



NDA 50-802

Dow Pharmaceutical Sciences  
1330A Redwood Way  
Petaluma, CA 94954-1169

Attention: Barry Calvarese  
Vice President, Regulatory and Clinical Affairs

Dear Mr. Calvarese:

We refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Clin-RA (clindamycin 1.0% and tretinoin 0.025%). Your formal dispute resolution request (FDRR) dated February 25, 2005, received February 28, 2005, submitted by your agent, Jur Strobos, M.D., concerns the December 7, 2004, letter issued by the Division of Dermatologic and Dental Drug Products (the Division). In your FDRR dated February 25, 2005, you disagree with the decision communicated in the letter that the application could not be approved because the contribution of tretinoin in the proposed combination product has not been established.

You specifically argue as to the appropriateness of the endpoints that we used to evaluate the treatment of acne vulgaris. This is based on the failure of the submitted trials (7001-G2HP-06-02 (06) and 7001-G2HP-07-02 (07) to provide substantial evidence for the co-primary endpoint, the Evaluator's Global Severity (EGS) score, to demonstrate that tretinoin contributes to the claimed effects of the proposed combination by a statistically significant percentage of patients who were scored as clear, or almost clear. You state your belief that such a demonstration of an effect of tretinoin by this analysis of the EGS score is not consistent with the advice of the Advisory Committee meeting of November 4-5, 2002.

You also argue that it is not necessary to show an effect on more than one endpoint (i.e., EGS score) in order to demonstrate contribution to the claimed effects of the proposed combination. Specifically, you argue that it is not necessary that the combination demonstrate a meaningful effect relative to its components in the EGS score in the acne vulgaris population and, therefore, that demonstration of an effect of the combination relative to its components on the lesion counts should be sufficient for approval.

A review of the administrative history for this application shows that we have had multiple meetings and discussions with you throughout the development program for Clin-RA. The record shows that we clearly informed you that the combination policy would be applicable to this new fixed-dose combination of clindamycin 1.0% and tretinoin 0.025%. More specifically, we informed you that it would be necessary to demonstrate an effect of each component to the claimed effects of the proposed combination product in adequate and well-controlled clinical trials in the target population for both primary endpoints (lesion counts and the EGS score). The design of the clinical program demonstrates that you clearly understood this requirement.

You do not dispute the need to demonstrate the contribution of the individual components in the FDRR by these pre-specified endpoints. Therefore, the applicability of our regulatory policy with regard to fixed-dose combinations is not in dispute. You dispute whether the data you submitted in the NDA adequately meet the recommended regulatory standard for approval of the indication of acne vulgaris.

Your clinical development program included two identical, four-armed, multi-center, randomized, double-blind, active- and vehicle-controlled, parallel Phase 3 trials, 7001-G2HP-06-02 (06) and 7001-G2HP-07-02 (07). These two Phase 3 studies were conducted in a population of patients with acne vulgaris using the pre-specified inclusion criteria of facial acne inflammatory lesions (papules and pustules) count no less than 20 but no more than 50, and facial acne non-inflammatory lesion (open and closed comedones) count no less than 20 but no more than 100.

You also conducted additional clinical trials that were designed to evaluate other important scientific and regulatory questions. These studies included a pharmacokinetic study and four dermal safety studies.

You note in the FDRR that your request for formal dispute resolution is based on “the issue of appropriate endpoints for the evaluation of topical products for the treatment of acne.” I disagree that an unfavorable action based on outcomes that were pre-specified and agreed to by you but which failed to demonstrate efficacy in the trials is a basis on which to address the issue of endpoint validity.

In the letter the Division concluded that “the contribution to efficacy of each component of your combination product was not adequately demonstrated”. Specifically, the contribution of tretinoin to efficacy was not adequately demonstrated. The Division directed you to address this deficiency by suggesting that “the contribution of tretinoin to the efficacy of this combination product should be documented in an additional clinical study”. In the FDRR, you disagree with the conclusion that the benefit of tretinoin in the combination has not been established, arguing instead that the efficacy data in question is based on an endpoint that is not validated and has been questioned as to its utility in a public advisory committee meeting in November 2002. You and your agent agree that the division’s expectation that the primary endpoints are a requirement in that they must show that tretinoin and clindamycin have an effect on both inflammatory, non-inflammatory, and total lesion counts, but assert that there was a verbal agreement<sup>1</sup> not reflected in the End of Phase 2 meeting minutes that allowed for an alternative dichotomized Evaluator’s Global or other endpoints where the Evaluator’s Global Scale proved invalid in order to gain approval.

At issue is the validity of the EGS endpoint for the study outcomes and whether alternative analyses are acceptable. I will analyze each of these issues separately.

#### Demonstration of a contribution of tretinoin to the claimed effects of the combination evidenced by EGS

It is apparent from reviewing the administrative record of this application that we considered the proposed product to be a significant new combination of active ingredients for an indication that had been previously granted for each of these single ingredients. It is also apparent that we expected you to demonstrate the safety and efficacy of this new combination, including the contribution of the individual active ingredients, in adequate and well-controlled trials in a population of acne vulgaris patients that could reasonably be expected to benefit from the fixed-dose combination.

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<sup>1</sup> Sponsor question # 2 for post action meeting of February 16, 2005.

There were a number of discussions between the Agency and you regarding the design of the clinical study program. You have not challenged in the FDRR the need to meet the combination policy and it is clear from the scope of the development program that you understood that approval would require a showing of substantial evidence of safety and effectiveness of the new combination as required under the statute. This is exemplified by the number and types of clinical trials included in your clinical development program.

It is also clear from the administrative history and the design of the individual clinical trials that your primary hypothesis regarding the utility of the EGS score reflected concurrence with this as a primary endpoint. The administrative record<sup>2</sup> also reflects that you were advised of the risk in the powering of your Phase 3 trials. You chose to undertake a 2:2:1:1 randomization based upon an expectation of a greater effect size for clindamycin. You chose to not perform exploratory Phase 2 trials to better characterize the effect size of each of the two components as a means of powering the Phase 3 trials.

It was only after you had failed to demonstrate an effect of tretinoin on this EGS scale, a pre-specified primary endpoint in each of the Phase 3 studies, that the risk of this in the Phase 3 trial design was fully evident. The clinical development program clearly demonstrated that your primary hypothesis about the effects of the individual components in the combination for both types of acne lesions was only partially correct since no statistically significant effect was demonstrated by the EGS efficacy endpoint in the ITT analyses (Appendix 1). Therefore, while the design of the Phase 3 pivotal studies was adequate for assessment of lesion counts, it was flawed with regard to assessment of the EGS, potentially due to the under powering of the trial.

You have raised other concerns regarding the validity of the EGS scale. The scale used in your Phase 3 trials closely mirrors the scale the Advisory Committee discussed at the November meeting (see Appendix 2). I am in agreement with the Division that an overall "global" assessment by the clinical evaluator is indeed important in the assessment of efficacy for this disease state.

You are responsible for the identification, recruitment and training of appropriately qualified clinical investigators. I do not agree that this scale, when used by qualified clinical investigators, would work differently for deeply pigmented individuals than for those less pigmented. Also, your assertion by that the EGS endpoint is susceptible to "gaming" by industry is spurious and this submission does not contain evidence to support this allegation.

Regarding scale validity, the scale was consistent with the proposed scale reviewed at the advisory committee meeting. The EGS data in both trials fail to demonstrate an effect for the combination compared to clindamycin. Regarding this endpoint, I acknowledge that it is unlikely that there are "perfect" patients who present an "exact fit" to the categories of the scale. The evaluator assessment and approximating patient appearance to the scale may potentially introduce variability of judgment and subjectivity to this assessment. However, unless you were to undertake careful photography for all subjects which you chose not to do, these clinical evaluator assessments would likely be balanced out across the treatment groups and any bias minimized, provided that proper randomization and blinding of the study was achieved .

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<sup>2</sup> End of Phase 2 Meeting Minutes, December 16, 2002

### Alternative Analyses based on the EGS

In the briefing package for the End of Phase 2 meeting, you proposed that, in addition to lesion counts, efficacy be based on an EGS score of "clear" or "almost clear," or a two-grade improvement from baseline. The Division advised you that, while two-grade improvement data could be submitted as supportive, the Division would measure efficacy by the proportion of subjects who are rated "clear" or "almost clear" at efficacy evaluation.

Given the concerns you have raised, this alternative analysis of a 2-grade reduction data will be further considered.

### **Two-Grade Improvement**

You submitted a supplemental set of analyses of the dichotomized EGS score to characterize the treatment effect for the proportion of subjects who showed at least a two-grade reduction or were rated as "clear" or "almost clear" in EGS score at Week 12. The findings of our statistical reviewer's analyses of the two-grade reduction data for the Clin-RA versus clindamycin comparison show:

**Statistical Reviewer's Table 5: Treatment Success and Modified Success Rates in the EGS Score at Week 12**

Analysis	Variable	Study 06			Study 07		
		Clin-RA (n = 420)	Clindamycin (n = 208)	p-value <sup>3</sup>	Clin-RA (n = 425)	Clindamycin (n = 218)	p-value <sup>3</sup>
ITT	Treatment						
	Treatment Success <sup>1</sup> rate	88 (21%)	34 (16%)	0.172	97 (23%)	38 (17%)	0.094
	Modified Success <sup>2</sup> rate	101 (24%)	38 (18%)	0.100	118 (28%)	44 (20%)	0.030
PP	Treatment						
	Treatment success <sup>1</sup> rate	79 (25%)	25 (16%)	0.037	81 (28%)	34 (21%)	0.130
	Modified Success <sup>2</sup> rate	90 (28%)	28 (18%)	0.020	100 (34%)	40 (25%)	0.031

<sup>1</sup> Treatment success is the Division's recommended co-primary efficacy endpoint, defined as clear or almost clear in the EGS score at week 12.  
<sup>2</sup> Modified success is defined as clear or almost clear or at least a 2-grade improvement from baseline in the EGS score at week 12.  
<sup>3</sup> p-value is based on CMH test adjusting for investigational group.

The ITT analyses for the two trials for your proposed "Modified Success Rate" demonstrates significance for Study 07 (p=0.030) but not for Study 06 (p=0.100).

### Summary of Findings

There is a clear expectation by us that there will be consistency in findings for the two co-primary endpoints to provide substantial evidence for efficacy for a product indicated for acne vulgaris. The submitted NDA for the combination of clindamycin and tretinoin was not approved based on the failure of the data to adequately substantiate efficacy for the contribution of the individual components as assessed by pre-specified co-primary endpoints of lesion counts and the EGS score.

As evidenced by the analyses in both trials for lesion counts, Clin-RA demonstrated a meaningful reduction in lesion counts for both inflammatory, non-inflammatory lesions, and total lesion counts in Study 06, and for inflammatory lesions and total lesion counts in Study 07. Clin-RA failed to demonstrate a significant difference in non-inflammatory lesion count reduction of the combination in Study 07 for both components and only for total lesion count reduction in the analysis for mean percent, not for the mean absolute reduction.

The data for the pre-specified EGS endpoint in the ITT analysis fail to meet statistical significance for tretinoin in both trials. The applicant's alternative analysis fails in the ITT analysis for Study 06. For

this post hoc analysis, there is a finding of statistical significance in the per protocol analysis for both trials.

I do not find that the submitted alternative analyses provide adequate evidence of efficacy for the indication of acne vulgaris. Overall, the NDA data does provide evidence for lesion count reduction of inflammatory lesions, but not consistently for the non-inflammatory lesions. However, in light of the failure to demonstrate an effect for the EGS co-primary endpoint, I am in agreement with the Division that an additional adequately designed trial, as was recommended in the December 7, 2004, letter is needed.

### Conclusions

The information provided in the February 25, 2005, FDRR and our documents related to this NDA have been closely and carefully reviewed. For the reasons stated above in the summary of findings, I do not concur with your assertion that the pre-specified endpoint of the Evaluator's Global Severity is not an appropriate endpoint in the evaluation of acne vulgaris. The efficacy of the combination for the indication of acne vulgaris in the intended population of use has not been adequately demonstrated. Therefore, I do not agree with your conclusion that the NDA for Clin-RA should be approved without additional clinical data. Your appeal, therefore, is denied.

I concur with the Division that an additional adequate and well-controlled clinical study is necessary to clearly demonstrate that clindamycin and tretinoin contribute to the claimed effects by the established co-primary endpoints.

I also concur with the Division that the additional study should be designed to assess both co-primaries with careful attention to study design, specifically, by appropriately powering the trial. I strongly encourage you to work with the Division to design the new study and also encourage you to consider submitting the study for Special Protocol Assessment before study initiation.

An alternative is to discuss with the Division taking your NDA to an advisory committee for review of the concerns you have raised.

While your request for immediate approval is denied, your assertion that an alternative indication may be substantiated based on additional analyses to support approval of the combination for a more limited indication would be subject to the same evidentiary standards. The acceptability of a narrower indication based on the evidence of an effect on inflammatory lesion counts in the absence of a meaningful effect on the EGS would not be acceptable.

If you wish to appeal this decision to the next level, your appeal should be directed to John Jenkins, M.D., Director, Office of New Drugs, Center for Drug Evaluation and Research. The appeal should be sent again through the Center's Dispute Resolution Project Manager, Kim Colangelo.

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If you have any questions concerning your appeal or this letter, call Ms. Colangelo at (301) 594-5479.

Sincerely,

Jonca C. Bull, M.D.

Director

Office of Drug Evaluation V

Office of New Drugs

Center for Drug Evaluation and Research

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**Appendix 1:**

**FDA Review: Comparison of Lesion Reduction from Baseline to Week 12 (ITT Analysis) Studies 06 and 07**

Lesion Type Mean (s.d.)	STUDY 06			
	Clin-RA (n = 420)	Clindamycin (n = 208)	Tretinoin (n = 417)	Vehicle (n = 207)
<b>Inflammatory</b>				
Mean baseline count	30.10 (8.64)	29.30 (8.38)	29.44 (8.40)	30.15 (8.43)
Mean number reduction	13.6 (13.0)	11.4 (12.0)	10.7 (12.9)	5.3 (15.6)
Mean % reduction	46.0% (42.2%)	39.7% (42.6%)	37.5% (42.3%)	19.5% (53.0%)
p-value (ranked ANOVA) <sup>1</sup>	NA	0.014	< 0.001	< 0.001
p-value (ranked ANOVA) <sup>2</sup>	NA	0.028	< 0.001	< 0.001
<b>Non-inflammatory</b>				
Mean baseline count	50.86 (22.21)	47.64 (20.77)	49.53 (21.13)	49.28 (22.00)
Mean number reduction	19.2 (21.7)	11.9 (19.4)	15.6 (20.6)	6.9 (23.1)
Mean % reduction	37.6% (37.8%)	24.1% (44.3%)	31.9% (40.0%)	13.5% (50.0%)
p-value (ranked ANOVA) <sup>1</sup>	NA	< 0.001	0.009	< 0.001
p-value (ranked ANOVA) <sup>2</sup>	NA	< 0.001	0.018	< 0.001
<b>Total</b>				
Mean baseline count	80.96 (25.69)	76.94 (23.57)	78.97 (24.20)	79.43 (24.50)
Mean number reduction	32.8 (28.5)	23.3 (26.4)	26.3 (28.0)	12.2 (32.7)
Mean % reduction	41.4% (33.2%)	31.3% (33.9%)	34.7% (34.8%)	16.5% (42.5%)
p-value (ranked ANOVA) <sup>1</sup>	NA	< 0.001	0.001	< 0.001
p-value (ranked ANOVA) <sup>2</sup>	NA	< 0.001	0.002	< 0.001
Lesion Type Mean (s.d.)	STUDY 07			
	Clin-RA (n = 425)	Clindamycin (n = 218)	Tretinoin (n = 429)	Vehicle (n = 216)
<b>Inflammatory</b>				
Mean baseline count	28.84 (8.15)	29.44 (8.18)	29.02 (8.07)	29.91 (8.50)
Mean number reduction	14.6 (12.5)	12.2 (14.5)	11.6 (12.8)	8.6 (13.6)
Mean % reduction	50.6% (48.8%)	43.6% (47.4%)	40.1% (42.5%)	31.7% (43.9%)
p-value (ranked ANOVA) <sup>1</sup>	NA	0.042	< 0.001	< 0.001
p-value (ranked ANOVA) <sup>2</sup>	NA	0.020	< 0.001	< 0.001
<b>Non-inflammatory</b>				
Mean baseline count	46.35 (21.0)	49.83 (22.39)	48.11 (21.55)	48.64 (21.34)
Mean number reduction	15.9 (21.9)	14.7 (21.7)	13.8 (27.9)	7.5 (26.0)
Mean % reduction	35.7% (43.5%)	30.1% (44.8%)	29.9% (48.2%)	18.5% (47.0%)
p-value (ranked ANOVA) <sup>1</sup>	NA	0.328	0.333	< 0.001
p-value (ranked ANOVA) <sup>2</sup>	NA	0.088	0.110	< 0.001
<b>Total</b>				
Mean baseline count	75.19 (24.23)	79.27 (25.52)	77.14 (24.73)	78.56 (24.81)
Mean number reduction	30.6 (29.2)	26.9 (28.6)	25.5 (34.7)	16.1 (32.9)
Mean % reduction	41.6% (37.8%)	35.9% (35.3%)	34.2% (39.3%)	23.2% (39.5%)
p-value (ranked ANOVA) <sup>1</sup>	NA	0.082	0.021	< 0.001
p-value (ranked ANOVA) <sup>2</sup>	NA	0.018	0.002	< 0.001

<sup>1</sup>p-values listed are the comparisons of mean absolute lesion reduction for Clin-RA vs. each of other three treatments.

<sup>2</sup>p-values listed are the comparisons of mean percent lesion reduction for Clin-RA vs. each of other three treatments.

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**Appendix 2: Evaluator's Global Severity Score**

Note: Dow used the Evaluator's Global Severity Scale that was proposed by the Agency as being reasonable at the Advisory Committee meeting of November 4, and 5, 2002

Score	Grade	Description
0	Clear	Normal, clear skin with no evidence of acne vulgaris
1	Almost clear	Rare non-inflammatory lesions present, with rare non-inflamed papules (papules must be resolving and may be hyper pigmented, though not pink-red)
2	Mild	Some non-inflammatory lesions are present, with few inflammatory lesions (papules/pustules only, no nodulo-cystic lesions)
3	Moderate	Non-inflammatory lesions predominate, with multiple inflammatory lesions: several to many comedones and papules/pustules only, and there may or may not be one small nodulo-cystic lesion.
4	Severe	Inflammatory lesions are more apparent, many comedones and papules/pustules, there may or may not be a few nodulo-cystic lesions
5	Very severe	Highly inflammatory lesions predominate, variable number of comedones, many papules/pustules, and many nodulo-cystic lesions.

**Statistical Reviewer's Table 4: EGS Score and Success at Week 12 (ITT Analysis) – Studies 06 and 07**

Distribution of EGS at wk 12 n (%)	STUDY 06			
	Clin-RA (n = 420)	Clindamycin (n = 208)	Tretinoin (n = 417)	Vehicle (n = 207)
Clear	5 (1%)	2 (1%)	4 (1%)	2 (1%)
Almost Clear	83 (20%)	32 (15%)	60 (14%)	16 (8%)
Mild	151 (36%)	83 (40%)	154 (37%)	57 (28%)
Moderate	153 (36%)	83 (40%)	180 (43%)	110 (53%)
Severe	18 (4%)	7 (3%)	18 (4%)	20 (10%)
Very Severe	0	1 (< 1%)	1 (< 1%)	2 (1%)
Percentage of patients with Clear or Almost Clear Comparison (p-value) <sup>1</sup>	88 (21%) NA	34 (16%) 0.172	64 (15%) 0.032	18 (9%) <0.001
Distribution of EGS at wk 12 n (%)	STUDY 07			
	Clin-RA (n = 425)	Clindamycin (n = 218)	Tretinoin (n = 429)	Vehicle (n = 216)
Clear	9 (2%)	3 (1%)	3 (1%)	1 (< 1%)
Almost Clear	88 (21%)	35 (16%)	60 (14%)	16 (7%)
Mild	172 (40%)	72 (33%)	151 (35%)	68 (31%)
Moderate	134 (32%)	90 (41%)	164 (43%)	103 (48%)
Severe	22 (5%)	17 (8%)	30 (7%)	28 (13%)
Very Severe	0	0	0	0
Not Reported	0	1	1	0
Percentage of patients with Clear or Almost Clear Comparison (p-value) <sup>1</sup>	97 (23%) NA	38 (17%) 0.094	63 (15%) 0.002	17 (8%) <0.001

<sup>1</sup> p-value is the comparison between Clin-RA and each of other three treatments and is based on CMH test adjusting for investigational group.

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

**FACSIMILE TRANSMITTAL SHEET**

**DATE:** March 22, 2005

<b>To:</b> Barry Calverese, MS, VP, Regulatory and Clinical Affairs	<b>From:</b> Jacquelyn Smith, Project Manager
<b>Company:</b> Dow Pharmaceutical Sciences	Division of Dermatologic and Dental Drug Products
<b>Fax number:</b> 707-793-0145	<b>Fax number:</b> 301-827-2075
<b>Phone number:</b> 707-793-2600	<b>Phone number:</b> 301-827-2027
<b>Subject:</b> NDA 50-802/DMETS <del>_____</del> comments	

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## FDA Fax Memo

**Date:** March 22, 2005

**Subject:** NDA 50-802

Dear Mr. Calvarese,

I notified you on December 9, 2004 via facsimile of the unacceptability per DMETS of ~~\_\_\_\_\_~~ as a proprietary name for NDA 50-802. In an email dated March 9, 2005, you requested more detail as to DMETS unacceptability determination. DMETS determination of unacceptability of the name "~~\_\_\_\_\_~~" is based on phonetic similarity and promotional concerns to "Zofran".

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Please submit an alternative proprietary name for DMETS review.

Regards,

Jacquelyn Smith  
Project Manager  
HFD-540

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## MEMORANDUM OF TELECON

**DATE:** March 9, 2005 **TIME:** 12: 00 PM

**APPLICATION NUMBER:** NDA 50-802

**DRUG PRODUCT:** Clin-RA Gel

**BETWEEN:**

Name: Barry Calvarese, VP, Regulatory & Clinical Affairs

Phone: (707) 793-2600

Representing: Dow Pharmaceutical Sciences

**AND**

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

Jonca Bull, M.D., Director, ODE V, HFD-105

Mary Jean Kozma-Fornaro, Chief Management Staff, DDDDP, HFD-540

Jacquelyn Smith, Regulatory Project Manager, DDDDP, HFD-540

The Sponsor was contacted to inform that the scheduled teleconference for later today, March 9, 2005, with the statisticians had to be cancelled because of the Dispute Resolution submission dated February 28, 2005. The March 9, 2005 teleconference was scheduled prior to the receipt of the Dispute Resolution.

In addition, the Office of Drug Evaluation V was not clear as to Medicis Pharmaceutical Corporation's role with regard to the Dispute Resolution submission. Dow Pharmaceutical Sciences is on record with the Agency as the Sponsor for NDA 50-802, but the Dispute Resolution was submitted by Medicis Pharmaceutical Corporation on Medicis Pharmaceutical Corporation letterhead. The Sponsor clarified that Medicis Pharmaceutical Corporation is the licensee for development of the Clin-RA product. The Sponsor also stated that they were unaware of the Dispute Resolution submission by Medicis Pharmaceutical Corporation until yesterday, March 8, 2005.

The Agency requested a letter from Dow which authorizes the request for Dispute Resolution submitted by Medicis Pharmaceutical Corporation as well as allowing further communication with Medicis Pharmaceutical Corporation. The Sponsor stated that a letter giving this authorization would be submitted.

**Addendum:** An authorization letter from Dow Pharmaceutical Sciences, dated March 8, 2005, was received on March 10, 2005.

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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration  
Rockville, MD 20857

NDA 50-802

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

Dear Mr. Calvarese:

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

We also refer to the meeting between representatives of your firm and the FDA on February 16, 2005. The purpose of the meeting was to discuss the briefing document submitted to the above referenced NDA.

The official minutes of that meeting are enclosed.

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

Sincerely,

*{See appended electronic signature page}*

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

Enclosure

**MEMORANDUM OF MEETING MINUTES**



**Meeting Date:** February 16, 2005, Time: 10:30 AM

**Location:** 9201 Corporate, N225

**Application:** NDA 50-802

**Indication:** Treatment of Acne Vulgaris

**Meeting ID:** 14759, Post NA Meeting

**Sponsor:** Dow Pharmaceutical Sciences

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

**Meeting Recorder:** Jacquelyn Smith, Project Manager

**FDA Attendees, Titles, and Office/Division:**

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

Stanka Kukich, M.D., Deputy Division Director, DDDDP, HFD-540

Mohamed Alesh, Ph.D., Team Leader, Biostatistics, DBIII, HFD-725

Shiowjen Lee, Ph.D., Biostatistics Reviewer, DBIII, HFD-725

Mat Soukup, Ph.D., Biostatistics Reviewer, HFD-725

Markham C. Luke, M.D., Ph.D., Team Leader, Dermatology, DDDDP, HFD-540

Brenda Carr, M.D., Clinical Reviewer, DDDDP

Jill Merrill, Ph.D., Pharmacology/Toxicology Reviewer, HFD-540

Jacquelyn Smith, Regulatory Project Manager, DDDDP, HFD-540

**Medicis Participants**

Todd Plott, MD, VP Clinical and Regulatory Affairs

Jur Strobos, MD, Medical Director

**Dow Pharmaceutical Sciences Participants**

Dr. Bhaskar Chaudhuri, President and CEO

Barry Calvarese, MS, VP Regulatory Affairs

John Quiring, Ph.D., Biostatistician

**Medical Consultants**

[REDACTED]

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**Purpose:**

To discuss the background and questions submitted in the briefing package dated January 10, 2005, with regard to the Not Approvable NDA action.

## Clinical

Discussion of the relevant historical background included mention that at the End-of-Phase 2 Meeting (December 16, 2002), the sponsor proposed to assess primary efficacy on the global scale by the proportion of subjects who were clear or almost clear on global assessment or who show a two-grade improvement on the global scale. In response to this proposal, the Division had advised that, while two-grade improvement data could be submitted as supportive, the Division would encourage measurement of efficacy by the proportion of subjects who are 'clear' or 'almost clear' on the dichotomized global scale at efficacy evaluation.

The sponsor asserted that the Division ignored the advice of the advisory committee that was held on November 4, 2002, it was felt by the committee that the Investigator's Global Assessment was not useful.

It was discussed that the sponsor's combination product, Clin-RA, contains the active ingredients clindamycin and tretinoin in a gel vehicle. The phase 3 protocols specified that the Evaluator's Global Severity Score would be dichotomized to success (clear or almost clear) or failure and that in the primary efficacy analyses for the comparison between Clin-RA Gel and clindamycin gel and tretinoin gel, superiority would be demonstrated if there was statistical significance in both (1) and (2);

(1) two of three of the following lesion counts:

- mean percent change from baseline at Week 12 in inflammatory lesion counts,
- mean percent change from baseline at Week 12 in non-inflammatory lesion counts,
- mean percent change from baseline at Week 12 in total lesion counts

(2) the percent of subjects who were "clear" or "almost clear" at Week 12, as judged by an Evaluator's Global Severity Score.

Additionally, the phase 3 protocols indicated that supplemental analyses would be conducted on the subset of subjects who had a baseline evaluator's Global Severity Score of severe and showed at least a two grade reduction in Global Severity Score at Week 12.

Pertaining to the specified primary analyses, the contribution of tretinoin to efficacy was not demonstrated for the dichotomized global assessment in either pivotal trial.

Additionally, the sponsor discussed that it was more difficult to assess for inflammation in African-American patients and asserted that that was possibly the reason why their original study was underpowered. The Agency queried the sponsor whether investigators more expert in assessing skin of color may be needed.

The sponsor also asserted that the patients with acne graded as severe may have hampered the total population achieving clear or almost clear. See Biostat comments regarding specific discussion.

The sponsor brought for discussion two primary areas of concern regarding how they could proceed in their development program:

**Sponsor Issue #1: Would a 2-arm study be acceptable?**

**Agency Response:** A two-armed study that demonstrates the superiority of the Clin-RA product compared to clindamycin in the product vehicle might be acceptable; however, the sponsor should provide a scientific rationale for not including a vehicle arm in the new study. In the proposed two-armed trial, the representation in the severe category and the Inclusion and Exclusion criteria should be the same as in the previously conducted Phase 3 trials. See also Biostatistics discussion below.

**Sponsor Issue #2: Would lesion counts be acceptable as the primary endpoint and global be taken as a secondary endpoint?**

**Agency Response:** The Agency does not agree that lesions counts should be the sole primary endpoint or that the global assessment should be relegated to a secondary endpoint.

**Biostatistics**

Results of Phase 3 studies 06 and 07 are summarized by the following:

Lesion Reduction –

- Clin-RA was superior to monads (clindamycin and tretinoin) and vehicle for inflammatory, non-inflammatory and total lesion reduction in Study 06.
- Clin-RA was superior to monads and vehicle for inflammatory and total lesion reduction in Study 07. Clin-RA was superior to vehicle for non-inflammatory lesion reduction, but not superior to monads.

Dichotomized IGA –

- Clear or almost clear – Clin-RA was superior to tretinoin and vehicle, but not superior to Clindamycin in Study 06 and Study 07.
- Clear or almost clear or at least a 2-grade reduction – Clin-RA was superior to Clindamycin in Study 07, but not in Study 06.
- At least a 2-grade improvement – Clin-RA was superior to Clindamycin in Study 07, but not in Study 06.

The comparisons of treatment arms for the two studies are presented below:

Endpoints	Study 06			Study 07		
	Clin-RA vs. Clindamycin	Clin-RA vs. Tretinoin	Clin-RA vs. Vehicle	Clin-RA vs. Clindamycin	Clin-RA vs. Tretinoin	Clin-RA vs. Vehicle
Infla.	0.028	< 0.001	< 0.001	0.020	< 0.001	< 0.001
Non-infla.	< 0.001	0.018	< 0.001	0.088	0.110	< 0.001
Total	< 0.001	0.002	< 0.001	0.018	0.002	< 0.001
Global	0.172	0.032	< 0.001	0.094	0.002	< 0.001

Modified Global <sup>a</sup>	0.100	NA	NA	0.030	NA	NA
2-grade Global <sup>b</sup>	0.150	NA	NA	0.026	NA	NA
<sup>a</sup> Sponsor's modified global – success is defined as IGA of clear, or almost clear, or at least a 2-grade improvement from baseline. <sup>b</sup> 2-grade Global – success is defined as at least a 2-grade improvement from baseline in IGA.						

During the meeting, the sponsor asserted that the Division's definition of success in the IGA (i.e., clear or almost clear) ignored the patients who had severe disease at baseline. In addition, the sponsor claimed that they enrolled a large percentage of severe disease patients as compared to other acne trials (about 30%). Therefore, the sponsor thought it would be reasonable that patients with at least a 2-grade improvement be considered as success.

*Meeting addendum: Review of the data for the two clinical trials shows:*

- *The percent of patients with severe/very severe disease at baseline were 11% for Study 06 and 18% for Study 07.*
- *For Study 06, totals of 13 (3.1%) and 4 (1.9%) patients who had severe IGA at baseline in Clin-RA and clindamycin, respectively, and who did not achieve clear or almost clear at week 12, achieved at least a 2-grade improvement in IGA. Adding these patients to success does not rescue the study.*
- *For Study 07, totals of 21 (5%) and 6 (2.8%) patients in Clin-RA and clindamycin, who had severe/very severe disease and who did not achieve clear or almost clear at week 12, had at least a 2-grade improvement. The superiority of Clin-RA to clindamycin would have been demonstrated by adding these patients to success.*

Based on the efficacy evaluation of the sponsor's clinical trial data, the Division concluded that the studies failed to establish the contribution of tretinoin to efficacy according to the Global Acne scale. Importantly, the studies were not powered for this co-primary endpoint at the IND stage. The Division had advised the sponsor at the End-of-Phase 2 meeting (dated 12/16/02):

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

The sponsor chose to proceed with their Phase 3 trials without powering the trials according to the dichotomized EGE. This is evident from the sponsor's submission of IND 65,531/SN-005 (dated 1/6/03) which stated on page 0015 that:

“During the meeting, Dow explained that there are no previous studies using the EGE from which to base power calculations; therefore, it is our risk to proceed with the current power calculations.”

The Division documented the sponsor’s statement which indicated that they are willing to take risks by proceeding with power calculation based only on percent change from baseline for inflammatory, non-inflammatory and total lesions, as conveyed to the sponsor on 3/27/03. Also, the sponsor’s limited power calculations were apparently based on a non-identical formulation with both clindamycin and tretinoin.

During the meeting, the sponsor raised the following issues about the Global evaluation as one of the co-primary efficacy endpoints for acne indication:

- It is insensitive to the change of non-inflammatory lesion counts.
- By requiring ‘clear’ or ‘almost clear’ as a criterion for success it does not measure all improvement in acne condition. For example, a patient with severe disease at baseline and achieve improvement of 2 grades on the scale but did not achieve clear or almost clear would be classified as failures.
- It is difficult to judge treatment success on patients with dark-color skin.
- ~~\_\_\_\_\_~~ proposed during the meeting that total lesion counts should be considered as the criterion for efficacy evaluation instead of the Global.

b(4)

In response the Agency stated that both inflammatory and non-inflammatory lesions contribute to the Global, however, inflammatory lesions are a more important component than non-inflammatory lesions for explaining the Global. Thus, the Global takes into account both types of lesions with more emphasis on the inflammatory lesions, unlike the total lesion counts which gives an equal weight to each of both lesion types.

The sponsor’s protocol pre-defined criterion for success in the Global is ‘clear’ or ‘almost clear’, and the Agency considered the 2-grade reduction as a supportive analysis.

The sponsor asserted that the advisory Committee members were not in favor of using the Global as a co-primary endpoint.

Following some discussion, the sponsor indicated that they are open to the possibility of conducting a new trial with two treatment arms to:

- Establish the contribution of tretinoin to the efficacy by comparing Clin-RA and Clindamycin.
- Evaluate the efficacy based on the reduction of lesion counts alone and use the dichotomized Global as a secondary endpoint (not co-primary).

In response,

- If elimination of some treatment arms is clinically acceptable, then the sponsor would need to provide argument that, based on the results from the previous trials (i.e., 06 and 07), significant efficacy findings for the eliminated arms would be maintained with a high probability.
- The patient population for such a trial should be similar to those two trials conducted previously (i.e., Study 7001-G2HP-06-02 and Study 7001-G2HP-07-02) in terms of disease severity, race, etc.

- The dichotomized Global is one of the needed co-primary efficacy endpoints in addition to the reduction of lesion counts (i.e., inflammatory, non-inflammatory, and total). The study should be powered for all co-primary efficacy endpoints. Success in the Global should be clear or almost clear.

*Meeting Addendum:*

*Inclusion of all treatment arms would make it easier to interpret study findings. This is relevant in particular if the response rates in the proposed new trial turn out to be inconsistent with those reported in the original trials (Study 06 and Study 07).*

**Project Management**

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

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/s/

Jonathan Wilkin  
3/18/05 03:04:12 PM

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**NDA 50-802**

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

Dear Mr. Calvarese:

We received your December 17, 2004 correspondence requesting a meeting to discuss the issues identified in our December 7, 2004 Not-Approvable Letter for **Clin-RA Gel**.

This is a Type C meeting, and is scheduled as follows:

Date: Wednesday, February 16, 2005  
Time: 10:00-11:00 AM, EST  
Location: 9201 Corporate Blvd., Rockville, MD 20850

Please provide the background information at least a month prior to the meeting. Submit the original copy to your NDA, and 12 copies, each marked "DESK COPY", directly to Sandy Childs at the above address. If we do not receive it by January 17, 2004, we may have to reschedule.

If you have any questions, call Sandy Childs, Consumer Safety Technician, at 301-827-2061.

Sincerely,

*{See appended electronic signature page}*  
Mary Jean Kozma-Fornaro  
Supervisor, Project Management Staff  
Division of Dermatologic & Dental Drug Products  
Office of Drug Evaluation V  
Center for Drug Evaluation and Research

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Suzanne Childs  
12/29/04 01:48:33 PM  
Signed for Mary Jean Kozma-Fornaro

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NDA 50-802

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

Dear Mr. Calvarese:

Please refer to your new drug application (NDA) dated February 6, 2004, received February 9, 2004, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for TRADENAME (clindamycin 1%, tretinoin 0.025%) Gel.

We acknowledge receipt of your submissions dated February 13, March 25, April 19, May 11, May 24, June 4, June 7, July 15, August 2, August 20, August 23, October 22, October 27 and November 8, 2004.

We completed our review and find the information presented is inadequate. Therefore, the application is not approvable under section 505(d) of the Act and 21 CFR 314.125(b). The deficiencies are summarized as follows:

The contribution to efficacy of each component of your combination product was not adequately demonstrated. Specifically, the contribution of tretinoin to efficacy was not adequately demonstrated.

To address this deficiency, the contribution of tretinoin to the efficacy of this combination product should be documented in an additional clinical study.

Although not the basis for the Not Approvable action for this application, the following issues should be addressed in the resubmission:

Chemistry:

1. 

2. 

  
**b(4)**  


1   Page(s) Withheld

Trade Secret / Confidential (b4)

Draft Labeling (b4)

Draft Labeling (b5)

Deliberative Process (b5)

11. T

12.

13.

14.

b(4)

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17.

When you respond to the above deficiencies, include a safety update as described at 21 CFR 314.50(d)(5)(vi)(b). The safety update should include data from all non-clinical and clinical studies of the drug under consideration regardless of indication, dosage form, or dose level.

1. Describe in detail any significant changes or findings in the safety profile.
2. When assembling the sections describing discontinuations due to adverse events, serious adverse events, and common adverse events, incorporate new safety data as follows:
  - Present new safety data from the studies for the proposed indication using the same format as the original NDA submission.
  - Present tabulations of the new safety data combined with the original NDA data.
  - Include tables that compare frequencies of adverse events in the original NDA with the retabulated frequencies described in the bullet above.
  - For indications other than the proposed indication, provide separate tables for the frequencies of adverse events occurring in clinical trials.

3. Present a retabulation of the reasons for premature study discontinuation by incorporating the drop-outs from the newly completed studies. Describe any new trends or patterns identified.
4. Provide case report forms and narrative summaries for each patient who died during a clinical study or who did not complete a study because of an adverse event. In addition, provide narrative summaries for serious adverse events.
5. Describe any information that suggests a substantial change in the incidence of common, but less serious, adverse events between the new data and the original NDA data.
6. Provide a summary of worldwide experience on the safety of this drug. Include an updated estimate of use for drug marketed in other countries.
7. Provide English translations of current approved foreign labeling not previously submitted.

Within 10 days after the date of this letter, you are required to amend the application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.120. If you do not follow one of these options, we will consider your lack of response a request to withdraw the application under 21 CFR 314.65. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

Under 21 CFR 314.102(d), you may request an informal meeting or telephone conference with this division to discuss what steps need to be taken before the application may be approved.

The drug product may not be legally marketed until you have been notified in writing that this application is approved.

Please also be reminded to submit appropriate patent certification at the time of the New Drug Application (NDA) submission.

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

Sincerely,

*{See appended electronic signature page}*

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

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Jonathan Wilkin  
12/7/04 04:02:39 PM

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# Memo

**To:** Jonathan Wilkin, MD  
Director, Division of Dermatologic and Dental Drug Products  
HFD-540

**From:** Felicia Duffy, RN, BSN  
Safety Evaluator, Division of Medication Errors and Technical Support  
Office of Drug Safety  
HFD-420

**Through:** Alina Mahmud, R.Ph., Team Leader  
Carol Holquist, R.Ph., Director  
Division of Medication Errors and Technical Support  
Office of Drug Safety  
HFD-420

**Date:** December 6, 2004

**Re:** ODS Consult 04-0290 [redacted] (Clindamycin and Tretinoin Topical Gel); NDA 50-802

b(4)

This memorandum is in response to a November 8, 2004 request from your Division for a review of the proprietary name [redacted] (NDA 50-802). Upon the initial steps in the proprietary name review process (EPD), the Division of Medication Errors and Technical Support (DMETS) had concerns about the phonetic similarity with [redacted] and the currently marketed drug product, Zofran.

b(4)

Zofran (ondansetron HCl) is an antiemetic drug product used in association with chemotherapy, radiation therapy and post-anesthesia. Zofran and [redacted] are almost identical in pronunciation. However, the products differ in indication for use, dosage forms, route of administration, and dosing regimen. DMETS recognizes these differences; however, when discussing the two names during an Expert Panel Discussion (EPD), it was extremely difficult to verbalize each name without seeking phonetic clarification about the name in question. Thus we anticipate several reports of potential error with this name pair. Due to the similarity in pronunciation, DMETS believes we can object to name based on 21 CFR 201.10(c)(5).

b(4)

As per discussion with the Division of Dermatologic and Dental Drug Products Project Manager, Jacquelyn Smith, on December 6, 2004, the Division concurs with DMETS' comments. Therefore, DMETS will not proceed with the safety review of the proposed proprietary name, [redacted], since the Division supports DMETS' objection of the name based on phonetic similarity to Zofran. We recommend the sponsor be notified immediately of the decision to reject the name based on the promotional concerns and request submission of an alternative proprietary name for NDA 50-802. Please forward the alternate name for DMETS review upon submission.

b(4)

If you have any questions or need clarification, please contact the medication errors project manager, Sammie Beam at 301-827-2102.

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/s/

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Felicia Duffy  
12/8/04 06:04:53 AM  
DRUG SAFETY OFFICE REVIEWER

Alina Mahmud  
12/8/04 07:45:08 AM  
DRUG SAFETY OFFICE REVIEWER

Carol Holquist  
12/8/04 07:59:25 AM  
DRUG SAFETY OFFICE REVIEWER

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

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**FACSIMILE TRANSMITTAL SHEET**

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**DATE:** November 29, 2004

<b>To:</b> Barry Calverese, MS, VP, Regulatory and Clinical Affairs	<b>From:</b> Jacquelyn Smith, Project Manager
<b>Company:</b> Dow Pharmaceutical Sciences	Division of Dermatologic and Dental Drug Products
<b>Fax number:</b> 707-793-0145	<b>Fax number:</b> 301-827-2075/2091
<b>Phone number:</b> 707-793-2600	<b>Phone number:</b> 301-827-2027
<b>Subject:</b> Old Antibiotic: Change from NDA 21-739 to NDA 50-802	

**Total no. of pages including cover:** 3

**Comments:**

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**Document to be mailed:**  YES  NO

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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration  
Rockville, MD 20857

NDA 50-802

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

Dear Mr. Calvarese:

Please refer to your New Drug Application (NDA) submitted February 6, 2004, under the Federal Food, Drug, and Cosmetic Act for ClinRA (clindamycin 1%, tretinoin 0.025%) Gel.

The ClinRA (clindamycin 1%, tretinoin 0.025%) Gel application that was previously numbered as NDA 21-739 has been re-numbered to NDA 50-802.

We refer to the guidance document issued by the Agency in May 1998, *Guidance for Industry and Reviewers Repeal of Section 507 of the Federal Food, Drug, and Cosmetic Act*. This guidance document defines the administrative actions required by the Agency for reviewing and approving antibiotic drug applications that were submitted after November 21, 1997. We also refer to the *Federal Register* notice Docket Number: 99N-3088, *Marketing Exclusivity and Patent Provisions for Certain Antibiotic Drugs* issued January 24, 2000, which lists the active drug substances, including any derivative thereof, that are directly affected by the repeal of Section 507.

All documentation regarding this application should be directed to NDA 50-802 from this date forward.

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

Sincerely,

{See appended electronic signature page}

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

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/s/

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Stanka Kukich  
11/26/04 01:58:12 PM  
sign off for Dr. Jonathan Wilkin, Division Director

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## REQUEST FOR CONSULTATION

TO (Division/Office):

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

FROM:

Jacquelyn Smith  
Project Manager  
Division of Dermatologic and Dental Drug Products

DATE:

November 17, 2004

IND NO.

NDA NO. 21-739

TYPE OF DOCUMENT

Tradename Request

DATE OF DOCUMENT:

November 8, 2004

NAME OF DRUG:

clindamycin, 1% - tretinoin,  
0.025%

PRIORITY CONSIDERATION

CLASSIFICATION OF DRUG:

3S

DESIRED COMPLETION DATE:

January 8, 2004  
PDUFA Date: December 9, 2004

NAME OF FIRM: Dow Pharmaceutical Sciences

### REASON FOR REQUEST

#### I. GENERAL

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

#### II. BIOMETRICS

STATISTICAL EVALUATION BRANCH

STATISTICAL APPLICATION BRANCH

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

#### III. BIOPHARMACEUTICS

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

#### IV. DRUG EXPERIENCE

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

#### V. SCIENTIFIC INVESTIGATIONS

CLINICAL

PRECLINICAL

#### COMMENTS/SPECIAL INSTRUCTIONS:

The Sponsor requests review of the following name:   
The previous tradename "Clin RA" was found unacceptable on October 5, 2004.

**b(4)**

**PDUFA DATE: December 9, 2004**

SIGNATURE OF REQUESTER

METHOD OF DELIVERY (Check one)

MAIL

HAND

SIGNATURE OF RECEIVER

SIGNATURE OF DELIVERER



# Dow Pharmaceutical Sciences

The D in Topicals R&D

Since 1977

*Via Federal Express*

November 8, 2004

Jonathan Wilkin, MD  
Division of Dermatological and Dental Drug Products  
Office of Drug Evaluation V  
Center for Drug Evaluation and Research  
Food and Drug Administration  
Central Document Mail Room  
9201 Corporate Boulevard, HFD-540  
Rockville, MD 20850

**RE: NDA 21-739 for Clin RA (clindamycin, 1%; tretinoin, 0.025%) Gel  
for the Indication of Acne Vulgaris**

**Amendment No. 0003: Request for Proprietary Name for Clin RA Gel  
Drug Product**

Dear Dr. Wilkin:

Dow Pharmaceutical Sciences (DPS) is in receipt of a facsimile message from Jacquelyn Smith, FDA Project Manager for the Clin RA project, dated October 19, 2004. In this message Ms. Smith informed the Sponsor that the Division of Medication Errors and Technical Support (DMETS) does not recommend the use of the proprietary name Clin RA Gel for this application, primarily due to concerns related to look-alike and/or sound-alike confusion with Clindagel and Cleocin. Additional concerns expressed by DMETS were the use of the dosage form in the proprietary name and the graphic presentation of the name.

After consideration of these and other issues, the Sponsor made a decision to change the proprietary name of this product to \_\_\_\_\_ Therefore, this Amendment 0003 is submitted as a formal request to change the name of the Clin RA Gel product to \_\_\_\_\_ from this date forward. **b(4)**

Copies of the revised carton and container labeling and the package insert, in Word, are enclosed in this submission as Attachment 1, Attachment 2, and Attachment 3, respectively. The submission also contains a Form FDA 356h.

Jonathan Wilkin, MD  
NDA 21-739 – Amendment No. 0003  
November 8, 2004  
Page 2

The facsimile received by Ms. Smith on October 19, 2004 also contained additional information on DMETS' review of the product's labels and labeling from a safety perspective and identified some areas of possible improvements to the labels and labeling, which might minimize potential user error. Please be advised that the Sponsor will consider these recommendations when finalizing labels and labeling for the \_\_\_\_\_ product.

b(4)

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

Should you require further information regarding this submission, please contact me by phone – 707.793.2600, by fax – 707.793.0145, or by e-mail – [bcalvarese@dowpharmsci.com](mailto:bcalvarese@dowpharmsci.com)

Sincerely,



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

/pm

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DEPARTMENT OF HEALTH AND HUMAN SERVICES  
FOOD AND DRUG ADMINISTRATION

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

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

FOR FDA USE ONLY

APPLICATION NUMBER

**APPLICANT INFORMATION**

NAME OF APPLICANT Dow Pharmaceutical Sciences	DATE OF SUBMISSION 11/8/04
TELEPHONE NO. (Include Area Code) 707-793-2600	FACSIMILE (FAX) Number (Include Area Code) 707-793-0145
APPLICANT ADDRESS (Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued): 1330A Redwood Way Petaluma, CA	AUTHORIZED U.S. AGENT NAME & ADDRESS (Number, Street, City, State, ZIP Code, telephone & FAX number) IF APPLICABLE

**PRODUCT DESCRIPTION**

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER (if previously issued) 21-739		
ESTABLISHED NAME (e.g., Proper name, USP/USAN name) Clindamycin and Tretinoin	PROPRIETARY NAME (trade name) IF ANY Clin RA Gel	
CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME (if any)	CODE NAME (if any)	
DOSAGE FORM: Topical Gel	STRENGTHS: Clindamycin: 1%, Tretinoin: 0.25%	ROUTE OF ADMINISTRATION: Topical

(PROPOSED) INDICATION(S) FOR USE:

Acne vulgaris

**APPLICATION DESCRIPTION**

APPLICATION TYPE (check one)	<input type="checkbox"/> NEW DRUG APPLICATION (CDA, 21 CFR 314.50)	<input type="checkbox"/> ABBREVIATED NEW DRUG APPLICATION (ANDA, 21 CFR 314.94)	<input type="checkbox"/> BIOLOGICS LICENSE APPLICATION (BLA, 21 CFR Part 601)
IF AN NDA, IDENTIFY THE APPROPRIATE TYPE	<input type="checkbox"/> 505 (b)(1)	<input checked="" type="checkbox"/> 505 (b)(2)	
IF AN ANDA, OR 505(b)(2), IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION			
Name of Drug	Holder of Approved Application		
TYPE OF SUBMISSION (check one)	<input type="checkbox"/> ORIGINAL APPLICATION	<input checked="" type="checkbox"/> AMENDMENT TO APENDING APPLICATION	<input type="checkbox"/> RESUBMISSION
	<input type="checkbox"/> PRESUBMISSION	<input type="checkbox"/> ANNUAL REPORT	<input type="checkbox"/> ESTABLISHMENT DESCRIPTION SUPPLEMENT
	<input type="checkbox"/> LABELING SUPPLEMENT	<input type="checkbox"/> CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT	<input type="checkbox"/> EFFICACY SUPPLEMENT
	<input type="checkbox"/> OTHER		

IF A SUBMISSION OF PARTIAL APPLICATION, PROVIDE LETTER DATE OF AGREEMENT TO PARTIAL SUBMISSION: \_\_\_\_\_

IF A SUPPLEMENT, IDENTIFY THE APPROPRIATE CATEGORY  CBE  CBE-30  Prior Approval (PA)

**REASON FOR SUBMISSION**

To request proprietary name for the Clin RA Gel product

PROPOSED MARKETING STATUS (check one)	<input checked="" type="checkbox"/> PRESCRIPTION PRODUCT (Rx)	<input type="checkbox"/> OVER THE COUNTER PRODUCT (OTC)
NUMBER OF VOLUMES SUBMITTED	2 copies	THIS APPLICATION IS <input checked="" type="checkbox"/> PAPER <input type="checkbox"/> PAPER AND ELECTRONIC <input type="checkbox"/> ELECTRONIC

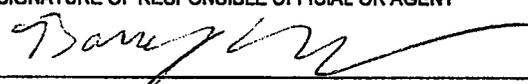
**ESTABLISHMENT INFORMATION (Full establishment information should be provided in the body of the Application.)**  
Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g. Final dosage form, Stability testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.

Establishment information provided in original electronic NDA submission

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

Dow Pharmaceutical Sciences IND 65,531: ~~DMF~~ ~~DMF~~  
~~FDA Registration~~ ~~DMF~~ ~~DMF~~ ~~DMF~~ ~~DMF~~ ~~DMF~~  
~~Registration #~~ ~~Registration~~

b(4)

This application contains the following items: (Check all that apply)		
<input type="checkbox"/>	1. Index	
<input checked="" type="checkbox"/>	2. Labeling (check one)	<input checked="" 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	
<input type="checkbox"/>	A. Chemistry, manufacturing, and controls information (e.g., 21 CFR 314.50(d)(1); 21 CFR 601.2)	
<input type="checkbox"/>	B. Samples (21 CFR 314.50 (e)(1); 21 CFR 601.2 (a)) (Submit only upon FDA's request)	
<input type="checkbox"/>	C. Methods validation package (e.g., 21 CFR 314.50(e)(2)(i); 21 CFR 601.2)	
<input type="checkbox"/>	5. Nonclinical pharmacology and toxicology section (e.g., 21 CFR 314.50(d)(2); 21 CFR 601.2)	
<input type="checkbox"/>	6. Human pharmacokinetics and bioavailability section (e.g., 21 CFR 314.50(d)(3); 21 CFR 601.2)	
<input type="checkbox"/>	7. Clinical Microbiology (e.g., 21 CFR 314.50(d)(4))	
<input type="checkbox"/>	8. Clinical data section (e.g., 21 CFR 314.50(d)(5); 21 CFR 601.2)	
<input type="checkbox"/>	9. Safety update report (e.g., 21 CFR 314.50(d)(5)(vi)(b); 21 CFR 601.2)	
<input type="checkbox"/>	10. Statistical section (e.g., 21 CFR 314.50(d)(6); 21 CFR 601.2)	
<input type="checkbox"/>	11. Case report tabulations (e.g., 21 CFR 314.50(f)(1); 21 CFR 601.2)	
<input type="checkbox"/>	12. Case report forms (e.g., 21 CFR 314.50 (f)(2); 21 CFR 601.2)	
<input type="checkbox"/>	13. Patent information on any patent which claims the drug (21 U.S.C. 355(b) or (c))	
<input type="checkbox"/>	14. A patent certification with respect to any patent which claims the drug (21 U.S.C. 355 (b)(2) or (j)(2)(A))	
<input type="checkbox"/>	15. Establishment description (21 CFR Part 600, if applicable)	
<input type="checkbox"/>	16. Debarment certification (FD&C Act 306 (k)(1))	
<input type="checkbox"/>	17. Field copy certification (21 CFR 314.50 (l)(3))	
<input type="checkbox"/>	18. User Fee Cover Sheet (Form FDA 3397)	
<input type="checkbox"/>	19. Financial Information (21 CFR Part 54)	
<input checked="" type="checkbox"/>	20. OTHER (Specify) Request for proprietary name	
<b>CERTIFICATION</b>		
<p>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:</p> <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 820.</li> <li>2. Biological establishment standards in 21 CFR Part 600.</li> <li>3. Labeling regulations in 21 CFR Parts 201, 606, 610, 660, and/or 809.</li> <li>4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR Part 202.</li> <li>5. Regulations on making changes in application in FD&amp;C Act section 506A, 21 CFR 314.71, 314.72, 314.97, 314.99, and 601.12.</li> <li>6. Regulations on Reports in 21 CFR 314.80, 314.81, 600.80, and 600.81.</li> <li>7. Local, state and Federal environmental impact laws.</li> </ol> <p>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.</p> <p>The data and information in this submission have been reviewed and, to the best of my knowledge are certified to be true and accurate.</p> <p><b>Warning:</b> A willfully false statement is a criminal offense, U.S. Code, title 18, section 1001.</p>		
SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT	TYPED NAME AND TITLE	DATE:
	Barry M. Calvarese, MS, VP Regulatory & Clinical Affairs	11/8/04
ADDRESS (Street, City, State, and ZIP Code)		Telephone Number
1330A Redwood Way, Petaluma, CA 94954-1169		( 707 ) 793-2600
<p>Public reporting burden for this collection of information is estimated to average 24 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:</p> <p>Department of Health and Human Services Food and Drug Administration CDER, HFD-99 1401 Rockville Pike Rockville, MD 20852-1448</p> <p>Food and Drug Administration CDER (HFD-94) 12229 Wilkins Avenue Rockville, MD 20852</p> <p>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.</p>		

15 Page(s) Withheld

Trade Secret / Confidential (b4)

Draft Labeling (b4)

Draft Labeling (b5)

Deliberative Process (b5)

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

/s/

-----  
Jacquelyn Smith  
11/17/04 09:54:21 AM

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On Original

**MEMORANDUM**

DEPARTMENT OF HEALTH AND HUMAN SERVICES  
Public Health Service  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Division of Drug Marketing, Advertising, and Communications

**Predecisional Agency Information**

---

Date: November 2, 2004  
From: Sonny Saini, Pharm.D. - DDMAC  
To: Jacquelyn Smith  
Re: ClinRA Gel (clindamycin, 1% - tretinoin, 0.025%)  
N 21-739

**Clinical Studies**

- The Clinical Studies section of the label states ' ~~\_\_\_\_\_~~  
~~\_\_\_\_\_~~ Is the overall improvement that is referred to in this statement statistically significant? If not, we recommend deleting this statement.

b(4)

**Indications and Usage**

- This section states " ~~\_\_\_\_\_~~  
~~\_\_\_\_\_~~ Is ClinRA Gel indicated for mild, moderate, or severe acne vulgaris? We recommend including this information in this section of the label.
- Is ClinRA Gel indicated as first line therapy for acne vulgaris? The Cleocin T label states "In view of the potential for diarrhea and pseudomembranous colitis, the physician should consider whether other agents are more appropriate." Should this statement be incorporated in the Indications and Usage section of this label?

b(4)

**Warnings**

- We recommend for ease of reading that the Warnings section not be presented in all capital letters.

**Adverse Reactions**

- This section states “ [REDACTED] b(4)  
[REDACTED]  
However, the table presents dry skin to occur with only a 2% incidence. Is this a misprint in the table?
- Can the statement “ [REDACTED] b(4)  
[REDACTED] be quantified?
- This section states [REDACTED] b(4)  
[REDACTED] Are all the adverse reactions reversible upon discontinuation of therapy? If not, we recommend stating specifically the ones that are reversible.

Appears This Way  
On Original

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

/s/

-----  
Sonny Saini  
11/8/04 01:38:59 PM  
DDMAC REVIEWER

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Dow Pharmaceutical Sciences

The D in Topicals R&D

Since 1977

RECEIVED

OCT 28 2004

MEGA / CDER

*Via Federal Express*

October 27, 2004

*2004/1*  
NEW CORRESP

Jonathan Wilkin, MD  
Division of Dermatological and Dental Drug Products  
Office of Drug Evaluation V  
Center for Drug Evaluation and Research  
Food and Drug Administration  
Central Document Mail Room  
9201 Corporate Boulevard, HFD-540  
Rockville, MD 20850

**RE: NDA 21-739 for Clin RA (clindamycin, 1%; tretinoin, 0.025%) Gel  
for the Indication of Acne Vulgaris**

**Amendment No. 0003: Request for Proprietary Name for Clin RA Gel  
Drug Product**

Dear Dr. Wilkin:

Dow Pharmaceutical Sciences (DPS) is in receipt of a facsimile message from Jacquelyn Smith, FDA Project Manager for the Clin RA project, dated October 19, 2004. In this message Ms. Smith informed the Sponsor that the Division of Medication Errors and Technical Support (DMETS) does not recommend the use of the proprietary name Clin RA Gel for this application, primarily due to concerns related to look-alike and/or sound-alike confusion with Clindagel and Cleocin. Additional concerns expressed by DMETS were the use of the dosage form in the proprietary name and the graphic presentation of the name.

After consideration of these and other issues, the Sponsor made a decision to change the proprietary name of this product to . Therefore, this Amendment 0003 is submitted as **b(4)** a formal request to change the name of the Clin RA Gel product to  from this date forward.

The facsimile received by Ms. Smith on October 19, 2004 also contained additional information on DMETS' review of the product's labels and labeling from a safety perspective and identified some areas of possible improvements to the labels and labeling, which might minimize potential user error. Please be advised that the Sponsor will consider these recommendations when finalizing labels and labeling for the  product.

DUPLICATE

**b(4)**

Jonathan Wilkin, MD  
NDA 21-739 – Amendment No. 0003  
October 27, 2004  
Page 2

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

Should you require further information regarding this submission, please contact me by phone – 707.793.2600, by fax – 707.793.0145, or by e-mail – [bcalvarese@dowpharmsci.com](mailto:bcalvarese@dowpharmsci.com)

Sincerely,



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

/pm

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On Original



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

<input type="checkbox"/>	1. Index
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<input type="checkbox"/>	18. User Fee Cover Sheet (Form FDA 3397)
<input type="checkbox"/>	19. Financial Information (21 CFR Part 54)
<input checked="" type="checkbox"/>	20. OTHER (Specify) Request for proprietary name

**CERTIFICATION**

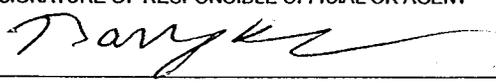
I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA.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

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

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

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

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

SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT 	TYPED NAME AND TITLE Barry M. Calvarese, MS, VP Regulatory & Clinical Affairs	DATE: 10/27/04
ADDRESS (Street, City, State, and ZIP Code) 1330A Redwood Way, Petaluma, CA 94954-1169		Telephone Number ( 707 ) 793-2600

Public reporting burden for this collection of information is estimated to average 24 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

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

Food and Drug Administration  
CDER (HFD-94)  
12229 Wilkins Avenue  
Rockville, MD 20852

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# Dow Pharmaceutical Sciences

The D in Topicals R&D

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October 22, 2004

Jonathan Wilkin, MD  
Division of Dermatological and Dental Drug Products  
Office of Drug Evaluation V  
Center for Drug Evaluation and Research  
Food and Drug Administration  
Central Document Mail Room  
9201 Corporate Boulevard, HFD-540  
Rockville, MD 20850

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OCT 25 2004

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N-000(BZ)

ORIG AMENDMENT

**RE: NDA 021739 for Clin RA (clindamycin, 1%; tretinoin, 0.025%) Gel  
for the Indication of Acne Vulgaris**

**Request for Information: Response to FDA Request of October 20, 2004,  
Plasma Samples and Extended Stability Data**

Dear Dr. Wilkin:

Dow Pharmaceutical Sciences (DPS) is submitting this Amendment 002 to the pending NDA application 021739, Clin RA Gel for the indication of acne vulgaris, as a result of a telephonic request for information on October 20, 2004 from Chandra Chaurasia, PhD, Reviewer, and Raman K. Baweja, PhD, RPh, Team Leader, of the Clinical Pharmacology & Biopharmaceutics team reviewing NDA 021739. Following are the requests for information, with a response from DPS for each request:

1. *For the PK study, Protocol 7001-G2-HP-C-02-02, please provide the date plasma samples were drawn from subjects and the date the samples were analyzed.*

**Response:** Samples were drawn on or about November 2, 2002 and were analyzed on December 10, 2002. Please see the attached spreadsheet for details regarding this information. (Attachment 1)

ORIGINAL

2. Please provide an explanation of the extended stability for clindamycin and tretinoin plasma samples and where this information may be found in the electronic NDA for Clin RA (clindamycin, 1%; tretinoin, 0.025%) Gel, NDA 21-739.

**Response:**

Clindamycin:

See ~~\_\_\_\_\_~~ Report DCN 11-520-V1\_am1, "First Amendment to the Report, Determination of Clindamycin in Heparinized Human Plasma by LC-MS-MS, Validation of the Analytical Method." Refer to page 4 of the study report. A measure of the extended stability of clindamycin in heparinized human plasma at -20°C (storage temperature) was evaluated at concentrations of 1.50 and 69.0 ng/mL. After 6 weeks of storage, the analytical results for the stability samples in each pool were within  $\pm 15\%$  of their theoretical concentrations, thus establishing an extended stability of 6 weeks. b(4)

The First Amendment to the ~~\_\_\_\_\_~~ Report DCN 11-520-V1\_am1 for clindamycin is found in the original electronic NDA in Section 6, Human Pharmacology and Bioavailability. It may be found by going to Section 6 Attachments - Attachment 6.2.1.2. b(4)

Tretinoin:

See ~~\_\_\_\_\_~~ Report DCN 11-380-V1\_am1, "First Amendment to the Report, Determination of all-trans-Retinoic Acid, 13-cis-Retinoic Acid, and 4-oxo-13-cis-Retinoic Acid in Heparinized Human Plasma by LC-MS-MS, Validation of the Analytical Method." Refer to page 4 of the study report. A measure of the extended stability of RA, 13-cis-RA, and 4-oxo-13-cis-RA in heparinized human plasma at -70°C (storage temperature) was evaluated at concentrations of 1.50 and 16.0 ng/mL. After 27 weeks of storage, the analytical results for at least two-thirds of the stability samples in each pool were within  $\pm 15\%$  of their theoretical concentrations, thus establishing an extended stability of 27 weeks. b(4)

The First Amendment to the ~~\_\_\_\_\_~~ Report DCN 11-380-V1\_am 1 for tretinoin was not submitted in the original electronic NDA. A copy is provided in this Amendment as Attachment 2. b(4)

Jonathan Wilkin, MD  
NDA 21-739 – Request for Information  
October 22, 2004  
Page 3

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

Should you require further information regarding this submission, please contact me by phone - 707.793.2600, by fax - 707.793.0145, or by e-mail – [bcalvarese@dowpharmsci.com](mailto:bcalvarese@dowpharmsci.com)

Sincerely,



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

/pm  
Enclosures

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

**FACSIMILE TRANSMITTAL SHEET**

**DATE:** October 19, 2004

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

**Total no. of pages including cover:** X 5

**Document to be mailed:**  YES  NO

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## FDA Fax Memo

**Date:** October 19, 2004

**Subject:** NDA 21-739

Dear Mr. Calvarese,

DMETS does not recommend the use of the proprietary name ClinRA Gel. In reviewing the proprietary name, the primary concerns related to look-alike and/or sound-alike confusion with Clindagel and Cleocin. Additionally, DMETS is concerned with the use of the dosage form in the proprietary name and the graphic presentation of the name.

- A. Clindagel may look and sound similar to ClinRA Gel. Four respondents (one verbal and three written) from the prescription studies interpreted the proposed name as Clindagel. Clindagel is indicated for topical treatment of acne vulgaris. Both names begin with the same four letters (clin) and end with the same four letters (agel) (see below). The only variance is the letter 'd vs. r' in the middle of the names. The letters "RA" of ClinRA Gel are capitalized in the proposed presentation; however, they will most likely not be capitalized in the scripted presentation, thus increasing the potential for error. Additionally, it is possible for the name to be scripted as one word 'Clinragel' subsequently increasing the orthographic similarity to Clindagel. Eight of the nine letters in each name are the same and appear in the same location of each name, thereby increasing the phonetic and orthographic similarity. Moreover, there are overlapping product characteristics, such as dose (small amount to affected area), dosage form (gel), frequency of administration (once daily), route of administration (topical), indication of use (acne vulgaris), and storage location (topicals). Whether the drugs are stored by proprietary name or by active ingredient, they could be stored alphabetically next to each other on pharmacy shelves. Both products contain 1% Clindamycin, however, ClinRA Gel also contains Tretinoin, which increases the adverse events profile for this product. Additionally Tretinoin has been identified as a teratogen. However, due to lack of studies conducted in humans to establish the safety of Clin RA Gel in pregnant women, there is an unknown level of teratogenicity associated with its use. This unknown level remains of concern. The potential for confusion and subsequent medication errors provides an increased level of concern involving this name pair. Thus, the orthographic and phonetic similarities, coupled with the overlapping product characteristics increase the potential for confusion and error involving Clindagel and ClinRA Gel.

C ■■■ D ■■■ E ■

C ■■■ R ■■■ E ■

*Clindagel*  
*Clinragel*

B. Cleocin may look and sound similar to ClinRA Gel when spoken or scripted. Four respondents from the prescription studies (three written and one verbal) responded with the root name 'Cleocin', incorporating a variety of modifiers into their responses [LA Gel (3), and CA Gel (1)]. Cleocin is an antibiotic indicated in the treatment of a variety of infections and acne. Both names begin with letters that may look similar when scripted (cleo vs. clin) (see below). Additionally, 'cin' may look similar to 'ra' if the letters are not clearly scripted. However, phonetically, they are different. Cleocin contains a long 'e' in the first syllable, whereas ClinRA Gel contains a short 'i' in the first syllable. Additionally, the last syllable is different, 'cin' is usually pronounced 'sin', whereas, 'RA' may be pronounced similar to 'ro' in rock. The most likely scenario where confusion may occur is with the Cleocin-T topical products (gel, lotion, topical solution, and pledgets). Although the dosage form uses a modifier 'T' in its proprietary name, post-marketing experience has demonstrated that modifiers are often omitted especially if practitioners feel they are not needed to distinguish a product. The modifier 'T' is part of only the topical Cleocin products proprietary names. Thus, the dosage formulation could be the identifying factor, and not the modifier. The most likely scenario would be that the name Cleocin and a dosage form would be included in the order (e.g. Cleocin Gel, Apply QD UD). All of these products contain 1% Clindamycin, and as such, the strength may not always be included. Thus, an order for ClinRA Gel could be interpreted as Cleocin Gel. There are overlapping product characteristics between these products, such as dose (small amount), dosage form (gel), frequency of administration (once daily), route of administration (topical), indication of use (acne), and storage location (topicals). Both products contain 1% Clindamycin, however, ClinRA Gel also contains Tretinoin, which increases the adverse events profile for this product. Although Tretinoin has been identified as a teratogen, the lack of clinical studies involving pregnant women with ClinRA Gel leaves an unknown teratogenicity risk, and remains a concern in the event of a medication error. The orthographic similarities and the product characteristics increase potential for error involving Cleocin and ClinRA Gel.

*Cleocin gel*

*Clinra gel*

C. In general, the Agency does not recommend including the dosage form in the proprietary name because a new dosage form might be introduced and cause future confusion. Thus, providing the dosage form, 'Gel', in the proprietary name, would be duplicative [e.g. ClinRA Gel, (1% Clindamycin and 0.025% Tretinoin Gel)]. Therefore, DMETS does not recommend the use of the modifier 'Gel' in the proposed proprietary name.

D. Additionally, DMETS reviewed the labels and labeling from a safety perspective. DMETS has identified the following area of possible improvement, which might minimize potential user error.

1. We note that the labels and labeling were submitted in black and white with text only. Thus, DMETS did not have the opportunity to evaluate and comment on the use of colors, color fonts and/or graphics, etc. Additionally, in order to equally represent the two components of this product (Clindamycin and Tretinoin), we recommend that the letters 'RA' be presented in the same color and font on the final printed labeling as the rest of the name, 'Clin'. See 21 CFR 201.6(b).
2. The dosage form should appear in conjunction with the established name (e.g. Clindamycin and Tretinoin 1%/0.025%, Gel).

Sincerely,

Jacquelyn Smith  
Project Manager  
DDDDP, HFD-540

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August 23, 2004

Jonathan Wilkin, MD
Division of Dermatological and Dental Drug Products
Office of Drug Evaluation V
Center for Drug Evaluation and Research
Food and Drug Administration
Central Document Mail Room # N 115
9201 Corporate Blvd. HFD-540
Rockville, Maryland 20850

N-000(Bm)
ORIG AMENDMENT

RE: NDA 21-739 for Clin RA (clindamycin, 1%; tretinoin, 0.025%) Gel
for the Indication of Acne Vulgaris

Response to FDA Facsimile Message Dated August 4, 2004

Dear Dr. Wilkin:

Dow Pharmaceutical Sciences (DPS) is in receipt of a facsimile from Jacquelyn Smith, FDA
Project Manager, dated August 4, 2004, requesting information for pending NDA application
21-739, Clin RA Gel for the indication of acne vulgaris. Following are the requests for
information, with a response from DPS for each request:

- 1. Please provide all available information regarding the outcomes of the pregnancies
that occurred in the pivotal trials. If the Pregnancy Outcome Forms were included in
the application, please identify their location in the submission.

Outcomes of Pregnancies – Clin RA Pivotal Trials

Protocol No. 7001-G2HP-06-02

Table with 2 columns: Site No./Subject No. and Pregnancy Outcome. Row 1: Site 603 / Subject 0494 - Site has been unable to reach patient about her pregnancy outcome. Row 2: Site 618 / Subject 1171 - On [redacted] Patient delivered a baby boy weighing 3345 grams, with a height of 49.5 cm, head circumference at .33 cm and Apgar score of 02 at one minute and 09 at five minutes.

b(6)

b(6)

Response to FDA Facsimile dated August 4, 2004  
August 23, 2004

Protocol No. 7001-G2HP-07-02

Site No./Subject No.	Pregnancy Outcome
Site 700 / Subject 1869	Patient had a voluntary abortion on _____ approximately _____ after last visit on July 14, 2003.
Site 701 / Subject 2227	Investigator attempted to contact Patient on 1/8/04, 1/22/04, 2/12/04, 3/11/04, 4/15/04 and 5/6/04, all with no answer. The site sent a Certified letter on 8/9/04 in an attempt to contact and obtain information from Patient, but again no response was received. It has been concluded that the Patient has been lost to follow up. The PI has no knowledge of the course or outcome of Patient's pregnancy.
Site 705 / Subject 2458	Patient stated on 6/7/04 that she delivered a healthy baby girl, weight 7 lbs., 14 oz., 21-3/4 inches in length, Apgar 9.9, on or about _____
Site 709 / Subject 2423	The Investigator attempted to call the Patient on 8/9/04 to determine outcome of her pregnancy. The phone had been disconnected. The Patient's chart was ordered from offsite storage on 8/10/04, but to date has not been received. A second phone call attempt was made to Patient at a different number on 8/16/04, but it was not a working number. A Certified letter was sent to Patient by Investigator on 8/16/04, and there has been no response to date. Once the site receives Patient's chart from offsite storage, an amended report of Patient's pregnancy outcome will be submitted to the FDA.

b(6)

b(6)

b(6)

b(6)

The Pregnancy Outcome Forms for both studies (Protocol 7001-G2HP-06-02 and Protocol 7001-G2HP-07-02) were not included in the NDA application, but are provided as **Attachment 1** to this communication.

- Please clarify the Certification/Disclosure Form for Norman B. Kanof, MD, as none of the boxes appear to have been checked (letter date May 22, [sic.] 2004).*

In the response to the FDA dated May 11, 2004, which included the Financial Disclosure form for Dr. Norman Kanof, as requested by FDA in a fax dated May 10, 2004, the box at the bottom of the Financial Disclosure is checked. It appears just above the signature and states: "OR [X] I hereby certify that none of the financial interests or arrangements listed above exist for myself, my spouse, or my dependent children."

For ease of review, a copy of Dr. Kanof's Financial Disclosure form is included with this response as **Attachment 2**.

Jonathan Wilkin, MD  
NDA 21-739 – ClinRA Gel  
Response to FDA Facsimile dated August 4, 2004  
August 23, 2004

Page 3

3. *Please clarify the proposed tradename, as it is variably referred to as "ClinRA" and "Clin-RA."*

The official tradename for this product is **Clin RA**, with a space, but no hyphen.

4. *Please provide status of study being conducted under protocol MP-1501-01 for purposes of collecting long-term safety data for the sponsor's product.*

In response to this request, an Interim Report for Protocol No. MP-1501-01 is provided in this submission as **Attachment 3**.

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

Should you require further information regarding this submission, please contact me or Gina Capioux, PhD, Associate Manager, Regulatory and Clinical Affairs, by phone - 707.793.2600, by fax - 707.793.0145, or by e-mail - [bcalvarese@dowpharmsci.com](mailto:bcalvarese@dowpharmsci.com) or [gcapioux@dowpharmsci.com](mailto:gcapioux@dowpharmsci.com)

Sincerely,



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

/pm  
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Center for Drug Evaluation and Research  
Food and Drug Administration  
Central Document Mail Room # N 115  
9201 Corporate Blvd. HFD-540  
Rockville, Maryland 20850

N-000(Su)  
ORIG AMENDMENT

**RE: NDA 21-739 for Clin RA (clindamycin, 1%; tretinoin, 0.025%) Gel  
for the Indication of Acne Vulgaris**

**120-Day Safety Update: Pregnancy Outcomes and Interim Report  
for Protocol No. MP-1501-01**

Dear Dr. Wilkin:

Dow Pharmaceutical Sciences (DPS) filed an electronic New Drug Application (NDA 21-739) for Clin RA Gel for the treatment of acne vulgaris on February 6, 2004.

Enclosed with this submission is the following new safety information obtained since the filing of NDA 21-739 on February 6, 2004, up to and including August 18, 2004, the cut-off date for this 120-Day Safety Update.

- Update on pregnancy outcomes for subjects in Phase 3 studies (Protocol 7001-G2HP-06-02 and 7001-G2.HP-07-02) **Attachment 1**
- and
- Interim Report, Protocol No. MP-1501-01: *"A Multi-Center, Open-Label, Long-Term Safety Trial of Clin RA Gel in the Treatment of Acne Vulgaris"* **Attachment 2**

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

Jonathan Wilkin, MD  
NDA 21-739, 120-Day Safety Update  
August 20, 2004  
Page 2

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

Sincerely,



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

/pm  
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Center for Drug Evaluation and Research  
Office of Drug Evaluation ODE 5

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**FACSIMILE TRANSMITTAL SHEET**

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**DATE:** August 4, 2004

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

**Total no. of pages including cover:** 3

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## FDA Fax Memo

**Date:** August 4, 2004

**Subject:** NDA 21-739/ClinRA Gel

Dear Mr. Calvarese,

1. Please provide all available information regarding the outcomes of the pregnancies that occurred in the pivotal trials. If the Pregnancy Outcome Forms were included in the application, please identify their location in the submission.
2. Please clarify the Certification/Disclosure Form for \_\_\_\_\_ A.D., as none of the boxes appear to have been checked (letter date May 22, 2004).
3. Please clarify the proposed tradename as it is variably referred to as "ClinRA" and "Clin-RA"
4. Please provide status of study being conducted under protocol MP-1501-01 for purposes of collecting long-term safety data for the sponsor's product.

b(6)

Sincerely,

Jacquelyn Smith  
Project Manager  
DDDDP, HFD-540

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August 2, 2004

N-800(25)

ORIG AMENDMENT

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

NA  
Blaw  
12 Aug 04

**RE: NDA 21-739 for ClinRA (clindamycin, 1%; tretinoin, 0.025%) Gel  
for the Indication of Acne Vulgaris**

**Response to FDA Facsimile Message Dated July 28, 2004**

Dear Dr. Wilkin:

Dow Pharmaceutical Sciences (DPS) is in receipt of a facsimile message from Jacquelyn Smith, FDA Project Manager, dated July 28, 2004, which requested that the following information be submitted in order to facilitate statistical review of NDA 21-739 for ClinRA Gel:

*"For each pivotal study, please submit an electronic SAS data set which includes patient ID, investigator ID, treatment group, Evaluator's Global Severity score at baseline, weeks 2, 4, 8 and 12, and an indicator that indicates if a subject was included in the per-protocol efficacy population."*

In accordance with this request, included with this letter is a compact disc containing a SAS data set with the requested information for each of the Phase 3 pivotal studies: Protocol numbers 7001.G2HP-06-02 and 7001.G2HP-07-02.

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

Jonathan Wilkin, MD  
NDA 21-739 – ClinRA Gel  
Response to FDA Facsimile dated July 28, 2004  
August 2, 2004

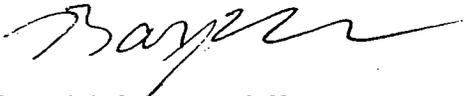
Page 2

Should you require further information regarding this submission, please contact me or Gina Capioux, PhD, Associate Manager, Regulatory and Clinical Affairs, by phone at 707.793.2600, by fax at 707.793.0145, or by e-mail at

[bcalvarese@dowpharmsci.com](mailto:bcalvarese@dowpharmsci.com)

[gcapioux@dowpharmsci.com](mailto:gcapioux@dowpharmsci.com)

Sincerely,



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

/pm  
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Center for Drug Evaluation and Research  
Office of Drug Evaluation ODE 5

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**DATE:** July 28, 2004

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

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## FDA Fax Memo

**Date:** July 28, 2004

**Subject:** NDA 21-739/ClinRA Gel

Dear Mr. Calvarese,

To facilitate statistical review, please submit the following:

For each pivotal study, please submit an electronic SAS data set which includes patient ID, investigator ID, treatment group, Evaluator's Global Severity score at baseline, weeks 2, 4, 8 and 12, and an indicator that indicates if a subject was included in the per-protocol efficacy population.

If you need further clarification, please contact me. Please submit this information as soon as possible.

Sincerely,

Jacquelyn Smith  
Project Manager  
DDDDP, HFD-540

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Office of Drug Evaluation ODE 5

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**FACSIMILE TRANSMITTAL SHEET**

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**DATE:** July 15, 2004

<b>To:</b> Barry Calverese, MS, VP, Regulatory and Clinical Affairs	<b>From:</b> Jacquelyn Smith, Project Manager
<b>Company:</b> Dow Pharmaceutical Sciences	Division of Dermatologic and Dental Drug Products
<b>Fax number:</b> 707-793-0145	<b>Fax number:</b> 301-827-2075
<b>Phone number:</b> 707-793-2600	<b>Phone number:</b> 301-827-2027

**Subject:** NDA 21-739/ClinRA Gel

**Total no. of pages including cover:** 3

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## FDA Fax Memo

**Date:** July 15, 2004

**Subject:** NDA 21-739/ClinRA Gel

Dear Mr. Calvarese:

We have been unable to locate the raw plasma concentration vs. time data for Phase 2 Clinical Protocol No. 7001.G2HP.C-02-02.

Please either provide this information in tabular form (for all analytical species of interest) along with the case report forms for the subject who had the elevated clindamycin plasma levels on day 14 or indicate where it may be found in your submission.

Please submit your response as soon as possible. Also, please inform us as to when you expect to submit the information.

Sincerely,

Jacquelyn Smith  
Project Manager  
DDDDP, HFD-540

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12229 Wilkins Avenue  
Rockville, Maryland 20852

N-000(RA)  
ORIG AMENDMENT

**RE: NDA 21-739 for ClinRA (clindamycin, 1%; tretinoin, 0.025%) Gel  
for the Indication of Acne Vulgaris**

**Response to FDA Facsimile Message Dated July 15, 2004**

Dear Dr. Wilkin:

Dow Pharmaceutical Sciences (DPS) is in receipt of a facsimile message from the Agency dated July 15, 2004, which requested the following:

*"We have been unable to locate the raw plasma concentration vs. time data for Phase 2 Clinical Protocol No. 7001.G2HP.C-02-02.*

*"Please either provide this information in tabular form (for all analytical species of interest) along with the case report forms for the subject who had the elevated clindamycin plasma levels on day 14 or indicate where it may be found in your submission."*

We are pleased to inform you that the requested information was sent to Jacquelyn Smith, FDA Project Manager, by way of e-mail transmission today. For review convenience, we are also providing this hard copy response in duplicate.

The data requested by the Agency may be found in the electronic submission of ClinRA NDA 21-739 in the following path:

N21739\hpbio\hupharm\Report 7001-G2HP-C-02-02.pdf

The data are on page 229 in Section 16.2.12 Pharmacokinetic Sampling – Listing 10.1.

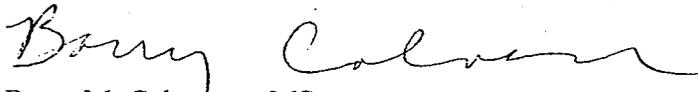
Jonathan Wilkin, MD  
NDA 21,739 – ClinRA Gel  
Response to FDA Facsimile dated July 15, 2004  
July 15, 2004

Page 2

In addition, DPS is providing two copies of the Case Report Form for Subject #007, the patient who had elevated clindamycin plasma levels on day 14, in the specified clinical study, 7001-G2HP.C-02-02.

Should you require further information regarding this response, please contact me or Gina Capioux, PhD, Associate Manager, Regulatory and Clinical Affairs, by phone at 707.793.2600, by fax at 707.793.0145, or by e-mail at  
[bcalvarese@dowpharmsci.com](mailto:bcalvarese@dowpharmsci.com)      [gcapioux@dowpharmsci.com](mailto:gcapioux@dowpharmsci.com)

Sincerely,



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

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## NDA/EFFICACY SUPPLEMENT ACTION PACKAGE CHECKLIST

Application Information		
NDA 50-802	Efficacy Supplement Type SE- N/A	Supplement Number N/A
Drug: Tradename ((clindamycin 1%, tretinoin 0.025%) Gel		Applicant: Dow Pharmaceuticals
RPM: Jacquelyn Smith	HFD-540	Phone # 301-827-2020
<p>Application Type: <input type="radio"/> 505(b)(1) <input checked="" type="radio"/> 505(b)(2)                      (This can be determined by consulting page 1 of the NDA Regulatory Filing Review for this application or Appendix A to this Action Package Checklist.)</p> <p><b>If this is a 505(b)(2) application, please review and confirm the information previously provided in Appendix B to the NDA Regulatory Filing Review. Please update any information (including patent certification information) that is no longer correct.</b></p> <p><input type="checkbox"/> Confirmed and/or corrected</p>	Listed drug(s) referred to in 505(b)(2) application (NDA #(s), Drug name(s)):	
<b>❖ Application Classifications:</b>		
<input type="checkbox"/> Review priority	<input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority	
<input type="checkbox"/> Chem class (NDAs only)	3S	
<input type="checkbox"/> Other (e.g., orphan, OTC)	N/A	
<b>❖ User Fee Goal Dates</b>	December 9, 2004	
<b>❖ Special programs (indicate all that apply)</b>	<input checked="" type="checkbox"/> None Subpart H <input type="checkbox"/> 21 CFR 314.510 (accelerated approval) <input type="checkbox"/> 21 CFR 314.520 (restricted distribution) <input type="checkbox"/> Fast Track <input type="checkbox"/> Rolling Review <input type="checkbox"/> CMA Pilot 1 <input type="checkbox"/> CMA Pilot 2	
<b>❖ User Fee Information</b>		
<input type="checkbox"/> User Fee	<input checked="" type="checkbox"/> Paid UF ID number 4688	
<input type="checkbox"/> User Fee waiver	<input type="checkbox"/> Small business <input type="checkbox"/> Public health <input type="checkbox"/> Barrier-to-Innovation <input type="checkbox"/> Other (specify) N/A	
<input type="checkbox"/> User Fee exception	<input type="checkbox"/> Orphan designation <input type="checkbox"/> No-fee 505(b)(2) (see NDA Regulatory Filing Review for instructions) <input type="checkbox"/> Other (specify) N/A	
<b>❖ Application Integrity Policy (AIP)</b>		



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

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

Yes  No

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

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

Yes  No

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

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

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

*If "No," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next box below (Exclusivity).*

*If "Yes," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007) and attach a summary of the response.*

❖ Exclusivity (approvals only) N/A	
<ul style="list-style-type: none"> <li>• Exclusivity summary</li> <li>• Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? (Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</li> </ul>	Exclusivity summary was in application..
<ul style="list-style-type: none"> <li>• Is there existing orphan drug exclusivity protection for the "same drug" for the proposed indication(s)? Refer to 21 CFR 316.3(b)(13) for the definition of "same drug" for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification.</li> </ul>	<input type="checkbox"/> Yes, Application # _____ <input type="checkbox"/> No
❖ Administrative Reviews (Project Manager, ADRA) (indicate date of each review)	N/A

General Information	
❖ Actions	
• Proposed action	<input type="checkbox"/> AP <input type="checkbox"/> TA <input type="checkbox"/> AE <input checked="" type="checkbox"/> NA
• Previous actions (specify type and date for each action taken)	N/A
• Status of advertising (approvals only)	<input type="checkbox"/> Materials requested in AP letter <input type="checkbox"/> Reviewed for Subpart H
❖ Public communications	
• Press Office notified of action (approval only)	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> Not applicable
• Indicate what types (if any) of information dissemination are anticipated	<input checked="" type="checkbox"/> None <input type="checkbox"/> Press Release <input type="checkbox"/> Talk Paper <input type="checkbox"/> Dear Health Care Professional Letter
❖ Labeling (package insert, patient package insert (if applicable), MedGuide (if applicable))	
• Division's proposed labeling (only if generated after latest applicant submission of labeling)	N/A
• Most recent applicant-proposed labeling	N/A
• Original applicant-proposed labeling	February 6, 2004
• Labeling reviews (including DDMAC, DMETS, DSRCS) and minutes of labeling meetings (indicate dates of reviews and meetings)	DMETS (10-5-04); DDMAC (11-8-04)
• Other relevant labeling (e.g., most recent 3 in class, class labeling)	N/A
❖ Labels (immediate container & carton labels)	
• Division proposed (only if generated after latest applicant submission)	
• Applicant proposed	February 6, 2004
• Reviews	
❖ Post-marketing commitments	
• Agency request for post-marketing commitments	
• Documentation of discussions and/or agreements relating to post-marketing commitments	N/A
❖ Outgoing correspondence (i.e., letters, E-mails, faxes)	X
❖ Memoranda and Telecons	X
❖ Minutes of Meetings	
• EOP2 meeting (indicate date)	December 16, 2002
• Pre-NDA meeting (indicate date)	October 1, 2003
• Pre-Approval Safety Conference (indicate date; approvals only)	N/A
• Other	
❖ Advisory Committee Meeting	
• Date of Meeting	N/A
• 48-hour alert	N/A
❖ Federal Register Notices, DESI documents, NAS/NRC reports (if applicable)	N/A

<b>Summary Application Review</b>	
❖ Summary Reviews (e.g., Office Director, Division Director, Medical Team Leader) <i>(indicate date for each review)</i>	
<b>Clinical Information</b>	
❖ Clinical review(s) <i>(indicate date for each review)</i>	12/7/04
❖ Microbiology (efficacy) review(s) <i>(indicate date for each review)</i>	3/3/04
❖ Safety Update review(s) <i>(indicate date or location if incorporated in another review)</i>	12/7/04
❖ Risk Management Plan review(s) <i>(indicate date/location if incorporated in another rev)</i>	N/A
❖ Pediatric Page(separate page for each indication addressing status of all age groups)	5/19/04
❖ Demographic Worksheet <i>(NME approvals only)</i>	N/A
❖ Statistical review(s) <i>(indicate date for each review)</i>	10/15/04
❖ Biopharmaceutical review(s) <i>(indicate date for each review)</i>	11/4/04
❖ Controlled Substance Staff review(s) and recommendation for scheduling <i>(indicate date for each review)</i>	N/A
❖ Clinical Inspection Review Summary (DSI)	
• Clinical studies	No DSI inspection
• Bioequivalence studies	No DSI inspection
<b>CMC Information</b>	
❖ CMC review(s) <i>(indicate date for each review)</i>	12/7/04
❖ Environmental Assessment	
• Categorical Exclusion <i>(indicate review date)</i>	12/7/04
• Review & FONSI <i>(indicate date of review)</i>	N/A
• Review & Environmental Impact Statement <i>(indicate date of each review)</i>	N/A
❖ Microbiology (validation of sterilization & product sterility) review(s) <i>(indicate date for each review)</i>	N/A
❖ Facilities inspection (provide EER report)	Date completed: 4/16/04 (X) Acceptable ( ) Withhold recommendation
❖ Methods validation	( ) Completed (X) Requested ( ) Not yet requested
<b>Nonclinical Pharm/Tox Information</b>	
❖ Pharm/tox review(s), including referenced IND reviews <i>(indicate date for each review)</i>	
❖ Nonclinical inspection review summary	N/A
❖ Statistical review(s) of carcinogenicity studies <i>(indicate date for each review)</i>	N/A
❖ CAC/ECAC report	N/A

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**Appendix A to NDA/Efficacy Supplement Action Package Checklist**

An application is likely to be a 505(b)(2) application if:

- (1) it relies on literature to meet any of the approval requirements (unless the applicant has a written right of reference to the underlying data)
- (2) it relies on the Agency's previous approval of another sponsor's drug product (which may be evidenced by reference to publicly available FDA reviews, or labeling of another drug sponsor's drug product) to meet any of the approval requirements (unless the application includes a written right of reference to data in the other sponsor's NDA)
- (3) it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)
- (4) it seeks approval for a change from a product described in an OTC monograph and relies on the monograph to establish the safety or effectiveness of one or more aspects of the drug product for which approval is sought (see 21 CFR 330.11).

Products that may be likely to be described in a 505(b)(2) application include combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations), OTC monograph deviations, new dosage forms, new indications, and new salts.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, please consult with the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007).

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ORIG AMENDMENT

June 7, 2004

RECEIVED

JUN 08 2004

MEGA/CDER

Central Document Room  
Food and Drug Administration  
12229 Wilkins Avenue  
Rockville, Maryland 20852

**RE: ClinRA NDA 21-739 Submission of June 4, 2004**

To Personnel in Central Document Room:

A submission to the above-referenced NDA, addressed to Dr. Jonathan Wilkin of the Dermatological and Dental Drug Products Division, was made by Dow Pharmaceutical Sciences on June 4, 2004. Two copies of a cover letter were sent, but unfortunately, the attachments to the letters were inadvertently omitted.

If you have not yet delivered the original letter with its copy to Dr. Wilkin, will you please see that the attached copies are appended to the two letters sent out on June 4. Federal Express confirmation shows that the June 4 submission was received in the Central Document Room today, June 7, 2004, by T. Jennings.

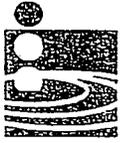
Thank you,

Paula Mueda  
Sr. Regulatory Specialist

/attachments

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**COPY**

*Via Federal Express*

June 4, 2004

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

RECEIVED  
JUN 08 2004

MEGA/CDER

**RE: NDA 21-739 for ClinRA (clindamycin, 1%; tretinoin, 0.025%) Gel  
for the Indication of Acne Vulgaris**

**Response to FDA Facsimile Message Dated May 25, 2004**

Dear Dr. Wilkin:

Dow Pharmaceutical Sciences (DPS) is in receipt of a facsimile message from the Agency dated May 25, 2004, which stated the following:

*"Your NDA submission presented only descriptive statistics for absolute lesion reduction from baseline to week 12. For each pivotal studies (7001-G2HP-06-02 and 7001-G2HP-07-02), please submit analyses of absolute change from baseline to week 12 in each inflammatory, non-inflammatory and total lesion count based on the ITT and PP populations.*

*"Please submit your response as soon as possible. Also, please inform us as to when you expect to submit the information."*

We are pleased to present the analysis of absolute lesion reduction that was requested.

The analysis was not part of the protocol or statistical plan finalized prior to unblinding. Just as the percent change in lesion counts, the reductions in absolute lesion counts failed to meet normality assumptions, as indicated by the p-value of several relevant tests being  $p < 0.05$  and in most cases  $p < 0.01$  (Shapiro-Wilk, Kolmogorov-Smirnov, Cramer-von Mises, and Anderson-Darling). Additionally, the skewness test of Zar rejected the hypothesis of symmetry ( $p < 0.0001$ ). This was observed for all lesion count variables in

Jonathan Wilkin, MD  
NDA 21,739 – ClinRA Gel  
Response to FDA Facsimile dated May 25, 2004  
June 4, 2004

Page 2

both pivotal trials' SAS datasets for the ITT and PP populations. The results of these tests are not documented in the NDA.

Because the data for the percent change and absolute lesion reductions fails to meet normality assumptions, the primary analysis was to be based on a non-parametric approach of ranking the percent change in lesion counts and then submitting the ranked data to an ANOVA. The ranked-ANOVA represents the data that best measured the central tendency of the dataset and further supports the prospective decision to use a rank transformation of the percent change from baseline as a theoretically sound method of analysis for the skewed distributions. The ranked-ANOVA is the data presented in the NDA.

Should you require further information regarding this submission, please contact me or Elena Serbinova, PhD, Associate Director, Regulatory and Clinical Affairs by phone at 707.793.2600, by fax at 707.793.0145, or by e-mail at

[bcalvarese@dowpharmsci.com](mailto:bcalvarese@dowpharmsci.com)      [eserbinova@dowpharmsci.com](mailto:eserbinova@dowpharmsci.com)

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

Sincerely,



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

/pm  
Enclosures

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

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**FACSIMILE TRANSMITTAL SHEET**

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**DATE:** May 25, 2004

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

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**Total no. of pages including cover:** 3

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**Document to be mailed:**                       YES                       NO

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

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## FDA Fax Memo

**Date:** May 25, 2004

**Subject:** NDA 21-739/ClinRA Gel

Dear Mr. Calvarese,

Your NDA submission presented only descriptive statistics for absolute lesion reduction from baseline to week 12. For each of the pivotal studies (7001-G2HP-06-02 and 7001-G2HP-07-02), please submit analyses of absolute change from baseline to week 12 in each of inflammatory, non-inflammatory and total lesion count based on the ITT and PP populations.

Please submit your response as soon as possible. Also, please inform us as to when you expect to submit the information.

Sincerely,

Jacquelyn Smith  
Project Manager  
DDDDP, HFD-540

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

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Jacquelyn Smith  
5/25/04 12:05:07 PM  
CSO

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MAY 25 2004

MEGA / CDER

*Via Federal Express*

May 24, 2004

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

N-200 (Bm)  
ORIG AMENDMENT

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

**Response to FDA Facsimile dated April 21, 2004 regarding potential Clinical review issue**

Dear Dr. Wilkin:

In response to a facsimile from the Agency dated and received by Dow Pharmaceutical Sciences (DPS) on April 21, 2004, DPS is submitting the enclosed information to address the Agency's comments regarding a potential review issue. Specifically, on page two of the faxed message, the Agency stated under the heading of "Clinical":

*"Regarding the Global Severity assessment, as discussed at the End-of-Phase 2 meeting, two-grade improvement data will be considered as supportive evidence of efficacy. Efficacy will be primarily assessed by the proportion of subjects who are 'clear' or 'almost clear' at efficacy evaluation (Week 12) and lesion counts."*

The data which follows addresses the Agency's request of the Sponsor:

*"Regarding the Global Severity assessment, please submit the supportive evidence of efficacy."*

During the December 16, 2002 End-of-Phase II meeting for ClinRA Gel, agreement was reached to provide an alternative analysis of the dichotomized Evaluator's Global Severity Score for subjects achieving 'clear,' 'almost clear' or a two-grade improvement at Week 12 as a supportive analysis. This analysis was included in the study protocol, because it is believed by the Sponsor and its consultant dermatologists that the dichotomized endpoint for

inclusion of only 'clear' and 'almost clear' subjects as 'successfully treated' is not realistic for subjects with a grade of 'severe' or 'very severe' at baseline. Because the protocol enrolled subjects as 'mild,' 'moderate,' 'severe' or 'very severe,' this analysis allows for 'severe' or 'very severe' subjects who have made a clinically meaningful improvement to be considered a success.

The Sponsor still maintains that the definition 'clear,' 'almost clear' or a two-grade improvement at Week 12 represents the most clinically meaningful primary endpoint and would offer the following data submitted in the ISE for NDA 21-739 in support of this position.

In pivotal clinical study 7001.G2HP-06-02 the proportion of ITT subjects achieving success by the proposed criteria showed a trend towards superiority ( $p=0.085$ , table 8.10) between the ClinRA and Clindamycin groups. In pivotal clinical study 7001.G2HP-07-02 the proportion of ITT subjects achieving success by these criteria reached a statistically significant difference ( $p=0.041$ , Table 8.10) between the ClinRA and Clindamycin groups. The inclusion of these more severe subjects widened the difference between the two treatments and lends support that ClinRA Gel is more efficacious than Clindamycin.

For the pooled ITT population (see ISE page 15, Table 8.10), the proportion of subjects achieving success by these criteria showed a statistically significant difference ( $p=0.008$ ) between the ClinRA and Clindamycin groups.

Additional support for inclusion of severe subjects is provided in the ISE sub-population of 'severe' subjects. In Table 8.52 (page 102, ISE), 120 subjects in the ClinRA Gel group had a baseline Global Score of 'severe,' and 47 (39%) obtained a 2-grade improvement. This can be compared to the 72 'severe' Clindamycin subjects; 20 (28%) of whom made a 2-grade improvement. The comparison showed a trend toward being statistically different ( $p=0.097$ ). Within the PP population (Table 8.53, page 103, ISE), out of the 84 subjects in the ClinRA Gel group with a Global Score of 'severe,' 41 (49%) obtained a 2-grade improvement. This can be compared to the 58 'severe' Clindamycin subjects; 18 (31%) of whom made a 2-grade improvement. The difference between ClinRA Gel and Clindamycin in the number of 'severe' subjects who made a two-grade improvement was statistically significant ( $p=0.036$ ).

The Sponsor prospectively included this criterion to include 'severe' subjects who make a meaningful improvement in the efficacy analysis.

The Sponsor would welcome the opportunity to better understand the Division's position for using the alternative criteria in judging the overall efficacy of the product.

Jonathan Wilkin, MD  
NDA 21,739 – ClinRA Gel  
Response to FDA Facsimile dated April 21, 2004  
May 24, 2004

Page 3

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

If there are questions regarding this submission, please contact me or Gina Capiiaux, PhD, Associate Manager of Regulatory and Clinical Affairs, at 707-793-2600, via fax at 707-793-0145, or by e-mail at:

[bcalvarese@dowpharmsci.com](mailto:bcalvarese@dowpharmsci.com)    [gcapiiaux@dowpharmsci.com](mailto:gcapiiaux@dowpharmsci.com).

Sincerely,



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

BMC/pm

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

**FAX TRANSMITTAL COVER**

TO: JACQUELYN SMITH, PROJECT MANAGER, CDER

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

FROM: Paula Mueda, Sr. Regulatory Specialist

RE: ClinRA NDA 21-739 - Investigator Financial Information

Jacquelyn,

Attached is a cover letter and the Certification/Disclosure Form for financial information regarding Investigator \_\_\_\_\_

b(6)

A hard copy of these documents will be sent to Dr. Wilkin's attention via Federal Express today.

Regards,

*Paula*

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Sent by: P. Mueda

Date: 5/11/2004



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*Via Facsimile & Federal Express*

May 11, 2004

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

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

Dear Dr. Wilkin:

Dow Pharmaceutical Sciences (DPS) is in receipt of a facsimile message dated May 10, 2004 from Jacquelyn Smith, Project Manager, requesting that financial disclosure information be provided to the Agency for                      (site 630, ClinRA study 7001-G2IIP-06-02).

b(6)

A copy of                      Certification/Disclosure Form is included with this letter. Should you require further information regarding this submission, please contact me or Gina Capioux, PhD, Associate Manager, Regulatory and Clinical Affairs. We may be reached by phone at 707.793.2600, by fax at 707.793.0145, or by e-mail at [bcalvarese@dowpharmsci.com](mailto:bcalvarese@dowpharmsci.com) [gcapioux@dowpharmsci.com](mailto:gcapioux@dowpharmsci.com)

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

Sincerely,

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

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Enclosure

1   Page(s) Withheld

       Trade Secret / Confidential (b4)

       Draft Labeling (b4)

       Draft Labeling (b5)

       Deliberative Process (b5)

  ✓   Privacy (b6)



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

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**FACSIMILE TRANSMITTAL SHEET**

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**DATE:** April 21, 2004

<b>To:</b> Barry Calverese, MS, VP, Regulatory and Clinical Affairs	<b>From:</b> Jacquelyn Smith, Project Manager
<b>Company:</b> Dow Pharmaceutical Sciences	Division of Dermatologic and Dental Drug Products
<b>Fax number:</b> 707-793-0145	<b>Fax number:</b> 301-827-2075/2091
<b>Phone number:</b> 707-793-2600	<b>Phone number:</b> 301-827-2027
<b>Subject:</b> NDA 21-739/ Filing Communication	

**Total no. of pages including cover:** 4

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## DEPARTMENT OF HEALTH &amp; HUMAN SERVICES

Public Health Service

Food and Drug Administration  
Rockville, MD 20857

NDA 21-739

**FILING COMMUNICATION**

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

Dear Mr. Calvarese:

Please refer to your February 6, 2004, new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for ClinRA (clindamycin 1%, tretinoin 0.025%) Gel.

We also refer to your submissions dated February 13 and March 25, 2004.

We have completed our filing review, and have determined that your application is sufficiently complete to permit a substantive review. Therefore, this application has been filed under section 505(b) of the Act on April 9, 2004 in accordance with 21 CFR 314.101(a).

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

Clinical:

Regarding the Global Severity assessment, as discussed at the End-of-Phase 2 meeting, two-grade improvement data will be considered as supportive evidence of efficacy. Efficacy will be primarily assessed by the proportion of subjects who are "clear" or "almost clear" at efficacy evaluation (Week 12) and lesion counts.

Biostatistics:

There is deviation of treatment assignments in the two pivotal studies.

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

Clinical:

Regarding the Global Severity assessment, please submit the supportive evidence of efficacy.

Biostatistics:

Please explain any deviation of treatment assignments in the two pivotal studies. This request was sent to you on April 6, 2004, and you agreed to respond by April 23, 2004.

NDA 21-739

Page 2

Please respond to the above requests for additional information. While we anticipate that any response submitted in a timely manner will be reviewed during this review cycle, such review decisions will be made on a case-by-case basis at the time of receipt of the submission.

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

Sincerely,

*{See appended electronic signature page}*

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

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Jonathan Wilkin  
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**FILING COMMUNICATION**

NDA 21-739

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

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

Sincerely,

*{See appended electronic signature page}*

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

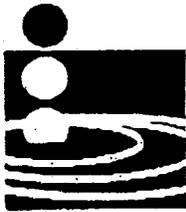
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Jonathan Wilkin  
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Dow Pharmaceutical Sciences  
1330A Redwood Way  
Petaluma, CA 94954-1169  
Phone: 707.285-1561  
Fax: 707.793.0145

## FAX TRANSMITTAL COVER

TO: JAQUELYN SMITH, PROJECT MANAGER, CDER

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

FROM: Paula Mueda, Sr. Regulatory Specialist

RE: NDA 21-739 – ClinRA – FDA Request for Information

Jacquelyn:

Attached is a copy of the cover letter for the submission we are sending to the Agency via Federal Express today. This facsimile message is sent as advance notice that the submission is going out today and that it should be delivered to the FDA Central Document Room tomorrow, April 20, 2004.

As noted, we will send two (2) Desk copies, with one electronic copy (CD) attached to one of the Desk copies.

Best regards,

A handwritten signature in cursive script, appearing to read "Paula".

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Sent by: P. Mueda

Date: 4/19/2004

**Dow Pharmaceutical Sciences**

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*Via Facsimile & Federal Express*

April 19, 2004

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

**Response to FDA Facsimile dated April 6, 2004 requesting information  
about any deviation in treatment allocation for Clinical pivotal trials**

Dear Dr. Wilkin:

In response to a facsimile dated and received by Dow Pharmaceutical Sciences (DPS) on April 6, 2004, requesting information about any deviation in treatment allocation to subjects enrolled in the two Clinical pivotal trials conducted for ClinRA Gel, we are providing you with supplemental listings of Subject Treatment Assignment (Listings 16.2.6.1.S) for the two Phase 3 studies (7001-G2HP-06-02 and 7001-G2HP-07-02). In the supplemental listings, three dates are provided: i) Enrollment date - the date subjects were screened (Visit 1), ii) Randomization date, the date subjects were randomized and received study medication; and iii) End of Study date, the date of the last study medication application. Per the protocol, drug supplies were to be dispensed sequentially from blocks (1 block=6 treatment kits randomized in a 2:2:1:1 ratio for each of the four treatment groups) to the subjects entering the study. In the two Phase 3 studies, 19 subjects were given treatment kits out of sequence. In all of these instances the entire block of kits was used, and therefore the integrity of the treatment ratios was maintained. In addition, in two instances, individual blocks were allocated out of sequence (Study 7001-G2HP-06-02 blocks containing kits 3265-3270 and 211-216); however, the kits within the block were distributed sequentially. Thus, these were not considered to be deviations from the protocol. A tabular summary of the treatment allocation deviations is provided in Appendix A.

As requested in a subsequent facsimile message on April 14 from Jacquelyn Smith, FDA Project Manager, DPS is providing the supplemental listings to the Agency in the form of two paper desk