

EXECUTIVE SUMMARY

BIOEQUIVALENCE OF THREE TRETINOIN GEL, 0.025% PRODUCTS

1. Objective

To evaluate the bioequivalence of three tretinoin gel, 0.25% products using the dermatopharmacokinetic method.

2. Subjects

- a. 49 subjects were evaluated
- b. 20 males and 29 females
- c. Ages 23-61 yrs (30.7 ± 9.4 , mean \pm SD)
- d. Caucasians = 41, Asians = 6, Hispanics = 2.

3. Products

- a. Three tretinoin gel, 0.025% products were evaluated (TABLE 1).
- b. Two products (A and C) were Q1 (qualitative) similar in their vehicle composition.
- c. One product (B) was Q1 different from the other two products (A or C) in vehicle composition.

TABLE I
Qualitative Composition Of Three 0.025% Tretinoin Gel Products

A	B	C
Ortho Pharmaceutical Corp	Bertek	Spears Pharmaceuticals
Butylated hydroxy toluene	Butylated hydroxy toluene	Butylated hydroxy toluene
Hydroxypropyl cellulose	Hydroxypropyl cellulose	Hydroxypropyl cellulose
Alcohol 90% (w/w)	Polyolprepolymer-2	Alcohol 90% (w/w)
	Ethanol 83% (w/w)	
	Denatured with <i>tert</i> -butyl alcohol and brucine sulfate	

4. Study Design [1]

- a. One hour before product application, forearms were wetted, cleansed with a gentle cleansing wash, rinsed under tepid water and blotted dry.
- b. Synchronous product application, asynchronous residual product removal.
- c. Drug uptake time points evaluated: 0.25, 0.50, 1.0 and 1.5 hours application
- d. Drug elimination time points evaluated: 3, 6, 9 and 12 hrs after residual product removal of a 1.5 hour application.
- e. Randomization schedule for product application
 - 1) Four anatomical regions on each forearm. Drug uptake time points of DPK profile randomly assigned to an anatomical region on right arm, Drug elimination time points of DPK profile randomly assigned to left arm.
 - 2) Three 1.13 sq cm skin sites in each anatomical region. Product randomized to skin site 1, 2, or 3. Randomization schedule on right arm same as left arm within a subject.
- f. Dose: 5 mg product/1.13 sq cm surface skin site.

- g. Protective non-occluding guard used over the skin sites to prevent accidental product removal.
 - h. Subjects wore loose long sleeved labcoats throughout the study to minimize light exposure to the product-treated skin sites.
 - i. Ten adhesive discs (D-squame®, CuDerm Corp.) used to harvest stratum corneum from each skin site. First adhesive discarded, and remaining 9 adhesive discs combined, immediately placed on dry ice, stored at -70°C until extracted and analyzed for tretinoin and isotretinoin by HPLC assay.
5. **HPLC assay** for quantitation of tretinoin and isotretinoin
- a. Validated for tretinoin and isotretinoin under gold light lab conditions according to Bioanalytical Assay Validation [2].
 - b. Precision $< 8\%$, Accuracy $> 96\%$ for adhesive disc spiked, extracted calibration standard curve 4-100 ng/mL.
 - c. Limit of quantification = 4 ng/mL.
 - d. Retention times: Tretinoin = 6.0 minutes, Isotretinoin = 5.0 minutes, and acetretin (internal standard) = 3.8 minutes.
6. **Pharmacokinetic parameters evaluated for tretinoin, isotretinoin and Total retinoids**
- a. C_{max}
 - b. T_{max}
 - c. AUC_{0-t}
 - d. T_{half}
7. **Statistical Analysis for Bioequivalence**
- a. C_{max} and AUC_{0-t} for tretinoin, isotretinoin and total retinoids
 - b. General Linear Models (GLM) procedure of SAS statistical program, in which effects for group, subjects and treatments were evaluated.
 - c. Analysis performed by Donald Schuirmann, Ph.D., FDA.
 - d. With and between subject variability
 - e. Bioequivalence was evaluated using the Average Bioequivalence Approach based on the ratio of average log-transformed responses [3].
 - 1) Products were considered bioequivalent if the 90% confidence interval for the ratio of the population geometric averages was contained completely within the 80-125% interval using the two, one sided t test [4].
 - 2) Products were considered bio-IN equivalent if the 95% confidence interval for the ratio of the population geometric averages was completely outside the 80-125% interval using the two, one sided t test.
8. **Results**
- a. **Dermatopharmacokinetic Method: C_{max} and AUC_{0-t}**
- 1) **Tretinoin**
 - a) The Ortho and Spear products are bioequivalent
 - b) The Bertek and Ortho products are NOT bioequivalent
 - 2) **Isotretinoin**
 - a) The Ortho and Spear products are bioequivalent
 - b) The Bertek and Ortho products are NOT bioequivalent

3) **Total Retinoid**

- a) The Ortho and Spear products are bioequivalent
- b) The Bertek and Ortho products are NOT bioequivalent

Clinical Trial Method

- a. Ortho and Spear products were clinically equivalent in terms of safety and efficacy [5] and FDA approved.
- b. Bertek product was NOT clinical equivalent in terms of efficacy, but 2 times more safe (less adverse events)[6] and FDA approved.

CONCLUSIONS

1. Tretinoin gels, 0.025%, which have similar qualitative (Q1) vehicle compositions (Ortho and Spear products) demonstrated equivalent clinical efficacy and safety and were determined to be bioequivalent by the dermatopharmacokinetic (DPK) method.
2. Tretinoin gels, 0.025%, which have different qualitative (Q1) vehicle compositions (Bertek and Ortho products) demonstrated NON equivalent clinical efficacy and safety and were determined to be bioINequivalent equivalent by the DPK method.
3. Thus, bioequivalence assessment by the DPK method agreed with the clinical efficacy and safety trial method assessments of bioequivalence.
4. These data support the use of the dermatopharmacokinetic method in assessing bioequivalence between multiple sources of topical tretinoin gel products.

References

1. Guidance for Industry: Topical Dermatological Drug Product NDAs And ANDAs - In Vivo Bioavailability, Bioequivalence, In Vitro Release, And Associated Studies. June 1998.
2. Shah VP, Midha KK, Dighe S, McGilveray IJ, Skelly JP, Yacobi A et al.: Analytical Methods Validation: Bioavailability, Bioequivalence, and Pharmacokinetic Studies: A Conference Report. *J Pharmaceut Sci* 1992; March:309-12.
3. Cox GEP, Cox DR. An analysis of transformations. *J Royal Statistical Society, series B*, 1964;26:211-52.
4. Schuirmann DJ. A Comparison Of The Two One-sided Tests Procedure and the power Approach for assessing the equivalence of Average Bioavailability. *J Pharmacokin Biopharm* 15 657-680 (1987).
5. Spear KL. "Skin Stripping Vs. Acne Bioequivalence Studies For Tretinoin Generics" Presentation to Dermatology Advisory Committee, November 17, 2000, Rockville, MD.
6. Tretinoin Gel, Topical, 0.025%. Approved Drug Products With Therapeutic Equivalence Evaluations, p 3-340, USDHHS, PHS, FDA, 2001.