

October 26, 1999

2615 '00 JAN 24 A11 :06

Roger Williams, M.D.
FDA-CDER
Mail Stop - HFD-001
Building WOC2,
1451 Rockville Pike
Rockville, Maryland 20852

Dear Dr. Williams,

It has come to my attention that data I presented on October 23, 1998 to a joint meeting of the Dermatologic and Ophthalmic Drug Advisory Committee and the Pharmaceutical Science Advisory Committee has been cited to support the contention that the DPK approach to topical bioequivalence is invalid. Since I have always been a strong supporter of the DPK approach, whether this be by tape stripping or other kinetic methods such as cadaver skin absorption, I wanted to reiterate the argument I made at the Advisory Committee meeting.

As you will recall, the conclusion of my presentation at the October 23rd meeting was simply that **tape stripping (DPK) is indeed a valid method by which to assess the bioequivalence of topical products. It works!** Data obtained from a series of studies conducted in my laboratory in which differences between two OTC 1% hydrocortisone creams were measured by three different methodologies (vasoconstrictor assay, tape stripping, cadaver skin permeation) were presented in support of my conclusion. The data showed that each of the three methods, one pharmacodynamic, one *in vivo* pharmacokinetic, and one *in vitro* pharmacokinetic, were capable of discerning that the two products were substantially different. Tape stripping was just as good as vasoconstrictor assay, a technique which has long been accepted by both the Agency and the dermatologic community.

One caveat that emerged from our work was that the number of tape strips taken is critical. It is necessary that a sufficient number of strips be taken so that what is being assayed is drug that has reached the deeper levels of the stratum corneum and not drug that is lying on the surface (in the furrows) of the skin. However, I do not view this as a limitation of the tape stripping method. Any method, when improperly conducted, will likely yield erroneous results. Increasing the number of strips taken from twelve to twenty-two was adequate in our hands to show differences between the two OTC hydrocortisone products. While it could be said that twelve strips are not adequate, **the conclusion of our work is that twenty-two strips are adequate.**

The procedure we have adopted is to take twenty-two strips, discard the first twelve (these are too heavily contaminated by drug on the surface of the skin, lying in the furrows) pool and analyze the last ten strips. The last ten strips represent drug in the mid to deeper levels of the stratum corneum, and relatively little contaminated by drug in the furrows. In our hands, complete removal of the stratum corneum from the forearm site with Transpore tape takes 30-40 strips on average. Increasing the number of tape strips taken from twelve to twenty-two is a

98D-0388

c17

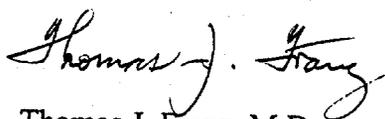
minor matter. Although it adds to the amount of time spent on each subject, it does not materially affect the conduct of the study nor does it present any additional risk or discomfort to the subjects. Twenty-two strips is no more painful than twelve strips; and, even with twenty-two strips, one is well above the living epidermis so that the chances for producing permanent hyperpigmentation or scarring are extremely remote. We have conducted four full DPK studies and several pilot DPK studies in the past four years, involving tape stripping of more than 200 subjects, and have never had a single adverse reaction or a single subject drop out because of pain.

Based on the hydrocortisone work we conducted, it is my recommendation that an adequate validation procedure be built into the tape stripping guidance. Each lab should be required to demonstrate their ability to detect differences between products known to be different, e.g. the two hydrocortisone products used in our study. The test "validation" products must differ in vehicle composition, however, not concentration, as differences in concentration can just as easily be detected by a faulty tape stripping procedure as a proper tape stripping procedure.

In conclusion, I feel that the tape stripping approach to bioequivalence testing is a valid methodology that has a firm theoretical basis at its roots. The driving force for the delivery of any topically applied drug to the living epidermis and dermis is the concentration of that drug in the stratum corneum. Therefore, the measurement of the change in stratum corneum drug concentration as a function of time, which is the objective of the DPK approach, is a valid means by which to compare a generic and innovator product for their ability to deliver drug to the deeper layers of the skin. Since their therapeutic effectiveness is dependent upon achieving a certain level of drug at the target site in the deeper layers of the skin, an equal delivery of drug to the target site translates to equal efficacy. (For one therapeutic class, the antifungals, the stratum corneum is itself the site of drug action. No better assay of bioequivalence can be envisioned for this class of compounds than direct assay of the target tissue.)

Based on the experience gained in my laboratory over the past four years, I can attest to the fact that the DPK approach to topical bioequivalence is quite workable and perfectly adequate to the task of making available to practitioners generic products whose efficacy can be assured. I have included a summary of the data presented at the Advisory Committee meeting last October 23rd. If further information is needed, please call. I would be more than willing to make a complete presentation of the hydrocortisone data, and other data obtained from the DPK studies we have already conducted, to the Agency at any time.

Sincerely,



Thomas J. Franz, M.D.

CC Janet Woodcock, M.D. ✓

ASSESSING THE VALIDITY OF STRATUM CORNEUM TAPE STRIPPING TO DETERMINE THE BIOAVAILABILITY/BIOEQUIVALENCE OF TOPICAL DRUG PRODUCTS

- OBJECTIVE:** To demonstrate that stratum corneum tape stripping is a valid method by which to assess the topical bioavailability or bioequivalence of topical drug products.
- SPECIFIC AIM:** To demonstrate that stratum corneum tape stripping can discriminate between two 1% hydrocortisone cream products of differing bioavailability.
- OUTLINE OF PLAN:**
- (1) OTC 1% hydrocortisone products were screened using the cadaver skin permeation model to identify two products of differing bioavailability.
 - (2) The two products identified in step 1, Hytone Cream 1% (Dermik Laboratories) and Cortizone-10 Cream (Thompson Medical Co.), were then tested in the human vasoconstrictor model to verify the difference in bioavailability by an independent method.
 - (3) The same two products identified in step 1 were then assessed by stratum corneum tape stripping to determine if this method could detect a difference in bioavailability.

METHODS:

Cadaver Skin Permeation

Multiple sections of dermatomed (0.25 mm) human trunk skin from the same donor were mounted on 0.8 cm² Franz cells and placed in a diffusion apparatus in which the dermal receptor solution was stirred magnetically at 600 RPM and its temperature maintained at 37°C. The epidermal surface was left open to ambient laboratory conditions. The integrity of each section was verified by measuring its permeability to tritiated water. Subsequently, test product was applied to a minimum of three sections of each donor skin at a dose of 8-10 mg/cm² and multiple donors were used for each product. At 4, 8, 12, 24, 30, 36 and 48 hours the receptor solution was removed in its entirety, replaced with fresh solution, and an aliquot taken for hydrocortisone assay by high performance liquid chromatography.

Vasoconstrictor Assay

The vasoconstrictor potency of two products (Hytone Cream 1% and Cortizone-10 Cream) as well as a positive control (Diprolene Ointment 0.05%) was tested in 18 normal

subjects. Four sites (2.5 cm diameter) were marked on each ventral forearm, dosed with 19 ± 0.1 mg of each product using a positive displacement pipette, and evenly spread over the entire site using a glass rod. Each of the three test products were applied to both forearms and the fourth site was used as a negative control.

Five minutes following application an occlusive polyethylene film (Saran Wrap) was placed over each forearm and held in place with an elastic cloth sleeve. At 16 hours after application the occlusive cover was removed and one hour later the site's skin color evaluated using a Minolta Chroma Meter (CR-300). The change in a* scale value between pre-dosing and 17 hours post-dosing was calculated for each site, and the two readings for each product averaged.

Stratum Corneum Tape Stripping

Stratum corneum tape-stripping studies were conducted on Hytone Cream 1% and Cortizone-10 Cream products. Six adult male and female subjects who were in good health and free of any skin disease were recruited. Test sites measuring 2x5 cm on the subject's volar forearm were marked, 19 mg of each product applied using a positive displacement pipette, and evenly spread over the entire site using a glass rod. The sites were protected, but not occluded. At eight hours post-dosing the sites were stripped twenty-two times with Transpore tape (#1527-1, 3M Health Care, St. Paul, MN). Each strip was applied, rubbed several times to ensure good contact and then removed in one continuous and rapid motion. All tape strips from a single site were pooled in groups (2, 5, 5, 5, 5), extracted and analyzed for hydrocortisone content by high pressure liquid chromatography.

RESULTS:

The results are presented in the accompanying Table and Figures.

TABLE I: Comparison of Hytone Cream 1% and Cortizone-10 Cream Bioavailability (Mean \pm SE)

Vehicle	Cadaver Skin Total Penetration (μg)	Cadaver Skin Peak Flux ($\mu\text{g}/\text{cm}^2/\text{hr}$)	<i>In Vivo</i> Vasoconstrictor Assay (Change in "a*" Value)
Cortizone-10 Cream	0.38 ± 0.13 (n=10) ^a	0.011 ± 0.003	-1.2 ± 0.3^b
Hytone 1% Cream	2.56 ± 0.42 (n=16)	0.091 ± 0.015	$1.9 \pm 0.3^{b,c}$
Un-treated Control			0.4 ± 0.3
Diprolene 0.05% Ointment			-2.3 ± 0.2^b

a. Statistical different $p < 0.001$ for Hytone vs Cortizone cream.

b. Significantly greater than un-treated control site; $p < 0.002$

c. Hytone 1% cream significantly greater than Cortizone-10 cream; $p < 0.014$

FIGURE 1
In Vitro Absorption of Hydrocortisone through Human Cadaver Skin

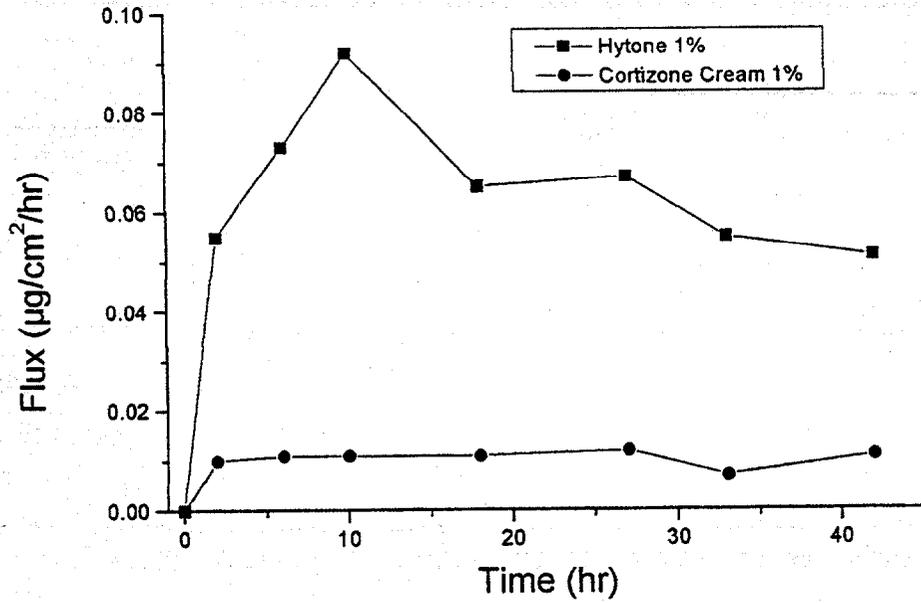
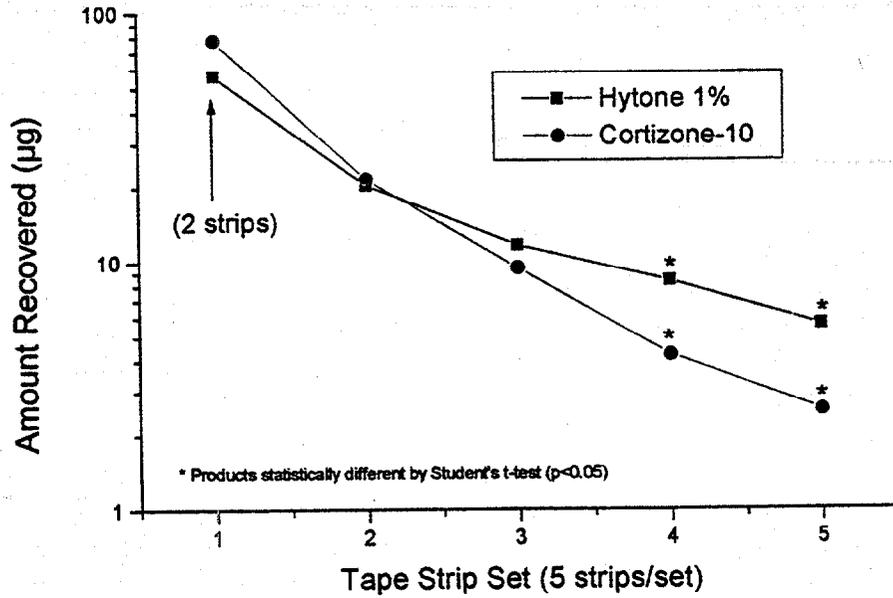


FIGURE 2
In Vivo Tape Stripping Study on 6 Subjects



CONCLUSIONS:

1. Hydrocortisone bioavailability was found to be significantly greater from Hytone Cream 1% than from Cortizone-10 Cream by two well recognized and independent methods, the human cadaver skin assay and the human vasoconstrictor assay.
2. Stratum corneum tape stripping was also found to be capable of demonstrating a significant difference in hydrocortisone bioavailability between the two products.
3. Given the sound theoretical basis upon which the tape stripping approach is based and the demonstration of acceptable sensitivity for the one test compound (hydrocortisone) examined here, it is expected that the tape stripping model will be a suitable method by which to demonstrate the bioavailability or bioequivalence of topical drug products. In practice, however, it is clear that adequate validation procedures for each drug, each laboratory, and each set of investigators/technicians within a lab must be established to insure that the test is properly conducted.