CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 76-458

BIOEQUIVALENCE REVIEW(S)

FLUOXETINE
ORAL SOLUTION, USP
20 mg (base)/5 mL
ANDA 76-458
Reviewer: F. Nouravarsani
76458W0702.doc

Par Pharmaceutical, Inc.
Spring Valley, NY
Submission Date:
July 15, 2002
September 10, 2002 (NC)

REVIEW OF A WAIVER REQUEST

INTRODUCTION:

Par Pharmaceutical, Inc. submitted an original ANDA for its test product, 20 mg (base)/5 mL Fluoxetine Oral Solution USP, and requested a waiver of bioequivalence study requirements based on 21 CFR 320.22(b)(3).

Reference Listed Drug (RLD) Product (Electronic Orange Book):

- Prozac® (Fluoxetine Hydrochloride) oral Solution, 20 mg (base)/5 mL by Lilly (NDA 20-101).
- The above listed product is coded AA.

The Following Information Is Found In The PDR (Electronic):

Prozac® (Fluoxetine Hydrochloride) is an antidepressant for oral administration.

The Oral Solution of Prozac® is manufactured by Eli Lilly and Company for Dista Products Company.

Fluoxetine Hydrochloride is a white to off-white crystalline solid with a solubility of 14 mg/mL in water.

Systemic Bioavailability: In man, following a single oral 40-mg dose, peak plasma concentrations of Fluoxetine are observed from 15 to 55 ng/mL after 6 to 8 hours.

The Oral Solution, Pulvule, Tablet, and Prozac® Weekly™ Capsule dosage forms of Fluoxetine are bioequivalent. Food does not appear to affect the systemic bioavailability of Fluoxetine, although it may delay its absorption by 1 to 2 hours, which is probably not clinically significant. Thus, Fluoxetine may be administered with or without food.

Metabolism: Fluoxetine is extensively metabolized in the liver to Norfluoxetine and a number of other unidentified metabolites. The only identified active metabolite, Norfluoxetine, is formed by demethylation of Fluoxetine.

Accumulation and Slow Elimination: The relatively slow elimination of Fluoxetine (elimination half-life of 1 to 3 days after acute administration and 4 to 6 days after chronic administration) and its active metabolite, Norfluoxetine (elimination half-life of 4 to 16 days after acute and chronic administration), leads to significant accumulation of these active species in chronic use and delayed attainment of steady state, even when a fixed dose is used.

Dosage and Administration: A dose of 20 mg/day, administered in the morning, is recommended as the initial dose for treatments of depression and obsessive-compulsive disorder. **Doses above 20 mg/day may be administered on a once a day (morning) or b.i.d. schedule (i.e., morning and noon) and should not exceed a maximum dose of 80 mg/day. The recommended dose for treatment of bulimia nervosa is 60 mg/day, administered in the morning.**

Therapy with prozac® may be continued for **several months or longer.**

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of trade secret and/or

confidential commercial

information from

BIOEQUIVALENCE REVIEW

COMMENTS:

1. Fluoxetine Oral Solution is listed in the USP 26/NF 21 (Electronic). The USP Fluoxetine Oral Solution contains an amount of Fluoxetine Hydrochloride equivalent to not less than 90.0 percent and not more than 110.0 percent of the labeled amount of fluoxetine. It may contain one or more preservatives. Its range of pH is 2.5 - 4.5.

The firm reported a pH of 3.5 for the test product (Volume B1.2, Page 628).

2. The Division of Bioequivalence currently grants a waiver of in vivo bioequivalence study requirements for Fluoxetine Oral Solution, 20 mg (base)/5 mL based on 21 CFR 320.22(b)(3).

3. [redacted]

Par Pharmaceutical, Inc. was contacted by a telephone call from the DBE on 12/05/02, and was asked to submit the concentration of each ingredient [redacted] responded by FAX on 12/06/02, and provided the requested data.

4. The amount of **"Sucrose"** in the test product is [redacted]% of the amount of "Sucrose" in the RLD product.

5. The amount of **"Glycerin"** in the formulation of the test product is [redacted] the amount of "Glycerin" in the formulation of the RLD product.

The labeling of the RLD product states that a dose of 20 mg/day, administered in the morning, is recommended as the initial dose for treatments of depression and obsessive-compulsive disorder. **Doses above 20 mg/day may be administered on a once a day (morning) or b.i.d. schedule (i.e., morning and noon) and should not exceed a maximum dose of 80 mg/day. The recommended dose for treatment of bulimia nervosa is 60 mg/day, administered in the morning. Therapy with prozac® may be continued for <u>several months or longer</u>.**

Therefore, consumption of Glycerin from the test product (——— mg/5 mL in a 20 mg/day dose or ——— mg/20 mL in a 80 mg/day dose) would be significantly higher than consumption of Glycerin from the RLD product (——— mg/5 mL in a 20 mg/day dose or ——— mg/20 mL in a 80 mg/day dose) (Attachment One).

6. The inactive ingredients, which are present in the flavors of "———Natural Peppermint Extract ——— " and "——————— Artificial Sweet Cream" are listed in the 21 CFR.

The substances listed under 21 CFR, 172.515 (Synthetic Flavoring Substances and adjuvants) are listed under PART 172 "Food Additives permitted for direct addition to food for human consumption".

The substance listed under 21 CFR 182.20 (Essential Oils, . . .) and the substances listed under 21 CFR 182.60 (Synthetic Flavoring Substances and Adjuvants) are listed under PART 182 "Substances Generally Recognized As Safe".

The substances listed under 21 CFR 184.1278, 184.1666, and 184.1293 are listed under PART 184 "Direct Food Substances Affirmed As Generally Recognized As Safe".

DEFICIENCIES:

1. The amount of Glycerin (——— mg/5 mL in a 20 mg/day dose or ——— mg/20 mL in a 80 mg/day dose) in the formulation of the test product is significantly different from the amount of Glycerin in the formulation of the RLD product.

The amount of Sucrose (——— mg/5 mL in a 20 mg/day dose or ——— mg/20 mL in a 80 mg/day dose) in the formulation of the test product is also different from the amount of Sucrose in the formulation of the RLD product.

The firm should consider to reformulate its test product, since the above differences may affect the bioequivalency of the test product to the RLD product.

2. The inactive ingredients, which are present in the flavors of " ——— Natural Peppermint Extract ——— " and " ——————— Artificial Sweet Cream" are listed in the 21 CFR.

However, the firm should submit information to support that using the proposed amounts of these ingredients daily for several months or longer, as it has been recommended in the labeling of the RLD product, either as a minimum amount (in a 20 mg/5 mL dose per day) or the maximum amount (in a dose of 80 mg/20 mL per day) are safe.

RECOMMENDATIONS:

1. The information submitted by Par Pharmaceutical, Inc. for its test product, Fluoxetine Oral Solution USP, 20 mg (base)/5 mL is found unacceptable by the Division of Bioequivalence.

2. The firm should be informed of the DEFICIENCIES.

Farahnaz Nouravarsani, 02/14/03

Farahnaz Nouravarsani, Ph.D.
Review Branch III
Division of Bioequivalence

RD INITIALED G. Singh
FT INITIALED G. Singh Gurjaip D Singh Date 2-14-03

Concur: _____ Date _____
Dale P. Conner, Pharm.D.
Director
Division of Bioequivalence

DO NOT CONCUR
BMcDaniel 3/31/03

F. Nouravarsani/Draft: 02-04-2003/76458W0702.doc

Attachment One:

Comparison of the amounts of "Glycerin" and "Sucrose" in the formulation of the test product with the amounts of "Glycerin" and "Sucrose" present in formulations of Fluoxetine Oral Solution, 20 mg (base)/5 mL:

	Ingredient		
NDA/ANDA	**Glycerin**		**Sucrose**
RLD, NDA #20-101: **(ORANGE BOOK)**			
TEST PRODUCT: **ANDA #76-458** **Par Pharmaceutical**			
ANDA #75-292 Nu-Pharm Inc. (ORANGE BOOK)			
ANDA #75-506 Teva Pharmaceuticals (ORANGE BOOK)			
ANDA #75-525 Hi-Tech Pharmacal CO. (ORANGE BOOK)			
——— ——— .			
ANDA #75-690 Alpharma USPD (ORANGE BOOK)			
ANDA #75-920 Mallinckrodt (ORANGE BOOK)			
ANDA #76-015 **Pharmaceutical Associates** **(ORANGE BOOK)**			
——— ———			
——— ———			
*: Amount of glycerin was calculated by the reviewer using the Specific Gravity of 1.249 reported in the USP 26/NF21.			

The amount of Glycerin (——— mg/5 mL in a 20 mg/day

dose or —— mg/20 mL in a 80 mg/day dose) in the formulation of the test product is significantly higher than the amount of Glycerin in the formulation of the RLD product. The amount of Glycerin (——— mg/5 mL in a 20 mg/day dose or ——— mg/20 mL in a 80 mg/day dose) in the ANDA 76-015 is also significantly higher than the amount of Glycerin in the RLD product. The sponsors of the above ANDAs (76-015 and 76-458) have not submitted any information to support that using the amounts of Glycerin daily for several months or longer, as it has been recommended in the labeling of the RLD product, either as a minimum amount (in a 20 mg/5 mL dose per day) or the maximum amount (in a dose of 80 mg/20 mL per day) are safe.

CC: ANDA 76-458
ANDA DUPLICATE
DIVISION FILE
FIELD COPY
HFD-658/F. Nouravarsani

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Printed in final on 02/14/03

Endorsements: (Final with Dates)
HFD-658/F. Nouravarsani, Farahnaz Nouravarsani, 02/14/03
HFD-658/G. Singh
HFD-650/D. Conner

BIOEQUIVALENCY - DEFICIENCY

SUBMISSION DATE:
7/15/2002

Waiver (W):

Strength: 20 mg (base)/5 mL

Outcome: UN

New Corres. (NC):
(9/10/2002)

Strength: 20 mg (base)/5 mL

Outcome: UN

FAX from _____
_____ :
(08/30/2002)
(12/06/2002)

Strength: 20 mg (base)/5 mL

Outcome: UN

OUTCOME DECISION: UN

WINBIO COMMENT: Unacceptable.

BIOEQUIVALENCY DEFICIENCIES TO BE PROVIDED TO THE APPLICANT

ANDA: 76-458 APPLICANT: Par Pharmaceutical, Inc.

DRUG PRODUCT: Fluoxetine Oral Solution USP
20 mg (base)/5 mL

The Division of Bioequivalence has completed its review of your submission(s) acknowledged on the cover sheet. The following deficiencies have been identified:

1. The amount of Glycerin (——— mg/5 mL in a 20 mg/day dose or ——— mg/20 mL in a 80 mg/day dose) in the formulation of your test product is significantly different from the amount of Glycerin in the formulation of the RLD product.

The amount of Sucrose (——— mg/5 mL in a 20 mg/day dose or ——— mg/20 mL in a 80 mg/day dose) in the formulation of your test product is also different from the amount of Sucrose in the formulation of the RLD product.

Please consider to reformulate your test product, since the above differences may affect the bioequivalency of your test product to the RLD product.

2. The inactive ingredients, which are present in the flavors of "——— Natural Peppermint Extract ——— and "——————— Artificial Sweet Cream" are listed in the 21 CFR.

However, please submit information to support that using the proposed amounts of these ingredients daily for several months or longer, as it has been recommended in the labeling of the RLD product, either as a minimum amount (in a 20 mg/5 mL dose per day) or the maximum amount (in a dose of 80 mg/20 mL per day) are safe.

3/31/03

Sincerely yours,

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

MAR 31 2003

Fluoxetine
Oral Solution, USP
20 mg (base)/5 mL
ANDA 76-458
Reviewer: Gur J.P. Singh
File #V:\FIRMSNZ\PAR\LTRS&REV\76458AD702.doc

Par Pharmaceutical, Inc.
Spring Valley, NY
Submission Date:
July 15, 2002
September 10, 2002

An Addendum to the Bioequivalency Review

The firm had submitted a request for the waiver of in vivo bioequivalence study requirements for its flouxetine oral solution USP 20 mg/mL. The request has been reviewed. Based on the attached review, the bioequivalence reviewer found deficiencies related to the amount of glycerin and sucrose and the proposed amounts of inactive ingredients present in the flavors of '—— natural Peppermint Extract —— ' and " ———————— '

The above deficiencies were discussed in meetings with the DBE senior management on February 24 and March 31, 2003. In those meetings it was recognized that:

- The amount of glycerin in the test product (—— mg) is less than the amount (——— mg) present in a marketed generic fluoxetine oral solution, 20 mg/ 5 mL (ANDA 76-015,).
- The DBE has previously accepted fluoxetine oral solutions with amount of sucrose greater or less than that used in the test product.
- As stated in the attached review, the inactive ingredients present in the flavors are listed under (a) 21 CFR 172.515, (b) under 21 CFR 182 (Substances generally recognized as safe, and (c) under 21 CFR 184 (Direct food substances affirmed as generally recognized as safe). The ingredients also have FEMA numbers

Based on the foregoing, it was determined the test product formulation is acceptable for a waiver of in vivo bioequivalence study requirements.

Recommendation:

The Division of Bioequivalence agrees that the information submitted by Par Pharmaceutical Inc., demonstrates that the test product, Fluoxetine Oral Solution, 20 mg/5 mL falls under 21 CFR Section 320.22(b)(3) of the Bioavailability/Biequivalence Regulations. The waiver of *in vivo* bioequivalence study for the proposed test product is granted. From the bioequivalence point of view, the Division of Bioequivalence deems the test oral solution formulation to be bioequivalent to Lilly's Prozac^{R} Oral Solution, 20 mg Base/5 mL.

The firm should be informed of the above recommendation

Gur J. P Singh, Ph.D.
Team Leader, Review Branch III
Division of Bioequivalence

Concur: _____ Date: 3/31/03
Barbara Davit, Ph.D.
Deputy Director
Division of Bioequivalence

Concur: _____ Date: 3/31/03
Dale P. Conner, Pharm.D.
Director
Division of Bioequivalence

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 75-458 APPLICANT: Par Pharmaceutical Inc.

DRUG PRODUCT: Fluoxetine Oral Solution USP, 20 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,

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

CC: ANDA #75-458
ANDA DUPLICATE
DIVISION FILE
HFD-651/ Bio Drug File
HFD-650/ Reviewer

3/31/03

Printed in final on ~~11/19/1999~~
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PAR 75458

Endorsements: (Final with Dates)
HFD-650/ Bio Reviewer, F Nouravarsani
HFD-658/ Bio Team Leader, GJP Singh GJPS 3-31-03
~~Team~~ HFD-650/ Bio Deputy Director, B. Davit BWD 3/31/03
HFD-650/ Bio Director, D. Conner 3/31/03

OFFICE OF GENERIC DRUGS
DIVISION OF BIOEQUIVALENCE

76-459

ANDA #~~75-690~~ SPONSOR : Par Pharmaceutical Inc.

DRUG AND DOSAGE FORM : **Fluoxetine Oral Solution**

STRENGTH(S) : 20 mg /5 mL

TYPES OF STUDIES : N/A

CLINICAL STUDY SITE(S) : N/A

ANALYTICAL SITE(S) : **N/A**

STUDY SUMMARY : The formulation is acceptable based on CFR 320.22 (b)(3)

DISSOLUTION : N/A

DSI INSPECTION STATUS

Inspection needed: YES / NO	Inspection status:	Inspection results:
First Generic __No_ New facility _____ For cause _____ Other _____	Inspection requested: (date) Inspection completed: (date)	

TEAM LEADER REVIEW BRANCH III: Gur J.P. Singh Ph.D.

INITIAL : Gurjpsingh DATE : 3-31-03

DEPUTY DIRECTOR, DIVISION OF BIOEQUIVALENCE, : Barbara M. Davit, Ph.D.

INITIAL : Barbara M Davit DATE : 3/31/03

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

INITIAL : JR **DATE :** 3/31/03