REFERENCE: ANDA 74-803
FLUOXETINE CAPSULES, USP 20 MG
AND SUPPLEMENTAL APPLICATION
FLUOXETINE CAPSULES, USP 10 MG

RESPONSE:

The smallest container/closure system included in the original application is for the package size of 100s using a 60 cc HDPE bottle with a 33 mm metal cap (Barr Code 07-0001). In accordance with your suggestion, Barr is proposing an additional container/closure system for the package size of 100s of a 60 cc HDPE bottle with a 33 mm SAF-LOK cap (Barr Code 07-0089) supplied by
The SAF-LOK cap combines a metal inner shell with a plastic, child-resistant outer shell and therefore provides the additional function of child-resistance. The SAF-LOK cap is equivalent in design, material construction (the inner shell, inner liner and inner seal of both caps are identical), and functionality to that of the 33 mm metal cap used to package this product. The SAF-LOK cap removal torque ranges fall within Barr's established ranges. Therefore, the stability data submitted in the application supports both the existing 33 mm metal cap (Barr Code 07-0001) and the proposed 33 mm SAF-LOK cap (Barr Code 07-0089). Please note that the change in Barr Code Number for the SAF-LOK cap was implemented for internal tracking purposes.

Enclosed please find the following documentation to support this additional container/closure system (see Pages 0135 through 0146):

- Packaging Master, MC# 0877013 (2/3/98)
- New Component Code Number Sheet for the cap (Barr code 07-0089)
- Barr Laboratories QA Packaging Component Inspection Report for the 33 mm SAF-LOK cap (Barr code 07-0089)
- Engineering diagram of the cap
- Authorization letter to reference DMF
- Specification sheet from
- Authorization letter to reference DMF for the PS 22 innerseal and the X-14 liner
- Technical data from on their Foamseal PS 22 liner
- Technical data from on their Closure X-14 Liner

REFERENCE: ANDA 74-803
FLUOXETINE CAPSULES, USP 20 MG
AND SUPPLEMENTAL APPLICATION
FLUOXETINE CAPSULES, USP 10 MG

Please note Barr has also updated its Packaging Master for the 100s size using the 60 cc bottle with a 33 mm metal cap as follows (see Page 0147):

- Added "USP" to product name (active raw material and finished product) to agree with USP 23, Seventh Supplement monographs
- Changed system for assigning revision number to make the number more informative, this includes a change to a Master Control Number ("MC#"). The first four numeric digits specify the product code, the next two numeric digits specify the packaging revision, and the last numeric digit specifies the site of packaging. For example,

0873	=	Product Code for Fluoxetine Capsules, USP 20 mg
01	=	Revision 1
3	=	

Barr will correct the Average Weight recording on both Packaging Masters to read "Average Capsule Weight" instead of "Average Tablet Weight" and submit the update in the next Annual Report.

COMMENT:

5. REGARDING LABORATORY CONTROLS:

A. REGARDING EXHIBIT LOT #5R87719:

I. PLEASE INDICATE THE MAKE, MODEL AND PRINCIPLE OF OPERATION (VERTICAL OR HORIZONTAL) OF THE HIGH SHEAR MIXERS.

REFERENCE: ANDA 74-803
FLUOXETINE CAPSULES, USP 20 MG
AND SUPPLEMENTAL APPLICATION
FLUOXETINE CAPSULES, USP 10 MG

RESPONSE:

As stated in the response to Comment 3A, the make, model and principle of operation of the high shear mixer is as follows:

Manufacturer:
Model: **Gral 600**
Mode of Operation: **Vertical**

COMMENT:

II. PLEASE INDICATE NOMINAL ENCAPSULATION SPEED AND ENVIRONMENTAL PARAMETERS.

RESPONSE:

As stated in the response to Comment 3C, the nominal encapsulation speed will be recorded and validated as part of Barr's normal process validation. The environmental parameters for lot #5R87719 were as follows: temperature limit: 59°F – 86°F, humidity: NMT %.

COMMENT:

B. REGARDING IN-PROCESS CONTROLS:

I. PLEASE SUBMIT SPECIFICATIONS FOR MONITORING BLEND UNIFORMITY DURING NORMAL PRODUCTION OF DRUG PRODUCT ALONG WITH ANY APPLICABLE JUSTIFICATION OR SUPPORTING DATA.

REFERENCE: ANDA 74-803
FLUOXETINE CAPSULES, USP 20 MG
AND SUPPLEMENTAL APPLICATION
FLUOXETINE CAPSULES, USP 10 MG

RESPONSE:

Barr Laboratories, Inc. commits to perform in-process testing for blend content uniformity. After sufficient data has been collected for the in-process testing (e.g., blend), Barr will submit a prior approval supplement before deleting testing at the blend stage.

The Analytical Specification Test Record used for release and the Acceptance Tests For In-Process and Finished Products have been revised to include blend content uniformity testing and specifications (see Pages 0148 through 0178).

COMMENT:

II. YOUR MASTER BATCH RECORD INDICATED THAT CAPSULE FILL WEIGHT WILL BE MONITORED BY AGGREGATE FILL WEIGHT AND NOT INDIVIDUAL FILL WEIGHTS, WHICH WILL NOT PROVIDE CONTROL OVER FILL WEIGHT VARIANCE. PLEASE SUBMIT SPECIFICATIONS FOR IN-PROCESS MONITORING OF INDIVIDUAL CAPSULE FILL WEIGHTS, ALONG WITH ANY NECESSARY JUSTIFICATION AND SUPPORTING DATA TO DEMONSTRATE ACCEPTABLE CAPSULE FILL WEIGHT AS WELL AS FILL WEIGHT VARIANCE.

RESPONSE:

Barr routinely monitors the capsule fill weight in two ways; aggregate and individual fill weights. While Barr personnel record the aggregate capsule fill weight on the manufacturing master (encapsulation monitoring record), they also monitor the individual capsule fill weights periodically throughout the encapsulation operation. These weights are recorded on individual weight tapes, which are then attached to the batch record. Enclosed on Pages 0179 through 0211 please find copies of the weight tapes containing the individual capsule fill weights for the submission batch as well as a summary report of all the weight tapes. The guidelines for determining acceptable capsule weights are covered by a standard operating procedure.

REFERENCE: ANDA 74-803
FLUOXETINE CAPSULES, USP 20 MG
AND SUPPLEMENTAL APPLICATION
FLUOXETINE CAPSULES, USP 10 MG

COMMENT:

C. WE NOTE THAT YOU HAVE INCLUDED COPIES OF YOUR VALIDATION SOP'S AS WELL AS VALIDATION STUDY RESULTS FOR EXHIBIT LOT #5R87719. WHILE THE VALIDATION DATA SUBMITTED MAY BE USEFUL FOR CLARIFICATION PURPOSES, PLEASE NOTE THAT APPROVAL OF THE APPLICATION DOES NOT INCLUDE APPROVAL OF SOP'S OR VALIDATION PROTOCOLS AND REPORTS WHICH ARE THE RESPONSIBILITY OF THE FIELD INVESTIGATOR.

RESPONSE:

Your comment is acknowledged.

COMMENT:

D. SECTION 1 OF YOUR ACCEPTANCE TESTS FOR IN-PROCESS & FINISHED PRODUCTS (METHOD NO. TM-419B) INCLUDES DESCRIPTION AND REFERENCE TO A 10 MG CAPSULE, WHICH HAS NOT BEEN INCLUDED IN THIS APPLICATION. PLEASE REMOVE ALL REFERENCES TO THE 10 MG CAPSULE FROM THE SPECIFICATIONS AND PROCEDURES IN THIS APPLICATION.

RESPONSE:

At this time Barr is amending it's application for Fluoxetine Capsules, USP 20 mg with the additional 10 mg strength. Therefore, Barr's Acceptance Tests for In-Process & Finished Products will continue to reference both the 10 mg and 20 mg strengths (see Part II for information on the 10 mg strength).

REFERENCE: ANDA 74-803 Page 20
FLUOXETINE CAPSULES, USP 20 MG
AND SUPPLEMENTAL APPLICATION
FLUOXETINE CAPSULES, USP 10 MG

COMMENT:

E. YOUR SPECIFICATIONS FOR RELATED COMPOUNDS AND MOISTURE ("REPORT RESULTS") ARE UNACCEPTABLE. PLEASE REVISE THESE SPECIFICATIONS TO INCLUDE LIMITS BASED ON DATA ACCRUED TO DATE.

RESPONSE:

Barr revised its release and stability specifications for Related Compounds and Moisture to include limits.

Specifically, Barr has set the following Related Compound Specifications based on the release data and 24 months of CRT stability data for the 10 mg and 20 mg strengths accrued to date:

Related Compounds Tests	Limits	
p-Triflouromethylphenol (Barr Impurity III)	NMT	%
4-Chlorobenzotriflouride (Barr Impurity IV)	NMT	%
Individual Unknown Impurities (excluding Impurities I and II)	NMT	%
Total Known and Unknown Impurities (excluding Impurities I and II)	NMT	%

REFERENCE: ANDA 74-803
FLUOXETINE CAPSULES, USP 20 MG
AND SUPPLEMENTAL APPLICATION
FLUOXETINE CAPSULES, USP 10 MG

Barr has adopted the USP 23, Supplement Seven method and specifications for related compounds. However, Barr Impurity I and Impurity II will be excluded from the calculations of the Individual Unknown Impurities and Total Known and Unknown Impurities for the finished product since they are process related and are being monitored in the drug substance under tight USP specifications. The Federal Register Notice/Volume 61, No. 54/Tuesday, March 19, 1996 provides the ICH Draft Guidelines on Impurities in New Drug Products and further supports the exclusion of Barr Impurity I and Impurity II. Specifically it states, "The specification for a new drug product should include limits for degradation products expected to occur under recommended storage conditions."

A summary of Barr's stability data through 24 months also supports Barr Impurity I and Impurity II as strictly process related compounds and not degradation products (see attached memorandum, "Justification to Exclude Two Process Related Compounds from the Calculation of Total Related Compounds in Fluoxetine Hydrochloride Capsules, USP 20 mg" dated 2/4/98, Pages 0212 through 0214).

Barr previously set a moisture specification of NMT % (only for stability testing) in its Acceptance Test For In-Process and Finished Products, TM-419C. This test method was submitted to the Division of Bioequivalence in a 6/6/97 response letter to FDA bioequivalence letter dated 6/10/96. Barr has since added a moisture specification of NMT % for release and revised the moisture specification for stability to NMT % based on additional data accrued (see memorandum on Pages 0212 through 0214 providing the rationale for this specification).

Barr has updated its Acceptance Test For In-Process and Finished Products, corresponding QC Analytical Specification Test Record, Marketed Product Stability Specification Sheet, and Stability Protocol accordingly (see Pages 0148 through 0178 and 0215 through 0221).

REFERENCE: ANDA 74-803
FLUOXETINE CAPSULES, USP 20 MG
AND SUPPLEMENTAL APPLICATION
FLUOXETINE CAPSULES, USP 10 MG

COMMENT:

F. YOUR FINAL PRODUCT SPECIFICATIONS (SPEC. #0877 - REV. 2) FAIL TO INCLUDE MOISTURE AS SHOWN IN THE METHODS (METHOD NO. TM-419B). PLEASE REVISE THE FINAL PRODUCT SPECIFICATIONS TO INCLUDE MOISTURE OR SUBMIT JUSTIFICATION FOR THE DELETION.

RESPONSE:

Barr has revised its finished product specifications to include the moisture specification of NMT %. Enclosed on Pages 0176 through 0178 please find a copy of Barr's QC Analytical Specification Test Record. In conjunction with the change, the statement "for stability testing only" originally placed after the moisture test in the Acceptance Test For In-Process and Finished Products has been removed (see Page 0149).

REFERENCE: ANDA 74-803
FLUOXETINE CAPSULES, USP 20 MG
AND SUPPLEMENTAL APPLICATION
FLUOXETINE CAPSULES, USP 10 MG

COMMENT:

6. REGARDING STABILITY:

YOU HAVE INDICATED THAT A LIGHT YELLOW COLORATION WAS NOTED IN THE GRANULATION WHERE THE GRANULATION WAS IN CONTACT WITH THE HARD GELATIN CAPSULES FOR SEVERAL OF THE SAMPLES TAKEN DURING ACCELERATED STABILITY TESTING AT ONE AND THREE MONTHS. CLOSE REVIEW OF THE INDIVIDUAL CAPSULE DISSOLUTION RESULTS SUBMITTED REVEALED INDIVIDUAL SAMPLES WHICH EXHIBITED DISSOLUTION VALUES AS LOW AS % WHEN THE MAJORITY OF THE CAPSULES EXHIBITED VALUES GREATER THAN %. PLEASE DISCUSS ANY POSSIBLE RELATIONSHIP BETWEEN THE APPARENT LOW VALUES FOR DISSOLUTION AND THE YELLOW COLORATION, AS WELL AS THE POTENTIAL FOR PELLICLE FORMATION. ALL ROOM TEMPERATURE STABILITY DATA ACCRUED TO DATE SHOULD BE SUBMITTED IN SUPPORT OF YOUR DISCUSSION.

RESPONSE:

Barr has conducted an extensive investigation into the possible cause(s) of the "light yellow coloration" found in the capsule contents in both CRT and accelerated stability samples and its possible impact on dissolution. Multiple hypotheses were explored including pellicle formation and the Maillard-reaction. In conclusion, as supported by the 24 month CRT stability data, the "light yellow coloration" of the capsule content has no adverse impact on the potency, impurity level or dissolution rate. In fact, no trends were observed in the CRT data up to 24 months and all stability results (including dissolution) for both the 10 mg and 20 mg strengths easily met specifications after 24 months storage under CRT conditions.

Enclosed please find Barr's Stability Summary Report RD97-224A dated February 20, 1998 and attached memorandum discussing this issue (Pages 0222 through 0251).

REFERENCE: ANDA 74-803 Page 24
FLUOXETINE CAPSULES, USP 20 MG
AND SUPPLEMENTAL APPLICATION
FLUOXETINE CAPSULES, USP 10 MG

Enclosed in Part II, Section XVII of this Amendment is a copy of Barr's Stability Summary Report through 24 months CRT stability storage for the 10 mg strength.

COMMENT:

B. LABELING DEFICIENCIES

1. GENERAL COMMENTS

WE RECOGNIZE YOUR INTENT TO MARKET THIS PRODUCT BEFORE THE PATENT EXPIRATION DATES OF THE LISTED DRUG. PLEASE NOTE, HOWEVER, THAT AFTER FEBRUARY 28, 1997, THE INFORMATION REGARDING OBSESSIVE COMPULSIVE DISORDER MUST BE INCLUDED IN YOUR LABELING.

RESPONSE:

Your comment is acknowledged. Barr has updated its labeling to include the information regarding obsessive compulsive disorder. A copy of the updated Insert is enclosed on Pages 0257 through 0267 in response to Comment 3.

COMMENT:

2. CONTAINER (100'S)

THE STRENGTH OF THIS PRODUCT IS EXPRESSED IN TERMS OF FLUOXETINE, AND WE SUGGEST CLARIFYING IT AS SUCH BY ADDING AN ASTERISK AFTER THE EXPRESSION OF STRENGTH ON THE MAIN PANEL AS FOLLOWS:

FLUOXETINE HYDROCHLORIDE CAPSULES

20 mg*

CAUTION: Federal law prohibits dispensing without prescription.

100 CAPSULES

*Each capsule contains: Fluoxetine Hydrochloride, equivalent to 20 mg fluoxetine.

RESPONSE:

Barr has updated its container labels to include an asterisk after the expression of strength on the main panel as suggested above. Please find (4) four draft container labels for the 100s package size on Pages 0252 through 0255. Also enclosed on Page 0256 is a side by side comparison of Barr's 20 mg strength new proposed container label versus the old proposed container label submitted with the application.

COMMENT:

3. INSERT

a. General

i. We recognize your intent to market this product before the patent expiration dates of the listed drug. Please note, however, that after February 28, 1997, the information regarding obsessive compulsive disorders must be included in your labeling.

ii. Italicize "*in vivo*" and "*in vitro*" where they appear in the insert labeling.

b. DESCRIPTION

i. Regarding the use of the phrase "and other ingredients". We refer you to USP XXIII, General Information, Chapter <1091>, Labeling of Inactive Ingredients, which states that a trade secret may be omitted from the list of inactive ingredients if the list states "and other ingredients". The chapter further states that an ingredient in considered to be a trade secret only if its presence confers a significant competitive advantage AND its identity cannot be ascertained by the use of modern analytical technology. If you still elect to use the phrase "and other ingredients" please provide supporting data concerning the "trade secret" status of these ingredients, if not, revise your labeling at the time of next printing to include all ingredients in the list of inactive ingredients. Also, include any dye(s) with your listing of inactive ingredients.

ii. Revise the first sentence in the third paragraph to read "Each capsule, for oral administration, contains..."

c. CLINICAL PHARMACOLOGY (Clinical Trials)

Revise to read, "fluoxetine" rather than "fluoxetine hydrochloride" throughout this subsection.

d. INDICATIONS AND USAGE

i. Delete the subsection heading, "Depression".

ii. Except in the first sentence, revise to read, "fluoxetine" rather than "fluoxetine hydrochloride" throughout this section.

e. CONTRAINDICATIONS

i. Except in the first sentence, revise to read, "fluoxetine" rather than "fluoxetine hydrochloride" throughout this section.

ii. Make the following revision in the penultimate sentence, "...within a minimum of ...".

iii. Make the following revision in the last sentence, "...doses [see *Accumulation and Slow Elimination* under **CLINICAL PHARMACOLOGY**]) should ...".

f. WARNINGS

In the last sentence, revise to read, "fluoxetine" rather than "fluoxetine hydrochloride":

g. PRECAUTIONS

i. Except in the following locations, revise to read, "fluoxetine" rather than "fluoxetine hydrochloride":

- the first sentence of this section.
- the "Suicide" subsection of the "General" subsection.
- the first sentence of the "Use in Patients with Concomitant Illness" subsection of the "General" subsection.
- the "Pregnancy" subsection.

ii. Revise the "Other Antidepressants" subsection of the "Drug Interactions" subsection as follows:

Other Antidepressants: In two studies, previously stable plasma levels of imipramine and desipramine have increased greater than 2 to 10-fold when fluoxetine has been administered in combination. This influence may persist for three weeks or longer after fluoxetine is discontinued. Thus, the dose of tricyclic antidepressant (TCA) may need to be reduced and plasma TCA concentrations may need to be monitored temporarily when fluoxetine is coadministered or has been recently discontinued (see *Accumulation and Slow Elimination* under **CLINICAL PHARMACOLOGY**, and *Drugs Metabolized by P450IID6* under Drug Interactions of **PRECAUTIONS**).

iii. Drug Interactions (Potential Effects of Coadministration of Drugs Tightly Bound to Plasma Proteins)

Revise to read "...warfarin...", rather than "Coumadin...".

iv. Nursing Mothers

Make the following revision in the last sentence, "...were 340 nm/mL...".

v. Usage in Children

Revise the section heading to read, Pediatric Use" and make the following revision, "...in pediatric patients have....".

h. ADVERSE REACTIONS

i. Except in the following locations, revise to read, "fluoxetine" rather than "fluoxetine hydrochloride":

- the first sentence of the "Commonly Observed" subsection.
- the first sentence of the "Associated with Discontinuation of Treatment" subsection.

- the penultimate subsection title.

ii. Incidence of Controlled Clinical Trials

A) Revise the first sentence to read, "The table that follows enumerates...".

B) Make the following revision in the first sentence of the second paragraph, "...that these figures cannot...".

C) Delete the title, "TABLE I".

iii. Other Events Observed During Premarketing Evaluation of Fluoxetine Hydrochloride

A) Make the following revision in the third sentence of the second paragraph, "...already listed in the table, those...".

B) Use formatting to increase the prominence of the terms, "frequent", "infrequent", and "rare".

iv. Postintroduction Reports

Revise as follows:

...the following: aplastic anemia, atrial fibrillation, cerebral vascular acceident, cholestatic jaundice, confusion, dyskinesia (including, for example, a case of buccallingual-masticatory syndrome with involuntary tongue protrusion reported to develop in a 77-year-old female after 5 weeks of fluoxetine therapy and which completely resolved over the next few months following drug discontinuation), eosinophilic dermatitis, gynecomastia, heart arrist hepatic failure/necrosis, hyperprolactinemia, immune-related hemolytic anemia, kidney failure, misues/abuse, movement disorders developing in patients with risk factors including drugs associated with such events and worsening of preexisting movement disorders, neuroleptic malignant syndrome-like events, pancreatitis, pancytopenia, priapism, pulmonary embolism, OT prolongation, sudden unexpected death, suicidal ideation, thrombocytopenia, thrombocytopenic purpura, baginal bleeding after drug withdrawal, and violent behaviors.

i. DRUG ABUSE AND DEPENDANCE

Except in the first sentence, revise to read, "fluoxetine" rather than "fluoxetine hydrochloride" throughout this section.

j. OVERDOSAGE

Except in the third paragraph of the "Management of Overdose" subsection, revise to read, "fluoxetine" rather than "fluoxetine hydrochloride".

k. DOSAGE AND ADMINISTRATION

i. Delete the subsection heading "Depression". Please note that "Initial Treatment" and "Maintenance/Continuation/ Extended Treatment" should appear with the same prominence as other subsections.

ii. Add the following text as the last two subsections:

REFERENCE: ANDA 74-803 Page 31
FLUOXETINE CAPSULES, USP 20 MG
AND SUPPLEMENTAL APPLICATION
FLUOXETINE CAPSULES, USP 10 MG

Switching Patients to a Tricyclic Antidepressant (TCA):

Dosage of a TCA may need to be reduced, and plasma TCA concentrations may need to be monitored temporarily when fluoxetine is coadministered or has been recently discontinued (see *Other Antidepressants* under Drug Interactions of **PRECAUTIONS**).

Switching Patients to or from Monoamine Oxidase Inhibitor:

At least 14 days should elapse between discontinuation of an MAOI and initiation of therapy with fluoxetine. In addition, at least 5 weeks, perhaps longer, should be allowed after stopping fluoxetine before starting an MAOI (see **CONTRAINDICATIONS** and **PRECAUTIONS**).

1. HOW SUPPLIED

Clarify that "20 mg" is equivalent to 20 mg fluoxetine and not of fluoxetine hydrochloride.

Please revise your container labels and package insert labeling, as instructed above, and submit final print labeling.

RESPONSE:

Enclosed on Pages 0257 through 0300 please find four (4) draft package brochures, which have been revised according to the Agency's recommendation. Also enclosed is a side by side comparison of Barr's updated proposed labeling versus the old proposed labeling submitted in the original application (see Pages 0301 through 0342). A copy of the reference product's brochure is also attached for informational purposes on Pages 0343 through 0351.

REFERENCE: ANDA 74-803 Page 32
FLUOXETINE CAPSULES, USP 20 MG
AND SUPPLEMENTAL APPLICATION
FLUOXETINE CAPSULES, USP 10 MG

COMMENT:

TO FACILITATE REVIEW OF YOUR NEXT SUBMISSION, AND IN ACCORDANCE WITH 21 CFR 314.94(A) (8) (IV), PLEASE PROVIDEA SIDE-BY-SIDE COMPARISON OF YOUR PROPOSED LABELING WITH YOUR LAST SUBMISSION WITH ALL DIFFERENCES ANNOTATED AND EXPLAINED.

RESPONSE:

Barr has provided a side-by-side comparison of their proposed labeling in accordance with 21 CFR 314.94(A) (8) (IV) (see Page 0256 and Pages 0301 through 0342).

REFERENCE: ANDA 74-803
FLUOXETINE CAPSULES, USP 20 MG
AND SUPPLEMENTAL APPLICATION
FLUOXETINE CAPSULES, USP 10 MG

Part II: Additional strength to pending application: Fluoxetine Capsules, USP 10 mg

The information on the additional 10 mg strength is provided in duplicate, both as an archival copy, and a review copy. The archival copy of the supplemental application is contained in blue binders and consists of 3 volumes. The review copy is divided into two parts. The chemistry, manufacturing and controls part of the review copy is contained in red binders and consists of 3 volumes. The bioequivalence part of the review copy is contained in orange binders and consists of 1 volume. The format of this application is in accordance with Office of Generic Drugs, Policy and Procedure Guide #30-91. The information submitted in this application is also in accord with the October 14, 1994 communication from Dr. Janet Woodcock, Director CDER.

An identical copy of this Major Amendment has been provided to the New Jersey District Office. A document certification is attached.

This completes the present response to the Agency's deficiency letter dated *July 9, 1996*. If you have any questions, please contact me by phone at (914) 353-8432 or by fax at (914) 353-3859.

Sincerely,

BARR LABORATORIES, INC.

/S/
Christine Mundkur
Regulatory Counsel and Director of
Regulatory Affairs

CM/egn
Enclosure

p:\ronnie\anda\fluoxeti.doc\respon.doc\110796.doc
7/11/97: 7/16/97

Barr Laboratories, Inc.

2 Quaker Road P.O. Box 2900 Pomona, NY 10970-0519 • 914/362-1100

August 18, 1998

ORIG AMENDMENT
N/AB

Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation & Research
FOOD AND DRUG ADMINISTRATION
Metro Park North II
7500 Standish Place
Room 150
Rockville, MD 20855

Via Facsimile
Via Federal Express

BIOEQUIVALENCE FACSIMILE AMENDMENT

REFERENCE: ANDA 74-803
FLUOXETINE CAPSULES, USP 10 MG AND 20 MG

Reference is made to our pending Abbreviated New Drug Application under Section 505(j) of the Federal Food, Drug and Cosmetic Act for Fluoxetine Capsules, USP 10 mg and 20 mg submitted on December 9, 1995.

Reference is also made to the telephone conversation between Karen Bonomi, Regulatory Affairs, Barr Laboratories, Inc. and Lizzie Sanchez, Project Manager, Division of Bioequivalence, OGD/FDA on August 10, 1998. During this conversation, Ms. Sanchez requested information regarding Barr's *In-Vitro* Comparative Dissolution Report No. RD98-034A for Fluoxetine Capsules, USP 10 mg that was submitted in the Major Amendment dated June 15, 1998. Accordingly, Barr is hereby providing the following information:

Barr Laboratories, Inc. originally conducted *in vitro* comparative dissolution testing on Barr's 10 mg submission batch 5R87618 compared to the Dista reference product 8NE08M in June and July 1995 (see Attachment 1). This original comparative dissolution testing for both the 10 mg and 20 mg strengths was conducted in 0.1 *N* HCl as the medium. In a January 8, 1998 facsimile comment letter, however, the Division of Bioequivalence requested Barr to change the dissolution medium from 0.1 *N* HCl to water. In addition, the Division requested Barr to reconduct the in vitro dissolution comparison simultaneously for both the test and reference products. The comment letter further provided that the lot numbers of the samples undergoing dissolution testing should be identical to those used in the in vivo study. In response to this comment letter, Barr submitted a Bioequivalence Amendment on April 29, 1998. In this Amendment, Barr provided the agency with an updated dissolution test method changing the

REFERENCE: **ANDA 74-803**
FLUOXETINE CAPSULES, USP 10 MG AND 20 MG
BIOEQUIVALENCE FACSIMILE AMENDMENT

medium to water as well as the revised *in vitro* comparative dissolution testing for the 20 mg strength using water as the medium for both products used in the in vivo study, Barr's 20 mg submission batch and the Dista product. Based on the agency's January 8, 1998 comment letter, Barr re-conducted the *in vitro* dissolution comparative study for the 10 mg strength using water as the medium. This dissolution comparative study was tested on the original Barr lot 5R87618 and the Dista reference lot 8NE08M that were originally tested in 1995 in accordance with the spirit of the agency's letter. The dissolution testing on both Barr's 10 mg test product and the reference product using water as the medium was performed on February 23, 1998 and the dissolution profiles were submitted in Section 6 of the June 15, 1998 Major Amendment. Please note that the expiration date of the reference lot 8NE08M manufactured by Dista Products Company was 9/1/96. This date was reported on the first and second pages of the *In Vitro* Comparative Study Report RD98-034A submitted in Section VI, pages 06-00007 and 06-00008. In addition, enclosed as Attachment 1 is a copy of the original dissolution comparative study report dated 11/07/95 demonstrating that the same Barr and Dista lots that were originally tested with 0.1 *N* HCl medium were also tested with water as the medium.

Barr Laboratories, Inc. is currently a party in a patent litigation with Eli Lilly regarding the Fluoxetine Capsules, USP 10 mg and 20 mg products. This litigation is ongoing, and therefore, Barr has not yet manufactured any validation batches. To manufacture a validation batch of Fluoxetine Capsules, USP would be too premature in the approval process with this ongoing litigation; the batch would expire prior to commercialization. This fact further supports Barr's decision to conduct the comparative dissolution testing using water as the medium on the original test and reference batches.

Lastly, the date of manufacture of the 10 mg submission batch 5R87618 was June 26, 1995.

In conclusion, Barr has provided the following documentation in response the agency's telephone request:

- In-Vitro Comparative Study Report No. RD98-034A dated 3/10/98 (water is medium)
- In-Vitro Comparative Study dated 11/07/95 (0.1*N* HCl is medium).
- Barr's Acceptance Tests for In-Process and Finished Products TM-419F (2/9/98). Please note that TM-419F was used to conduct the dissolution testing for Report No. RD98-034A and is Barr's current test method.

Barr Laboratories, Inc.

REFERENCE: **ANDA 74-803**
FLUOXETINE CAPSULES, USP 10 MG AND 20 MG
BIOEQUIVALENCE FACSIMILE AMENDMENT

If you have any questions concerning this Facsimile Amendment, please contact me by phone at (914) 353-8432 or by fax at (914) 353-3859.

Sincerely

BARR LABORATORIES, INC.

Elizabeth Noble for

Christine Mundkur,
Regulatory Counsel and Director of
Regulatory Affairs

CM/kdb
Enc.

This submission in comprised of Pages 1 through 40.

5/25/99 Telephone Amendment to CMC Reviewer

Barr Laboratories, Inc.

2 Quaker Road P.O. Box 2900 Pomona, NY 10970-0519 • 914/362-1100

May 21, 1999

Office of Generic Drugs
Center for Drug Evaluation and Research
FOOD AND DRUG ADMINISTRATION
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, Maryland 20855-2773

NDA ORIG AMENDMENT
N/FA

TELEPHONE AMENDMENT

REFERENCE: **ANDA 74-803**
FLUOXETINE CAPSULES, USP 10 MG AND 20 MG

Reference is made to our pending Abbreviated New Drug Application submitted under Section 505(j) of the Federal Food, Drug and Cosmetic Act for Fluoxetine Capsules, USP 10 mg and 20 mg.

Reference is also made to Barr's Minor Amendment dated April 12, 1999 and to the May 13, 1999 telephone conversation between Glen Smith, Review Chemist, Div. of Chemistry II, OGD/CDER/FDA and Christine Mundkur, Vice President Quality and Regulatory Counsel, Barr Laboratories, Inc.

Mr. Smith requested that Barr change their proposed specification for Impurity I, drug product, from: NMT % to NMT % to match USP 23/NF 18, Supplement 7. Accordingly, Barr has changed their specification for Impurity I for the drug product to NMT %. Attached please find the following documents:

- Barr's Quality Control Analytical Specifications & Test Record, Fluoxetine Capsules, USP 10 mg
- Barr's Quality Control Analytical Specifications & Test Record, Fluoxetine Capsules, USP 20 mg
- Barr's Marketed Product Stability Specification/Test Record, Fluoxetine Capsules, USP 10 mg
- Barr's Marketed Product Stability Specification/Test Record, Fluoxetine Capsules, USP 20 mg
- Barr's Acceptance Tests for In-Process & Finished Products, TM-419G

When USP adopts the PF Sep./Oct. 98 specification of NMT % for Impurity I, Barr will adopt this specification for both its release and stability testing and submit the changes in the Annual Report in accordance with 21 CFR 314.70 (d).

OFFICE OF GENERIC DRUGS
FOOD AND DRUG ADMINISTRATION

REFERENCE: **ANDA 74-803**
FLUOXETINE CAPSULES, USP 10 MG AND 20 MG

An identical copy of this Telephone Amendment has been provided to the New Jersey District Office. A document certification is attached.

This completes the present Telephone Amendment. If you have any questions, please contact me by phone at (914) 353-8432 or by fax at (914) 353-3859.

Sincerely,

BARR LABORATORIES, INC.

Christine Mundkur
Vice President, Quality and Regulatory
Counsel

CM/egn
Enc.

cc: New Jersey District Filed Office

This Submission is comprised of **Pages 01 through 39.**

Barr Laboratories, Inc.

2 Quaker Road P.O. Box 2900 Pomona, NY 10970-0519 • 914/362-1100

June 7, 1999

ORIG AMENDMENT

FA

Office of Generic Drugs
Center for Drug Evaluation and Research
FOOD AND DRUG ADMINISTRATION
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, Maryland 20855-2773

TELEPHONE AMENDMENT

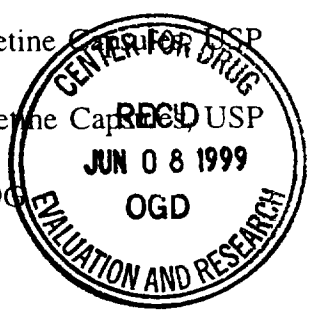
REFERENCE: **ANDA 74-803**
FLUOXETINE CAPSULES, USP 10 MG AND 20 MG

Reference is made to our pending Abbreviated New Drug Application submitted under Section 505(j) of the Federal Food, Drug and Cosmetic Act for Fluoxetine Capsules, USP 10 mg and 20 mg.

Reference is also made to Barr's Minor Amendment dated April 12, 1999 and to the May 27, 1999 telephone conversation between Glen Smith, Review Chemist, Div. of Chemistry II, OGD/CDER/FDA and Christine Mundkur, Vice President Quality and Regulatory Counsel, Barr Laboratories, Inc.

Mr. Smith requested that Barr change their proposed specification for Total Known and Unknown Impurities, drug product, to include Barr Impurity I and II. Barr has made this change and, consequently, has changed their specification for Other Individual Unknown Impurities to include Impurity II and change the name to Other Individual Impurities. This latter change was made to account for the known Impurity II in the drug product. Attached please find the following documents:

- Barr's Quality Control Analytical Specifications & Test Record, Fluoxetine Capsules, USP 10 mg
- Barr's Quality Control Analytical Specifications & Test Record, Fluoxetine Capsules, USP 20 mg
- Barr's Marketed Product Stability Specification/Test Record, Fluoxetine Capsules, USP 10 mg
- Barr's Marketed Product Stability Specification/Test Record, Fluoxetine Capsules, USP 20 mg
- Barr's Acceptance Tests for In-Process & Finished Products, TM-4190



When USP adopts the PF Sep./Oct. 98 specifications for Fluoxetine Capsules, USP, Barr will adopt these specifications for both its release and stability testing and submit the changes in the Annual Report in accordance with 21 CFR 314.70 (d).

An identical copy of this Telephone Amendment has been provided to the New Jersey District Office. A document certification is attached.

This completes the present Telephone Amendment. If you have any questions, please contact me by phone at (914) 353-8432 or by fax at (914) 353-3859.

Sincerely,

BARR LABORATORIES, INC.

Christine Mundkur
Vice President, Quality and Regulatory
Counsel

CM/egn
Enc.

cc: New Jersey District Filed Office

This Submission is comprised of **Pages 01 through 39.**

Barr Laboratories, Inc.

2 Quaker Road P.O. Box 2900 Pomona, NY 10970-0519 • 914/362-1100

March 7, 2000

Office of Generic Drugs
Center for Drug Evaluation and Research
FOOD AND DRUG ADMINISTRATION
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, Maryland 20855-2773

NDA DRUG AMENDMENT

MINOR AMENDMENT

REFERENCE: **ANDA 74-803**
FLUOXETINE CAPSULES, USP 10 MG AND 20 MG

Reference is made to our pending Abbreviated New Drug Application submitted under Section 505(j) of the Federal Food, Drug and Cosmetic Act for Fluoxetine Capsules, USP 10 mg and 20 mg.

Reference is also made to Barr's July 23, 1999 correspondence and the Agency's letter dated August 2, 1999 in which the following is stated:

COMMENT:

Review of the data submitted in your correspondence dated July 23, 1999 shows that your drug product fails to meet compendial specifications through the proposed expiry dating when the amounts of Impurity I ((±) 1-Phenyl-3-methylamino-1-propanol) are included in the determination of Individual and Total Impurities. Please submit stability data demonstrating conformance to compendial requirements in support of the proposed 24 month expiration date.

CENTER FOR DRUG EVALUATION AND RESEARCH
REC'D
MAR 0 8 2000
OGD

3-10-00

REFERENCE: ANDA 74-803
FLUOXETINE CAPSULES, USP 10 MG AND 20 MG

RESPONSE:

Barr manufactured two additional batches; one 10 mg strength and one 20 mg strength and placed each batch into its long-term and accelerated stability program. The stability data demonstrates conformance to compendial requirements in support of the proposed 24 month expiration date.

Please note that Barr changed the packaging and labeling site as follows:

From

To

On February 14, 2000 through February 23, 2000, the Baltimore District inspected the manufacturing and packaging operations at the site and found it to be in compliance with current Good Manufacturing Practices. Enclosed is Barr's Certifications and Assurance of Controlled Manufacturing in Conformance With Good Manufacturing Procedures for the site.

In addition, the procedure for testing in-process blend content uniformity was improved to eliminate possible segregation of blend powder within the sample vials, thereby increasing the accuracy and precision of the test. The approved procedure specifies to test a portion of sample powder (equivalent to one theoretical capsule fill weight). The revised procedure specifies that the entire contents of the sample vial (up to 3.4 times the theoretical capsule fill weight) is rinsed. The working standard concentration range for Fluoxetine Capsules was previously validated in Method Validation Report No. FLU-083195. Therefore, no additional method validation is necessary for this change. Please note that the specification for blend uniformity testing, sample size, and procedures for testing and re-testing have been reviewed and approved by the New York and New Jersey District Offices, Office of Compliance and the U.S. Attorneys Office in accordance with the "Barr Decision" and subsequent Court Order. Based on these prior agreements between Barr and FDA concerning blend content uniformity testing, Barr will adhere to a Stage 2 RSD specification of NMT % .

In accordance with USP 24/NF 19, Supplement 1, Barr also changed the dissolution tolerance from NLT % (Q) to NLT % (Q).

REFERENCE: **ANDA 74-803**
FLUOXETINE CAPSULES, USP 10 MG AND 20 MG

In support of this Minor Amendment please find the following:

1. Table of Contents

2. Certification and Assurance of Controlled Manufacturing in Conformance With Good Manufacturing Procedures

3. Finished Product Documentation – 10 mg strength, Batch 308769R01
   - 3.1 Executed Batch Record - Manufacturing
   - 3.2 Executed Batch Record - Packaging
   - 3.3 Testing Specifications and Data
   - 3.4 Copy of Barr's Acceptance Tests for In-Process and Finished Product, TM-419J, and QC Analytical Specifications & Test Record for the 10 mg strength
   - 3.5 Stability Report

4. Finished Product Documentation – 20 mg strength, Barr Batch 308779R01
   - 4.1 Executed Batch Record – Manufacturing
   - 4.2 Executed Batch Record – Packaging
   - 4.3 Testing Specifications and Data
   - 4.4 Copy of Barr's Acceptance Tests for In-Process and Finished Product, TM-419J and QC Analytical Specifications & Test Record for the 20 mg strength (see Section 3.4 for a copy of the test method)
   - 4.5 Stability Report

REFERENCE: **ANDA 74-803**
FLUOXETINE CAPSULES, USP 10 MG AND 20 MG

An identical copy of this Minor Amendment has been provided to the New Jersey and Baltimore District Offices. A document certification is attached. Please note that Barr is also submitting, under separate cover, its response dated 3/8/00 to the New Jersey District's July 1, 1999 FDA Record of Inspections Observation (483). This response concerns similar issues raised in the Office of Generic Drug's 8/2/99 comment letter.

This completes Barr's Minor Amendment. If you have any questions, please contact me by phone at (914) 353-8432 or by fax at (914) 353-3859.

Sincerely,

BARR LABORATORIES, INC.

Christine Mundkur
Vice President Quality and
Regulatory Counsel

This submission is comprised of **Pages 01 through 0159.**

Barr Laboratories, Inc.

2 Quaker Road P.O. Box 2900 Pomona, NY 10970-0519 • 914/362-1100

March 17, 2000

Office of Generic Drugs
Center for Drug Evaluation and Research
FOOD AND DRUG ADMINISTRATION
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, Maryland 20855-2773

NDA DRUG AMENDMENT

MINOR AMENDMENT

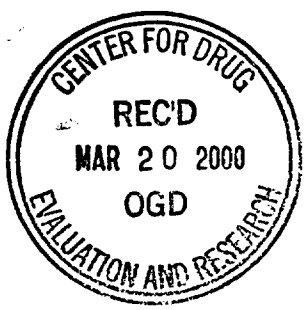
REFERENCE: **ANDA 74-803**
FLUOXETINE CAPSULES, USP 10 MG AND 20 MG

Reference is made to our pending Abbreviated New Drug Application submitted under Section 505(j) of the Federal Food, Drug and Cosmetic Act for Fluoxetine Capsules, USP 10 mg and 20 mg.

Reference is also made to Barr's March 7, 2000 Minor Amendment submitted in response to the Agency's letter dated August 2, 1999. As requested by Tim Ames, FDA during a March 15, 2000 telephone conversation with Christine Mundkur, Barr, we are hereby requesting withdrawal of our March 7, 2000 Minor Amendment and are submitting a new Minor Amendment response to the Agency's August 2, 1999 letter which stated:

COMMENT:

> Review of the data submitted in your correspondence dated July 23, 1999 shows that your drug product fails to meet compendial specifications through the proposed expiry dating when the amounts of Impurity I ((±) 1-Phenyl-3-methylamino-1-propanol) are included in the determination of Individual and Total Impurities. Please submit stability data demonstrating conformance to compendial requirements in support of the proposed 24 month expiration date.



OFFICE OF GENERIC DRUGS
FOOD AND DRUG ADMINISTRATION

REFERENCE: ANDA 74-803
Fluoxetine Capsules, USP 10 mg and 20 mg

RESPONSE:

Barr manufactured two additional batches; one 10 mg strength and one 20 mg strength and placed each batch into its long-term and accelerated stability program. The stability data demonstrates conformance to compendial requirements in support of the proposed 24 month expiration date. Both batches were packaged in their entirety. Enclosed please find the executed batch records and corresponding stability data for these newly manufactured submission batches.

An identical copy of this Minor Amendment has been provided to the New Jersey District Office. A document certification is attached. Please note that Barr also submitting, under separate cover, its response to the New Jersey District's July 1, 1999 FDA Record of Inspections Observation (483). This response concerns similar issues raised in the Office of Generic Drug's 8/2/99 comment letter.

This completes Barr's Minor Amendment. If you have any questions, please contact me by phone at (914) 353-8432 or by fax at (914) 353-3859.

Sincerely,

BARR LABORATORIES, INC.

Christine Mundkur
Vice President Quality and
Regulatory Counsel

This submission is comprised of **Pages 0001 through 0040**.

Barr Laboratories, Inc.

2 Quaker Road P.O. Box 2900 Pomona, NY 10970-0519 • 914/362-1100

April 18, 2000

Office of Generic Drugs
Center for Drug Evaluation and Research
FOOD AND DRUG ADMINISTRATION
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, Maryland 20855-2773
Attention: Gary Buehler
Acting Director

VIA FACSIMILE: (301) 443-3839
ORIGINAL VIA FEDERAL EXPRESS

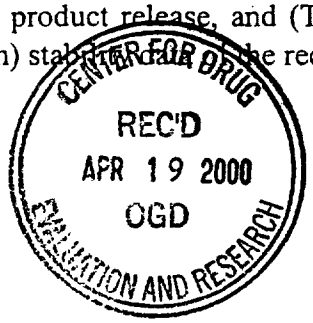
TELEPHONE AMENDMENT

REFERENCE: **ANDA 74-803**
FLUOXETINE CAPSULES, USP 10 MG AND 20 MG

Reference is made to our pending Abbreviated New Drug Application submitted under Section 505(j) of the Federal Food, Drug and Cosmetic Act for **Fluoxetine Capsules, USP 10 mg and 20 mg.**

Reference is also made to the April 2000 phone conversation between Tim Ames, Project Manager, OGD, FDA and Christine Mundkur, Barr Laboratories, Inc. regarding Barr's March 7, 2000 Minor Amendment. Mr. Ames requested that Barr submit 6 month CRT stability data on samples pulled on 2/28/00 as well as additional information on the impurity profiles, particularly the impurity profile for the 10 mg that was just below the total impurities specification at 3 month CRT conditions. Mr. Ames suggested Barr review the 3 and 6 month CRT stability profiles of the recently manufactured 10 mg and 20 mg batches (submitted with the Minor Amendment).

Accordingly, Barr reviewed the drug substance, finished product release, and (T0), accelerated (one, two, and three month) and CRT (three and six month) stability data of the recent batches.



... Continued

4/19/00

REFERENCE: **ANDA 74-803**
FLUOXETINE CAPSULES, USP 10 MG AND 20 MG

The data to date shows that the individual known impurities, unknown impurities, and total impurities are well within specification and remain consistent through 6 month CRT. Therefore, Barr's Fluoxetine Capsules, USP Products are expected to meet the impurities specifications through the proposed 24 month expiration dating period.

In support of Barr's conclusions, we are including the following documents:

- Updated Interim Stability Report for Fluoxetine Capsules, USP 10 mg and 20 mg
- Detailed review of impurity profiles
- Representative impurities/degradation product chromatograms from initial release, 3 month CRT and 6 month CRT

If you have any questions, please contact me by phone at (914) 353-8432 or by fax at (914) 353-3859.

Sincerely,

BARR LABORATORIES, INC.

Christine Mundkur
Regulatory Counsel and
Director of Regulatory Affairs

cc: New Jersey District Field Office

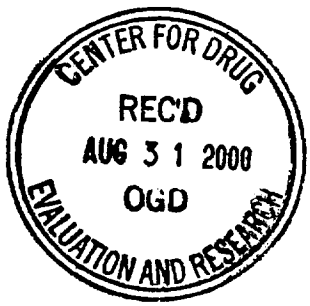
Barr Laboratories, Inc.

2 Quaker Road • P.O. Box 2900 • Pomona, NY 10970-0519 • 845/362-1100

NEW CORRESP
NC

August 30, 2000

Privileged and Confidential
VIA FEDERAL EXPRESS



Gary Buehler
Acting Director
Office of Generic Drugs (HFD-600)
Center for Drug Evaluation & Research
Food and Drug Administration
7500 Standish Place
Rockville, MD 20855

Re: ANDA No. 74 - 803: Barr Laboratories, Inc.
Fluoxetine Capsules, USP 10 mg & 20 mg
Meeting Request - 180 Day Market Exclusivity

To Whom It May Concern:

Barr Laboratories, Inc. ("Barr") hereby submits this correspondence and meeting request to our Abbreviated New Drug Application ("ANDA") (ANDA No. 74 - 803) for Fluoxetine Capsules, USP 10 mg and 20 mg. 21 C.F.R. § 314.102 (a), (e) (1999). Given that Barr is the first paragraph IV filer on Eli Lilly's ("Lilly") '081 and '549 patents, and given the Federal Circuit's recent ruling of invalidity of the '549 patent, Barr is entitled by law to a full 180 days of market exclusivity.

For the reasons fully described in the attached Exclusivity Statement, Barr submits that the agency is prohibited by statute from approving all subsequent fluoxetine capsules ANDAs until Barr's generic exclusivity has expired. Barr's exclusivity should commence upon commercial marketing of the products, which will occur after expiration of the '081 patent and, if awarded, after Lilly's pediatric exclusivity. At the very least, Barr's exclusivity period will not begin until the district court enters judgment pursuant to the Federal Circuit's mandate, and that Barr's exclusivity will not run concurrently with any pediatric exclusivity awarded to Lilly.

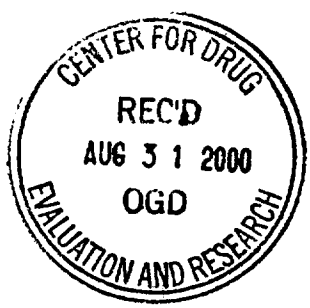
Because the agency's application of the statute in this situation will have a profound impact on Barr, the generic industry and American consumers, and because this situation has not previously been before the agency, Barr submits that a meeting with appropriate agency officials is clearly warranted. The purpose of the meeting will be to confirm that Barr's fluoxetine capsules are entitled to a full 180 days of market exclusivity under 21 U.S.C. § 355(j)(5)(B)(iv), regardless of whether Lilly is awarded pediatric exclusivity. Any other application of the statute to Barr's fluoxetine capsules, will render the 180 day exclusivity provision meaningless, vitiating the congressional incentive for future patent challenges.

We will contact your office next week concerning this meeting request. In the meantime, should you have any questions, please contact me at (845) 353 – 8432.

Sincerely,

Christine Mundkur, Esq.
Vice President, Quality and Regulatory Counsel
Barr Laboratories, Inc.

cc: Cecelia M. Parise
Kimberly Dettelbach
Elizabeth H. Dickinson



Barr Laboratories, Inc.

2 Quaker Road • P.O. Box 2900 • Pomona, NY 10970-0519 • 845/362-1100

July 31, 2001

Office of Generic Drugs
Center for Drug Evaluation and Research
FOOD AND DRUG ADMINISTRATION
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, Maryland 20855-2773

NEW CORRESP
NC

AMENDMENT

REFERENCE: **ANDA 74-803**
FLUOXETINE CAPSULES, USP 10MG AND 20 MG

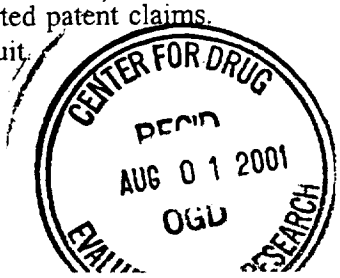
Reference is made to Barr's tentatively approved Abbreviated New Drug Application submitted under Section 505(j) of the Federal Food, Drug, and Cosmetic Act for **Fluoxetine Capsules, USP 10 mg and 20 mg**, dated December 9, 1995. Reference is also made to Barr's May 22, 2001 minor amendment for the 20 mg strength.

Barr is requesting final agency approval of the 20 mg strength of Fluoxetine Capsules, USP. In accordance with the tentative approval letter from the Agency, dated June 14, 2000, Barr is forwarding a copy of the final judgement from the District Court for the Southern District of Indiana, dated July 27, 2001, as well as the Federal Circuit's opinion, dated May 30, 2001, and the mandate that issued therefrom dated July 26, 2001.

Barr is entitled to final approval for its 20 mg fluoxetine capsules when Eli Lilly's pediatric exclusivity expires on August 2, 2002. In December 1995, Barr filed the first ANDA seeking to market 20 mg fluoxetine capsules, a generic version of Eli Lilly's Prozac® brand anti-depressant product. Barr's ANDA contained a paragraph IV certification to both patents Lilly listed in the Orange Book in connection with Prozac®, U.S. Patent Nos. 4,314,081 ("the '081 patent") and 4,626,549 ("the '549 patent").

Barr timely notified Lilly of Barr's paragraph IV certification and, in April, 1996, Lilly initiated a patent infringement action against Barr in the United States District Court for the Southern District of Indiana. In that suit, Lilly asserted that Barr's marketing of fluoxetine hydrochloride for its then-labeled uses would infringe claim 5 of the '081 patent, which claims the fluoxetine hydrochloride compound and claim 7 of the '549 patent, which claims the use of fluoxetine hydrochloride to inhibit the uptake of serotonin.

Lilly asserted only claim 5 of the '081 patent and claim 7 of the '549 patent against Barr and, thus, those two claims were the only patent claims at issue in the *Lilly v. Barr* litigation. On January 25, 1999, the District Court entered judgment in favor of Lilly and against Barr on both of the asserted patent claims. Barr filed a timely appeal of this order to the U.S. Court of Appeals for the Federal Circuit.



REFERENCE: **ANDA 74-803**
FLUOXETINE CAPSULES, USP 10MG AND 20 MG

On May 30, 2001, the Federal Circuit affirmed the District Court's finding that claim 5 of the '081 patent was valid, but reversed the District Court's finding regarding claim 7 of the '549 patent. The panel found that claim 7 of the '549 patent was invalid on double patenting grounds. *Eli Lilly & Co. v. Barr Labs*, 251 F.3d 955, 972 (Fed. Cir. 2001). This opinion replaced an earlier opinion by the same panel, dated August 8, 2000, which had been vacated by the Federal Circuit *en banc*. *See Eli Lilly & Co. v. Barr Labs*, 222 F.3d 973, 988 (Fed. Cir. 2000). On July 26, 2001, the Federal Circuit issued a judgment and mandate (copy attached) directing the District Court to vacate its January 25, 1999 order.

On July 27, 2001, the District Court entered the Federal Circuit's mandate on the District Court docket and, in doing so, the Court "ordered and adjudged that this cause is affirmed-in-part, reversed-in-part and vacated, in accordance with the decision of the Federal Circuit Court of Appeals, entered May 30, 2001." Simply put, the Court vacated its January 25, 1999 order and entered judgment in favor of Barr, and against Eli Lilly because claim 7 of the '549 patent is invalid. A copy of the relevant docket entry is attached. Because Lilly successfully demonstrated that the '081 patent was valid and infringed, Lilly became eligible for a six-month period of pediatric exclusivity following the expiration of the '081 patent. Since the '081 patent expired on February 2, 2001, Lilly's pediatric exclusivity period ends on August 2, 2001. Thus, as a result of Lilly's pediatric exclusivity and the District Court's entry of the Federal Circuit's mandate, Barr is entitled to final approval on August 2, 2001. As the FDA is aware, Barr is entitled to 180 days of exclusivity for its 20 mg fluoxetine capsules, which Barr contends begins on August 2, 2001.

An identical copy of this Amendment has been provided to the New Jersey and Baltimore District Offices. A document certification is attached.

This completes Barr's amendment requesting final approval for Fluoxetine Capsules, USP 20 mg. If you have any questions concerning this submission, please contact me by phone at (845) 353-8432 or by fax at (845) 353-3859.

Sincerely,

BARR LABORATORIES, INC.

Christine Mundkur
Vice President of Quality and
Regulatory Affairs

Enclosure

Barr Laboratories, Inc.

2 Quaker Road • P.O. Box 2900 • Pomona, NY 10970-0519 • 845/362-1100

July 24, 2001

NEW CORRESP
NC

Office of Generic Drugs
Center for Drug Evaluation and Research
FOOD AND DRUG ADMINISTRATION
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, Maryland 20855-2773

VIA FACSIMILE: 301 443-3847
VIA FedEx

LABELING FACSIMILE

REFERENCE: **ANDA 74-803**
FLUOXETINE CAPSULES, USP 10 MG AND 20 MG

Reference is made to our tentatively approved Abbreviated New Drug Application submitted under section 505(j) of the Federal Food, Drug, and Cosmetic Act for Fluoxetine Capsules, USP 20 mg.

Reference is also made to the telephone conversation between Adolph Vezza, Labeling Review Branch, FDA and Christine Mundkur, Barr Laboratories, Inc. on July 24, 2001 in which Mr. Vezza requested Barr commit to making the labeling changes specified in FDA's June 22, 2001 facsimile at the time of Barr's next printing.

Accordingly, Barr hereby commits to making all of the labeling changes specified in the Agencies' June 22, 2001 letter at the time of their next printing.

This completes the present Labeling Facsimile. If you have any questions, please contact me by phone at (845) 353-8432 or by fax at (845) 353-3859.

Sincerely,

BARR LABORATORIES, INC.

Christine Mundkur
Vice President, Quality and Regulatory Counsel

Enc.
cc: Adolph Vezza – Labeling Review Branch

Barr Laboratories, Inc.

2 Quaker Road • P.O. Box 2900 • Pomona, NY 10970-0519 • 845/362-1100

July 19, 2001

Office of Generic Drugs
Center for Drug Evaluation and Research
FOOD AND DRUG ADMINISTRATION
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, Maryland 20855-2773

ORIG AMENDMENT
N/AF

VIA FACSIMILE: 301 443-3847
VIA FedEx

LABELING AMENDMENT

REFERENCE: **ANDA 74-803**
FLUOXETINE CAPSULES, USP 10 MG AND 20 MG

Reference is made to our tentatively approved Abbreviated New Drug Application submitted under section 505(j) of the Federal Food, Drug, and Cosmetic Act for Fluoxetine Capsules, USP 20 mg.

Reference is also made to the Agency's June 22, 2001 facsimile from the Labeling Review Branch that stated the following:

Labeling Deficiencies:

1. GENERAL COMMENTS:
   a. FDA does not authorize certifications with respect to patents that claim a use for the reference listed drug for which the applicant is not seeking approval. The statute required patent certifications, e.g. Paragraph(s) I, II, III, IV, only if the patent claims a use for the reference listed drug for which the applicant is seeking approval (Section 505(j)(2)(A)(vii) of the Act). The statute requires an applicant to make a patent statement when a method of use patent does not claim a use for which the applicant is seeking approval (Section 505(j)(2)(A)(viii)).

      We note that you have challenged U.S. Patent 4626549 by filing a Paragraph IV Certification. However, your proposed insert labeling does not contain the method of use covered by the aforementioned patent. Please amend your patent information and revise your insert labeling as appropriate.

      We acknowledge that you have requested an opinion on this issue with this submission. Please be informed that it is still under consideration by the Agency.

b. For additional guidance regarding your patent certification we refer you to the Agency's letter dated March 16, 2001.

Response:

The paragraph IV certification provided in the original ANDA continues to be correct in that Barr proposes to market its product for the treatment of depression and U.S. Patent 4626549 ("'549") claims using fluoxetine to block seratonin uptake, which is the undisputed mechanism through which fluoxetine treats depression. However, because Barr never intended to market its product for the treatment of appetite disorders covered by the '549 patent and because the agency suggested in its March 16, 2000 letter that it is reasonable to conclude that bulimia nervosa could be considered an appetite disorder covered by the '549 patent, Barr elected to delete the bulimia nervosa indication from Barr's proposed labeling. Therefore, in order to clarify the original paragraph IV certification to reflect the fact that Barr is not pursuing the bulimia indication, Barr is enclosing the attached section viii statement under section 505 (j)(2)(A)(viii) stating that ANDA 74-803 is not seeking approval for the use of treating bulimia nervosa.

2. INSERT

a. GENERAL COMMENTS
   i. "U.S." rather than "US" throughout the text of the insert.
   ii. "coadministered" and "coadministration" (delete hyphens)

b. DESCRIPTION
   First sentence-"...oral administration; it is also marketed for the treatment of premenstrual dysphoric disorder (Sarafem™, fluoxetine hydrochloride). It is chemically unrelated..."

REFERENCE: ANDA 74-803
FLUOXETINE CAPSULES, USP 10 MG AND 20 MG

DRAFT

c. CLINICAL PHARMACOLOGY

i. Absorption, Distribution, Metabolism, and Excretion, Metabolism, first sentence-"...other unidentified..." (delete comma)

ii. Clinical Trials

Depression, second paragraph, first sentence-"...fluoxetine 20 mg..." (delete hyphens – two instances)

d. PRECAUTIONS

Drug Interactions, Warfarin – "anticoagulant" (delete hyphen)

e. ADVERSE REACTIONS

Table 2 – Delete the second row (two by two hyphens)

f. DOSAGE AND ADMINISTRATION

Switching Patients to a Tricyclic Antidepressant (TCA)-"...under PRECAUTIONS, Drug Interactions)."

g. HOW SUPPLIED

i. "...of fluoxetine (present as the hydrochloride) are..."

iii. Add the statement "Sarafem™ is a trademark of Eli Lilly".
iv. Add the statement "PROTECT FROM LIGHT".
v. Add "[see USP]" to the end of the storage temperature recommendations.

OFFICE OF GENERIC DRUGS
FOOD AND DRUG ADMINISTRATION

REFERENCE: ANDA 74-803
FLUOXETINE CAPSULES, USP 10 MG AND 20 MG

DRAFT

Response:

According to the June 22, 2001 phone conversation between Christine Mundkur, Barr Laboratories, and Bob West, FDA, Barr will be making the proposed labeling changes and submitting them post approval in the Annual Report since they are all minor in nature. Specifically, they deal with the following: grammatical changes (deletion of hyphens, commas, and periods); addition of "Sarafem™" wording; deletion of a table row that contains no text; addition of descriptive words; and a change from lower to upper case letters for "PROTECT FROM LIGHT". These are all changes that are typically requested to be submitted in the Annual Report.

This completes the present Labeling Amendment. If you have any questions, please contact me by phone at (845) 353-8432 or by fax at (845) 353-3859.

Sincerely,

BARR LABORATORIES, INC.

Christine Mundkur
Vice President, Quality and Regulatory Counsel

Enc.
Cc: Cecelia Parise, Special Assistant
Adolph Vezza – Labeling Review Branch

This Submission is comprised of **Pages 01 through 04**

labeling review
drafted 6/21/01
A. Vega

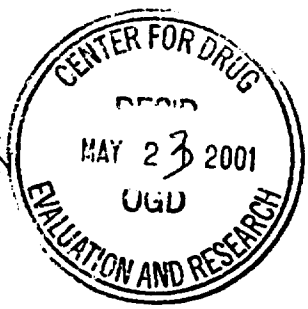
Barr Laboratories, Inc.

2 Quaker Road • P.O. Box 2900 • Pomona, NY 10970-0519 • 845/362-1100

May 22, 2001

Noted NAF.
B. McNeil
6/1/01

Office of Generic Drugs
Center for Drug Evaluation and Research
FOOD AND DRUG ADMINISTRATION
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, Maryland 20855-2773



ORIG AMENDMENT
N/AM
5/30/01

MINOR AMENDMENT

REFERENCE: **ANDA 74-803**
FLUOXETINE CAPSULES, USP 10 MG AND 20 MG

Reference is made to our tentatively approved Abbreviated New Drug Application submitted under Section 505(j) of the Federal Food, Drug and Cosmetic Act for Fluoxetine Capsules, USP 10 mg and 20 mg.

Reference is also made to the Agency's June 14, 2000 tentative approval letter in which the following is stated:

"...please submit an amendment at least 60-days (but not more than 90 days) prior to the date you believe your application will be eligible for final approval. Your amendment should identify changes, if any, in the conditions under which the drug product was tentatively approved and should include documentation such as a copy of a final order or judgement from the Court of Appeals...or any other relevant information. The amendment should also provide updated information such as final printed labeling, chemistry, manufacturing, and controls data as appropriate."

Barr is expecting to be eligible for final approval on August 2, 2001 with 180 days exclusivity for the 20 mg strength. We believe another generic company will be granted 180 days exclusivity for the 10 mg strength. Accordingly, we are hereby submitting a Minor Amendment for the 20 mg strength identifying changes in the conditions under which the drug product was tentatively approved and providing a status on the case at the court of appeals. We will be submitting a Minor Amendment for the 10 mg strength 60 to 90 days prior to being eligible for final approval.

Reference is also made to a June 1, 2001 telephone conversation between Christine Mundkur, VP Quality and Regulatory Counsel, Barr Laboratories, and Bob West, Acting Deputy Director, OGD/FDA in which Mr. West stated that the following changes would be accepted as a Minor Amendment.

5/31/01

I. Site Changes:

- New packaging and alternate analytical testing site of Since Barr no longer has facilities at the packaging site under which the application was tentatively approved, it is necessary to file for as a packaging site. It is also necessary to file for as an additional analytical testing site to the already approved due to the high volume of the product.

II. Test Method and Specification Changes:

III. Manufacturing and Packaging Changes:

IV. Labeling Changes:

- Updated labeling in accordance with FDA's March 16, 2001 correspondence and Eli Lilly's last approved labeling, including a "protect from light" statement. Please note that references to the 10 mg strength were removed. In the March 16, 2001 correspondence directed to Barr's fluoxetine capsule products, FDA stated that generic manufacturers, like Barr, may omit from their fluoxetine product labels an indication for bulimia nervosa. Barr decided to remove references to the bulimia nervosa indication (see Section IV for a detailed explanation concerning the bulimia nervosa indication). In so doing, we followed specific instructions received from Adolph Vezza, Div. of Labeling and Program Support, OGD/FDA received during an April 6, 2001 phone conversation held with Barr personnel (Christine Mundkur, Vice President Quality and Regulatory Counsel, Nancy Westcott, Regulatory Affairs Labeling Specialist, and Elisabeth Noble Gray, Technical Group Leader, Regulatory Affairs).
- Changed product capsule description from barr/877 to barr 20/877 at the request of Barr's Sales and Marketing Department. The above affected documents reflect this change (annual reportable change).

Barr commits to place the first batch of the 100's Heat Seal CRC in its long-term stability program in support of all of the above changes. Supporting documentation for these changes is provided in the four enumerated sections that follow.

Court of Appeals Information

Eli Lilly filed a petition for a rehearing; the Court of Appeals has not yet ruled on this rehearing request. On August 9, 2000 the United States Court of Appeals, Eli Lilly and Co. v. Barr Laboratories, Inc., 222F. 3d 973 (Fed. Cir. 2000) issued an opinion holding that the '549 patent was invalid but that the '081 patent was valid. The '081 patent expired on February 2, 2001.

An identical copy of this Minor Amendment has been provided to the New Jersey and Baltimore District Offices. A document certification is attached.

This completes Barr's Minor Amendment. If you have any questions, please contact me by phone at (845) 353-8432 or by fax at (845) 353-3859.

Sincerely,

BARR LABORATORIES, INC.

Christine Mundkur
Vice President Quality and
Regulatory Counsel

Barr Laboratories, Inc.

2 Quaker Road • P.O. Box 2900 • Pomona, NY 10970-0519 • 845/362-1100

November 1, 2000

Privileged and Confidential
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NDA CORRESP

NAT
13-NOV-2000

Gary Buehler
Acting Director
Office of Generic Drugs (HFD-600)
Center for Drug Evaluation & Research
Food and Drug Administration
7500 Standish Place
Rockville, MD 20855

Re: ANDA No. 74 – 803: Barr Laboratories, Inc.
Fluoxetine Capsules, USP 10 mg & 20 mg
Supplement to Exclusivity Statement

To Whom It May Concern:

Barr Laboratories, Inc. ("Barr") hereby submits this correspondence to our Abbreviated New Drug Application ("ANDA") (ANDA No. 74 – 803) for Fluoxetine Capsules, USP 10 mg and 20 mg. Barr is supplementing our original Exclusivity Statement dated August 30, 2000. Since submitting its Statement, Barr has had discussions with various individuals from the Office of Generic Drugs and FDA's General Counsel's office. In light of these conversations, Barr submits this supplement to ANDA No. 74 – 803.

For the reasons fully described in the attached Supplement to Exclusivity Statement, Barr submits that pediatric exclusivity and generic exclusivity run consecutively, not concurrently. The plain language of the statute is clear that Congress intended pediatric exclusivity and generic exclusivity to harmoniously co-exist. Additionally, the legislative history of the pediatric exclusivity provision demonstrates that Congress did not intend this extension to interfere with generic exclusivity.

Finally, the Supplement to Exclusivity Statement addresses the Agency's informal inquiry regarding the relevance, if any, of its decision on Citizen Petition No. 99P-1271/PSA 1 and PSA2 (the Cisplatin Petition). As set forth in Barr's Supplement, the Cisplatin Petition is not relevant to the case of fluoxetine hydrochloride.

If you have any questions, please contact me at (845) 353 – 8432.

Sincerely,

Christine Mundkur, Esq.
Vice President, Quality and Regulatory Counsel
Barr Laboratories, Inc.

cc: *Cecelia M. Parise*
Kimberly Dettelbach
Elizabeth H. Dickinson

Stamped Copy 1/7/96

Barr Laboratories, Inc.

2 Quaker Road P.O. Box 2900 Pomona, NY 10970-0519 • 914/362-1100

December 9, 1995

Office of Generic Drugs
Center for Drug Evaluation & Research
FOOD AND DRUG ADMINISTRATION
Metro Park North II
7500 Standish Place
Room 150
Rockville, MD 20855

We are submitting herewith, in duplicate, an Abbreviated New Drug Application under Section 505(j) of the Federal Food, Drug and Cosmetic Act for Fluoxetine Hydrochloride Capsules, 20 mg.

The application is provided both as an archival copy, and a review copy. The archival copy of the application is contained in blue binders and consists of volumes. The review copy is divided into two parts. The chemistry, manufacturing and controls part of the review copy is contained in red binders and consists of 3 volumes. The bioequivalence part of the review copy is contained in orange binders and consists of volumes. The format of this application is in accordance with Office of Generic Drugs, Policy and Procedure Guide #30-91. The information submitted in this application is also in accord with the October 14, 1994 communication from Dr. Janet Woodcock, Director CDER and Mr. Ronald Cheesemore (ORA). As a result of this policy, detailed facilities descriptions and equipment listings as well as specific SOPs are not contained in this application. They are, however, kept current and are available for review and inspection by FDA District Field Investigators.

Included in this application, and in accordance with the Generic Drug Enforcement Act of 1992, a Debarment Certification Statement with a List of Convictions Statement is provided for this application. In addition, in accordance with the FDA's Final Rule (Federal Register, Vol. 58, No. 172, September 8, 1993), a "Field Copy" of this application has been forwarded to the New Jersey District Office.

Your earliest acknowledgment to this application will be very much appreciated.

Sincerely,

BARR LABORATORIES, INC.

Herbert G. Luther, Ph.D.
Director Scientific Affairs

RECEIVED
DEC 11 1995
GENERIC DRUGS