OFFICE OF CLINICAL PHARMACOLOGY REVIEW

NDA	**50-819**
Submission Letter Date(s)	**12/21/2007, 2/19/2008**
PDUFA Due Date	**10/26/08**
Brand Name	**Acanya Gel (pending brand name approval)**
Generic Name	**Aqueous gel containing clindamycin phosphate 1.2% and benzoyl peroxide 2.5%**
Primary Reviewer	**Jang-Ik Lee, Pharm.D., Ph.D.**
Primary Review Team Leader	**Lydia Velazquez, Pharm.D.**
OCP Division	**DCP 3**
OND Division	**ODE3/DDDP**
Sponsor	**Dow Pharmaceutical Sciences, Inc.**
Relevant IND(s)	**IND 41,733**
Submission Type	**505(b)(2)**
Formulation; Strength(s)	**Aqueous gel; clindamycin phosphate 1.2%, benzoyl peroxide 2.5% in 50 g jar**
Proposed indication	**Topical treatment of acne vulgaris in patients 12 years or older**
Proposed Dosage and Administration	**Applied to the affected areas on the face once daily.**

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1 EXECUTIVE SUMMARY

Acanya Gel® is a combination product with two active ingredients of clindamycin phosphate 1.2% and benzoyl peroxide 2.5% in an aqueous gel formulation. This submission is a 505(b)(2) application referencing BenzaClin Topical Gel® (NDA 50-756 approved in September 20, 2000) containing clindamycin phosphate 1.2% and benzoyl peroxide 5% as a listed drug product. (b) (4)

The applicant has requested a waiver for pediatric studies (see Section *2.3.2.2 Pediatric Patients*). In terms of in vivo bioavailability, the applicant has submitted study report 2104-047-051-053-056, entitled "In Vitro Percutaneous Absorption of Clindamycin and Benzoyl Peroxide from BenzaClin, (b) (4) (1/2.5), **(b) (4)** , and Duac Topical Gel Using Intact Human Skin from Two Healthy Donors", in order to obtain a waiver of the in vivo bioavailability study requirement. In vitro bioavailability studies are allowed under the provisions §320.24 but only when the tests have been shown to correlate with in vivo bioavailability ((b)(1)(ii)) or the test is such that it ensures human in vivo bioavailability ((b)(5)) neither of which conditions are met by this study.

The applicant also submitted the study report DPS 07-07-2005-001, "A Phase 3 Bioequivalence Study of **(b) (4)** Gel to BenzaClin", to support the clinical bridge for 505(b)(2) application purpose. The study does not compare in vivo bioavailability of the active ingredients; but instead assesses clinical outcomes between **(b) (4)** Gel (clindamycin phosphate 1.2%/benzoyl peroxide 5%), (b) (4) and BenzaClin Topical Gel®, the listed product. It should be noted that the proposed product is not a pharmaceutical equivalent of either of these "reference" products as is it contains a (b) (4) amount of benzoyl peroxide than either **(b) (4)** Gel® or BenzaClin® (2.5% vs. 5%)

At the present time the proposed brand name, 'Acanya Gel®' has not been approved. In this submission, the applicant used other unapproved product names for Acanya Gel® such as (b) (4) Gel, (b) (4) (1/2.5) Gel and IDP-110 Gel.

1.1 Recommendation

The clinical pharmacology information included in this application is not adequate to support the approval of the proposed product, Acanya Gel®. Specifically, the application does not contain adequate in vivo bioavailability information required by 21 CFR §320. The clinical pharmacology review team reminded the applicant of such requirement during the End-of-Phase-2 and pre-NDA meetings.

(b) (4)

In order for NDA 50-819 to be approved, the applicant is required to conduct a 'maximum use systemic exposure (MUSE)' bioavailability study in the targeted patient population to determine the extent of systemic absorption of the active ingredients in Acanya Gel® in comparison to the listed drug BenzaClin Gel®. Elements of the said study should include:

a) Highest frequency of dosing in the proposed label for Acanya® Gel and BenzaClin® Gel.
b) Greatest duration of dosing in the above mentioned labels
c) Use of to-be-marketed formulation
d) Maximum total involved surface area to be treated at one time per labeling
e) Amount applied per square centimeter to be documented
f) Method of application/site preparation should be documented
g) Sensitive and validated analytical method to measure active and potential metabolite(s).

Should the Division of Dermatological and Dental Drug Products (DDDDP) determine that there is sufficient safety and efficacy information in the clinical studies database for approval we would still recommend that the study outlined above be conducted as a Phase IV post marketing commitment. This is in keeping with previous precedent and underscores the need for such information in drug development.

This recommendation should be communicated to the clinical division and subsequently to the applicant.

1.2 Phase 4 Commitments

The clinical pharmacology information submitted in this application is not adequate to support the approval of the proposed product. However, if as a result of overall regulatory determination by the DDDDP based on the efficacy and safety of the submitted clinical study results, a decision is made to approve the application, an in vivo bioavailability study will be required to be conducted post approval. Under these circumstances just described, the clinical pharmacology review team recommends conducting a 'maximum use systemic exposure (MUSE)' bioavailability study in the targeted patient population under maximal use conditions in comparison to the listed product, BenzaClin Gel® as a Phase IV commitment.

1.3 Summary of Clinical Pharmacology Findings

The applicant did not assess the characteristics of clindamycin or benzoyl peroxide absorption in subjects with acne vulgaris. Instead, the applicant performed an in vitro skin permeation study (2104-047-051-053-056) using dermatomed healthy human abdominal skin mounted to Bronaugh flow-through diffusion cells. The amount of drug in the receptor fluid, the dermis and the epidermis was measured after a single application (5 mg/cm^2) of the proposed (Acanya Gel®) or listed drug products (BenzaClin Topical Gel®, Duac Gel®) using a high performance liquid chromatographic (HPLC) method.

Although **clindamycin** concentrations could not be quantified (below the limit of quantitation [LOQ]) and compared in dermis samples and receptor solutions, the concentrations in epidermis samples were consistently above the LOQ (200 ng/sample) for all compared products. However,

due to large cell-to-cell (coefficient of variation [CV] up to 133%) and donor-to-donor (difference up to 3.5 fold) variability, and small number of skin donors (n = 2), the clindamycin recovery in the epidermis could not be reliably compared between the proposed and listed drug products.

Benzoyl peroxide was not detectable in the receptor solution or the dermis for any of the products. Although benzoyl peroxide was detected in a few epidermis samples, benzoyl peroxide concentrations were not quantifiable (lower than the LOQ, 40 μg/sample). Because benzoyl peroxide concentrations were not detectable or quantifiable, the extent of benzoyl peroxide absorption could not be compared between the proposed and listed drug products.

Benzoic acid was not detectable in dermis samples. Although benzoic acid was detected in receptor solutions and epidermis samples, benzoic acid concentrations were not quantifiable due to the LOQ. The LOQ of benzoic acid in receptor solution (400 ng/mL) is approximately 3% of applied dose when the solution is collected for 6 hours. Thus, by detecting benzoic acid in the samples, the extent of benzoyl peroxide absorption could not be compared between the proposed and listed drug products.

The HPLC method used in the study showed poor recovery of all analytes from receptor solutions (as low as 30% in benzoyl peroxide recovery).

Based on the results of the in vitro study summarized above, the extent of percutaneous absorption of clindamycin and benzoyl peroxide can not be reliably compared between the proposed and listed drug products since the drug concentrations were unquantifiable or highly variable and there were only two skin donors. Furthermore, in diseases where there is a disruption of the skin, in vitro study result is not acceptable as a surrogate for in vivo bioavailability.

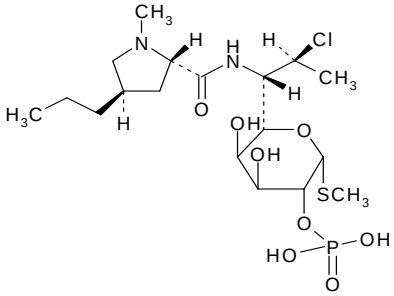
Note: The Optional Intra-Division Clinical Pharmacology Briefing was held on September 29, 2008. The attendees include Captain E. Dennis Bashaw, PharmD., Commander Lydia Velazquez, PharmD, and Jang-Ik Lee, Pharm.D., Ph.D.

2 QUESTION-BASED REVIEW

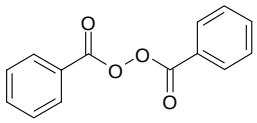
2.1 General Attributes

2.1.1 What are the highlights of the chemistry and physical-chemical properties of the drug substance and the formulation of the drug product?

Acanya Gel is a topical combination product with two active ingredients of clindamycin phosphate 1.2% and benzoyl peroxide 2.5% in an aqueous gel formulation. Clindamycin phosphate is a water-soluble ester of the semi-synthetic antibiotic produced by a 7(S)-chloro-substitution of the 7(R)-hydroxyl group of the parent antibiotic lincomycin. The chemical name for clindamycin phosphate is Methyl 7-chloro-6,7,8-trideoxy-6-(1-methyl-trans-4-propyl-L-2-pyrrolidinecarboxamido)-1-thio-L-threo-α-D-galacto-octopyranoside 2-(dihydrogen phosphate). Benzoyl peroxide is an antibacterial and keratolytic agent. The structural formula for clindamycin phosphate and benzoyl peroxide are represented below:



Clindamycin phosphate
(molecular weight, 504.97)



Benzoyl peroxide
(molecular weight, 242.23)

The chemical composition of Acanya Gel is shown in the table below.

Ingredient	%w/w	Quantity per 50 g Jar (g)
Clindamycin Phosphate, USP	1.20[1]	[redacted]
[redacted] Benzoyl Peroxide, USP	2.50[2]	
Propylene Glycol, USP	[redacted]	
Carbomer 980		
Potassium Hydroxide, NF		
Purified Water, USP		

[1] Equivalent to 1% w/w clindamycin
[2] Based on [redacted] benzoyl peroxide

(b) (4)

(b) (4)

2.1.2 What are the proposed mechanism(s) of action and therapeutic indication(s)?

Clindamycin binds to the 50S ribosomal subunits of susceptible bacteria and prevents elongation of peptide chains by interfering with peptidyl transfer, thereby suppressing bacterial protein synthesis. The clinical relevance of this in the treatment of acne vulgaris is unknown. Benzoyl peroxide is an oxidizing agent with bactericidal and keratolytic effects.

Acne vulgaris is a multifactorial disease, resulting from interplay of keratination abnormalities, excess sebaceous gland secretion, bacterial growth and inflammatory immune reactivity. Given the pathogenesis of acne, combination therapies affecting multiple etiologic factors have been shown to have significant benefit in acne treatment. This has been demonstrated with the combination of antibiotics (clindamycin or erythromycin) and keratolytic agents (tretinoin or benzoyl peroxide). In clinical practice, it is common for physicians to prescribe both topical benzoyl peroxide and a topical antibiotic for the treatment of acne. An example of combination products includes BenzaClin Gel (Sanofi Aventis, NDA 50-756).

2.1.3 What are the proposed dosage(s) and route(s) of administration?

Acanya Gel should be applied (b) (4) once daily (b) (4) Acanya Gel is not for oral, ophthalmic or intravaginal use.

2.2 General Clinical Pharmacology

2.2.1 What are the design features of the clinical pharmacology and clinical studies used to support dosing or claims?

The applicant has performed one Phase 2 study (DPS-07-12-2005-002) and two identical Phase 3 studies (DPSI-06-22-2006-012, DPSI-06-22-2006-017) which have provided clinical support for the efficacy of Acanya Gel. Male and female subjects 12 years or older were included in the studies. Dosing in the Phase 2 study was once or twice daily for 12 weeks, and in the 2 Phase 3 studies, it was once daily for 12 weeks. The gel was applied as a thin coating (a dab the size of a pea) that is gently rubbed into the skin on the face. All studies included subjects having between 17 and 40 acne inflammatory lesions, 20 and 100 non-inflammatory lesions, and 2 or fewer nodules.

2.2.2 What is the basis for selecting the response endpoints or biomarkers and how are they measured in clinical pharmacology and clinical studies?

The primary efficacy endpoints were absolute change from baseline to Week 12 in mean inflammatory lesion counts and percent of subjects who achieve a two-point reduction at Week 12 in the Evaluator's Global Severity Score (EGSS) from baseline.

2.2.3 Are the active and or relevant moieties in the plasma (or other biological fluid) appropriately identified and measured to assess pharmacokinetic and pharmacodynamic parameters and exposure response relationships?

No blood sample was collected from study subjects enrolled in any clinical study to assess pharmacokinetics, pharmacodynamics or exposure-response relationships.

2.2.4 Exposure-Response

2.2.4.1 What are the characteristics of the exposure-response relationships for efficacy? If relevant, indicate the time to the onset and offset of the desirable pharmacological response or clinical endpoint.

The exposure-efficacy response relationships have not been characterized in this 505(b)(2) application.

2.2.4.2 What are the characteristics of the exposure-response relationships for safety?

The exposure-safety response relationships have not been characterized in this 505(b)(2) application.

2.2.4.3 Does this drug prolong the QT or QTc interval?

No clinical study has been performed to determine the effect of Acanya Gel on QT interval.

2.2.4.4 Is the dose and dosing regimen selected by the Sponsor consistent with the known relationship between dose-concentration-response, and are there any unresolved dosing or administration issues?

The proposed dose is not based on a dose-concentration-response relationship but rather the approved dose of the listed product (BenzaClin Gel) and fixed dose studies conducted by the applicant.

2.2.5 What are the pharmacokinetic characteristics of the drug and its major metabolite?

2.2.5.1 What are the single dose and multiple dose pharmacokinetic parameters?

No clinical pharmacokinetic study has been conducted for this application.

2.2.5.2 How do the pharmacokinetics in healthy volunteers compare to those in patients?

No clinical pharmacokinetic study has been conducted for this application.

2.2.5.3 What are the characteristics of drug absorption?

The applicant did not assess the characteristics of clindamycin or benzoyl peroxide absorption in humans. Instead, the applicant performed an in vitro skin permeation study (2104-047-051-053-056), entitled "In Vitro Percutaneous Absorption of Clindamycin and Benzoyl Peroxide from BenzaClin, (b) (4) (1/2.5), (b) (4), and Duac Topical Gel Using Intact Human Skin from Two Healthy Donors," using dermatomed human abdominal skin from 2 healthy donors, obtained from elective surgeries. The purpose of the study was to compare the percutaneous absorption of clindamycin and benzoyl peroxide from Acanya Gel ((b) (4) 1/2.5) with that from BenzaClin Topical Gel (approved, NDA 50-756), Duac Topical Gel (approved, NDA 50-741) and (b) (4) All comparators contain the same amount of clindamycin (1%) but 2-fold larger amount of benzoyl peroxide (5%) than Acanya Gel.

The in vitro study used Bronaugh flow-through diffusion cells in 5 replicates with a single 24-hour application of product 5 mg to 1 cm^2 mounted skin area. The receptor fluid containing phosphate buffered saline with 0.1% sodium azide and 4% bovine serum albumin was continuously pumped under the skin at a flow rate of nominally 1.5 ml/hr and collected at 6-hour intervals. After 24 hours, the product residue remaining on the surface of the skin was removed by tape-stripping technique, and the epidermis and the dermis were separated by blunt dissection. The amount of drug in the receptor fluid, the epidermis and the dermis was measured using a high performance liquid chromatographic (HPLC) method.

Based on the results of the in vitro study, the extent of percutaneous absorption of clindamycin and benzoyl peroxide can not be reliably compared between the proposed and listed products since the drug concentrations were unquantifiable or highly variable. Furthermore, an in vitro study using non-diseased normal skin is not likely to reflect the clinical situation (inflamed skin) for the following reasons:

1. The use of non-viable skin can alter the permeation properties of the skin (e.g. storage conditions).

2. The use of normal skin instead of diseased skin, which due to the disrupted stratum corneum in diseased skin, can markedly affect drug penetration.

3. The preparation of the skin samples usually requires the microtoming of the skin to a uniform layer, a situation that is neither physiologic nor relevant to diseased skin.

<u>Absorption of Clindamycin</u>

As shown in Table 1 below, only 1 out of the 160 assayed receptor solutions contained clindamycin levels above the limit of quantification (LOQ, 2.0 ng/mL). The solution was Cell (b) (4) for (b) (4) Gel assayed to contain 2.54 ng/mL at the 12-hour sampling point. In the

dermis, clinidamycin was detected in some cells. However, none of the dermis samples contained clindamycin concentrations above the LOQ (200 ng/sample). Since clindamycin could not be quantified in receptor solution and in the dermis, the extent of clindamycin skin absorption can not be compared between studied products using the receptor solution or dermis samples.

Table 1: Clinicdamycin concentrations measured in vitro skin permeation study using Bronaugh flow-through diffusion cells after the application of gel product 5 mg/cm^2

Clindamycin * below LOQ	Cell ID	Receptor Phase (ng/mL) Hour(s) 6	12	18	24	Skin Tissue (ng/sample) Epidermis	Dermis
BenzaClin Gel Donor 1	A1	(b) (4)					
	A2						
	A3						
	A4						
	A5						
(b) (4) 1/2.5 Donor 1	C1						
	C2						
	C3						
	C4						
	C5						
(b) (4) Donor 1	D1						
	D2						
	D3						
	D4						
	D5						
Duac Gel Donor 1	E1						
	E2						
	E3						
	E4						
	E5						
BenzaClin Gel Donor 2	F1						
	F2						
	F3						
	F4						
	F5						
(b) (4) 1/2.5 Donor 2	H1						
	H2						
	H3						
	H4						
	H5						
(b) (4) Donor 2	I1						
	I2						
	I3						
	I4						
	I5						
Duac Gel Donor 2	J1						
	J2						
	J3						
	J4						
	J5						

The clindamycin concentrations in the epidermis were consistently above the limit of quantification (200 ng/sample, Table 1). Due to large cell-to-cell (coefficient of variation [CV] up to 133%) and donor-to-donor (difference up to 3.5 fold) variability, and a small number of skin donors (n = 2) as shown in table 2 below, the clindamycin recovery in the epidermis can not be reliably compared between studied products.

Table 2: Clinicdamycin recovery in vitro skin permeation study using Bronaugh flow-through diffusion cells after the application of gel product 5 mg/cm^2

Donor	Formulation	Recovery (ng/cm^2)	% Dose Applied
Donor 1	(b) (4) 1/2.5	349 ± 142	1 ± 0
	(b) (4) (b) (4)	1586 ± 2105	3 ± 4
	Duac Gel	699 ± 386	2 ± 1
	BenzaClin Gel	1985 ± 1781	4 ± 4
Donor 2	(b) (4) 1/2.5	1234 ± 823	3 ± 2
	(b) (4) (b) (4)	1324 ± 826	3 ± 2
	Duac Gel	2354 ± 1532	5 ± 3
	BenzaClin Gel	1251 ± 401	3 ± 1

Absorption of Benzoyl Peroxide / Benzoic Acid

Benzoyl peroxide was detectable in the epidermis in some cells as shown in Table 3. However, the concentrations of benzoyl peroxide were not quantifiable (below the LOQ). The LOQ values were 400 ng/mL in receptor solution, and 40 µg/sample in both epidermis and dermis samples. Benzoyl peroxide was not detectable in the receptor solution or dermis for any of the formulations studied. Because benzoyl peroxide concentrations were not quantifiable, the extent of benzoyl peroxide absorption could not be compared between studied products using benzoyl peroxide concentrations.

Table 3: Benzoyl peroxide detected in vitro skin permeation study using Bronaugh flow-through diffusion cells after the application of gel product 5 mg/cm^2

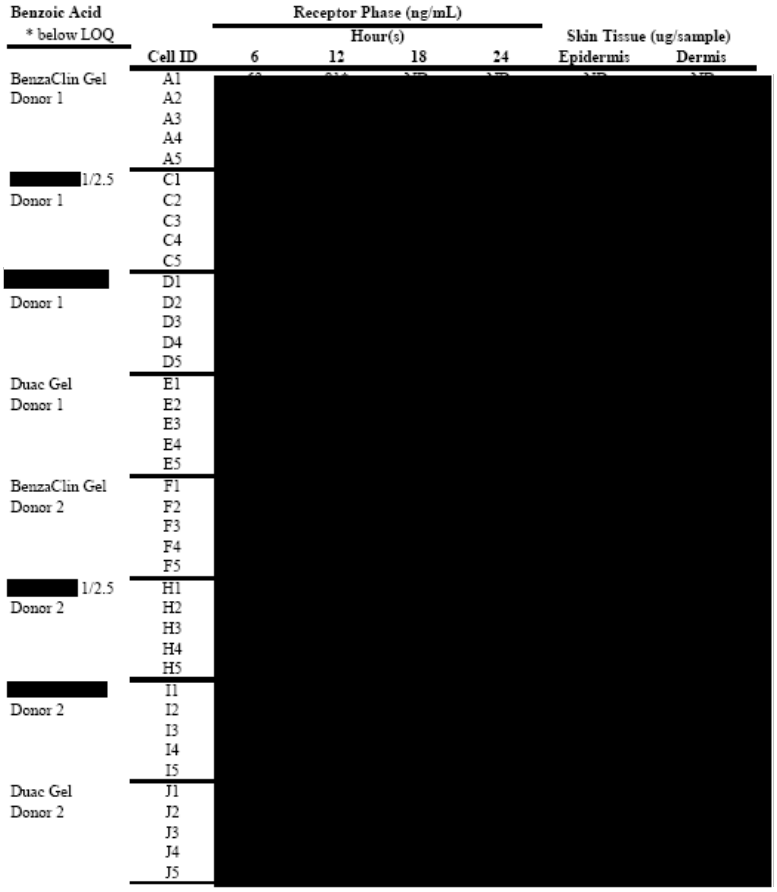
Benzoyl Peroxide * below LOQ		Receptor Phase (ng/mL) Hour(s)				Skin Tissue (ug/sample)	
	Cell ID	6	12	18	24	Epidermis	Dermis
BenzaClin Gel Donor 1	A1	(b) (4)					
	A2						
	A3						
	A4						
	A5						
(b) (4) 1/2.5 Donor 1	C1						
	C2						
	C3						
	C4						
	C5						
(b) (4) Donor 1	D1						
	D2						
	D3						
	D4						
	D5						
Duac Gel Donor 1	E1						
	E2						
	E3						
	E4						
	E5						
BenzaClin Gel Donor 2	F1						
	F2						
	F3						
	F4						
	F5						
(b) (4) 1/2.5 Donor 2	H1						
	H2						
	H3						
	H4						
	H5						
(b) (4) Donor 2	I1						
	I2						
	I3						
	I4						
	I5						
Duac Gel Donor 2	J1						
	J2						
	J3						
	J4						
	J5						

As shown in Table 4 below, benzoic acid was detectable in all cells 6 hours after all product applications, most cells 12 hours after most product applications, and a few cells 18 or 24 hours after some product applications. The concentrations of benzoic acid were quantifiable (LOQ, 200 ng/mL, approximately 2.7% of applied dose) in the receptor solution in some cells 6 and 12 hours after the application of **(b) (4)** Gel, but not quantifiable 18 and 24 hours after application of any product. The maximum concentration of 269 ng/mL measured in **(b) (4)** Gel application was approximately 3.6% of applied dose. In the epidermis, benzoic acid was detectable in most cells with Donor 1 skin and in a few cells with Donor 2 skin. None of the detected benzoic acid in the epidermis was quantifiable (LOQ, 40 µg/sample). In the dermis, benzoic acid was not detected in any cell.

These results are consistent with the literature findings that benzoyl peroxide was rapidly metabolized to benzoic acid during skin absorption. However, the extent of benzoyl peroxide absorption could not be compared between the proposed and listed products using benzoic acid concentrations since the concentrations were quantifiable only a few samples. The applicant noted that the limit of detection for benzoic acid was 35 ng/mL in receptor solution, and the 2% of the applied benzoyl peroxide dose with an applied 5-mg dose to 1 cm^2 of skin over 12 hours

would be equivalent to an assay value of approximately 150 ng/mL of benzoic acid in the receptor solution when fully metabolized.

Table 4: Benzoic acid concentrations measured in vitro skin permeation study using Bronaugh flow-through diffusion cells after the application of gel product 5 mg/cm^2



2.2.5.4 What are the characteristics of drug distribution?

No drug distribution study has been performed for this application.

2.2.5.5 Does the mass balance study suggest renal or hepatic as the major route of elimination?

No mass balance study has been performed for this application.

2.2.5.6 What are the characteristics of drug metabolism?

No metabolism study has been performed for this application.

2.2.5.7 What are the characteristics of drug excretion?

No excretion study has been performed for this application.

2.2.5.8 Based on pharmacokinetic parameters, what is the degree of linearity or nonlinearity in the dose-concentration relationship?

The degree of linearity in dose-response relationship has not been performed for this application.

2.2.5.9 How do the pharmacokinetic parameters change with time following chronic dosing?

No clinical pharmacokinetic study has been performed for this application.

2.2.5.10 What is the inter- and intra-subject variability of pharmacokinetic parameters in volunteers and patients, and what are the major causes of variability?

No clinical pharmacokinetic study has been performed for this application.

2.3 Intrinsic Factors

2.3.1 What intrinsic factors influence exposure and/or response, and what is the impact of any differences in exposure on efficacy or safety responses?

The impact of intrinsic factors on efficacy and safety response has not been evaluated in this application.

2.3.2 Based upon what is known about exposure-response relationships and their variability and the groups studied, healthy volunteers vs. patients vs. specific populations, what dosage regimen adjustments, if any, are recommended for each of these groups? If dosage regimen adjustments are not based upon exposure-response relationships, describe the alternative basis for the recommendation.

2.3.2.1 Elderly

A geriatric study has not been performed in this application. Given that acne vulgaris normally is a disease associated with younger patients, geriatric data is not needed to support this application.

2.3.2.2 Pediatric Patients

Safety and effectiveness of Acanya Gel in pediatric patients under the age of 12 have not been established. Clinical trials of Acanya Gel included patients 12 to 17 years of age.

The applicant requested a waiver for pediatric studies since Acanya Gel does not represent a meaningful therapeutic benefit over existing treatments for pediatric patients and is not likely to be used in a substantial number of patients younger than 12 years.

2.3.2.3 Gender

No study was conducted to evaluate the effect of gender on the clinical pharmacology of Acanya Gel.

2.3.2.4 Race

No study was conducted to evaluate the effect of race on the clinical pharmacology of Acanya Gel.

2.3.2.5 Renal impairment

No study was conducted to evaluate the effect of renal impairment on the clinical pharmacology of Acanya Gel.

2.3.2.6 Hepatic impairment

No study was conducted to evaluate the effect of hepatic impairment on the clinical pharmacology of Acanya Gel.

2.3.2.7 What pregnancy and lactation use information is there in the application?

Based on the proposed labeling, the pregnancy category is C. There are no well-controlled trials in pregnant women treated with Acanya Gel. It also is not known whether Acanya Gel can cause fetal harm when administered to a pregnant woman. Acanya Gel should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

It is not known whether clindamycin is excreted in human milk after topical application of Acanya Gel. However, orally and parentally administered clindamycin has been reported to appear in breast milk. Because of the potential for serious adverse reactions in nursing infants, a decision should be made whether to (b) (4) Acanya Gel, taking into account the importance of the drug to the mother.

2.4 Extrinsic Factors

2.4.1 What extrinsic factors (drugs, herbal products, diet, smoking, and alcohol use) influence dose-exposure and/or -response and what is the impact of any differences in exposure on response?

No analysis was conducted to evaluate the effect of the extrinsic factors on the clinical pharmacology of Acanya Gel.

2.4.2 Drug-drug interactions

Based on the proposed labeling, Acanya Gel should not be used in combination with erythromycin-containing products due to its clindamycin component. In vitro studies have shown antagonism between erythromycin and clindamycin. The clinical significance of this in vitro antagonism is not known. This is consistent with BenClin Gel labeling.

Concomitant topical acne therapy should be used with caution because a possible cumulative irritancy effect may occur, especially with the use of peeling, desquamating, or abrasive agents.

In the proposed labeling, the applicant states that clindamycin has been shown to have neuromuscular blocking properties that may enhance the action of other neuromuscular blocking agents. Therefore, Acanya Gel should be used with caution in patients receiving such agents. The applicant was requested to provide the source of this information and the pertinence of this information is under discussion at the completion of this review.

2.4.3 What issues related to dose, dosing regimens, or administration are unresolved and represent significant omissions?

The dose, dosing regimen and administration other than the proposed ones have not been tested in this 505(b)(2) application.

2.5 General Biopharmaceutics

This section is not applicable to this application since in vivo bioavailability study has not been conducted.

2.6 Analytical

2.6.1 How are the active moieties identified and measured in the plasma in the clinical pharmacology and biopharmaceutics studies?

In vitro skin permeation study, clindamycin, benzoyl peroxide and benzoic acid residing in the epidermis, dermis and receptor solution samples were identified and measured using a mass spectrometric method. The mass spectrometric conditions were optimized for the most abundant ion transition of clindamycin at m/z (b) (4) and benzoic acid and benzoyl peroxide at m/z (b) (4). The ionization mode was APCI in the positive ion mode for clindamycin and negative mode for benzoic acid and benzoyl peroxide.

2.6.2 Which metabolites have been selected for analysis and why?

In the in vitro permeation study, benzoic acid in the epidermis, dermis, and receptor solution samples was measured as the major metabolite because benzoyl peroxide is rapidly and predominantly metabolized to benzoic acid during skin absorption.

2.6.3 For all moieties measured, is free, bound, or total measured? What is the basis for that decision, if any, and is it appropriate?

The total amount of the analytes in the specimens was measured. This is appropriate to determine the percutaneous absorption of the analytes.

2.6.4 What bioanalytical methods are used to assess concentrations?

The concentrations of clindamycin, benzoyl peroxide and benzoic acid in the epidermis, dermis and receptor solution samples were measured by a reversed phase HPLC method with UV and mass spectroscopic detection (HPLC/UV/MS/MS). The method includes the sample preparation

along with typical chromatographic and mass spectrometric operating conditions and parameters. Receptor solution containing the analytes was diluted 1:1 using (b) (4) The resulting solution was centrifuged and the supernatant analyzed by the HPLC method. The epidermis and dermis samples containing the analytes were extracted using (b) (4) . The samples were homogenized and then centrifuged. A portion of the supernatant was then diluted 1:10 with a solution of (b) (4) The resulting solution was then analyzed by the HPLC method. The HPLC column used for the separation was a (b) (4) . A gradient elution program was employed using (b) (4)

2.6.4.1 What is the range of the standard curve? How does it relate to the requirements for clinical studies? What curve fitting techniques are used?

For clindamycin assay, an assay range of 200 to 10,000 ng/sample was established for epidermis and dermis samples, while a range of 2.0 to 100 ng/mL for receptor fluid. For benzoic acid assay, a range of 40 to 400 µg/sample was established for epidermis and dermis samples, while a range of 400 to 4000 ng/mL for receptor fluid. For benzoyl peroxide assay, a range of 40 to 400 µg/sample was established for epidermis and dermis samples, while a range of 400 to 4000 ng/mL for receptor fluid.

2.6.4.2 What are the lower and upper limits of quantification?

The table below summarizes the LOQ values determined for each analyte in each specimen.

	Receptor Solution	Epidermis	Dermis
Analyte	**(ng/mL)**	**(µg /sample)**	**(µg /sample)**
clindamycin	2.0	0.20	0.20
benzoic acid	200.0	40.0	40.0
benzoyl peroxide	400	40.0	40.0

The table below summarizes the values for limits of detection determined for each analyte in each specimen.

	Receptor Solution	Epidermis	Dermis
Analyte	**(ng/mL)**	**(µg/sample)**	**(µg /sample)**
clindamycin	0.2	0.004	0.004
benzoic acid	35.0	4.5	4.5
benzoyl peroxide	120	3.3	3.3

2.6.4.3 What are the accuracy, precision, and selectivity at these limits?

See Section 2.6.4.5 below

2.6.4.4 What is the sample stability under the conditions used in the study (long-term, freeze-thaw, sample-handling, sample transport, autosampler)?

The sample stability has not been reported.

2.6.4.5 What is the QC sample plan?

The quality control samples for low, medium and high concentrations were run in triplicates. The low concentrations were the same as the lower LOQs. The performance of the quality controls for each analyte in each specimen is summarized in the table below. All analytes showed poor recovery from receptor solution as shown in bold figures in the table.

Analyte	Specimen (unit)	Concentration	Accuracy (% Recovery)	Precision (% CV)
Clindamycin	Epidermis (ng/sample)	200	109	5
		1000	111	5
		4000	**120**	0
	Dermis (ng/sample)	200	103	2
		1000	111	1
		4000	113	0
	Receptor Fluid (ng/mL)	2	87	8
		10	**129**	4
		40	**136**	8
Benzoic Acid	Epidermis (µg/sample)	40	108	1
		160	101	10
		320	103	1
	Dermis (µg/sample)	40	98	6
		160	106	2
		320	98	2
	Receptor Fluid (ng/mL)	400	**73**	11
		1600	**70**	6
		3200	**74**	14
Benzoyl Peroxide	Epidermis (µg/sample)	40	94	1
		160	96	9
		320	108	7
	Dermis (µg/sample)	40	83	11
		160	101	1
		320	103	2
	Receptor Fluid (ng/mL)	400	**37**	20
		1600	**49**	17
		3200	**30**	7

3 DETAILED LABELING RECOMMENDATIONS

The following changes are recommended. ~~ABC~~ indicates deletion of text from and ABC indicates insertion of new text to the labeling text proposed by the Sponsor.

(b) (4)

(b) (4)

4 APPENDICES

4.1 Package Insert (Proposed and Annotated)

Please refer to \\Cdsesub1\evsprod\NDA050819\0000\m1\us\114-labeling\1141-draft-labeling\11412-annotated-draft-labeling-text\annotated-draft-labeling-text.pdf

Appears This Way On Original

4.2 Summary of Individual Studies

No clinical pharmacology study was performed in humans for this application.

4.3 Consult Reviews

No consult review was requested.

Appears This Way On Original

4.4 OCPB Filing/Review Form

Office of Clinical Pharmacology and Biopharmaceutics

New Drug Application Filing and Review Form

General Information about the Submission

	Information		Information
NDA Number	50-819	**Brand Name**	(b) (4) Gel
OCPB Division (I, II, III)	DCP3	**Generic Name**	1.2 % clindamycin phospahte , 2.5 % benzoyl peroxide
Medical Division	HFD-540	**Drug Class**	Anti microbial
OCPB Reviewer	Abi Adebowale	**Indication(s)**	Treatment of acne vulgaris in patients 12 years and older
OCPB Team Leader	Lydia Velazquez	**Dosage Form**	Gel
Letter Date	21st December, 2007	**Dosing Regimen**	(b) (4)
Application Receipt Date	26th December, 2007	**Route of Administration**	Topical
Estimated Due Date of OCPB Review	26th August, 2008	**Sponsor**	Dow Pharmaceutical Sciences, Inc.
PDUFA Due Date	26th, October, 2008	**Priority Classification**	Standard 505 (b) (2) application *Reference Listed Drugs are Benzaclin Topical Gel and Duac Topical Gel*
		IND Number	41,733

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Study Numbers If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	X			
Tabular Listing of All Human Studies	X			
HPK Summary	X			
Labeling	X			
Reference Bioanalytical and Analytical Methods	X			Sponsor needs to direct me to the validation report for the assay method used in study # 2104-047-051-053-056 (In vitro percutaneous absorption)
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:				
multiple dose:				
Patients-				
single dose:				
multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:				

hepatic impairment:				
PD:				
Phase 2:				
Phase 3:				
PK/PD:				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability:				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference (IR):				
Bioequivalence studies -				
traditional design; single / multi dose:	X	1		Study # DPS-07-07-2005-001- (b) (4) (b) (4)
replicate design; single / multi dose:				
Food-drug interaction studies:				
Dissolution:				
(IVIVC):				
Bio-wavier request based on BCS				
BCS class				
III. Other CPB Studies				
Genotype/phenotype studies:				
Other (in vitro percutaneous absorption study)	X	1		Study #2104-047-051-053-056
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies		2		

Filability and QBR comments

Types and #'s of studies and supplementary information (literature review) are adequate to conduct a review	"X" if yes X	**Comments** Send IR to sponsor to direct me to, or provide, the validation report for the analytical method used to measure clindamycin, benzoyl peroxide and benzoic acid in study #2104-047-051-053-056: In Vitro Percutaneous absorption of Clindamycin and Benzoyl peroxide from Benzaclin, (b) (4) (1/2.5), (b) (4) and DUAC Topical Gel using intact human skin from two healthy donors Sponsor already responded
Application filable?	X	Reasons if the application is not filable (or an attachment if applicable) For example, is clinical formulation the same as the to-be-marketed one?
Comments sent to firm?	**No**	Comments have been sent to firm (or attachment included). FDA letter date if applicable.
QBR questions (key issues to be considered)	What is the systemic exposure of clindamycin and benzoyl peroxide from (b) (4) Gel and how does it compare to the currently marketed products?	
Other comments or information not included above		
Primary reviewer Signature and Date	**Abi Adebowale (02/11/08)**	
Secondary reviewer Signature and Date	**Lydia Velazquez**	

End of Document

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

/s/

Jang-Ik Lee
9/29/2008 03:21:40 PM
BIOPHARMACEUTICS

Lydia Velazquez
9/29/2008 03:53:46 PM
BIOPHARMACEUTICS