CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-320

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

Clinical Pharmacology Review

NDA	22-320	**Submission Date(s)**	February 8th, 2008 and July 15th, 2008
Proposed Brand Name		Epiduo	
Generic Name		Adapalene 0.1 % / Benzoyl Peroxide 2.5 % Gel	
Reviewer		Abimbola Adebowale, Ph.D.	
Team Leader		Lydia Velazquez, Pharm.D.	
OCP Division		DCP-3	
OND division		HFD-540	
Applicant		Galderma Laboratories, L.P. Forth Worth, Texas	
Relevant IND(s)		67,801	
Submission Type; Code		505 (b) (2) NDA Application	
Formulation; Strength(s)		Gel	
Indication		Topical Treatment of *Acne Vulgaris* in patients 12 years and older	

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1 Executive Summary

Adapalene/Benzoyl Peroxide Gel, is a new a fixed-dose retinoid and antimicrobial combination drug product intended for the topical treatment of *acne vulgaris* in patients who are 12 years of age and older. Adapalene and benzoyl peroxide are currently marketed as monotherapy for the treatment of acne vulgaris. Adapalene is currently marketed for the topical treatment of acne vulgaris at a concentration of 0.1 % (cream,

gel, and solution) and 0.3 % (gel). The NDAs for adapalene 0.1% solution (NDA 20-338) and adapalene 0.1% gel (NDA 20-380) were approved on May 31st, 1996. Adapalene 0.1 % cream (NDA 20-748) was approved on May 26th, 2000. Adapalene 0.3 % cream (NDA 21-753) was approved on June 19th, 2007. Benzoyl peroxide is also currently marketed for the topical treatment of acne vulgaris in concentrations ranging from 2.5 % to 10 % in prescription and nonprescription drug products.

Please note that the terms "adapalene/benzoyl peroxide gel" and "Epuido" gel are used interchangeably in this review document.

1.1 Recommendations

The clinical pharmacology and biopharmaceutics information included in this submission is acceptable. We recommend that the labeling changes in Section 3 and 4.1 (included in the product package insert) be conveyed to the applicant.

1.2 Phase IV Commitments

Not Applicable

1.3 Summary of Clinical Pharmacology and Biopharmaceutics Findings

Overview of the Clinical pharmacology Drug Development Program

The clinical pharmacology program for adapalene/benzoyl peroxide gel consisted of 2 in vivo pharmacokinetic (PK) studies (SRE.2685 and SRE.18097). These studies were conducted in subjects with *acne vulgaris*. For this application only one in vivo PK study (SRE.18097) is considered pivotal. Study SRE 2685 was not reviewed in detail because the formulation used in this study was not the to-be-marketed formulation, and the study utilized an analytical method with a sensitivity (LOQ=0.25 ng/mL) that was not considered to be optimal. In addition, the duration of study SRE 2685 was 10 days which was not considered to be representative of steady state conditions because retinoids are generally known to reach steady state at around 15 days. Therefore, this study was repeated in SRE.18097 using the to-be-marketed formulation, with a duration of 30-days and a more sensitive analytical method (LOQ=0.1 ng/mL). It is noted that this repeat study was conducted based on advice provided by the FDA at a Pre-IND meeting held with the applicant on July 28th, 2003.

Only adapalene plasma concentrations were evaluated in these studies. Benzoyl peroxide plasma concentrations were not assessed in either study because of its complete and rapid metabolism to benzoic acid in the skin. Since benzoic acid is an endogenous compound and it is also widely used as a food additive (that is considered safe in humans), the applicant stated that it would be difficult to accurately evaluate treatment-related exposure of benzoic acid.

In the biopharmaceutics section, the applicant also provided in vitro data from three percutaneous absorption studies (SRE.4700, SRE. 4708 and SRE.4781) that evaluated the release of the individual active substances, both from the monads and from the fixed

combination product. The in vitro percutaneous components of these studies were not reviewed because 1) in vitro percutaneous studies for this indication is not an acceptable method for assessing exposure of the drug product and 2) studies SRE. 4700 and SRE. 4708 did not use the to-be-marketed formulation. Although study SRE. 4781 used the to-be-marketed formulation, the in vitro data (conducted with healthy skin) will not add any benefit to the information obtained from the in vivo studies conducted in patients with diseased skin for the reason mentioned above.

It is noted that Studies SRE 4700 and 4708 were previously submitted to NDA 21-753 (Adapalene gel 0.3 %) and not reviewed. The clinical pharmacology reviewer stated that these studies were not reviewed because they were considered to be exploratory in nature for formulation development. However, for study # 4708, the applicant included some metabolism data which may be relevant to this drug product. Therefore, the metabolism data is reviewed in this document.

Systemic Exposure:

The systemic exposure of adapalene in subjects with acne vulgaris was assessed under maximal use conditions in the pivotal PK study, SRE.18097. This was a single-center, double-blind, randomized, active-controlled, parallel-group study. Twenty (20) acne vulgaris subjects were treated once daily for 30 days with 2 grams of either adapalene 0.1%/benzoyl peroxide 2.5% gel (N=10) or adapalene 0.1 % gel (N=10), applied to the face, upper part of the chest, and upper part of the back (approximately 1000 cm^2) corresponding to approximately 2 mg/cm^2. Blood samples for the determination of adapalene plasma concentrations were collected on Days 1, 10, 21, and 30 at the following times: before the study medication application (pre-dose) and 2, 4, 6, 8, 10, 12, and 24 hours following application. Additionally, on Day 30, blood samples were also collected at 36, 48, and 72 hours following the study medication application.

Two of the 10 subjects (20 %) treated with adapalene/benzoyl peroxide gel and 3 of 10 (30 %) subjects treated with adapalene gel, 0.1% had quantifiable (LOQ = 0.1 ng/mL) adapalene plasma concentrations, ranging between 0.1 ng/mL to 0.21 ng/mL. The pharmacokinetic parameters derived from the quantifiable concentrations obtained in these five subjects are shown in the table below.

Table 1: Pharmacokinetic Parameters of Adapalene

Treatment	Subject	Day	C_{max} (ng/mL)	T_{max} (h)	$AUC_{(0-24h)}$ (ng h/mL)
Adapalene/Benzoyl Peroxide Gel, the fixed combination	13	21	0.1266	0	1.9945
	16	30	0.2086	12	NA
Adapalene Gel, 0.1%, the monad	1	10	0.1611	12	2.6481
	1	21	0.1261	6	1.2623
	15	30	0.1392	24	NA
	21	30	0.1101	6	NA

NA: Not applicable due to fewer than three consecutive quantifiable concentrations available.

No accumulation of adapalene was observed over time. The results of the study suggested that the systemic exposure of adapalene following topical application of the adapalene/benzoyl peroxide gel for 30 days to subjects with acne vulgaris is comparable to that obtained following topical application of adapalene 0.1 % gel alone under the same conditions. This suggests that the presence of benzoyl peroxide in the adapalene/benzoyl peroxide combination gel may not affect the plasma concentrations of adapalene. However, since intra-subject comparisons are not possible and the number of subjects with plasma levels was small, definitive conclusions can not be made.

There were 6 samples obtained from 4 subjects that were re-assayed by the applicant due to initial high plasma values of adapalene that were considered to be unexpected values within the concentration-time profile. Four of the 6 re-assayed samples were collected from three of the twelve (25%) subjects (subject #'s 1, 8 and 15) in the adapalene gel group. Subject #'s 1 and 8 had one re-assayed sample each and Subject # 15 had two re-assayed samples. The remaining two re-assayed samples were collected from one of the twelve (8%) subject (subject #16) in the adapalene 0.1 %/benzoyl peroxide 2.5 % gel group. Three of the re-assayed samples were reported as BLQ which was the mean of the repeat values obtained. These samples (one sample per subject) were from three subjects (subject #1, 15 and 16).

However, the remaining 3 re-assayed samples had concentration values that were not reportable due to insufficient volume of plasma available to duplicate the repeat analysis for verification purposes and therefore not resolved. The non reportable plasma sample values were ⌜ ⌟ of adapalene for subject #8 (day 30, 10h), and for subject #15 (day 33, 72h) from the adapalene gel group, respectively. The third non reportable plasma sample value was ——— of adapalene for subject #16 (day 30, 8h) from the adapalene/benzoyl peroxide gel group. b(4)

Based on previous clinical pharmacology findings for adapalene, the highest initial plasma concentration of adapalene ——— obtained from the 3 unresolved samples is at least 50 % less than the highest concentration of adapalene ——— obtained following application of the approved 0.3 % adapalene gel (NDA 21-753); which is a higher concentration of adapalene than what is proposed for marketing in this application. In addition, the applicant stated that there were no treatment related systemic adverse b(4)

events recorded for the four subjects (#'s 1, 8, 15 and 16) who had their samples re-assayed.

Previous PK studies for currently approved adapalene 0.1 % gel or cream also indicated that following the application of 2g of either the cream or the gel to 1000 cm^2 of acne involved skin for 5 days for the cream and up to 3 months for the gel, the plasma concentrations of adapalene reported were < 0.38 ng/mL. For the most part, the systemic exposure obtained for adapalene following the application of Epiduo is comparable to historical data for the monad except in the case of the 3 unresolved plasma samples.

In Vitro Metabolism Study

The *in vitro* metabolism of ^{14}C-adapalene from Adapalene/Benzoyl Peroxide Gel (not the to-be--marketed formulation) and ^{14}C- Adapalene Gel, 0.1% was investigated in study SRE.4708 using Reconstructed Human Epidermis (RHE). Parent adapalene was the only radioactive component found in all of the samples analyzed. There were no metabolites detected in the RHE samples analyzed following application of ^{14}C- Adapalene /Benzoyl Peroxide Gel or ^{14}C- Adapalene Gel, 0.1%. Therefore, under the experimental conditions of this study, no metabolites of adapalene were identified following the application of ^{14}C- Adapalene 0.1 % /Benzoyl Peroxide 2.5 % Gel or ^{14}C- Adapalene Gel, 0.1%.

Signatures:

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An OCPB Briefing was held on October 23rd, 2008.

2 Question-Based Review

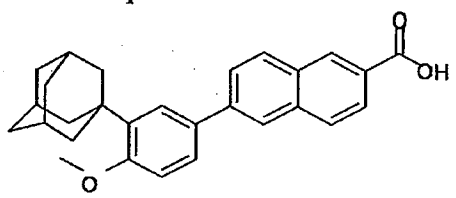
2.1 General Attributes of the drug

Q ***What are the highlights of the chemistry and physical-chemical properties of the drug substance?***

EPIDUO (adapalene 0.1% and benzoyl peroxide 2.5%) Gel is a retinoid and antimicrobial fixed-dose combination gel product with two active ingredients.

Adapalene is a naphthoic acid derivative with retinoid-like properties. The chemical name for adapalene is (6-[3-(1-adamantyl)-4-methoxyphenyl]-2-naphthoic acid). It has the following structural formula:

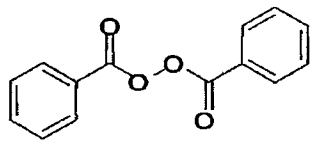
Adapalene:



Molecular formula: $C_{28}H_{28}O_3$ Molecular weight: 412.5

Benzoyl Peroxide is a lipophilic oxidizing agent that localizes in both bacterial and keratinocyte cell membranes. The chemical name for benzoyl peroxide is dibenzoyl peroxide. It has the following structural formula:

Benzoyl Peroxide:



Molecular formula: $C_{14}H_{10}O_4$ Molecular weight: 242.23

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

Indication: Epuido gel is indicated for the topical treatment of *acne vulgaris* in patients aged 12 years and older.

Mechanism of Action: **Adapalene** acts on retinoid receptors. Mechanistically, adapalene binds to specific retinoic acid nuclear receptors but it does not bind to the

cystolic receptor protein. Although the exact mode of action of adapalene is unknown, it is suggested that topical adapalene normalizes the differentiation of follicular epithelial cells resulting in decreased microcomedone formation.

Benzoyl peroxide is an antibacterial agent which is believed to act by oxidizing proteins, including bacterial proteins, and reducing the population of *Propionibacterium acnes* which are usually abnormally present in the acne-affected pilosebaceous unit.

Therefore,ada palene and benzoyl peroxide act through different, but complementary, mechanisms that affect different aspects of acne therapy.

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

Epiduo gel is to be applied to acne affected areas (e.g. forehead, chin, each cheek, and trunk) of the skin once daily ——— after washing gently with a non-medicated cleanser. b(4)

2.2 General Clinical Pharmacology

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

Table 2: Tabular listing of clinical pharmacology and Phase 3 clinical studies:

Study Number	Objective of the Study	Study Design and Number of Subjects	Test Product (s), Dosage Regimen and Study Duration
RD.03.SRE.2685	Assessment of pharmacokinetics	Single-centre, randomized, parallel group, investigator-blind, active-controlled in subjects with acne vulgaris Number of Subjects: N=16 (8 for the fixed combination and 8 for Adapalene Monad) Age: 19-35 years old	Study Drug: Adapalene/Benzoyl Gel ***(Not the to-be-marketed formulation)*** Control Adapalene 0.1% Gel, Dose: ~ 2 g/day applied to the face, upper back and upper chest Study Duration: 10 Days
RD.06.SRE.18097	Assessment of pharmacokinetics	Single-centre, randomized, parallel group, double-blind, active-controlled in	Study Drug: Adapalene/Benzoyl Gel ***(To-be-marketed***

		subjects with acne vulgaris Number of Subjects: N=24 (12 the fixed combination and 12 Adapalene Monad) Age: 18-34 years old	***formulation (TBMF))*** Control: Adapalene 0.1% Gel, Dose: ~ 2g/day applied to the face, upper back and upper chest Study Duration: 30 Days
RD.06.SRE.18094	Assessment of efficacy and safety	Multi-centre, randomized, parallel group, double-blind, active-controlled and vehicle-controlled in subjects with acne vulgaris Number of Subjects: N=517 (149 the fixed combination, 148 Adapalene Monad, 149 Benzoyl Peroxide, and 71 Vehicle Gel) Age: 12-56 years old	Study Drug: Adapalene/Benzoyl Peroxide Gel ***(TBMF)*** Controls Adapalene 0.1% Gel, Benzoyl Peroxide 2.5 % Gel, Vehicle gel Dose: Once daily application in the evening to the face and trunk, if needed Study Duration: 12 weeks
RD.06.SRE.18087	Assessment of efficacy and safety	Multi-centre, randomized, parallel group, double-blind, active-controlled and vehicle-controlled in subjects with acne vulgaris Number of Subjects: N=1668 (415 in the fixed combination and 420 Adapalene Monad, 415 Benzoyl Peroxide, and 418 Vehicle Gel) Age: 12-58 years old	Study Drugs: Adapalene/Benzoyl Peroxide Gel ***(TBMF)*** Controls: Adapalene 0.1% Gel, Benzoyl Peroxide 2.5 % Gel Vehicle gel Dose: Once daily application in the evening to the face and trunk, if needed Study Duration: 12 weeks
RD.06.SRE.18089	Assessment of long-	Multi-centre, open-	Study Drugs:

	term safety and efficacy	label, no control in subjects with acne vulgaris Number of Subjects: N=452 Age: 12-50 years old	Adapalene/Benzoyl Peroxide Gel *(TBMF)* Dose: Once daily application in the evening to the face and trunk, if needed Study Duration 12 Months

Q ***What is the basis for selecting the response endpoints, i.e., clinical or surrogate endpoints and how were they measured in clinical pharmacology and clinical studies?***

The primary site of acne vulgaris is the face, followed by the back, chest, and shoulders. Clinically, acne vulgaris presents with several types of lesions, both inflammatory (papules, pustules and nodules) and non-inflammatory (open and closed comedones, also known as "blackheads" and "whiteheads", respectively).

The co-primary efficacy endpoints were Success Rate, Percent Change in Inflammatory, Percent Change in Non-inflammatory, and Percent Change in Total Lesion Counts at Week 12. Success Rate was defined as the proportion of subjects with an Investigator's Global Assessment (IGA) Score of '0' or '1' (clear/almost clear) on the global, static, dichotomized, six-point scale.

Q ***Were the active moieties in the plasma (or other biological fluid) appropriately identified and measured to assess pharmacokinetic parameters and exposure-response relationships?***

Yes, refer to section 2.6 for further details.

Q ***What are the characteristics of the exposure-response relationships (dose-response, concentration-response) for efficacy and safety?***

Exposure-Response for Efficacy: No exposure-response analysis for efficacy was conducted. The applicant stated that the concentrations of the components in the Epiduo combination product are based on the established efficacy and safety of adapalene (0.1 %) and benzoyl peroxide (2.5 %) currently in clinical use.

Exposure-Response for Safety: The applicant stated that dose-response for local safety was evaluated in the dose-finding study SRE .2674 conducted in healthy subjects (n=60). The local irritability (irritation potential) of the fixed-combination of adapalene 0.1 % with benzoyl peroxide 2.5 % was compared to adapalene 0.1 %/benzoyl peroxide 5 % in fixed combination, as well as to marketed products of benzoyl peroxide formulations ranging from 2.5 % to 10 %. The applicant stated that the local tolerability of the fixed-

combination of adapalene 0.1 % with benzoyl peroxide 2.5 % was similar to both 2.5 % and 5 % benzoyl peroxide formulations alone. While the fixed-combination of adapalene 0.1 % with benzoyl peroxide 5 % was significantly more irritating than either 5 % or 10 % benzoyl peroxide formulations alone. Therefore, the lower dose fixed combination was selected for further development (see clinical review for further details).

Q What is the systemic exposure of Epiduo Gel under maximal use conditions?

The systemic exposure of adapalene in subjects with acne vulgaris was assessed under maximal use conditions in the pivotal PK study, SRE.18097. This was a single-center, double-blind, randomized, active-controlled, parallel-group study. Twenty (20) acne vulgaris subjects were treated once daily for 30 days with 2 grams of either adapalene/benzoyl gel (N=10) or adapalene 0.1 % gel (N=10), applied to the face, upper part of the chest, and upper part of the back (approximately 1000 cm^2) corresponding to approximately 2 mg/cm^2. Blood samples for the determination of adapalene plasma concentrations were collected on Days 1, 10, 21, and 30 at the following times: before the study medication application (pre-dose) and 2, 4, 6, 8, 10, 12, and 24 hours following application. Additionally, on Day 30, blood samples were also collected at 36, 48, and 72 hours following the study medication application. Quantifiable plasma concentrations of adapalene obtained are summarized in the table below.

Table 3: Plasma Concentrations of Adapalene

[illegible] (0.1 ng/mL)

Subject	Day	0h	2h	4h	6h	8h	10h	12h	24h	36h	48h	72h
Treatment with Adapalene/Benzoyl Peroxide Gel, the fixed combination												
13	1	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ			
	10	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ			
	21	[illegible]							BLQ			
	30	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ
16	1	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ			
	10	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ			
	21	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ			
	30	BLQ	BLQ	BLQ	BLQ	[a]	BLQ	—	BLQ	BLQ	BLQ	BLQ
Treatment with Adapalene Gel, 0.1%, the monad												
1	1	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ			
	10	BLQ	BLQ	[illegible]					[illegible]			
	21	[illegible]						BLQ	BLQ			
	30	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ
15	1	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ			
	10	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ			
	21	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ			
	30	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	—	BLQ	BLQ	[a]
21	1	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ			
	10	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ			
	21	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ			
	30	BLQ	BLQ	BLQ	—	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ

b(4)

b(4)

BLQ: Below the limit of quantification (0.1 ng/mL).

[a] Missing data. There are no bioanalytical data for this time point.

As shown in Table 3 above, two of the 10 subjects (20 %) treated with adapalene/benzoyl peroxide gel and 3 of 10 (30 %) subjects treated with adapalene gel, 0.1% had quantifiable (LOQ = 0.1 ng/mL) adapalene plasma concentrations ranging between 0.1 ng/mL and 0.2 ng/mL.

The pharmacokinetic parameters derived from the quantifiable concentrations obtained in these five subjects are shown in the table below.

Table 4: Pharmacokinetic Parameters of Adapalene

Treatment	Subject	Day	C_{max} (ng/mL)	T_{max} (h)	AUC_{t0-24h}(ng h/mL)
Adapalene/Benzoyl Peroxide Gel, the fixed combination	13	21	0.1268	0	1.9945
	16	30	0.2086	12	NA
Adapalene Gel, 0.1%, the monad	1	10	0.1611	12	2.6481
	1	21	0.1261	6	1.2623
	15	30	0.1392	24	NA
	21	30	0.1101	6	NA

NA: Not applicable due to fewer than three consecutive quantifiable concentrations available.

Reviewer's Comments:

There were 6 samples obtained from 4 subjects that were re-assayed by the applicant due to initial high plasma values of adapalene that were considered to be unexpected values within the concentration-time profile. Four of the 6 re-assayed samples were collected from three of the twelve (25%) subjects (subject #'s 1, 8 and 15) in the adapalene gel group. Subject #'s 1 and 8 had one re-assayed sample each and Subject # 15 had two re-assayed samples. The remaining two re-assayed samples were collected from one of the twelve (8%) subject (subject #16) in the adapalene 0.1 %/benzoyl peroxide 2.5 % gel group. Three of the re-assayed samples were reported as BLQ which was the mean of the repeat values obtained. These samples (one sample per subject) were from three subjects (subject #1, 15 and 16).

However, the remaining 3 re-assayed samples had concentration values that were not reportable due to insufficient volume of plasma available to duplicate the repeat analysis for verification purposes and therefore not resolved. The non reportable plasma sample values were ⌜ ⌟ *of adapalene for subject #8 (day 30, 10h), and for subject #15 (day 33, 72h) from the adapalene gel group, respectively. The third non reportable plasma sample value was* ——— *of adapalene for subject #16 (day 30, 8h) from the adapalene/benzoyl peroxide gel group.* b(4)

Based on previous clinical pharmacology findings for adapalene, the highest initial plasma concentration of adapalene ——— *obtained from the 3 unresolved samples is at least 50 % less than the highest concentration of adapalene* ——— *obtained* b(4)

following application of the approved 0.3 % adapalene gel (NDA 21-753); which is a higher concentration of adapalene than what is proposed for marketing in this application. In addition, the applicant stated that there were no treatment related systemic adverse events recorded for the four subjects (#'s 1, 8, 15 and 16) who had their samples re-assayed.

No accumulation of adapalene was observed over time. The results of the study suggested that the systemic exposure of adapalene following topical application of the adapalene/benzoyl peroxide gel for 30 days to subjects with acne vulgaris is comparable to that obtained following topical application of adapalene 0.1 % gel alone under the same conditions. This data suggests that the presence of benzoyl peroxide in the adapalene/benzoyl peroxide combination gel may not affect the plasma concentrations of adapalene. However, since intra-subject comparisons are not possible and the number of subjects with plasma levels was small, definitive conclusions can not be made.

Previous PK studies for currently approved adapalene 0.1 % gel or cream also indicated that following the application of 2g of either the cream or the gel to 1000 cm^2 of acne involved skin for 5 days for the cream and up to 3 months for the gel, the plasma concentrations of adapalene reported were < 0.38 ng/mL. For the most part, the systemic exposure obtained for adapalene following the application of Epiduo is comparable to historical data for the monad except in the case of the 3 unresolved plasma samples.

Q. What are the metabolism, distribution and excretion of adapalene and benzoyl peroxide?

Adapalene: The metabolism, distribution and excretion of adapalene were characterized in the approved NDAs for adapalene 0.1 % gel and cream and adapalene: 0.3 % gel. A summary of the findings from these NDAs is presented below:

Metabolism and Excretion: The metabolism and excretion of adapalene was submitted (Study PK 91005 (DCa/JF/92-020)) and reviewed (by Dr. A. Dorantes) in approved NDA 20-338 for Adapalene topical solution. Adapalene was reported to be metabolized extensively *in vitro* in human hepatocytes. The possible structures of adapalene metabolites were submitted (Study RDS.03.SRE.4518) and reviewed (Dr. L. Zhang) in approved NDA 21-753 for Adapalene Gel 0.3 %. The possible structures of adapalene metabolites proposed involved either O-demethylation or hydroxylation, or combinations of these processes to the methoxy benzene ring of adapalene. The studies however, failed to completely characterize any of the metabolites. Excretion appears to be primarily by the biliary route.

The *in vitro* metabolism of ^{14}C-adapalene from Adapalene/Benzoyl Peroxide Gel (not the to-be--marketed formulation) and ^{14}C- Adapalene Gel, 0.1% was investigated in study SRE.4708 using Reconstructed Human Epidermis (RHE). A review of this study in this application indicated that parent adapalene was the only radioactive component found in all of the samples analyzed. There were no metabolites detected in the RHE samples analyzed following application of ^{14}C- Adapalene /Benzoyl Peroxide Gel or ^{14}C-

Adapalene Gel, 0.1%. Therefore, under the experimental conditions of this study, no metabolites of adapalene were identified following the application of ^{14}C- Adapalene 0.1 % /Benzoyl Peroxide 2.5 % Gel or ^{14}C- Adapalene Gel, 0.1%.
Protein Binding: The blood and plasma protein binding of adapalene has been submitted (Study TILL/9042 (DC/JF/91-143)) and reviewed (by Dr. A. Dorantes) in approved NDA 20-338 for Adapalene topical solution. The total plasma protein binding of adapalene in human blood *in vitro* was reported to be greater than 99 % with adapalene bound primarily to lipoproteins and human serum albumin.

Benzoyl Peroxide: Previous Agency findings of approved products containing benzoyl peroxide reported that after topical application, benzoyl peroxide is absorbed by the human skin where it is converted to benzoic acid. It is then absorbed as benzoic acid into the systemic circulation and excreted in the urine.

Q. Does Epuido gel prolong QT intervals?

There was no QT/QTc study conducted with the Adapalene/Benzoyl Peroxide gel.

The applicant stated that considering the scope of ICH E 14 guideline, there is no rationale to perform a QT/QTc study on Adapalene/Benzoyl Peroxide gel knowing that:

- ***the Adapalene/Benzoyl peroxide Gel is a fixed-combination of two approved drugs of established safe use with no reported effect on cardiac repolarization;***
- ***the topical route of administration of the fixed-combination is the same as for adapalene and benzoyl peroxide;***
- ***the combination's active ingredients are used at their lowest dose and therapeutic regimen;***
- ***systemic exposure to the individual ingredients of the fixed-combination is low and comparable to the approved and marketed monotherapies;***
- ***the combination product was developed in the same indication and population as the individual active ingredients already approved.***

Reviewer's Comments: The clinical reviewer (Dr. J. Liedtka) is currently reviewing the applicants' rationale for not conducting a QT/QTc study (see clinical review for further details). This reviewer agrees with bullet #4 of the applicant's rationale that refers to systemic exposure.

2.3 Intrinsic Factors

Q. What intrinsic factors influence exposure (PK usually) and/or response?

No specific studies were conducted to evaluate the effect of intrinsic factors on the exposure or response of the active components of Epuido gel.

2.4 Extrinsic Factors

Q What extrinsic factors influence exposure and/or response?

No specific studies were conducted to evaluate the effect of extrinsic factors (e.g. drug-drug interactions) on the exposure or response of Epuido gel.

2.5 General Biopharmaceutics

Drug Product Composition: The quantitative composition of the drug product is provided in the table below:

Table 5 Adapalene/Benzoyl Peroxide Gel: Qualitative and Quantitative Composition

Components	Function	Percent Formula (w/w)	Quantity per 1 g
Active Components			
Adapalene	Active Ingredient	0.10	0.001
Benzoyl Peroxide	Active Ingredient; antimicrobial	2.50	0.025
Excipients			
Simulgel 600 PHA[3]	Gelling agent		
Docusate Sodium			
Edetate Disodium			
Glycerin			
Poloxamer 124			
Propylene Glycol			
Purified Water			

b(4)

b(4)

[1] This overage was discussed in IND 067,801 SN: 019 and accepted by FDA CMC reviewer (memo dated February 3, 2004) [3] Simulgel 600 PHA (copolymer of acrylamide and sodium acryloyldimethyltaurate, isohexadecane, polysorbate 80, sorbitan oleate) is a non-compendial component.

Reviewer's Comment: The formulation (555.610) used in the Bioavailability study (SRE.18097) and the Phase 3 clinical studies was the same as the to-be-marketed formulation.

2.6 Analytical Section

Q Were the bioanalytical methods used adequately validated?

Adapalene plasma concentrations were determined by High Performance Liquid Chromatography (HPLC) and fluorescence detection after enzymatic hydrolysis with Helix Pomatia juice.

b(4)

Table 6: BioAnalytical Method and Validation:

Method	Reversed-phase HPLC with fluorescence detection
Compound	Adapalene
Internal Standard	CD1871
Matrix	Human Plasma
Accuracy (% Bias) ***Inter-Day*** ***Intra-Day***	 88.4 to 99.9 % 86.7 to 101.6 %
Precision (% CV) ***Inter-Day*** ***Intra-Day***	 3.4 to 6.9 % 0.5 to 7.8 %
Standard curve range	0.1 to 10 ng/mL ($r > 0.99$)
Sensitivity (LOQ)	0.1 ng/mL (CV % = 8.5 and Accuracy = 99.9 %)
Recovery	104.8 % to 110.6 % (mean = 108.0 (2.7 %))
Specificity	There was no interference at the retention time of interest
Stability	Stable in human plasma at approximately -20 °C after 3 freeze-thaw cycles (< 8 % degradation) and in human plasma at approximately -20 °C after at least seven weeks (<11.4 % degradation)
Conclusion	**Method validation is acceptable**

3 Detailed Labeling Recommendations

Please see labeling changes in product package insert in Section 4.1 below. This reviewer's changes are shown as ***deletions*** which are ***"strikethroughs"*** and ***additions which*** are ***"underlined"***.

4 Appendices

4.1 Proposed Package Insert (Original)

11 Page(s) Withheld

_____ Trade Secret / Confidential (b4)

✓ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

Withheld Track Number: Clin Pharm/Bio- 1

4.2 Individual Study Reviews:

Study No. SRE 18097

Title: A Pharmacokinetic Study to Determine the Systemic Exposure to Adapalene During Dermal Application of Either a Fixed-Combination of Adapalene 0.1% and Benzoyl Peroxide 2.5% (Adapalene and Benzoyl Peroxide Topical Gel) Gel or Adapalene 0.1% Topical Gel for 30 Days in Subjects with Acne Vulgaris.

Objectives:
This study was conducted to assess systemic exposure to adapalene in subjects with acne vulgaris during once daily dermal treatment for 30 days with two grams of Adapalene plus BPO Gel or Adapalene Gel on the face, upper part of the chest, and upper part of the back.

Study Design:

This was a single-center, double-blind, randomized, active-controlled, parallel-group study to assess adapalene plasma concentration over a 30 day period and observe trends in safety and efficacy. A total of 24 male or female subjects between 18 and 35 years of age with acne vulgaris ((A minimum of 20 but not more than 50 inflammatory (papules and pustules) lesions on the face (excluding the nose), A minimum of 30 but not more than 100 non-inflammatory lesions (open comedones and closed comedones) on the face (excluding the nose)) were enrolled. Screening evaluations were conducted within 14 days prior to the start of the study.

Subjects reported to the clinic every morning on each study day up to Day 30 to have the study medication applied by a trained nurse or study technician. Subjects were required to take a shower in the morning at least 1 hour before study medication application. The nurse or study technician instructed subjects to wash their face and body with —— cleanser every morning from Day 1 through Day 30. The subjects were then to rinse thoroughly with water and dry themselves with a clean towel prior to study drug application. On the morning of Day 1 through Day 30 between 7:30 and 9:30 (±30 minutes), subjects received a once-daily 2 grams application of the study medication (either Adapalene + BPO Gel or Adapalene Gel) to the face, upper part of the chest, and upper part of the back. The study medication was applied to a total body surface area of approximately 1000 cm^2 or 2 mg/cm^2 on the face, upper part of the chest, and upper part of the back.

b(4)

Reviewer's Comments: A 30-day treatment period was considered appropriate because the terminal apparent T 1/2 following topical administration of Adapalene 0.3 % gel (NDA 2-753) was 7-51 hours (mean = 17.2(10.2) hrs). Therefore for a T 1/2 of 51 hours it will take about11 days for the drug to achieve Steady State. In addition, retinoids are generally known to reach steady state at around 15 days. It is also noted that this repeat

study was conducted based on discussions with the FDA at a Pre-IND meeting held with the applicant on July 28th, 2003.The use of — daily to wash the treatment area and the effect of utilizing such a product may have a favorable outcome on the study results in terms of efficacy in this study and other clinical trials. However, Dr. J. Ledtka, the medical reviewer informed me that — cleanser is considered to be a gentle cleanser and this was acceptable for the patients to use as a non-medicated cleanser in the clinical trials. She also added that this was consistent with the current clinical practice for the treatment of acne.

b(4)

Identity of the Investigational Drug Products:

TEST MATERIAL ADMINISTRATION		
	Investigational Product	
Trade Name	NA	NA
Name of Active Ingredient	Adapalene 0.1% and Benzoyl Peroxide 2.5%	Adapalene 0.1%
Formulation	Gel	Gel
Formulation Number/ Batch Number	555.610/051*03	555.613/048*03
Dosing Schedule	2 g daily application for a total of 30 days	
Route of Administration	Topical	
Storage Requirements	Store at or below 25° C (77° F) – Do not refrigerate	
External Appearance	White to very pale yellow opaque gel	
Packaging (primary)	— tube, 45 g tubes	
Manufacturer	Galderma Laboratories, SA Development Industrial Touviere- BP17 74540 Alby-Sur-Cheran France	

b(4)

Reviewer's Comments: The drug product used in the bioavailability study was a commercial batch size of — scale. In this study, the drug was applied in the morning however, in the clinical trials it was applied in the evening which is consistent [ ] It is not clear whether there is a diurnal difference in the PK of adapalene. However, this morning application is consistent with the way it was administered in the PK studies conducted for the approved drug products of adapalene. For the approved topical adapalene drug products, the application of the medication in the morning was considered acceptable even though the approved label recommends application in the evening.

b(4)

Administration of the Study Products:

The study medication was applied to the face, upper part of the chest, and upper part of the back (approximately 1000 cm^2 of body surface area) by qualified staff. According to the 2 mg/cm^2 application rule, subjects received two grams daily of the study medication as follows:

- Approximately 1.0 gram to the upper back
- Approximately 0.5 grams to the upper chest

- Approximately 0.5 grams to the face

The entire face was treated except the upper and lower eyelids and the lips. Medication was applied with protective gloves and rubbed in until no visible mass of the gel was observed on the surface of the skin. It was determined that two grams of study medication were equivalent to 2 mL. The study medication was delivered with a syringe and the exact amount was measured by the gradations on the syringe, assuring, as accurately as possible, that the volume of study medication in the syringe was equal to a two grams application. To be more precise, the study site weighed the study medication tubes, the syringe, and gloves pre- and post-application and documented the weights on the site's drug dispensing forms. The difference between the pre- and post-application weights of the syringe and gloves was calculated by the study site.

Prior and Concomitant Therapy:
The use of concomitant systemic medications (except paracetamol, vitamins, minerals, or oral contraceptives) was prohibited during the study. No topical treatment other than the test material was permitted. Subjects were permitted to use a moisturizer as required for the symptomatic relief of skin dryness or irritation; however, the use of any moisturizers was to be documented in the Case Report Form (CRF).

PK Sampling:

Blood samples for the determination of adapalene plasma concentrations were collected on Days 1, 10, 21, and 30 before the morning study medication application (pre-dose) and 2, 4, 6, 8, 10, 12, and 24 hours following application (post-dose), and additionally, at 36, 48, and 72 hours following the last study medication application at End of Treatment/ Day 30. Subjects remained overnight in the clinic the night prior to pharmacokinetic (PK) blood sampling on Days 1, 10, 21 and 30. Pre-dose blood samples were collected as scheduled, study medication was applied and subjects were discharged from the clinic on Days 2, 11, and 22 following collection of the 24- hour post-dose blood sample. On Day 31, subjects were discharged from the clinic following collection of the 36-hour post-dose blood sample.

During the Day 32 and Day 33 visits, subjects visited the clinic in the morning for scheduled tests and procedures and were discharged from the clinic on Day 32 following the collection of the 48-hour post-dose blood sample and on Day 33 following the collection of the 72-hour post-dose blood sample (A total of 35 blood samples).

Bioanalytical Methods:

Adapalene plasma concentrations were determined by high performance liquid chromatography (HPLC) and fluorescence detection after enzymatic hydrolysis with Helix Pomatia juice (consists of a mixture of ß-glucuronidase and arylsulfatase). The method allowed the quantification of the compound with a limit of quantification (LOQ) of 0.1 ng/mL.

b(4)

Pharmacokinetic Variables and Statistical Plans:
Where sufficient data were available, the following pharmacokinetic parameters of adapalene were determined by non-compartmental analysis: C_{max}, T_{max} and $AUC_{(0\text{-}24h)}$: All data were summarized using descriptive statistics.

Efficacy Assessments:
Facial lesion counts (inflammatory and non-inflammatory) were assessed and recorded at Screening, Baseline/ Day 1, and End of Treatment/ Day 30

Safety Assessments: The following local cutaneous safety variables (erythema, scaling, dryness and stinging/burning sensation) were assessed at separate locations (the face, upper part of the chest, and upper part of the back) using a four-point scale of 0 to 3/none to severe.

The following assessments were performed to record systemic safety: Physical Examination, Vital Signs, Virology Screen, Urine Drug Screen, and Laboratory Screen (Hematology: white blood cell (WBC) count with differential, red blood cell (RBC) count, hemoglobin, hematocrit, platelet count, Blood Chemistry: glucose, sodium, potassium, chloride, blood urea, nitrogen (BUN), creatinine, uric acid, phosphorus, calcium, cholesterol, triglycerides, alkaline phosphatase, aspartate aminotransferase (AST), alanine, aminotransferase (ALT), total bilirubin, and direct bilirubin).

Reviewer's Comments: This reviewer did not review the efficacy and safety assessments. See clinical review for details of the review of these assessments.

Results:

Study Population: A total of 24 subjects were enrolled and randomized to treatment, 12 each in the Adapalene + BPO Gel and the Adapalene Gel treatment groups. Among the 24 subjects treated, there were 11 males and 13 females. The mean age (S.D.) of all subjects was 22.8 (4.68) years, and ranged from 18 to 34 years. Thirteen subjects (54.2%) were Caucasian, 8 subjects (33.3%) were Hispanic and 3 subjects (12.5%) were Black.

Of the 24 subjects treated, 20 completed the study as scheduled, 10 in each treatment group. Two subjects in the Adapalene + BPO Gel group discontinued from the study due to "Subject Request:" Subject No. 003 was having difficulty with her work schedule, and Subject No. 020 had conflicts with her personal life and children. In the Adapalene Gel group, two subjects (Subjects No. 002 and No. 005) discontinued due to "other" reasons which were stated by the Investigator as missing multiple blood samplings for PK analyses.

Mean percent of total body surface area (BSA) treated at Baseline was comparable between treatment groups, with mean values of 5.49% for the Adapalene + BPO Gel and 5.28% for the Adapalene Gel group.

Reviewer's Comments: It is noted that this is the percentage of total BSA and not percentage BSA of diseased skin (i.e. face, upper chest and upper back). However, the amount (2g/day) applied in the study was at the high end when compared to the mean (SD) daily medication usage of adapalene/benzoyl peroxide gel in the two pivotal phase 3 studies (RD.06.SRE.18094, and RD.06.SRE. 18087) which was 0.78 (0.51) g/day and 0.69 (0.55) g/day, respectively. In addition 2 g/day dose was used in the previous maximal use PK studies for the approved 0.1% adapalene drug products and was considered acceptable.

Pharmacokinetics:

Plasma Concentrations:

Only 2 of 24 subjects (8.3 %) had quantifiable adapalene concentrations in at least three consecutive plasma samples during any sampling period. Subject No. 013 (Adapalene + BPO Gel) had at least three consecutive quantifiable concentrations during one sampling period (Day 21), while Subject No. 001 (Adapalene Gel) had at least three consecutive quantifiable concentrations during two sampling periods on Days 10 and 21. Therefore, the only three plasma profiles obtained were flat, with no marked concentration peak as shown in Figure 1 below:

Figure 1: Plasma Concentration of Adapalene versus Time Profiles following application of Adapalene/Benzoyl Peroxide combination

b(4)

Quantifiable concentrations were observed for one subject in the Adapalene + BPO Gel group (Subject No. 016) and two other subjects in the Adapalene group (Subjects No. 015 and No. 021); however, the quantifiable concentrations occurred in only one or two samples throughout the sampling period. There was no evidence of accumulation of adapalene during the course of the study in either treatment group.

Table 2 Plasma concentrations of Adapalene

Plasma concentrations (ng/mL) ; Treatment: Adapalene + Benzoyl Peroxide

Subject N°	Day	0h	2h	4h	6h	8h	10h	12h	24h	36h	48h	72h
3	1	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ			
	10	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ			
	21	*	*	*	*	*	*	*	*			
	30	*	*	*	*	*	*	*	*	*	*	*
4	1	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ			
	10	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ			
	21	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ			
	30	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ
6	1	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ			
	10	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ			
	21	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ			
	30	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ
7	1	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ			
	10	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ			
	21	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ			
	30	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ
10	1	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ			
	10	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ			
	21	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ			
	30	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ
11	1	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ			
	10	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ			
	21	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ			
	30	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ
13	1	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ			
	10	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ			
	21	[illegible]						[illegible]	BLQ			
	30	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ
16	1	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ			
	10	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ			
	21	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ			
	30	BLQ	BLQ	BLQ	BLQ	**	BLQ	[illegible]	BLQ	BLQ	BLQ	[illegible]
18	1	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ			
	10	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ			
	21	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ			
	30	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ
20	1	BLQ	BLQ	BLQ	*	*	*	*	*			
	10	*	*	*	*	*	*	*	*			
	21	*	*	*	*	*	*	*	*			
	30	*	*	*	*	*	*	*	*	*	*	*
22	1	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ			
	10	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ			
	21	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ			
	30	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ
24	1	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ			
	10	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ			
	21	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ			
	30	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ

b(4)

b(4)

**: Missing data (discontinued subject).*
***: Missing data (No bioanalytical data).*
BLQ: Below the limit of quantification (0.1 ng/mL).

Plasma concentrations (ng/mL); Treatment: Adapalene

Subject N°	Day	0h	2h	4h	6h	8h	10h	12h	24h	36h	48h	72h
1	1	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ			
	10	BLQ	BLQ	⌜					⌟			
	21	⌜					⌟	BLQ	BLQ			
	30	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ
2	1	BLQ	BLQ	BLQ	*	*	*	*	*			
	10	*	*	*	*	*	*	*	*			
	21	*	*	*	*	*	*	*	*			
	30	*	*	*	*	*	*	*	*	*	*	*
5	1	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ			
	10	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ			
	21	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ			
	30	*	*	*	*	*	*	*	*	*	*	*
8	1	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ			
	10	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ			
	21	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ			
	30	BLQ	BLQ	BLQ	BLQ	BLQ	**	BLQ	BLQ	BLQ	BLQ	BLQ
9	1	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ			
	10	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ			
	21	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ			
	30	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ
12	1	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ			
	10	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ			
	21	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ			
	30	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ
14	1	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ			
	10	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ			
	21	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ			
	30	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ
15	1	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ			
	10	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ			
	21	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ			
	30	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ		BLQ	BLQ	**
17	1	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ			
	10	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ			
	21	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ			
	30	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ
19	1	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ			
	10	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ			
	21	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ			
	30	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ
21	1	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ			
	10	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ			
	21	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ			
	30	BLQ	BLQ	BLQ	—	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ
23	1	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ			
	10	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ			
	21	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ			
	30	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ

b(4)

b(4)

b(4)

**: Missing data (discontinued subject).*
***: Missing data (No bioanalytical data; See Paragraph 5).*
BLQ: Below the limit of quantification (0.1 ng/mL).

Reviewer's Comments: Plasma concentrations ranged between ⌜ ⌟ in 2 subjects (#'s 13 and 16) for Adapalene + BPO and ⌜ ⌟ in 3 subjects (#'s 1, 15 and 21) for Adapalene alone.

b(4)

Pharmacokinetic Parameters:

Administration	Subject	Day	Cmax (ng/mL)	Tmax (h)	AUC(0-24h) (ng h/mL)
Adapalene + BPO Gel	13	21	0.1266	0	1.9945
	16	30	0.2086	12	NA
Adapalene Gel	1	10	0.1611	12	2.6481
	1	21	0.1261	6	1.2623
	15	30	0.1392	24	NA
	21	30	0.1101	6	NA

Reviewer's comments: The Cmax values of 0.21 ng/mL (adapalene/benzoyl peroxide gel) and 0.16 ng/mL (adapalene gel) correspond to a systemic exposure of 0.51nM and 0.39 nM concentrations of adapalene, respectively. These nanomolar concentrations would be considered to be minimal in terms of systemic exposure.

For the adapalene/benzoyl peroxide group, both subjects were female (Subject # 13 was a 23 year old female and # 16 was a 26 year old female). For the adapalene group 1 subject was female and 2 subjects were male (Subject #1 was a 26 year old female, # 15 was a 19 year old male and # 21 was a 31 year old male). Therefore, the limited number of quantifiable concentrations obtained does not suggest a meaningful difference in the systemic exposure obtained between the females and the males.

Bioanalytical Method:

Table 3: Analytical Method and Validation:

Method	Enzymatic hydrolysis with Helix Pomatia Juice, liquid-liquid extraction followed by reversed-phase HPLC with fluorescence detection
Compound	Adapalene
Internal Standard	CD1871
Matrix	Human Plasma
Accuracy (% Bias) ***Inter-Day*** ***Intra-Day***	 88.4 to 99.9 % 86.7 to 101.6 %
Precision (% CV) ***Inter-Day*** ***Intra-Day***	 3.4 to 6.9 % 0.5 to 7.8 %
Standard curve range	0.1 to 10 ng/mL ($r > 0.99$)
Sensitivity (LOQ)	0.1 ng/mL (CV % = 8.5 and Accuracy = 99.9 %)
Recovery	104.8 % to 110.6 % (mean = 108.0 (2.7 %)
Specificity	There was no interference at the retention time of interest

Stability	Stable in human plasma at approximately -20 °C after 3 freeze-thaw cycles (< 8 % degradation) and in human plasma at approximately -20 °C after at least seven weeks (<11.4 % degradation)
Conclusion	**Method validation is acceptable**

The applicant stated that in three samples (see table 4 below), concentrations above 0.2 ng/mL were observed upon initial analysis but were below the LOQ upon sample re-analysis. For this reason, concentrations were not reported for these samples.

Table 4: Re-assays for Pharmacokinetics Reasons:

Subject No	Sample identification	Initial value	Reason for re-assay	Repeat values	Reported value	Reason for reported value
001	Day30 6h		1	BLQ BLQ	BLQ	1
008	Day30 10h		1	BLQ	NR	2
015	Day32 48h		1	BLQ BLQ	BLQ	1
015	Day33 72h		1	BLQ	NR	2
016	Day30 8h		1	BLQ	NR	2
016	Day31 36h		1	BLQ BLQ	BLQ	1

b(4)

REASONS FOR RE-ASSAY:
1). Unexpected value within time-concentration profile
REASONS FOR REPORTED VALUE:
1). Repeats differ by 15% and mean of repeat is >15% of original - Mean of repeats is reported.
2). Repeat and original differ by >30% - Not reportable value

Reviewer's Comments: The applicant stated that the reason for the re-assay was because these values were considered to be unexpected values within the time-concentration profile of adapalene. Summarized in the table below is the concentration-time data for the subjects and days of the samples re-assayed with the initial values (bolded) inserted instead of the repeat values:

Table 5:

	Plasma Concentrations (ng/mL):Treatment: Adapalene (A) and Adapalene plus Benzoyl Peroxide (AB)												
Subject #	TX	Day	0h	2h	4h	6h	8h	10h	12h	24h	36h	48h	72h
1	A	30	BLQ	BLQ	BLQ	—	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ
8	A	30	BLQ	BLQ	BLQ	BLQ	BLQ	—	BLQ	BLQ	BLQ	BLQ	BLQ
15	A	30	BLQ	BLQ	BLQ	BLQ	BLQ	Missing	BLQ	—	BLQ	—	
16	AB	30	BLQ	BLQ	BLQ	BLQ	—	BLQ	—	BLQ	—	BLQ	—

For the initial values in red, repeat analysis were reportable; For the initial values in blue repeat analysis were non reportable

b(4)

The tables above indicate that:

- *There were 6 samples obtained from 4 subjects that were re-assayed by the applicant due to initial high plasma values of adapalene that were considered to be unexpected values within the concentration-time profile.*
- *Four of the 6 re-assayed samples were collected from three of twelve (25%) subjects (subject #'s 1, 8 and 15) in the adapalene gel group. Subject #'s 1 and 8 had one re-assayed sample each and Subject # 15 had two re-assayed samples. The remaining two re-assayed samples were collected from one of twelve (8%) subjects (subject #16) in the adapalene 0.1 %/benzoyl peroxide 2.5 % gel group.*
- *The initial concentration values ⌜ ⌟ obtained for Subject # 1 (day 30, 6h) and Subject #8 (day 30, 10h) were inconsistent with the other values (all BLQ) obtained for both subjects at the other sampling time points.* b(4)
- *It is noted that the mean of the repeat values for subject # 1 (day 30, 6h) was BLQ, however, for subject # 8 (day 30, 10h) the value was non-reportable because the applicant did not have sufficient sample available to duplicate the repeat value obtained.*
- *The initial concentration values ⌜ ⌟ obtained for Subject #'s 15 (day 32, 48h) and Subject #16 (day 31, 36h) were not totally inconsistent with the other values obtained for both subjects at the other sampling time points. However, it is noted that the mean of the repeat values for both subjects was BLQ.* b(4)
- *The initial concentration values ⌜ ⌟ obtained for Subject # 15 (day 33, 72h) and Subject #16 (day 30, 8h) were also not totally inconsistent with the other values obtained for both subjects at the other sampling time points. It is also noted that the concentration values were non-reportable for both subjects because the applicant did not have sufficient sample available to duplicate the repeat value obtained.*
- *Therefore, three of the re-assayed samples were reported as BLQ which was the mean of the repeat values obtained. These samples (one sample per subject) were from three subjects (#'s 1, 15 and 16).*
- *However, the remaining 3 re-assayed samples had concentration values that were not reportable due to insufficient volume of plasma available to duplicate the repeat analysis for verification purposes and therefore not resolved. The non reportable plasma sample values were ⌜ ⌟ of adapalene for subject #'s 8 (day 30, 10h), 15 (day 33, 72h) from the adapalene gel group, and ——— of adapalene for subject #16 (day 30, 8h) from the adapalene/benzoyl peroxide gel group, respectively.* b(4)

Based on previous clinical pharmacology findings for adapalene, the highest initial plasma concentration of adapalene ——— obtained from the 3 unresolved samples is at least 50 % less than the highest concentration of adapalene ——— obtained following application of the approved 0.3 % adapalene gel (NDA 21-753). In addition, the applicant stated that there were no systemic or cutaneous adverse events recorded for the four subjects (#'s 1, 8, 15 and 16) who had their samples re-assayed. b(4)

Applicants' Conclusion: Daily application of Adapalene + BPO Gel or Adapalene Gel under maximized conditions for 30 days resulted in comparable low systemic exposure to adapalene. Plasma concentrations were below LOQ (0.1 ng/mL) in most subjects. Adapalene concentrations reached quantifiable levels (between 0.1 and 0.2 ng/mL) in two subjects treated with Adapalene + BPO Gel and three subjects treated with Adapalene Gel.

Reviewer's Comments: This reviewer agrees with the applicant's study results and conclusions. In addition, the data demonstrates that the presence of benzoyl peroxide in the Adapalene 0.1 %/Benzoyl Peroxide 2.5 % gel combination may not affect the systemic exposure of adapalene.

In Vitro Studies

Table 9 Summary of *In Vitro* Studies

Study Report No. (Country) Location	Type of Study	Test Article	Product ID / Batch No.	Tissue Preparation and Dose Application	Parameters
SRE.4700 (France)	Liberation and cutaneous penetration in diffusion cell system	Adapalene 0.1% / benzoyl peroxide 2.5% gel Adapalene 0.1%/Encapsulated benzoyl peroxide 2.5% gel Adapalene 0.1% gel Benzoyl peroxide 2.5% gel	555.059 / 1F2 555.058 / 1F2 555.060 / 1F1 555.061 / 1F1	Excised human skin (3 female donors) in glass diffusion cells Finite dose of 10 mg per cm^2 applied for 16 hours	Distribution in total skin and collected fractions
SRE.4708 (France)	Permeation and metabolism	^{14}C-Adapalene 0.1%/ benzoyl peroxide 2.5% gel ^{14}C-Adapalene 0.1% gel Gel vehicle	555.606 / R1 555.568 / R1 555.562P / 1F1	Reconstructed human epidermis (RHE) Finite dose of 10 mg per cm^2 applied for up to 24 hours	Adapalene and potential metabolite concentrations
SRE.4781 (France)	Liberation and cutaneous penetration in diffusion cell system	Adapalene/Benzoyl Peroxide Gel Adapalene 0.1% Gel Differin® Gel Benzoyl Peroxide 2.5% Gel Cutacnyl® 2.5	555.610 / 051*03 555.613 / 048*03 NA / 5051016 555.611 / 043*03 NA / 4020016	Excised human skin (11 female, 1 unknown donors) in glass diffusion cells Finite dose of 10 mg per cm^2 applied for 16 hours	Distribution in total skin and collected fractions

Reviewer's Comments: In the biopharmaceutics section, the applicant also provided in vitro data from three percutaneous absorption studies (SRE.4700, SRE. 4708 and SRE.4781) that evaluated the release of the individual active substances, both from the monads and from the fixed combination product. The in vitro percutaneous absorption component of these studies were not reviewed because study SRE. 4700 and SRE. 4708 did not use the to-be-marketed formulation. Although study SRE. 4781 used the to-be-marketed formulation the in vitro data (conducted with healthy skin) will not add any benefit to the information obtained from the in vivo studies conducted in patients with diseased skin.

It is noted that Studies SRE 4700 and SRE 4708 were previously submitted to NDA 21-753 (Adapalene gel 0.3 %) and not reviewed. The clinical pharmacology reviewer stated that these studies were not reviewed because they were considered to be exploratory in nature for formulation development. However, for study # 4708, the applicant included

some metabolism data which may be relevant to this drug product. Therefore a review of this metabolism data was performed below.

Synopsis of Study Report No. RDS.03.SRE.4708

This review will focus only on the metabolism data. The percutaneous absorption component will not be reviewed for reasons already mentioned.

Title: Permeation and Metabolism of ^{14}C-Adapalene Formulated Alone or in Combination with Benzoyl Peroxide in the Same Formulation through Reconstructed Human Epidermis

Objective: To compare the percutaneous absorption and the metabolism of ^{14}C-adapalene from a formulation (# 555.568/R1) containing adapalene alone at 0.1 % (w/w) or from the same formulation (# 555.606/R1) containing adapalene at 0.1 % (w/w) in combination with benzoyl peroxide at 2.5 % (w/w).

Reviewer's comment: It is noted that the formulation # 555.606/R1 for the adapalene/BPO combination used in this study is not the proposed to-be-marketed formulation.

Study Site: Galderma R&D, Cedex, France

Experimental Procedure

A reconstructed human epidermis (RHE) model was used. The RHE was supplied by [redacted]. The RHE were placed on 6-well plates. A finite dose (10 mg per cm^2) of each formulation and 50 µL of ^{14} C- testosterone solution (i.e. 5 nmoles, 1.450 µg) was applied directly onto the cornified side of six RHE (surface area of each = 0.63 cm^2). Negative controls (six untreated RHE) were run in parallel. b(4)

The RHE preparations were incubated at 37°C and flushed with 5% CO_2 prior to testing and throughout the 24 hour test period. At various incubation times 1, 2, 3, 6, and 24 hours, the culture medium was withdrawn from the receiver chamber for metabolic sample analysis and was replaced by fresh culture medium. At the end of the 24-hour exposure period, the surface excess was removed and the RHEs were retained for analysis. Total radioactivity content of each sample was measured by liquid scintillation counting prior to metabolic profiling, which was performed using a high pressure liquid chromatographic (HPLC) method with radioactive detection. ^{14}C-labelled testosterone was used as a positive control to qualify the RHE to serve as a model for *in vitro* drug metabolism. Additionally, cell viability and integrity were also assessed at the end of the study, using a 3-(4,5 Dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide reduction assay (MTT assay).

General Study Design:

Each sample was labeled (A, B, C, D or E) according to the tissue treatment:

A: Adapalene/benzoyl Peroxide gel placebo

B: 14C –Adapalene 0.1 % gel
C: 14C Adapalene 0.1 %/benzoyl Peroxide 2.5 %
D: Untreated
E: ^{14}C-Testosterone
Eight 6-well plates were seeded with 6 epidermal tissues (N=48 RHE) an treated as follows

	Plates 1 to 3: Permeation and metabolisation assays					
Plate N°1:	E MET, RA	E MET, RA	E MET, RA	E MET, RA	E MET, RA	E MET, RA
Plate N°2:	B MET, RA	B MET, RA	B MET, RA	B MET, RA	B MET, RA	B MET, RA
Plate N°3:	C MET, RA	C MET, RA	C MET, RA	C MET, RA	C MET, RA	C MET, RA

Sample Analysis: All samples (culture medium and RHE homogenates) were assayed for total radioactivity content by liquid scintillation counting. A metabolic profile was performed on the following samples:

[^{14}C]-Adapalene; RHE homogenates and culture media
[^{14}C]-testosterone; culture media

Samples having identical sampling time and treatment were pooled. After a 10-minute refrigerated centrifugation (1500g), the supernatant was collected and processed for HPLC analysis using radioactive detection.

Data Analysis: Chromatographic profiles obtained from the different treatment were compared. The metabolic peaks found in the different samples will be expressed in terms of area % of all integrated peaks of the chromatogram.

Results and Conclusions:
Testosterone Metabolism: An extensive metabolism of testosterone was observed after the 24-hour exposure period in the RHE. The radioactivity for ^{14}C was distributed over two different fractions (M1 and the unchanged drug). In the last collected medium (6-24 hours), M1 represented 100 % of the total radioactivity eluted indicating an extensive metabolism of testosterone (see table below). These results suggest that the RHE used in this study were qualified to serve as a model for *in vitro* drug metabolism.

TABLE E: Individual and cumulated levels of Testosterone and M1 in the culture medium (Mean values ± SEM, N=6)

Incubation time	Total µg eq	M1 µg eq	M1 Radioactivity eluted (%)	Testosterone µg	Testosterone Radioactivity eluted (%)
0-1H	0.31 ± 0.01	0.10 ± 0.01	30.69 ± 2.37	0.22 ± 0.01	69.31 ± 2.37
1-2 H	0.34 ± 0.01	0.15 ± 0.00	43.48 ± 0.72	0.19 ± 0.01	56.52 ± 0.72
2-3 H	0.24 ± 0.00	0.14 ± 0.00	56.48 ± 1.54	0.11 ± 0.01	43.52 ± 1.54
3-6 H	0.24 ± 0.01	0.19 ± 0.01	81.07 ± 3.69	0.05 ± 0.01	18.93 ± 3.88
6-24 H	0.16 ± 0.01	0.16 ± 0.01	100.00 ± 0.00	/	/
0-24 H	1.26 ±0.03	0.70 ± 0.02	NA	0.56 ± 0.01	NA

[14] C-Adapalene Metabolic Profile

In the RHE samples, liquid scintillation counting indicated that the radioactivity was distributed over one single fraction identified as the unchanged drug (i.e. Adapalene). Only unchanged adapalene was detected. There were no metabolites detected in the RHE samples analyzed following application of ^{14}C- Adapalene /Benzoyl Peroxide Gel or ^{14}C-Adapalene Gel, 0.1%. In addition, due to the low quantity of radioactivity recovered through the RHE, no significant chromatographic peaks were detected in the culture medium.

Therefore, under the experimental conditions of this study, no metabolites of adapalene were identified following the application of ^{14}C- Adapalene 0.1 % /Benzoyl Peroxide 2.5 % Gel or ^{14}C- Adapalene Gel, 0.1%.

Reviewer's Comments: The data obtained in this study suggests that the RHE model may not be a good model for in vitro drug metabolism of adapalene.

b(4)

4.3 Consult Reviews (including Pharmacometric Reviews): Not Applicable

4.4 Cover Sheet and OCP 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	22-320	**Brand Name**	Epiduo Gel
OCPB Division (I, II, III)	DCP3	**Generic Name**	Adapalene 0.1 % / benzoyl Peroxide 2.5 %
Medical Division	HFD-540	**Drug Class**	Retinoid and Antimicrobial Combination Product
OCPB Reviewer	Abi Adebowale, Ph.D.	**Indication(s)**	Treatment of acne vulgaris in patients 12 years and older
OCPB Team Leader	Lydia Velazquez, Pharm.D.	**Dosage Form**	Gel
		Dosing Regimen	Apply a pea-sized amount to the acne affected areas of the skin once daily [redacted] after washing gently with a non-medicated cleanser
Date of Submission, Internal Filing Date	February 8th 2008 March 24th, 2008	**Route of Administration**	Topical
		Sponsor	Galderma USA
PDUFA Due Date	December 8th, 2008	**Priority Classification**	4S
Clinical Division Due Date	October 8th, 2008	**IND Number**	67,801

b(4)

Clinical Pharmacology and Biopharmaceutics 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	1	1	RDS.03.VRE.34016

I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Studies using other Human Biomaterials				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:				
multiple dose:				
Patients-				
single dose:				
multiple dose:	X	2	2	Study # SRE 2685 in acne vulgaris patients (daily applications for 100 days) *Not to-be-marketed formulation* Study # SRE. 18097 in acne vulgaris patients (daily application for 30 days) Batch Number 555.610/051*03 (*to-be-marketed formulation)*
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/race:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
PD (HEALTHY OR PATIENTS):				
Phase 1 or 2:				
Phase 3:				
PK/PD (HEALTHY OR PATIENTS):				
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:				
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies:				
Dissolution:				
(IVIVC):				
Bio-wavier request based on BCS				
BCS class				
III. Other CPB Studies				
Genotype/phenotype studies:				

Other (in vitro percutaneous absorption study)	X	3	1	RDS.03.SRE.4700 (permeation), RDS.03.SRE.4781 (permeation) and RDS.03.SRE. 4708 (permeation and metabolism)
Chronopharmacokinetics				
Pediatric development plan	X			
Literature References				
Total Number of Studies		6	3	

Fileability and QBR comments

	"X" if yes X	Comments
		The applicant only used the TBMF in the PK study # SRE.18097 the batch size was [redacted] which is [redacted] of the Commercial Batch size of: [redacted]
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?	Yes	Comments have been sent to firm (or attachment included). FDA letter date if applicable.

QBR questions (key issues to be considered)	Does adapalene affect the systemic exposure of benzoyl peroxide and vice versa when used as a combination product in acne vulgaris patients?
Other comments or information not included above	
Primary reviewer Signature and Date	**Abi Adebowale 03/19/08**
Secondary reviewer Signature and Date	**Lydia Velazquez**

b(4)

CC: NDA 22-320, HFD-850 (P.Lee), HFD-540 (K. Bhatt), DCP3 (L. Velazquez, A.Adebowale, H. Ahn, and D. Bashaw)

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

/s/

Abi Adebowale
10/24/2008 03:47:24 PM
BIOPHARMACEUTICS

Lydia Velazquez
10/27/2008 06:50:18 PM
BIOPHARMACEUTICS

Office of Clinical Pharmacology and Biopharmaceutics

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b(4)

Clinical Pharmacology and Biopharmaceutics Information

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Tabular Listing of All Human Studies	X			
HPK Summary	X			
Labeling	X			
Reference Bioanalytical and Analytical Methods	X	2		RDS.03.VRE.34016
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Studies using other Human Biomaterials				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:				
multiple dose:				
Patients-				
single dose:				
multiple dose:	X	2		Study # SRE 2685 in acne vulgaris patients (daily applications for 100 days) *Not to-be-marketed formulation* Study # SRE. 18097 in acne vulgaris patients (daily application for 30 days) Batch Number 555.610/051*03
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				

Other comments or information not included above	
Primary reviewer Signature and Date	**Abi Adebowale 03/19/08**
Secondary reviewer Signature and Date	**Lydia Velazquez**

CC: NDA 22-185, HFD-850 (P.Lee), HFD-540 (K. Bhatt), DCP3 (L. Velazquez, A.Adebowale, H. Ahn, D. Bashaw)