CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 50-741

CLINICAL PHARMACOLOGY and BIOPHARMACEUTICS REVIEW(S)

SEP 1 2000

Clinical Pharmacology/Biopharmaceutics Review

Clindamycin Phosphate 1% and
Benzoyl Peroxide 5% Gel
NDA 50-741 AZ
Clindoxyl Gel
Reviewer: E.D. Bashaw, Pharm.D.
MWH

Stiefel Labs.
Oak Hill, NY

Submission Date:
March 6, 2000

Review of a Major Amendment

Application Background

Clindoxyl Gel is a combination product containing clindamycin phosphate (equal to 1% clindamycin) and benzoyl peroxide 5% in a gel base for use in the treatment of acne vulgaris. During the original review of this application in mid-1997 it was revealed that the supplier of clindamycin for Stiefel ——— , was under investigation by the Agency for violation of CGMP (current good manufacturing procedures). Specifically, as it relates to this application, inspection of the drug substance manufacturing site revealed that the proper procedures and manufacturing controls were not being followed. Subsequent to this investigation ——— went out of business. Under the Agency's Application Integrity Policy, all applications using drug product from ——— were viewed as suspect. On the basis of the lack of validation of the drug product material, the original NDA submission was cited as non-approvable in a letter to the sponsor dated May 14, 1997.

Biopharmaceutic Background

One of the issues cited in the May 14th, 1997 letter was the lack of an adequate determination of in vivo bioavailability. Through discussion with the sponsor it was decided that an in vitro determination using cadaver skin would be sufficient to demonstrate in vivo bioavailability. This was based on our experience with topical clindamycin solutions which under conditions of exaggerated use have a very poor bioavailability i.e. <<5%. In addition the use of an in vitro system would allow us to determine the degree of penetration of the benzoyl peroxide component of this product. Normally, this cannot be done in humans due both to its short biologic half-life and its ubiquitous nature as a common food preservative. In this submission the sponsor has submitted the results of in vitro release testing using Clindoxyl Gel, Cleocin-T, and a single entity benzoyl peroxide product.

In Vitro Testing

Study Title: Determination of Clindamycin Phosphate and Benzoyl Peroxide Percutaneous Absorption In Vitro Using the Finite Dose Human Cadaver Skin Model.

Investigators:

Study Site:

Products Used	Brand Name	Lot #	Exp.
Test Product	Clindoxyl Gel	D1025	9/00
Benzoyl Peroxide Reference	PanOxyl AQ 5 Gel	D0392	10/00
Clindamycin Reference	Cleocin-T Topical Soln.	51BXM	4/00

Investigational Formulation:

Ingredients	PERCENT
Benzoyl Peroxide	5%
Clindamycin Phosphate	%*
Carbomer 940	
Dimethicone	
Disodium Lauryl Sulfosuccinate	%
Edetate Disodium	
Glycerin	
Silicon Dioxide	%
Methylparaben	%
Poloxamer	
Purified Water	%
Sodium Hydroxide	%

* equal to 1% Clindamycin

Methods

Results

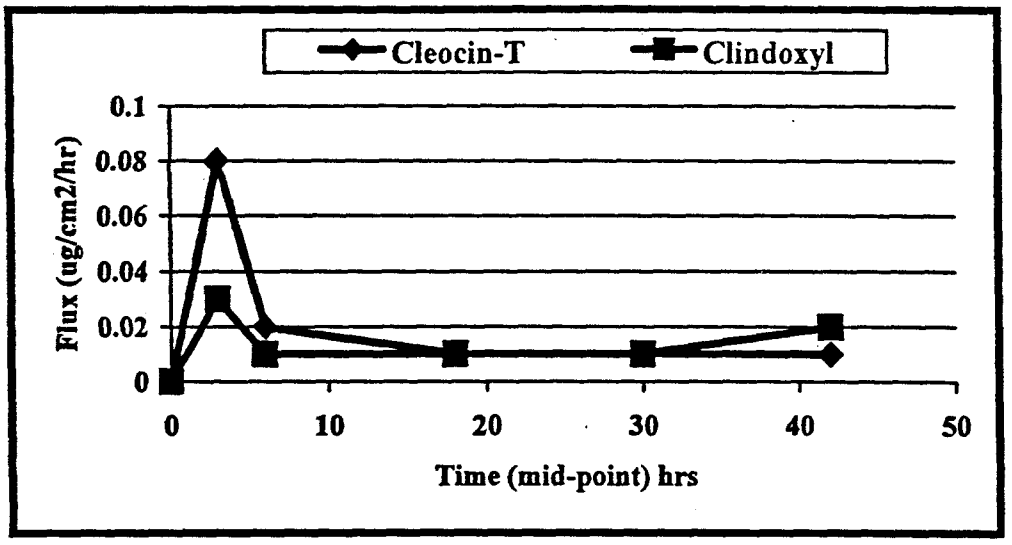
Clindamycin Phosphate

As expected from previous in vivo studies the degree of percutaneous absorption of clindamycin phosphate was very low with less than 1% of the applied dose being detected in the receptor fluid (cumulative). Between the two products significantly more clindamycin phosphate was recovered from the surface of the skin from Cleocin-T than from the Clindoxyl treated cells. This is most likely due to an interaction between benzoyl peroxide and clindamycin phosphate occurring on the skin. [It is known that clindamycin phosphate is unstable in the presence of benzoyl peroxide in the presence of light and heat.] Reproduced below is a summary of the individual data attached as Tables I and II.

% of Applied Dose
Mean +/- S.E., N=33

	Clindoxyl	Cleocin-T
Total Absorbed	0.70+/-0.28	0.78+/-0.25
Dermis	0.00+/-0.00	0.00+/-0.00
Epidermis	1.07+/-0.64	1.64+/-0.33
Surface Wash	27.31+/-5.79	62.03+/-4.49
Total Recovered	28.98+/-5.81	64.32+/-4.71

Reproduced below is a graphical representation of the flux data per mid-point of the observation interval.



As expected the data indicates that Cleocin-T has a faster in vitro penetration. Given that it is a solution and the Clindoxyl product is a gel, this finding is in keeping with expectations.

Clindamycin Hydrochloride

Because of the potential for the clindamycin phosphate to form the hydrochloride salt after contact with the cadaver skin and/or the receptor fluid, the sponsor also attempted to determine the amounts of clindamycin hydrochloride present in the system as well. Unfortunately the results of this analysis were complicated by an interfering substance which yielded values of clindamycin hydrochloride in great excess of the amount applied. While the sponsor did not attempt to identify this compound, they do speculate that the interfering substance is likely a byproduct of a reaction between clindamycin phosphate and benzoyl peroxide. This theory is supported by the observation that the no such interference was seen for the Cleocin-T cells. Reproduced below is a summary of the individual data attached as Tables III and IV.

% of Applied Dose
Mean +/- S.E., N=33

	Clindoxyl	Cleocin-T
Total Absorbed	1.39+/-0.45	1.73+/-0.57
Dermis	10.67+/-4.07	0.70+/-0.37
Epidermis	45.16+/-18.13	1.12+/-0.75
Surface Wash	149.19+/-48.53	5.18+/-4.33
Total Recovered	205.68+/-34.45	9.22+/-4.64

The sponsor also points out that the actual amount that reaches the receptor fluid is similar between the two samples (1.39% vs. 1.73%). They also speculate that the design of the study (using a 48hr contact time) may have contributed to the formation of this interfering species. This portion of the study is unevaluable.

Benzoyl Peroxide

As expected very little benzoyl peroxide was detected in the receptor fluid after 48 hrs. This is most likely due to its instability, ie. it's propensity to oxidize other compounds in and on the skin to form benzoic acid. Reproduced below is a summary of the individual data attached as Tables V and VI.

% of Applied Dose
Mean +/- S.E., N=28

	Clindoxyl	Panoxyl AQ
Total Absorbed	0.05+/-0.05	0.00+/-0.00
Dermis	0.11+/-005	0.14+/-0.07
Epidermis	0.63+/-0.21	1.83+/-1.07
Surface Wash	18.18+/-6.11	25.49+/-9.53
Total Recovered	18.96+/-6.22	27.47+/-9.71

Benzoic Acid

Compared to the benzoyl peroxide data, appreciably more benzoic acid appeared in the receptor fluid after 48hrs. Even so if one adds the amount of drug absorbed as both benzoic acid and benzoyl peroxide, less than 6% of the total dose was recovered in the receptor fluid using sink conditions for 48hrs. Again the in vitro data validates the previously mentioned assumptions that benzoyl peroxide would be poorly absorbed and that the majority of what was absorbed would be benzoic acid. Reproduced below is a summary of the individual data attached as Tables VII and VIII.

% of Applied Dose
Mean +/- S.E., N=28

	Clindoxyl	Panoxyl AQ
Total Absorbed	5.50+/-2.49	5.22+/-1.60
Dermis	3.15+/-1.47	3.28+/-1.10
Epidermis	4.91+/-1.58	7.37+/-1.66
Surface Wash	11.91+/-4.57	3.74+/-0.79
Total Recovered	25.60+/-3.61	18.01+/-2.48

Conclusions

The data from the in vitro studies presented here validates our previously held views that both clindamycin and benzoyl peroxide are poorly absorbed across intact skin. While it

could be expected that in diseased skin, ie. skin with acne vulgaris, absorption might be increased, it is clear, from the small amounts absorbed here that these amounts would still be very small and of no systemic pharmacologic interest (pseudomembraneous colitis).

Recommendation

From a clinical pharmacology and biopharamceutics perspecitve, the sponsor has adequately addressed the biopharmaceutic issues raised in the May 14th , 1997 non-approval letter. The following comments are being provided to the sponsor for future reference.

Comments

1.) Because of the importance of validation of the integrity of the skin samples in the Franz cell appartaus, the sponsor should include in their report all of the results of sample integrity testing, i.e., individual TEWL values.
2.) Because of the noted analytical problems cited in this study the sponsor is reminded that demonstration of adequate analytical validation is crucial to the acceptance of the data presented. In their future NDA submissions the sponsor should provide the necessary analytical validation data needed to validate the methods used in support of both in vivo and in vitro studies.

/S/ 9/1/00

E. Dennis Bashaw, Pharm.D.
Team Leader,
Combined HFD-540/550/560 PK Team
Division of Pharmaceutical Evaluation-III

Secondary Review, Arzu Selen, Ph.D., Dep. Dir. DPE-III, /S/ 9/1/2000

NDA 50-741 ORIG
HFD-540
HFD-540 (CINTRON)
HFD-880 (BASHAW, LAZOR, SELEN)

ACROSS DONOR SUMMARY: FLUX AND MASS BALANCE: Clindamycin Phosphate

Project: Steifel
Date: 12/29/99

All Flux values are ug/cm2/hr
All % are percent of applied dose.

Table I

Product: Cleocin-T

Sample	Donor 1	Donor 2	Donor 3	Donor 4	Donor 5	Donor 6	Donor 7	Donor 8	Mean	SE	Mid-t (hr)
1									0.08	0.03	3
2									0.02	0.01	9
3									0.01	0.00	18
4									0.01	0.00	30
5									0.01	0.00	42
Total Abs (ug):	0.81	0.45	0.57	na	0.20	1.20	1.24	0.00	0.64	0.18	
% Abs:	0.89	0.49	0.62	na	0.22	1.32	1.90	0.00	0.78	0.25	
% Derm:	0.00	0.00	0.00	0.00	na	na	0.00	0.00	0.00	0.00	
% Epi:	0.68	1.88	0.69	1.81	na	na	2.12	2.68	1.64	0.33	
% Surface:	63.12	43.46	56.92	63.61	na	na	74.85	70.21	62.03	4.49	
% Total Rec:	64.70	45.83	58.23	65.42	na	na	78.87	72.90	64.32	4.71	

Product: Clindoxyl Gel

Table II

Sample	Donor 1	Donor 2	Donor 3	Donor 4	Donor 5	Donor 6	Donor 7	Donor 8	Mean	SE	Mid-t (hr)
1									0.03	0.01	3
2									0.01	0.00	9
3									0.01	0.01	18
4									0.01	0.01	30
5									0.02	0.01	42
Total Abs (ug):	0.07	0.41	0.55	na	0.05	1.12	0.23	1.40	0.55	0.20	
% Abs:	0.08	0.45	0.61	na	0.06	1.23	0.35	2.15	0.70	0.28	
% Derm:	0.00	0.00	0.00	0.00	na	na	0.00	0.00	0.00	0.00	
% Epi:	0.44	0.00	0.00	0.29	na	na	1.66	4.03	1.07	0.64	
% Surface:	40.84	26.53	33.20	30.44	na	na	0.00	32.82	27.31	5.79	
% Total Rec:	41.36	26.98	33.80	30.73	na	na	2.01	38.99	28.98	5.81	

ACROSS DONOR SUMMARY: FLUX AND MASS BALANCE CLINDAMYCIN HYDROCHLORIDE

Project: Steifel
Date: 12/29/99

All Flux values are ug/cm2/hr
All % are percent of applied dose.

Table III

Product: Cleocin-T

Sample	Donor 1	Donor 2	Donor 3	Donor 4	Donor 5	Donor 6	Donor 7	Donor 8	Mean	SE	Mid-t (hr)
1									0.10	0.04	3
2									0.03	0.01	9
3									0.03	0.01	18
4									0.05	0.02	30
5									0.04	0.01	42
Total Abs (ug):	2.09	4.52	2.01	0.00	0.90	0.95	1.49	0.00	1.50	0.52	
% Abs:	2.30	4.97	2.21	0.00	0.99	1.04	2.30	0.00	1.73	0.57	
% Derm:	0.00	0.00	1.04	2.28	na	na	0.86	0.00	0.70	0.37	
% Epi:	0.00	0.00	4.29	2.42	na	na	0.00	0.00	1.12	0.75	
% Surface:	0.13	26.64	0.20	0.62	na	na	3.48	0.00	5.18	4.33	
% Total Rec:	2.43	31.62	7.48	7.16	na	na	6.63	0.00	9.22	4.64	

Table IV

Product: Clindoxyl Gel

Sample	Donor 1	Donor 2	Donor 3	Donor 4	Donor 5	Donor 6	Donor 7	Donor 8	Mean	SE	Mid-t (hr)
1									0.08	0.03	3
2									0.03	0.01	9
3									0.02	0.01	18
4									0.03	0.01	30
5									0.03	0.01	42
Total Abs (ug):	0.00	2.45	0.81	na	2.77	1.27	1.10	0.00	1.20	0.41	
% Abs:	0.00	2.69	0.89	na	3.04	1.40	1.69	0.00	1.39	0.45	
% Derm:	26.63	10.51	1.77	17.11	na	na	8.03	0.00	10.67	4.07	
% Epi:	78.33	111.75	3.53	56.16	na	na	17.20	3.99	45.16	18.13	
% Surface:	65.83	10.26	141.30	102.04	na	na	330.64	245.06	149.19	48.53	
% Total Rec:	170.79	135.20	146.17	175.31	na	na	357.56	249.05	205.68	34.45	

ACROSS DONOR SUMMARY: FLUX AND MASS BALANCE BENZOYL PEROXIDE

Project: Stiefel
Date: 12/29/99

All Flux values are ug/cm2/hr
All % are percent of applied dose.

Product: Clindoxyl Gel

Table V

Sample	Donor 1	Donor 2	Donor 3	Donor 4	Donor 5	Donor 6	Donor 7	Donor 8	Mean	SE	Mid-t (hr)
1									0.00	0.00	3
2									0.04	0.04	9
3									0.00	0.00	18
4									0.00	0.00	30
5									0.00	0.00	42
Total Abs (ug):	na	na	1.01	0.00	0.00	0.00	0.00	0.00	0.17	0.17	
% Abs:	na	na	0.29	0.00	0.00	0.00	0.00	0.00	0.05	0.05	
% Derm:	na	na	0.19	0.00	0.24	0.23	0.00	0.00	0.11	0.05	
% Epi:	na	na	0.00	1.15	1.09	0.50	0.94	0.09	0.63	0.21	
% Surface:	na	na	28.21	34.75	31.49	9.40	4.44	0.80	18.18	6.11	
% Total Rec:	na	na	28.64	35.89	32.82	10.13	5.38	0.89	18.96	6.22	

Product: Panoxyl

Table VI

Sample	Donor 1	Donor 2	Donor 3	Donor 4	Donor 5	Donor 6	Donor 7	Donor 8	Mean	SE	Mid-t (hr)
1									0.00	0.00	3
2									0.00	0.00	9
3									0.00	0.00	18
4									0.00	0.00	30
5									0.00	0.00	42
Total Abs (ug):	na	na	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	
% Abs:	na	na	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	
% Derm:	na	na	0.22	0.00	0.39	0.25	0.00	0.00	0.14	0.07	
% Epi:	na	na	1.05	0.76	7.11	1.15	0.93	0.00	1.83	1.07	
% Surface:	na	na	44.24	60.52	27.39	15.14	5.21	0.46	25.49	9.53	
% Total Rec:	na	na	45.52	61.27	34.89	16.53	6.13	0.46	27.47	9.71	

ACROSS DONOR SUMMARY: FLUX AND MASS BALANCE BENZOIC ACID

Project: Steifel
Date: 12/29/99

All Flux values are ug/cm2/hr
All % are percent of applied dose.

Table VII

Product: Clindoxyl Gel

Sample	Donor 1	Donor 2	Donor 3	Donor 4	Donor 5	Donor 6	Donor 7	Donor 8	Mean	SE	Mid-t (hr)
1									1.18	0.84	3
2									0.34	0.15	9
3									0.37	0.13	18
4									0.53	0.24	30
5									0.35	0.22	42
Total Abs (ug):	na	na	61.04	2.11	18.97	9.72	11.59	5.34	18.13	8.90	
% Abs:	na	na	17.44	0.60	5.42	2.78	4.64	2.14	5.50	2.49	
% Derm:	na	na	0.85	2.94	9.88	4.07	0.66	0.53	3.15	1.47	
% Epl:	na	na	3.34	12.36	1.81	2.90	3.24	5.84	4.91	1.58	
% Surface:	na	na	7.50	8.29	0.96	3.48	29.41	21.80	11.91	4.57	
% Total Rec:	na	na	28.09	25.99	18.06	13.23	37.94	30.31	25.60	3.61	

Table VIII

Product: Panoxyl

Sample	Donor 1	Donor 2	Donor 3	Donor 4	Donor 5	Donor 6	Donor 7	Donor 8	Mean	SE	Mid-t (hr)
1									0.94	0.27	3
2									0.46	0.12	9
3									0.36	0.11	18
4									0.55	0.20	30
5									0.38	0.17	42
Total Abs (ug):	na	na	42.09	26.79	9.86	10.32	10.54	4.13	17.29	5.85	
% Abs:	na	na	12.02	7.65	2.82	2.95	4.22	1.65	5.22	1.60	
% Derm:	na	na	1.67	2.24	7.79	5.31	1.99	0.71	3.28	1.10	
% Epl:	na	na	11.88	12.47	3.59	6.76	6.76	2.76	7.37	1.66	
% Surface:	na	na	3.90	4.49	0.63	3.32	3.49	6.60	3.74	0.79	
% Total Rec:	na	na	29.47	17.26	14.82	18.34	16.44	11.71	18.01	2.48	

MAY 12 1997

Clinical Pharmacology/Biopharmaceutics Review

Clindamycin Phosphate 1%
Benzoyl Peroxide 5% Gel
NDA 50-741
Clindoxyl™ Gel
Reviewer: E.D. Bashaw, Pharm.D.

Stiefel Labs, Inc.
Oak Hill, NY 12460
Submission Date: 5/14/96

Review of an NDA

Background

This NDA is for a topical combination of clindamycin phosphate 1% and benzoyl peroxide 5% for use in the treatment of acne vulgaris. Both of the individual ingredients are available as single entity products for the same condition, clindamycin as Cleocin-T® and benzoyl peroxide as Oxy-5™ (among others). The theory behind the combination is that as each ingredient works via a different mechanism of action (clindamycin as a topical antibiotic and benzoyl peroxide as a drying agent), a combination product would produce superior results relative to either single entity.

Pharmacokinetic Overview

The submitted NDA contains no in vivo pharmacokinetic studies done with Clindoxyl® Gel or with either entity alone. In the submission, the applicant cites a number of in vivo pharmacokinetic trials from the published literature showing little or no systemic absorption of clindamycin following the topical administration of Cleocin-T® solution. It is the applicant's contention that the topical penetration (i.e., systemic availability) of clindamycin will be lower than that of the Cleocin-T® solution due to the fact that their product is a gel and not alcoholic solution. The applicant contends that the lack of a gel matrix in Cleocin-T® results in a faster rate of absorption and better systemic availability relative to their product. The citing of a number of articles in their NDA package indicating the low systemic absorption of Cleocin-T® is evidence, according to the applicant, that the degree of systemic availabilitiy will be unquantifiable due to analytical limits.

Because of the low drug levels seen with the original Cleocin-T® NDA, Dr. Rabi Patniak of the Division of Bioequivalence, Office of Generic Drugs, was consulted as to the requirements for approval of generic Cleocin-T® generic products. He indicated that for any proposed generic of Cleocin-T® solution, the Office of Generic Drugs requries the demonstration of clinical a/k/a pharmacodynamic equivalence for their approval. This is due to the demonstrated low and erratic nature of clindamycin levels after topical administration from the published literature.

As for the benzoyl peroxide component of this drug product, a survey of both the published literature and the review files indicate that benzoyl peroxide has a very short biologic

half-life. It is rapidly converted into benzoic acid by both the action of skin microflora and by the blood. Benzoic acid is converted in the liver to hippuric acid and excreted in the urine.

Labeling

At this time, NDA 50-741 is not approvable due to deficiencies associated with the manufacture and processing of the final drug substance. Because of this, labeling comments will be deferred until a resubmission.

Comments

If 100% absorption from the Clindoxyl formulation is assumed for clindamycin and the total amount from the tube (45 gm) is applied, the total systemic exposure would be less than that from an IV dose of Cleocin. Because "diarrhea, bloody diarrhea, and colitis (including pseudomembranous colitis) have been reported with the use of topical and systemic clindamycin" [quoted from proposed package insert], it would be beneficial to know if clindamycin exposure is greater from the Clindoxyl formulation than the topical administration of clindamycin alone. The relative percutaneous absorption of benzoyl peroxide should also be evaluated.

Recommendation

At the present time the applicant has provided neither an assessment of the degree of or relative nature of the in vivo percutaneous absorption of clindamycin and benzoyl peroxide from Clindoxyl® Gel. Instead the applicant has presented copies of articles showing the low and variable degree of clindamycin absorption from Cleocin-T® and a discussion of the fate of topically applied benzoyl peroxide. As part of the re-submission of this application the applicant should provide an in vitro assessment of the percutaneous absorption of both clindamycin and benzoyl peroxide from Clindoxyl® gel, Cleocin-T® solution, and a single entity product of benzoyl peroxide. Provided that these in vitro studies show that the rate and/or extent of in vitro percutaneous penetration is less than that of Cleocin-T® or the single entity benzoyl peroxide product, then in vivo bioavailability testing will not be required. If such studies show enhanced percutaneous penetration for the Clindoxyl® gel dosage form, then an assessment of the in vivo percutaneous absorption of Clindoxyl® gel in man will be required. The Division of Pharmaceutical Evaluation III will review and provide comment to submitted protocols that address the above recommendation.

/S/ 5/12/97

E. Dennis Bashaw, Pharm.D.
Senior Pharmacokineticist (HFD-550)
Division of Pharmaceutical Evaluation III

Secondary Review, John Lazor, Pharm.D /S/ 5/12/97

CC: NDA 50-741 (ORG)

HFD-540/Div File
HFD-540/CSO/White
HFD-880 (Bashaw)
HFD-880 (Div File)
CDR (B. Murphy)
HFD-344 (Viswanathan)

U.S. Food and Drug Administration

MEMO

TO: Vicky Lutwak, Project Manager, HFD-540

From: E. Dennis Bashaw, Pharm.D. /S/
Team Leader, ODE-V Combined PK Review Team
Div. of Pharmaceutical Evaluation-III, HFD-880

RE: Clindoxyl PK Labeling

After evaluating the supplied labeling in the current NDA re-submission, the following revised pk section is proposed:

CLINICAL PHARMACOLOGY
A comparative study of the pharmacokinetics of _____ and 1% clindamycin solution alone in 78 patients indicated that mean plasma clindamycin levels during the four week dosing period were < 0.5 ng/ml for both treatment groups.

Benzoyl peroxide has been shown to be absorbed by the skin where it is converted to benzoic acid. Less than 2% of the dose enters systemic circulation as benzoic acid.

The revised section does not imply, as the sponsor's previous version did, that the two products are "bioequivalent" and attempts to put the data into a proper perspective.

APPEARS THIS WAY
ON ORIGINAL