

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 cm² 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.

Absorption of Clindamycin

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, clindamycin 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: Clindamycin concentrations measured in vitro skin permeation study using Bronaugh flow-through diffusion cells after the application of gel product 5 mg/cm²

Clindamycin * below LOQ	Cell ID	Receptor Phase (ng/mL)				Skin Tissue (ng/sample)	
		Hour(s)				Epidermis	Dermis
		6	12	18	24		
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: Clindamycin recovery in vitro skin permeation study using Bronaugh flow-through diffusion cells after the application of gel product 5 mg/cm²

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/cm²

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

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 cm² 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/cm²

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

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) [REDACTED] and benzoic acid and benzoyl peroxide at m/z (b) [REDACTED]. The ionization mode was APCI in the positive ion mode for clindamycin and (4) [REDACTED] 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