{day}$  for both males and females in the low, mid, and high-dose groups, respectively.
3. The committee commented that the passage in the protocol (under section 3.5) that pertains to early termination of the study is unclear. It is recommended that the sponsor contact the division for guidance prior to conducting an early termination.
4. The protocol calls for obtaining blood and urine samples from 20 animals per gender per group during week 52 for assessing blood chemistry and urinalysis. The committee recommends that the protocol be modified to include 5 satellite animals per sex per group (including the control groups), that blood and urine samples be obtained from the satellite animals during week 52 for assessment of blood and urine chemistry (to obtain information about calcium metabolism, as these data may be a useful means of assessing effective systemic exposure to calcitriol), and that samples not be obtained from main-study animals.
5. The committee expressed concern about the fact that toxicokinetic data will not be obtained in the study due to the absence of an assay of sufficient sensitivity. The committee recommends that the sponsor consider conducting a separate study, run concurrently with the bioassay under conditions identical to those of the bioassay, in which it may be possible to assess systemic exposure through use of radiolabeled calcitriol. For example, a study might be initiated at the same time as the bioassay, using animals of the same strain and age, with treatment of the animals in exactly the same manner and with the same materials as in the bioassay. Following an appropriate period of treatment (e.g., 52 weeks) blood and urine samples could be obtained to permit correlation of pharmacodynamic values, particularly calcium data, with exposure data. Treatment could continue for an appropriate period (e.g., one week) to permit recovery from the blood collection procedure. The final treatment of each animal would involve use of test material that had been spiked with radiolabeled calcitriol. Blood samples could be obtained at appropriate time points during the 24 hours following the final treatment for assessment of activity, and the data used to calculate standard pharmacokinetic parameters (including AUC values). The data would be most useful if the fractional activity associated with different metabolites at each time point was known. While conduct of such a study is not a requirement, the committee noted that the sponsor will ultimately be responsible for analysis of data from the bioassay, including correlation of exposure with tumor frequency, and, if possible, comparison of systemic exposure values achieved in the bioassay with exposure values observed clinically.

**Executive CAC Recommendations and Conclusions concerning the proposed 104 week topical bioassay in mice:**

6. The committee recommended that the number of animals of each gender in each treatment or control group be increased to 60.
7. The committee recommended exposure levels of 0.3, 0.6, and 1 ppm (equating to approximately 0.3, 0.6, and 1  $\mu\text{g}/\text{kg}/\text{day}$ ) for both males and females.
8. The committee commented that the passage in the protocol (under section 3.5) that pertains to early termination of the study is unclear. It is recommended that the sponsor contact the division for guidance prior to conducting an early termination.
9. The committee recommended that blood collections scheduled for week 52 not be conducted in main study animals (to avoid unnecessarily stressing the animals). It is recommended that the protocol be modified to include 5 satellite animals per gender per group (including the control group) and that blood and urine samples be collected from these animals during week 52 of treatment. The samples should be analyzed in a standard battery of clinical pathology assessments (particularly those that pertain to calcium metabolism). The sponsor may attempt to measure the concentration of calcitriol in blood samples obtained at the anticipated time of maximum concentration of calcitriol if it so chooses. The committee commented that data from these animals that describe calcium metabolism may be a useful means of comparing relative (effective) systemic exposures to calcitriol if useful toxicokinetic data are not available.
10. The committee recommends that the sponsor consider obtaining detailed systemic exposure data in a separate study that involves use of radiolabeled material, as discussed under point 5, above. That study, if conducted, should utilize methodology as similar to the methodology employed in the bioassay as possible.
11. The committee commented that the exact formulations of the test materials used should be clearly indicated when the final report of the study is submitted (not necessarily in the study report, if the formulation is regarded as a trade secret, but in the same submission to the agency).

**Jim Farrelly, Ph.D.**  
**Acting Chair, Executive CAC**

cc:\n  
/Division File, HFD-540  
/AJacobs, HD-540  
/NSee, HFD-540  
MOwens, HFD-540  
/AScifried, HFD-024

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this page is the manifestation of the electronic signature.**

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James Farrelly  
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Pre-IND/EOP2  
11/15/1999

**MEMORANDUM OF MEETING**

Meeting Date: November 15, 1999

Time: 1:00 PM

Meeting ID: 4995

Location: N200A

Purpose of Meeting: Pre-IND/End of Phase 2 for Calcitriol ointment 3 µg/g for the topical treatment of psoriasis.



Meeting Chair: Jonathan K. Wilkin, M.D., Director, Division of Dermatologic and Dental Drug Products

Meeting Recorder: Victoria Lutwak, Project Manager, Division of Dermatologic and Dental Drug Products, DDDDF, HFD-540

**FDA Attendees:**

Robert DeLap, Director, ODE 5

Jonathan K. Wilkin, M.D., Director, DDDDF, HFD-540

Ramzy Labib, M.D., Medical Officer, DDDDF, HFD-540

Steve Hathaway, Ph.D., Acting Chemistry Team Leader, DDDDF, HFD-540

Norman See, Ph.D., Pharmacologist/Toxicologist, DDDDF, HFD-540

R. Srinivasa, Ph.D., Biostatistics Team Leader, HFD-725

Sue-Chih Lee, Ph.D., Biopharmaceutics, HFD-880

Victoria Lutwak, Project Management, DDDDF, HFD-540

**Galderma Attendees:**

Maurizio Mariani, M.D. Ph.D., DABT, Director of Development

Klana Rizova, M.D. Ph.D., Medical Advisor

Michael Tusey, Ph.D., Project Leader

Oliver Watts, Ph.D., Director of Pharmaceutical Development

Maryse Coroller, Ph.D., Toxicology

Sebastian Genevo, Pharm.D., Manager Dossier & Regulatory Issues US

Aza-Belen Irgaray, Pharm.D., Corporate Regulatory Affairs Manager

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**Chemistry, Manufacturing, and Controls:**

Calcitriol is a well-established drug substance, marketed for oral and intravenous routes of administration. Two CMC questions are presented as follows:

- *Does the FDA agree that no further stability data beyond that submitted to the DMF are necessary to support an NDA?*

This is a review issue. Without a letter authorizing reference, a commitment cannot be given at this time. However, it should be noted that many DMF holders do not routinely submit stability updates to their drug substance DMFs; the report submitted with the meeting package dates from 1995. Therefore, we recommend that such information be requested from the DMF holder. An alternative approach would be to obtain the pertinent drug substance stability data directly from the DMF holder, and then to submit those in the IND. This approach would obviate the need to request a letter of authorization or an update to the DMF. (It would still be necessary to provide assurance that no changes would be made to the drug-substance manufacturing processes by the DMF holder without prior notification.)

*Since the active ingredient is present at a low dosage, it has not been possible to identify or monitor oxidative degradation products. Will it be acceptable to monitor only the active ingredient in the finished product stability studies?*

Again, this is a review issue. However, usually it is expected that the stability studies will be able to detect degradation products. If the analytical methods are capable of detecting the degradation products, the presence of any such degradants below the limit of quantitation should be no problem. Forced degradation studies should be performed on both drug substance and drug product under the recommended conditions (i.e., heat, acid, base, oxidation, and light). We expect that any degradants seen in the drug substance forced-degradation study would be looked for during the analyses of drug product which has been subjected to the same conditions. Where such impurities in drug product cannot be detected or are below the limit of quantitation, you might propose omission of regulatory specifications for these impurities. The rationale, data, and interpretive analysis of the results would then be reviewed in the IND submission.

The following additional comments are offered:

1. For reference, UV-visible spectra should be provided for the drug substance, all appropriate components of the drug product, and all identified degradation products and synthetic byproducts.
2. We recommend that you consider performing forced photodegradation studies on the drug product.
3. Your stability studies report package sizes of 10 and 100 gms. Please clarify which size or sizes will be used in the clinical trials, and submit appropriate container/closure descriptions.

b(4)

b(4)

**Pharmacology/Toxicology:**

*Pharm Question 1: Concurrence is sought that additional studies of duration longer than 6 months by oral or parenteral routes in a non-rodent species may be waived.*

*Pharm Question 2: Concurrence is sought that [a 28-day dermal toxicity study in dogs and a 6-month dermal toxicity study in rats] will complement adequately the dermal safety profile of calcitriol in the proposed formulation.*

*Pharm Question 3: Concurrence is sought that no further studies are needed to assess the genotoxic potential of calcitriol.*

*Pharm Question 4: Concurrence is sought that carcinogenicity studies with calcitriol ointment in laboratory animals may be waived.*

*Pharm Question 5: Concurrence is sought that a photo-carcinogenicity study with calcitriol ointment may be waived.*

**Response:** These matters can only be decided during review of an IND for the product. It seems plausible that the 28-day topical dermal rat and rabbit toxicology studies may adequately support eight-week clinical studies when taken in conjunction with the total calcitriol database, assuming the studies are found to have been properly designed and executed, and provided that adequate data concerning sensitization potential are submitted. Additional topical dermal toxicology studies may be required to support the Phase 3 studies if the rat and rabbit studies were deficient (e.g., use of improper test materials, failure to monitor critical factors, failure to prevent the animals from licking the application site, failure to obtain toxicokinetic data, etc.).

At this time, it appears that an appropriate battery of nonclinical studies to support filing of a NDA for calcitriol ointment may include:

1. A nine-month topical dermal toxicology study in an appropriate non-rodent species (rabbits or pigs are generally preferred for topical dermal studies). It is recommended that the study include toxicokinetic evaluation and complete clinical pathology and histopathology. These data should be submitted prior to initiation of any clinical studies of longer than eight weeks duration.

2. Apparently calcitriol has been assessed in an Ames test and in a micronucleus assay. It is recommended that a mouse lymphoma TK locus assay in L5178Y cells be performed to further develop the genetic toxicology of the drug substance.

3. A photocarcinogenicity study.

4. Either a two-year topical dermal carcinogenicity bioassay or a Tg.AC assay.

5. Additional phototoxicity and photoallergenicity data may be needed, depending on the quality of the existing data.

However, it should be emphasized that the perceived data requirements may change during review of the IND. All pivotal toxicology studies should be conducted in compliance with Good Laboratory Practices regulations (21 CFR 58). The sponsor is invited to submit draft protocols for pivotal toxicology studies to the division for comment prior to initiation of those studies.

**Biopharmaceutics:**

To submit the application under 505(b)(1)

Our comments for the existing PK studies (H.141.605 & H.141.6002) are as follows:

Total recovery of radioactivity was low, which raises questions regarding the reliability of the study.

In both studies, 1 gram of ointment was applied to lower back of each subject (300 sq. cm). This surface area is far less than the proposed use of up to 35% of BSA.

The study with multiple applications was conducted for 4-5 weeks. Since the skin conditions change with time, timing for sample collection can impact on systemic absorption. The sponsor did not demonstrate that 4-5 weeks represent the time to reach maximal exposure.

Since the purpose of the PK study is to determine the maximal exposure, the sponsor should conduct a study in patients with maximal involved surface area as intended for clinical use. Timing of sample collections should be such that maximal exposure can be captured.

To submit application under 505(b)(2)

Under 505 (b)(2) the sponsor will need to compare the plasma level profile from their product to an approved product. As the indication they are pursuing is not one currently covered by an NDA (and in fact would require a lower dose) the sponsor will have to demonstrate that the plasma levels of their product are either equivalent to or inferior to the currently approved product. This demonstration would then potentially allow the sponsor to use this comparison to support their safety database.

Since a comparison with another product will be made, the variability should be taken into account in sample size calculations.

**CLINICAL:**

**Question 1:**

The sponsor intends calcitriol ointment 3µg/g to be indicated for the treatment of psoriasis, with twice daily applications. Concurrence is sought that the available data from Phase 1 and Phase 2 studies are appropriate to start Phase 3 program and to support an NDA.

**Response:**

The submitted data did not include any full reports or protocols. However, from the submitted summaries, it appears that the sponsor may be ready for Phase 3 studies.

The detailed protocol and results of the dose ranging study, H.141.5012/M may need further review. It appears that this study involved severe psoriasis which is not included in the indication sought. Its applicability for the

indication is doubtful. Also, it is not clear why the data of the primary parameter show better results for the 3µg/g ointment compared to the lower concentrations (difference between means, table 3 page US-226), whereas the data of the secondary parameter do not support this result (mean percent reduction, table 4 page US-227). It is possible that the differences shown in the primary parameter are in fact attributable to the lower baseline severity in the 3µg/g ointment population (table 4).

The topical safety studies should be carried out using the to-be-marketed formulation

**Question 2:**

Concurrence is sought that the planned Phase 3 clinical studies outlined in the package will be required and that the protocol designs are adequate to support the filing of an NDA for the product.

**Response:**

Protocols numbers: 18053 & 18054 (Identical except that the former has safety labs not included in the latter).

1. The rationale for the first week of vehicle treatment of both arms is not clear. It may affect labeling. The use of bland marketed emollients may be preferable.
2. Pregnancy and breast feeding exclusions may affect labeling. The sponsor should submit data to support the pregnancy rating C.
3. Only mild and moderate Chronic Plaque Psoriasis patients will be enrolled. Amount applied daily is limited to a maximum of 30 gm ointment. This will be reflected in labeling. The sponsor should describe any safety margins with the 30 gram/day dose.
4. There are no provisions for compliance with the pediatric rule.
5. The primary efficacy parameters: The investigator's global assessment dichotomized to success/failure is recommended. Success is recommended to include only clear or almost cleared. The risk benefit ratio is important in defining the level of severity of psoriasis in patients to be included in the clinical studies. All lesions should be treated and evaluated regarding erythema, scaling and plaque thickness. Scalp lesions may be excluded. At least more than one target lesion should be assessed in each patient. Information about efficacy in knee/elbow lesions as compared to trunk lesions will be needed.
6. The secondary efficacy variable(s) should preferably include all treated lesions rather than a single target lesion.
7. Laboratory safety assessments are included in one study only. Because of concern about calcium homeostasis with this treatment, it is recommended to include these laboratory safety assessments in both studies.

**Additional Clinical items necessary before the sponsor can file the NDA submission;**

1. Long term safety study including at least 300 patients of all ages, pregnant and lactating, unless there is a convincing rationale for any exclusion.
2. The Topical safety studies (submitted) should be with the final to be marketed formulation. Information on the relapse rate will be important in the risk benefit assessment.

**Biostatistics:**

1. As indicated by the medical officer, the Division recommends the dichotomized static global assessment as a primary efficacy variable in the Phase 3 trials.
2. Based on the primary efficacy variable recommended, the sponsor needs to redo the sample size/power calculations for their Phase 3 trials.
3. The division recommends ITT population to be used for superiority trials, and ITT is defined as all subjects randomized and dispensed study medication, active or vehicle. The sponsor is reminded that all discontinued subjects should be included in the ITT population.

4. In Phase 3 trials, the primary efficacy analysis should be adjusted for center and the center x treatment interaction should be formally tested using 0.1 level of significance.

5. For Phase 3 trials, the Division recommends that in each center, at least 10 subjects be randomized to each treatment arm. Further, to ensure more homogeneous results across the centers, the Division recommends having a fewer number of centers, with each center having larger enrollments.

6. In Phase 3 trials, the primary efficacy hypotheses should be stated in the protocol in advance.

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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:

*For 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(e).*

3. 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.
4. 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.

Minutes Preparer: Victoria Lutwak  
Victoria Lutwak/Project Manager, DDDDP

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