CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 75265

BIOEQUIVALENCE REVIEW(S)

OFFICE OF GENERIC DRUGS
DIVISION OF BIOEQUIVALENCE

ANDA # 75-265 **SPONSOR:** Spear Pharmaceuticals, Inc..
DRUG & DOSAGE FORM: Tretinoin Cream USP
STRENGTH: 0.05%
TYPE OF STUDY: SD SDF MULT OTHER In vitro release testing and Waiver Request
STUDY SITE: CLINICAL: NA **ANALYTICAL:**

STUDY SUMMARY:
From the bioequivalence point of view, Spear Pharmaceuticals, Inc. has met the requirement of in vitro drug release testing on its Tretinoin Cream USP 0.05% and the application is approvable pending approval of the clinical studies on the 0.025% and 0.1% strengths.

DISSOLUTION : Not applicable

PRIMARY REVIEWER: James E. Chaney, Ph.D. **BRANCH:** I
INITIAL: /S/ **DATE:** 11/24/98

BRANCH CHIEF: Yih Chain Huang, Ph.D. **BRANCH:** I
INITIAL: /S/ **DATE:** 11/24/98

DIRECTOR, DIVISION OF BIOEQUIVALENCE: Dale P. Conner, Pharm.D.
INITIAL: /S/ **DATE:** 11/26/98

DIRECTOR, OFFICE OF GENERIC DRUGS:
INITIAL: _____ **DATE:** _____

BIOEQUIVALENCY COMMENTS

ANDA: 75-265 APPLICANT: Spear Pharmaceuticals

DRUG PRODUCT: Tretinoin Cream USP 0.05%

The Division of Bioequivalence has completed its review and has no further questions at this time.

Please note that the bioequivalency comments provided in this communication are preliminary. These comments are subject to revision after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling, or other scientific or regulatory issues. Please be advised that these reviews may result in the need for additional bioequivalency information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

Sincerely yours,

/S/

Dale P. Conner, Pharm. D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

BIOEQUIVALENCY COMMENTS

ANDA: 75-265 APPLICANT: Spear Pharmaceuticals

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Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

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HFD-652/ J. Chaney /S/
HFD-652/ Y. Huang 7/13/98
HFD-617/ L. Sanchez
HFD-650/ D. Conner 7/21/98

BIOEQUIVALENCY - ACCEPTABLE

9e. STUDY/DISSOLUTION (*in vitro* Release) Strengths: 0.025%, 0.05%, and 0.10% Cream

Outcome: (AC)

Outcome Decision:
(AC) Acceptable

WINBIO COMMENTS:

From the bioequivalence point of view, Spear Pharmaceuticals, Inc. has met the requirement of *in vitro* drug release testing on its Tretinoin Cream USP 0.05% and the application is approvable pending approval of the clinical studies on the 0.025% and 0.1% strengths.

Tretinoin Cream USP 0.05%	Spear Pharmaceuticals, Inc.
ANDA 75-265	Fort Meyers, FL
Reviewer: James Chaney	Submission Date:
WP #75265W.D97	December 2, 1997

REVIEW OF *IN VITRO* RELEASE DATA and WAIVER REQUEST

I. BACKGROUND AND INTRODUCTION

The firm has three product strengths, 0.1% (ANDA 75-213), 0.05% (ANDA 75-265), and 0.025% (ANDA 75-264). The firm was advised by the Office of Generic Drugs, in a letter dated October 15, 1997, that it could request a waiver of *in vivo* bioequivalence study for the intermediate strength, 0.05%, provided the following criteria are met:

1. The proposed product's active and inactive ingredients are qualitatively and quantitatively the same as the reference listed drug.
2. The firm conducts acceptable *in vivo* bioequivalence studies with clinical endpoints for tretinoin cream 0.1% and 0.025%, comparing the test product to the reference listed drug and placebo (vehicle), evaluating both safety and efficacy. The safety studies should include comparative skin irritation and sensitization tests for both strengths.
3. The firm provides additional comparative data, (e.g., in vitro release testing, physico-chemical properties comparison, etc.) for each strength of the proposed product and the reference listed drug, and the data are acceptable.

The product for which a waiver is being sought is the generic equivalent of Retin-A Cream 0.05%, the reference listed drug which is manufactured and marketed by Ortho Pharmaceutical Corporation (originally the R.W. Johnson Company) under NDA 17-522 approved on July 19, 1974.

All inactive ingredients are qualitatively the same as the reference listed drug (Table 1). In addition, physicochemical properties all compare nearly identically between the test and reference product for all three strengths. The physicochemical data for the intermediate strength is shown in Table 2.

Table 1. Comparative Formulation of Test and Reference Tretinoin 0.05% Creams

Ingredients	Spear %W/W	Ortho %W/W	IIG (1996) Limits for Topical Creams
Tretinoin, USP	0.05	0.05	
Xanthan Gum,			0.3-0.75%
Polyoxyl 40 Stearate,			0.45-8.8
Stearyl Alcohol, NF			1-30%
Stearic Acid,			1.2-22.5%
Isopropyl Myristate,			1-10%
Butylated Hydroxytoluene,			0.02-0.1%
Sorbic acid,			0.05-0.2%
Purified Water,			

*This level represents a overage to assure product potency throughout the shelf life. Acceptable content limits per USP 23, Suppl 1 p2511 are 90-120%.

Table 2. Comparative Physicochemical Properties Of Ortho Pharmaceutical's Retin-A (Tretinoin) Cream 0.05% (Reference Listed Drug) with Spear Pharmaceuticals' Tretinoin Cream USP 0.05% (Generic Equivalent)

PHYSICOCHEMICAL PROPERTY	REFERENCE Retin-A 0.05% Cream Lot 26N661	GENERIC Tretinoin 0.05%Cream Lot 702710
Description	Normal	Normal
pH (10% solution)		
Specific gravity @ 25°C		
Apparent Viscosity (cps)[2]		
Tretinoin Content (%w/w)		
Isotretinoin Content (% w/w)		
Other Related Substances (% Area)	e	le
Spreadability (mm)		

Batch homogeneity for tretinoin cream USP 0.025, 0.05, and

0.1% strengths is acceptable with CVs ranging from [redacted].

Bioequivalence studies with clinical endpoints were done and submitted for Tretinoin 0.1% (ANDA 75-213) and Tretinoin 0.025% (ANDA 75264). These studies are under review.

II. METHODS

Comparative *in vitro* release data was generated from the generic formulations and the corresponding reference listed drugs (0.1, 0.05, and 0.025% strengths). The comparative *in vitro* release experiments on the 0.1, 0.05, and 0.025% strengths were performed by [redacted] group at the University of [redacted], in accordance with SUPAC-SS.

The model uses [redacted] diffusion chambers that allow for sequential sampling of the receptor solution while maintaining the membrane at a controlled temperature and humidity. A small amount of product was applied to the outer surface of the synthetic membrane and drug diffusion was measured by monitoring its rate of appearance in the receptor solution bathing the inner surface of the synthetic membrane.

Quantification of tretinoin in the collected samples was accomplished using a validated [redacted] method.

Membrane rate of release regression slopes were compared per the "Guidance for Industry, Nonsterile Semisolid Dosage Forms, Scale-Up and Postapproval Changes: Chemistry, Manufacturing, and Controls; In Vitro Release Testing and *In vivo* Bioequivalence Documentation" (SUPAC 5/97).

Six chambers were utilized to determine the rate of release behavior of each product. Linear regression slopes were calculated for each chamber (cumulative release vs. square root of time, $\mu g/cm^2/hr^{1/2}$). The regression slopes for the individual chambers were evaluated as indicated in the SUPAC 5/97 guidance.

III. RESULTS

Cumulative Release: The terminal phase of the project included three studies of 12 chambers each (6 chambers per product). Table 3 shows the cumulative release of tretinoin as a function of time.

Table 3. Cumulative Release of Tretinoin ($\mu g/cm^2$) Versus Square Root of Time								
Time (min)	Time (hr)	Root Time $(min)^{1/2}$	0.025%		0.05%		0.10%	
			Retin-A	Spear	Retin-A	Spear	Retin-A	Spear
15	0.25	0.50						
30	0.5	0.71						
60	1	1.00						
90	1.5	1.22						
120	2	1.41						

Data quality was assessed by regression linearity (cumulative release vs. square root of time) and degree of scatter. The correlation coefficients (r, as determined by linear regression for each chamber) were greater than 0.98 for all chambers (the current limit for method validation is 0.95). The relative standard deviation (%CV) for these studies ranged between 5% and 19%.

Regression Slopes: Table 4 shows the regression slopes for the six products ($\mu g/cm^2/hr^{1/2}$) as well as the mean, standard deviation, and %CV for each product.

Table 4. Regression Slopes [Cumulative Release of Tretinoin *vs* Square Root of Time] ($\mu g/cm^2/hr^{1/2}$)						
Chamber #	Retinoin-A	Spear	Retinoin-A	Spear	Retinoin-A	Spear
	0.025%	0.025%	0.05%	0.05%	0.10%-	0.10%
1						
2						
3						
4						
5						
6						
Ave						
SD						
%CV						

Non-Parametric Statistical Analysis: Table 5 shows the results of the non-parametric tests as specified by the SUPAC guidelines for each product potency (0.025%, 0.05%, and 0.1%). For this analysis, the reference products are the Retin-A creams and the generic products are the Spear creams. The test itself is a simple ranked test. Ratios of the test product slope divided by

the reference product slope were calculated for all permutations. This resulted in 36 permutations that were then ranked from lowest to highest. If the 8th and 29th ranked ratios were within the range of 75% to 133%, the products were considered to have equivalent rates of release.

Table 5 shows that the rate of release of the Spear creams are equivalent to the corresponding strengths of Retin-A creams.

Table 5. Results of Non-Parametric Statistical Test Specified by SUPAC Guidelines

Strength	**0.025%**	**0.05%**	**0.10%**
Low	84.56%	77.98%	84.32%
High	106.27%	111.09%	100.17%
	Passed @ First Stage	Passed @ First Stage	Passed @ First Stage

IV. COMMENTS

1. All inactive ingredients are qualitatively the same as the reference listed drug. All inactive ingredients are quantitatively the same as the reference listed drug except for stearic acid which is in the test product and % in the reference product. Both of these values fall within in the 1996 Inactive Ingredient Guide range of 1.2-22.5% for topical creams. Furthermore, the formulations of the 0.025%, 0.05% and 0.10% strength tretinoin creams are proportional for all the inactive ingredients.

2. Comparative *in vitro* release data demonstrate no statistically significant differences in release rates between the three generic equivalents and the corresponding reference listed drugs.

3. Batch homogeneity for tretinoin cream USP 0.1, 0.05, and 0.025% strengths is acceptable.

4. The calculation of the Non-Parametric Statistical Test were confirmed by the reviewer's calculations (Attached Table 7).

5. The reviewer determined by calculation that the mean regression slope ratios between strengths for test and reference products are nearly equal as shown in Table 6.

Table 6. Comparison of Regression Slopes								
Strength	Test			Reference			T/R Ratios of Ratios Between Strengths	
	Mean	Ratios Between Strengths		Mean	Ratios Between Strengths			
0.1%	22.85	1.65	--	25.14	1.69	--	0.98	--
0.05%	13.86		1.95	14.91		1.97		0.99
0.025%	7.11	--		7.55	--		--	

6. The firm has appropriately validated the procedures.

7. The comparative physicochemical data for the all three strengths is acceptable.

V. RECOMMENDATION

From the bioequivalence point of view, Spear Pharmaceuticals, Inc. has met the requirement of *in vitro* drug release testing on its Tretinoin Cream USP 0.05% and the application is approvable pending approval of the clinical studies on the 0.025% and 0.1% strengths.

/S/

James E. Chaney, Ph.D.
Division of Bioequivalence
Review Branch I

RD INITIALED YCHuang
FT INITIALED YCHuang /S/ Date 5/13/98

Concur: /S/ Date 5/21/98
Dale P. Conner, Pharm.D.
Director, Division of Bioequivalence

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Table 7. Analysis of *In Vitro* Release Data (ANDA #75265) Based on Methodology From the SUPAC-SS Guidance

							Obs. #	T/R (0.025%)	T/R (0.05%)	T/R (0.10%)
		TEST (0.025%)					1			
	7.87	6.65	8.38	5.53	7.05	7.19	2			
7.88							3			
7.60							4			
REF 7.14							5			
(0.025%) 7.87							6			
7.85							7			
6.96							8			
		90% CI: 84-106					9			
							10			
The test slopes are listed across the top of the table,							11			
the reference slopes are listed down the left margin							12			
of the table, and the individual T/R ratios are the							13			
entries in the body of the table.							14			
							15			
		TEST (0.05%)					16			
	12.87	13.66	14.46	15.06	11.32	15.79	17			
15.11							18			
11.61							19			
REF 14.52							20			
(0.05%) 17.18							21			
12.29							22			
18.73						.84	23			
		90% CI: 78-111					24			
							25			
							26			
		TEST (0.10%)					27			
	25.05	24.90	24.45	19.94	21.30	21.43	28			
28.97							29			
24.90							30			
REF 25.01							31			
(0.10%) 22.97							32			
23.64							33			
25.33							34			
		90% CI: 84-100					35			
							36			

(Table 6 Cont'd). Analysis of in Vitro Release Data (ANDA #75265) Based on Methodology From the SUPAC-SS Guidance

							Obs. #	R0.05% /R0.1%	T0.05% /T0.1%	R0.025% /R0.05%	R0.05% /R0.1%
	TEST (0.025%)										
	7.87	6.65	8.38	5.53	7.05	7.19	1				
12.87							2				
13.66							3				
TEST 14.46							4				
(0.05%) 15.06							5				
11.32							6				
15.79						46	7				
	90% CI: 45-59						8				
							9				
	TEST (0.05%)						10				
	12.87	13.66	14.46	15.06	11.32	15.79	11				
25.05							12				
TEST 24.90							13				
(0.1%) 24.45						65	14				
19.94						9	15				
21.30							16				
21.43							17				
	90% CI: 53-69						18				
							19				
	REF (0.025%)						20				
	7.88	7.60	7.14	7.87	7.85	6.96	21				
15.11							22				
11.61							23				
REF 14.52							24				
(0.05%) 17.18							25				
12.29							26				
18.73							27				
	90% CI: 42-62						28				
							29				
	REF (0.05%)						30				
	15.11	11.61	14.52	17.18	12.29	18.73	31				
28.97							32				
REF 24.90							33				
(0.1%) 25.01							34				
22.97							35				
23.64											
25.33	0					4					
	90% CI: 49-69										