

**CENTER FOR DRUG EVALUATION AND RESEARCH**

*APPLICATION NUMBER:*

**ANDA 75-250**

**BIOEQUIVALENCE REVIEW(S)**

\_\_\_\_\_ Syrup  
 Prednisolone Sodium Phosphate  
 15 mg/5 ml syrup  
 NDA #75-250  
 Reviewer: J. Lee  
 75250W.N97

WE Pharmaceuticals, Inc.  
 Ramona, California  
 Submission date:  
 November 10, 1997

**Review of a Request for Waiver**

The sponsor has submitted an application for \_\_\_\_\_ 15 mg/5 ml syrup {prednisolone sodium phosphate oral solution} and has requested a waiver of in-vivo bioequivalence testing under 21 CFR 320.22 (b)(3).

This application was accepted under a suitability petition (Docket #87P-0235/CP), filed on July 14, 1987 and accepted on November 4, 1987, which allows for a change in strength from the RLD (from 5 mg/5 ml to 15 mg/5 ml).

A formulation comparison of the test/reference products is presented below:

	_____	Pediapred®
	per 5 ml	per 5 ml
Prednisolone Sodium Phosphate	20.16 mg	6.7 mg
-as base equivalent	15 mg	5 mg
_____	_____	---
_____	_____	---
_____	_____	---
Glycerin	_____	---
Sodium saccharin	_____	---
Sorbitol	-----	_____
_____	_____	---
Edetate disodium	-----	_____
Methylparaben	-----	_____
Sodium phosphate, dibasic	-----	_____
Sodium biphosphate	-----	_____
FD&C Blue #1 _____	_____	---
FD&C Red #40 _____	_____	---
Artificial grape flavor	_____	---
Raspberry _____ flavor	-----	_____
Purified water	_____	_____

Comment:

1. The test formulation conforms to OGD's Inactive Ingredients Guideline.

Recommendation:

1. The Division of Bioequivalence finds that the information submitted by WE Pharmaceuticals, Inc. demonstrates that \_\_\_\_\_ 15 mg/5 ml syrup falls under 21 CFR 320.24 (b)(6) of Bioavailability/Bioequivalence Regulations. The Division of Bioequivalence recommends that the waiver of an in-vivo bioavailability study be granted.

*J. Lee 3/9/98*

J. Lee  
Division of Bioequivalence  
Review Branch II

RD INITIALED SNERURKAR  
FT INITIALED SNERURKAR

*[Signature]* 3/9/1998

Concur: *Dale P. Conner* Date: *3/24/98*

Dale Conner, Pharm. D.  
Director, Division of Bioequivalence

JLee/jl/03-05-98

cc: NDA #75-250 (original, duplicate), HFD-630, HFD-655 (Lee, Patnaik), Drug File, Division File

E L E C T R O N I C M A I L M E S S A G E

Date: 10-Mar-1998 11:43am EST  
From: Rabindra Patnaik  
PATNAIK  
Dept: HFD-651 MPN2 130  
Tel No: 301-827-5847 FAX 301-594-0181

TO: Shrinivas Nerurkar (NERURKAR )  
CC: Dale Conner (CONNERD )  
CC: Jenny Lee [HFD-655] (LEEJ )  
CC: Donald Hare (HARE )  
CC: Rabindra Patnaik (PATNAIK )

Subject: Prednisolone sodium phosphate solution,15mg/ml

Vijay:

This is a post'62 product (salt, although prednisolone is a DESI drug) and seems to have a wide therapeutic range. The labeling recommends a dose from 5 mg to 60 mg and for certain conditions, upto 200 mg. This is the rationale for the approval of the suitability petition of the higher strength (equiv. to base 15mg/ml). Thus,, there are no safety issues involved for this strength. Furthermore, if I recall, all excipients are within the approved ranges. Next questions are: are the formulations for the 5 mg and 15 mg similar? If not, is there any component that may affect the absorption of the drug? If I recall, this drug does not seem to have absorption problem. If the answers are "no" to these questions and it is a true solution, I do not see why we can not grant the waiver.

Thanks.

Rabi.



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Fisons Corporation  
Attention: Mr. John Glasby  
Two Preston Court  
Bedford, MA 01730

Best Possible Copy

Food and Drug Administration  
Rockville MD 20857

APPEARS THIS WAY  
ON ORIGINAL

NOV 4 1987

Docket 87P-0235/CP

Dear Mr. Glasby:

Reference is made to your petition filed July 14, 1987 requesting permission to file an Abbreviated New Drug Application (ANDA) for the following drug product: Prednisolone Sodium Phosphate Oral Solution, eq to 15 mg base/5 mL. The listed drug product to which you refer in your petition is Prednisolone Sodium Phosphate Oral Solution eq to 5 mg base/5 mL manufactured by your firm.

We have reviewed your petition under Section 505(j)(2)(C) of Federal Food, Drug, and Cosmetic Act (Act), and have determined that it is approved. This letter represents the Agency's determination that an ANDA may be submitted for the above-referenced product.

Your request involves a change in strength from the listed reference drug product (i.e., from 5 mg/5 mL to 15 mg/5 mL). The type of change you request is the type of change authorized under Section 505(j)(2)(C) of the Act.

Under Section 505(j)(2)(C)(i) of the Act the Agency will approve a petition seeking a strength which differs from the strength of the listed reference drug product unless it finds that investigations must be conducted to show the safety and effectiveness of the differing strength.

The Agency has determined that the change in strength for this specific product does not pose questions of safety or effectiveness. The basis for this determination is that although you propose a change in concentration from 5 mg/5 mL to 15 mg/5 mL, the doses, uses and administration of the proposed product are the same as those of the listed product. The labeling of the listed drug product indicates that doses may vary from 5 mL-60 mL (5 mg-60 mg) per day. In addition, for certain disease states doses of up to 200 mL (200 mg) daily may be required. Your proposed product is merely offered as an alternative dosage strength designed for patients who, because of their individual dosage requirements, would require volumes of 15 mL or larger of the listed drug product. Thus, there are no investigations that would be required to demonstrate safety or effectiveness of the proposed product and therefore, an ANDA may be submitted.

The approval of this petition to allow an ANDA to be submitted for the above referenced product does not mean that the Agency has determined that the ANDA will be approved for the product. The determination that an ANDA will be approved is not made until the ANDA itself is submitted and reviewed by the Agency.

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page 2

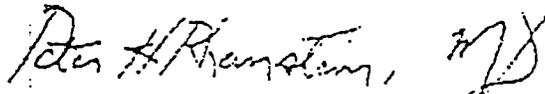
APPEARS THIS WAY  
ON ORIGINAL

To permit review of your ANDA submission you must submit all information required under Section 505(j)(2)(A) and (B) of the Act. To be approved the product will, among other things, be required to meet current bioequivalence requirements under Section 505(j)(2)(A)(iv) of the Act. We suggest that you contact the Director, Division of Bioequivalence at (301) 443-0181 to determine the specific requirements for this product. During the review of your application, the Agency may require the submission of additional information.

The listed drug product to which you refer in your ANDA must be the one upon which you based this petition. In addition, you should refer in your ANDA to the petition docket number above, and include a copy of this letter in the ANDA submission.

A copy of this letter approving your petition will be placed on public display in the Dockets Management Branch, HFA-305, Room 4-62.

Sincerely yours,



Peter H. Rheinstein, M.D., J.D., M.S.  
Director, Office of Drug Standards  
Center for Drugs and Biologics

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 75-250

APPLICANT: WE Pharmaceuticals, Inc.

DRUG PRODUCT: \_\_\_\_\_ 15 mg/5 ml syrup

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,



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

CC: ANDA 75-250  
ANDA DUPLICATE  
DIVISION FILE  
HFD-650/ Nerurkar for BioSign Off List *Jan 3/9/98*  
HFD-655/ J. Lee *l.f. 3/5/98*  
BIO DRUG FILE

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BIOEQUIVALENCY - ACCEPTABLE

6. **WAIVER (WAI)** Strengths: 15 mg/5 ml  
Outcome: **AC**

OUTCOME DECISIONS:  
**AC** - Acceptable **NC** - No Action

WINBIO COMMENTS:  
Waiver granted per 21 CFR 320.22 (b)(3) and suitability petition  
87P-0235/CP.

OFFICE OF GENERIC DRUGS  
DIVISION OF BIOEQUIVALENCE

ANDA/AADA # 75-250 SPONSOR: WE Pharmaceuticals

DRUG: \_\_\_\_\_

DOSAGE FORM: syrup

STRENGTHS/(s): 15 mg / 5 ml

TYPE OF STUDY: Single\_\_ Multiple\_\_ Fasting\_\_ Fed\_\_  N/A

STUDY SITE:

N/A

STUDY SUMMARY:

Waiver granted 21 CFR 320.22 (b)(3)  
and suitability petition 97P-0235/cp

ISSOLUTION:

N/A

PRIMARY REVIEWER: Jenny Lee BRANCH: II

INITIAL: E. Lee DATE 3/5/98

TEAM LEADER: S. Nerurkar, Ph.D BRANCH: II

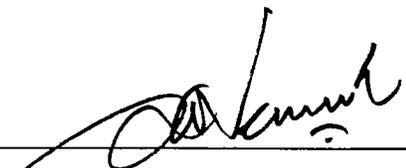
INITIAL: SN DATE 3/24/98

DIRECTOR, DIVISION OF BIOEQUIVALENCE: Dale Conner, Pharm.D

INITIAL: \_\_\_\_\_ DATE \_\_\_\_\_

DIRECTOR, OFFICE OF GENERIC DRUGS:

INITIAL: \_\_\_\_\_ DATE \_\_\_\_\_

 3/9/98

CC: ANDA 75-250  
ANDA DUPLICATE  
DIVISION FILE  
HFD-650/ Nerurkar for BioSign Off List  
HFD-655/ J. Lee *q.f.* 3/5/98  
BIO DRUG FILE

*AW* 3/9/98

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BIOEQUIVALENCY - ACCEPTABLE

6. WAIVER (WAI)

Strengths: 15 mg/5 ml

Outcome: AC

OUTCOME DECISIONS:

AC - Acceptable

NC - No Action

WINBIO COMMENTS:

Waiver granted per 21 CFR 320.22 (b)(3) and suitability petition  
87P-0235/CP.

Prednisolone Sodium Phosphate  
 15 mg/5 ml syrup  
 ANDA #75-250  
 Reviewer: J. Lee  
 75250W.500

WE Pharmaceuticals, Inc.  
 Ramona, California  
 Submission date:  
 May 26, 2000

**Review of a Waiver Amendment**

The waiver request in this application was originally reviewed and found acceptable by DBE [see rev 3/24/98, J.Lee]. This application has not been approved. Recently, the sponsor has reformulated the product due to the Agency's concerns about the amount of alcohol in a pediatric drug product. Other changes implemented in the new formulation as stated by the sponsor are as follows:

1. Changed FD&C Blue— dye to FD&C Blue #1 in order to eliminate a color change that occurred in previous batches.
2. Alcohol was removed, per FDA request and \_\_\_\_\_ was added to buffer the revised formulation product to a pH of 6.0 - 7.0
3. \_\_\_\_\_ was replaced by \_\_\_\_\_
4. \_\_\_\_\_ was removed and replaced with methylparaben and \_\_\_\_\_

As noted in the original review, this application was accepted under a suitability petition (Docket #87P-0235/CP), filed on July 14, 1987 and accepted on November 4, 1987, which allows for a change in strength from the RLD (from 5 mg/5 ml to 15 mg/5 ml).

Note also that this drug product is no longer using the trade name \_\_\_\_\_ per request by the Labeling Division.

A formulation comparison of the test/reference products is presented below:

	<u>WE Pharm</u> (old) per 5 ml	<u>WE Pharm</u> (new) per 5 ml	<u>Pediapred</u> <sup>®</sup> per 5 ml
Prednisolone Sodium Phosphate	20.16 mg	20.16 mg	6.7 mg
-as base equivalent	15 mg	15 mg	5 mg
_____	_____	---	---
_____	_____	---	---
_____	_____	---	---
Glycerin	_____	_____	---
Sodium saccharin	_____	_____	---

Sorbitol	----	---	_____
	_____	---	---
Edetate disodium	----	---	_____
Methylparaben	----	_____	_____
Sodium phosphate, dibasic	----	_____	_____
Sodium biphosphate	----	_____	_____
FD&C Blue #1 _____*	_____	_____	---
FD&C Red #40 _____*	_____	_____	---
Artificial grape flavor	_____	_____	---
Raspberry _____ flavor	----	---	_____
Purified water	_____	_____	_____
_____	---	_____	---
_____	---	_____	---
_____	---	_____	---
Propylene glycol	---	_____	---

\* in IIG

\*\* amount of artificial grape flavor \_\_\_\_\_ in the formulation is \_\_\_\_\_ % according to batch records.

Breakdown of artificial grape flavor : \_\_\_\_\_, in formulation:

<u>Ingredient</u>	<u>% of flavor</u>	<u>% of total formulation</u>
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Comment:

1. Although the sponsor states that FD&C Blue dye was changed from \_\_\_\_\_ to #1, we note that the original formulation already contained #1 dye and not \_\_\_\_\_ dye. The chemist reviewer also noted this fact and has asked for a clarification from the sponsor.
2. There were other changes in the formulation not spelled out in the four point summary outlined above: (1) a reduction in the amount of \_\_\_\_\_ (2) an increase in the amount of \_\_\_\_\_ (3) a very small decrease in the amount of \_\_\_\_\_ (4) introducing propylene glycol into the new formulation.
3. All flavor components/colors are  $\leq$  \_\_\_\_\_ % of total formulation or are in the IIG.

Recommendation:

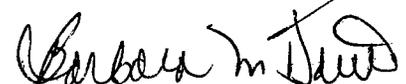
1. The Division of Bioequivalence agrees that the information submitted by WE Pharmaceuticals, Inc. demonstrates that prednisolone sodium phosphate 15 mg/5 ml syrup falls under 21 CFR 320.24 (b)(6) of Bioavailability/Bioequivalence Regulations.

R. Lee 11/2/00

J. Lee  
Division of Bioequivalence  
Review Branch II

RD INITIALED SNERURKAR  
FT INITIALED SNERURKAR

 11/9/2000

Concur:  Date: 11/29/00

 Dale Conner, Pharm. D.  
Director, Division of Bioequivalence

JLee/jl/11-02-00

cc: NDA #75-250 (original, duplicate), HFD-630, HFD-655 (Lee, Patnaik), Drug File,  
Division File

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 75-250                      APPLICANT: WE Pharmaceuticals, Inc.

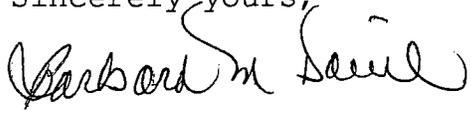
DRUG PRODUCT: Prednisolone Sodium Phosphate Syrup, 15 mg/5 ml

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,

*for* 

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

CC: ANDA 75-250  
ANANDA DUPLICATE  
DIVISION FILE  
HFD-651/ Bio Drug File  
HFD-650/ Reviewer

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Endorsements: (Final with Dates)

HFD-655/ JLee *f.f. 11/21/00*

HFD-655/ Bio team Leader

HFD-650/ D. Conner *Bm D 11/29/00*

*for*

*11/9/00*

BIOEQUIVALENCY - ACCEPTABLE

submission date: May 26, 2000

6. **WAIVER** (WAI)

Strengths: 15 mg/5 ml

Outcome: **AC**

7

Outcome Decisions: **AC** - Acceptable

WinBio Comments:

Waiver granted per 21 CFR 320.24 (b) (6)

**OFFICE OF GENERIC DRUGS  
DIVISION OF BIOEQUIVALENCE**

ANDA #: 75-250

SPONSOR: WE Pharmaceuticals

DRUG AND DOSAGE FORM: Prednisolone Na PO<sub>4</sub> Syrup

STRENGTH(S): 15mg/5ml

TYPES OF STUDIES: N/A

CLINICAL STUDY SITE(S): N/A

ANALYTICAL SITE(S): N/A

STUDY SUMMARY: <sup>Acceptable</sup> ~~per 21 CFR 320.24 (c)(6)~~

DISSOLUTION: 12/4/01 - Recognize there is a new RLD - Orosol  
Does not need a new bio-equivalent - P. Lee

**DSI INSPECTION STATUS**

Inspection needed: YES / <u>(NO)</u>	Inspection status:	Inspection results:
First Generic <u>No?</u>	Inspection requested: (date)	
New facility _____	Inspection completed: (date)	
For cause _____		
Other _____		

PRIMARY REVIEWER: J. Lee

BRANCH: II

INITIAL: P. Lee

DATE: 11-3-00

TEAM LEADER: SG Nerurkar

BRANCH: II

INITIAL: [Signature]

DATE: 11/9/2000

DIRECTOR, DIVISION OF BIOEQUIVALENCE: DALE P. CONNER, Pharm. D.

INITIAL: Barbara M. Sant DATE: 11/29/00

CC: ANDA 75-250  
ANDA DUPLICATE  
DIVISION FILE  
HFD-651/ Bio Drug File  
HFD-650/ Reviewer

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Endorsements: (Final with Dates)

HFD-655/ JLee *f.f.* 11/2/00

HFD-655/ Bio team Leader

*for* HFD-650/ D. Conner *Bmg* 11/29/00

*[Signature]* 11/9/00

BIOEQUIVALENCY - ACCEPTABLE

submission date: May 26, 2000

6. **WAIVER** (WAI)

Strengths: 15 mg/5 ml

Outcome: **AC**

7

Outcome Decisions: **AC** - Acceptable

WinBio Comments:

Waiver granted per 21 CFR 320.24 (b) (6)