CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

74803

CORRESPONDENCE

ANDA 74-803

Barr Laboratories, Inc.
Attention: Herbert G. Luther, Ph.D.
2 Quaker Road
Pomona, New York 10970-0519

JUL 9 1996

Dear Dr. Luther:

This is in reference to your abbreviated new drug application dated December 9, 1995, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act, for Fluoxetine Hydrochloride Capsules, 20 mg.

The application is deficient and, therefore, not approvable under Section 505 of the Act for the following reasons:

A. Chemistry Deficiencies

1. Regarding synthesis:

DMF has been found to be deficient. A letter has been sent to the holder identifying these issues. All deficiencies must be corrected before the approval of this application.

2. Regarding raw material controls:

a. Please revise your specifications for Fluoxetine Hydrochloride to replace "Report Results" for Related Substances and "See Test Record for Limits" for Particle Size with specifications based on data accrued to date.

b. Please revise your specifications for Fluoxetine Hydrochloride to include tests for Melting Point and Moisture.

c. Since the drug substance exists as a racemic mixture, please revise you specifications to include testing for optical rotation to ensure that a racemic mixture is used.

d. Your Assay specification ( )%) is not consistent with the supplier's specification of)%. Please revise your specification to be consistent with the supplier or submit justification and supporting data for the wider specification.

e. Regarding the Reference Standards for Fluoxetine Hydrochloride and Related Compounds:

i. Please indicate the source of reference standards for Fluoxetine Hydrochloride as well as all Related Compounds.

ii. Please describe any in-house qualification procedures or purification steps used for all reference standards prior to use.

iii. Please submit supplier and in-house (if applicable) Certificates of Analysis for your reference standards for Fluoxetine Hydrochloride as well as all Related Compounds.

3. Regarding manufacturing and processing:

a. Please revise your Master Batch Record to include the manufacturer, model, and mode of operation (Vertical or Horizontal) of the High Shear Mixer.

b. Please revise your Master Batch Record to include Oscillator/Mesh settings for screening the granulation.

c. Please revise your Master Batch Record to include the rate of encapsulation (nominal or range in capsules/hour) as well as any limits on environmental conditions (e.g. temperature, relative humidity) for the encapsulation process.

4. Regarding container/closure systems:

a. Please submit USP <671> Containers-Permeation testing results for the proposed container/closure system.

a. We strongly suggest that the smallest container/closure system included in the application be equipped with a child resistant closure. Please 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.

ii. Please indicate nominal encapsulation speed and environmental parameters.

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.

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.

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.

d. Section 1 of your Acceptance Tests for In-Process & Finished Products 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.

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.

f. Your final product specifications (Spec. #0877 - Rev. 2) fail to include Moisture as shown in the methods Please revise the final product specifications to include Moisture or submit justification for the deletion.

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.

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.

2. CONTAINER (100s)

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.

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 is 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 ng/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 accident, cholestatic jaundice, confusion, dyskinesia (including, for example, a case of buccal-lingual-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 pneumonia, epidermal necrolysis, exfoliative dermatitis, gynecomastia, heart arrest, hepatic failure/necrosis, hyperprolactinemia, immune-related hemolytic anemia, kidney failure, misuse/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, QT prolongation, sudden unexpected death, suicidal ideation, thrombocytopenia, thrombocytopenic purpura, vaginal bleeding after drug withdrawal, and violent behaviors.

i. DRUG ABUSE AND DEPENDENCE

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:

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 a 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.

To facilitate review of your next submission, and in accordance with 21 CFR 314.94(a)(8)(iv), please provide a side-by-side comparison of your proposed labeling with your last submission with all differences annotated and explained.

Please note that we reserve the right to request further changes in your labels and/or labeling based upon further changes in the approved labeling of the listed drug or upon further review of the application prior to approval.

The file on this application is now closed. You are required to take an action described under 21 CFR 314.120 which will either amend or withdraw the application. Your amendment should respond to all the deficiencies listed. A partial reply will not be considered for review, nor will the review clock be reactivated until all deficiencies have been addressed. The response to this letter will be considered a MAJOR amendment and should be so designated in your cover letter. You will be notified in a

separate letter of any deficiencies identified in the bioequivalence portion of your application. If you have substantial disagreement with our reasons for not approving this application, you may request an opportunity for a hearing.

Sincerely yours,

/S/ 7/5/96

Frank O. Holcombe, Jr., Ph.D.
Director
Division of Chemistry II
Office of Generic Drugs
Center for Drug Evaluation and Research

ANDA 74-803
75-810

MAR 16 2001

Barr Laboratories, Inc.
Attention: Christine Mundkur
2 Quaker Road
P.O. Box 2900
Pomona, NY 10970-0519

Dear Madam:

The Office of Generic Drugs (OGD) has reconsidered its position regarding the applicability of a listed patent to portions of the labeling of the reference listed drug, Prozac®, (fluoxetine hydrochloride) NDA 18-936, NDA 20-101 and NDA 20-974. This relates to U.S. patent number 4,626,549, which is listed in the Orange Book as covering two uses of fluoxetine hydrochloride. Use 84 is described by the NDA holder as " a method of blocking the uptake of monoamines by brain neurons in animals." Use 154 is described as "a method of treating animals suffering from an appetite disorder." Specifically, the Agency has concluded that applicants may remove statements related to "appetite disorders" from the proposed ANDA labeling. The Agency permits firms to omit from the labeling indications that are protected by patent and/or exclusivity pursuant to Section 505(j)(2)(A)(viii) of the Federal Food Drug and Cosmetic Act and 21 C.F.R. § 314.94(a)(8)(iv).

The labeling of the reference listed drug, Prozac®, includes the following indication: "*Bulimia Nervosa* --Prozac® is indicated for the treatment of binge-eating and vomiting behaviors in patients with moderate to severe bulimia nervosa." We find that it is reasonable to consider bulimia an appetite disorder. One of the definitions in Dorland's Illustrated Medical Dictionary, 28th Edition, characterizes bulimia as an "abnormally increased appetite; hyperorexia".

Therefore, ANDA applicants may omit the statements related to "appetite disorders" from the labeling of their generic version of fluoxetine hydrochloride. The applicants are permitted to amend their paragraph IV (PIV) patent certification to the '549 patent to assert that the labeling does not infringe the patent or that the patent is invalid or unenforceable for some of the claims and also include a statement under Section 505(j)(2)(A)(viii) and 21 CFR § 314.94(a)(12)(iii) (a "section viii statement") that indicates that the method of use patent does not claim a use for which the ANDA applicants are seeking approval for other claims. In this case, because the '549 patent apparently contains a number of different claims described by the NDA holder as covering different uses, the section viii statement will essentially assert that the ANDA applicants are not seeking approval for one or more of the multiple uses claimed in the patent. In addition, the ANDA applicants are requested to specify the use(s) they are deleting from the labeling.

If you have any questions regarding this correspondence, please contact Cecelia Parise, R.Ph., Special Assistant for Regulatory Policy, Office of Generic Drugs, at (301) 827-5845.

Sincerely

/S/ for

Gary Buehler
Acting Director
Office of Generic Drugs
Center for Drug Evaluation and Research

3/16/2001

ANDA 74-803

JUN 10 1996

Barr Laboratories, Inc.
Attention: Herbert G. Luther
2 Quaker Road
Post Office Box D2900
Pomona, NY 10970-0519

Dear Dr. Luther:

Reference is made to the Abbreviated New Drug Application, submitted on December 9, 1995, for Fluoxetine Hydrochloride Capsules, 20 mg.

The Office of Generic Drugs has reviewed the bioequivalence data submitted and the following comments are provided for your consideration:

1. Regarding the single dose fasting study, please provide the following information which was missing from the submission:

   a. Stability data regarding the effect of room temperature storage during handling of the samples.

   b. The batch/lot size for the test product, the assay potency and content uniformity data for both the test and reference products. In addition, the date of manufacture of the test product should be included.

2. The Physician's Desk Reference (PDR), 49 Ed. (pages 943-947) report the following statements:

   * A dose of 20 mg/day, administered in the morning, is recommended as the initial dose.

   * Studies comparing fluoxetine 20, 30, 40 and 60 mg/day to placebo indicate that 20 mg/day is sufficient to obtain a satisfactory antidepressant response.

   * 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.

   In your study, three capsules of 20 mg fluoxetine were administered to each subject. Please explain the rationale

for administering a dosage which is three times higher than the recommended starting dose.

3. Provide a brief description on the analytical methodology procedure.

4. Due to the fact that the labeling of the reference listed drug (RLD) indicates that the drug may be administered with or without food and also "food does not appear to affect the systemic bioavailability of the drug", a food study is required for this product to demonstrate that the generic formulation will behave similarly to the RLD formulation under both fasting and non-fasting conditions.

   The single-dose post-prandial bioequivalence study should use a three-way crossover design comparing equal doses of the test and reference products. The study should be conducted in a random, three-treatment (Treatments 1&2: the test and reference products should be dosed immediately after standard breakfast, Treatment 3: the test product should be dosed under fasting conditions), three-period, cross-over design using a minimum of 18 healthy subjects. An adequate wash-out period between periods 1, 2, and 3 dosing should be applied.

   Note: The standard breakfast should be as follows:

   one buttered English muffin
   one fried egg
   one slice of American cheese
   one slice of Canadian bacon
   one serving of hashed brown potatoes
   eight fluid ounces (240 mL) of whole milk
   six fluid ounces (180 mL) of orange juice.

5. Please submit a comparative dissolution study for both the test and reference drug products, performed as part of the same experiment (within 8-10 working days). The dissolution data should include the number of capsules (not less than 12), type and volume of the medium, the method that has been used, and the date the testing was performed. The dissolution testing should be done on capsules from the same lot number that was used in the *in vivo* bioequivalence study. The comparative dissolution profiles (in a side-by-side tabular format, if possible) should be submitted with raw dissolution data, the dissolution mean, the range (high, low), and the percentage of coefficient of variation (%C.V.), and date(s) of analysis.

As described under 21 CFR 314.96 an action which will amend this application is required. The amendment will be required to address all of the comments presented in this letter.

Should you have any questions, please call Mark Anderson, Project Manager, at (301) 594-0315. In future correspondence regarding this issue, please include a copy of this letter.

Sincerely yours,

/S/

Keith K. Chan, Ph.D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

NAI "Methods Validation information" 3/4/96 file

Barr Laboratories, Inc.

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

4/5/96

BIOAVAILABILITY

NEW CORRESP
NC

February 22, 1996

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

RECEIVED
FEB 23 1996
GENERIC DRUGS

REFERENCE: **ANDA 74-803**
FLUOXETINE HYDROCHLORIDE CAPSULES, 20 mg
ADDITIONAL COPIES (3) OF ANALYTICAL METHODS & VALIDATION

Reference is made to our pending Abbreviated New Drug Application dated *December 9, 1995* submitted under Section 505(j) of the Federal Food, Drug and Cosmetic Act for **FLUOXETINE HYDROCHLORIDE CAPSULES, 20 mg**.

The following response is to your letter dated *February 21, 1996* in which the following is stated:

> However, in the interim, please submit three additional copies of the analytical method and descriptive information needed to perform the tests on the samples (both the bulk active ingredient(s) and finished dosage form) and validate the analytical methods. Please do not send samples unless specifically requested to do so. If samples are required for validation, we will inform you where to send them in a separate communication.

RESPONSE:

Three additional copies of the analytical methods and validation reports for the bulk active ingredient and finished product are provided as separately bound review (red) copies. The following information is enclosed:

....continued

REFERENCE: ANDA 74-803
FLUOXETINE HYDROCHLORIDE CAPSULES, 20 mg

XVI. ANALYTICAL METHODS

1. Methods for New Drug Substance
   a. Test Methods, Specifications and Data
   b. Method Validation

2. Methods for Finished Drug Product and Stability Testing
   a. Test Methods, Specifications and Data
   b. Method Validation

The above referenced items are duplicates of Section XVI, Pages 16-00001 to 16-00179 of our original Application The three review copies contain this cover letter with a complete duplicate copy of Section XVI. The archival copy consists solely of the cover letter, since this information was previously submitted in the original application.

This completes the response to the comment in the Agency's letter dated *February 21, 1996.*

Sincerely,

BARR LABORATORIES, INC.

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

NAI "Patent Notice"

Barr Laboratories, Inc.

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

4/5/96

March 13, 1996

ORIG NEW CORRES

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

RECEIVED

MAR 1 4 1996

REFERENCE: **ANDA 74-803**
FLUOXETINE HYDROCHLORIDE CAPSULES, 20 mg

Reference is made to our pending Abbreviated New Drug Application dated *December 9, 1995* submitted under Section 505(j) of the Federal Food, Drug and Cosmetic Act for **FLUOXETINE HYDROCHLORIDE CAPSULES, 20 mg.**

At this time, we hereby amend our Application by certifying that Barr Laboratories, Inc., on February 28, 1996, served Eli Lilly & Co. (the patent and NDA holder) with the required Notice in accordance with 21 U.S.C. 355(j)(2)(B)(i) and (ii) with regard to U.S. Patent No. 4,314,081 and U.S. Patent No. 4,626,549.

This Notice met the content requirement as set forth in 21 C.F.R. 314.95(c).

This completes the present Amendment to our Application.

Sincerely,

BARR LABORATORIES, INC.

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

Noted 3-22-96

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

NTC "Patent Notice" 4/5/96

March 14, 1996

NEW CORRESP
NC

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

RECEIVED
MAR 15 1996
GENERIC DRUGS

REFERENCE: **ANDA 74-803**
FLUOXETINE HYDROCHLORIDE CAPSULES, 20 mg
AMENDMENT TO A PENDING APPLICATION

Reference is made to our pending Abbreviated New Drug Application dated *December 9, 1995* submitted under Section 505(j) of the Federal Food, Drug and Cosmetic Act for **FLUOXETINE HYDROCHLORIDE CAPSULES, 20 mg**.

At this time, we hereby amend our Application by providing evidence which verifies that Barr Laboratories, Inc., on February 28, 1996, served Eli Lilly & Co. (the patent and NDA holder) with the required Notice in accordance with 21 U.S.C. 355(j)(2)(B)(i) and (ii) with regard to U.S. Patent No. 4,314,081 and U.S. Patent No. 4,626,549.

Enclosed as Page 1 is a copy of the Return Receipt from Eli Lilly & Co. for the Notice which was delivered to Eli Lilly & Co. on March 4, 1996.

This completes the present Amendment to our Application and Patent Certification commitment as contained in our original Application, Page 1.

Sincerely,

BARR LABORATORIES, INC.

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

This Submission is comprised of **Page 1**.

NAL
"Patent infringed!"
7/2/96
ORIG NEW CORRES

FINNEGAN, HENDERSON, FARABOW, GARRETT & DUNNER, L.L.P.
1300 I STREET, N.W.
WASHINGTON, DC 20005-3315

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FACSIMILE 202•408•4400

BRUSSELS OFFICE:
AVENUE LOUISE 326, BOX 37
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WRITER'S DIRECT DIAL NUMBER
202/408-4068

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MINATO-KU, TOKYO 105, JAPAN
TELEPHONE 011•813•3431•6943
FACSIMILE 011•813•3431•6945

April 17, 1996

Food & Drug Administration
Office of Generic Drugs
(HFD-600)
7500 Standish Place
Rockville, Md. 20855

Via Federal Express

RECEIVED
APR 18 1996
GENERIC DRUGS

Re: Fluoxetine Hydrochloride Capsules, 20 mg
Abbreviated New Drug Application No. 74-803
Notification of Filing of Legal Action for Patent Infringement

Sir:

We represent Eli Lilly and Company ("Lilly"), owner of U.S. Patent Nos. 4,314, 081 and 4,626,549. We are sending you this letter on behalf of our client under 21 C.F.R. § 314.107(f)(2) to notify you of the following:

(1) On February 28, 1996, Mark E. Waddell of Bryan Cave L.L.P. sent a letter to Lilly by certified mail stating that the sender represented Barr Laboratories, Inc. ("Barr") and was providing information pursuant to section 505(j)(2)(B) of the Food, Drug and Cosmetic Act. The letter included the following information:

(i) The FDA has received an abbreviated new drug application by Barr containing bioavailability or bioequivalence data or information with respect to fluoxetine hydrochloride 20 mg capsules.

(ii) The abbreviated new drug application number is 74-803.

(iii) The established name, as defined in section 502(e)(3) of the Food, Drug and Cosmetic Act, of the proposed drug product is fluoxetine hydrochloride capsules, 20 mg.

(iv) The active ingredient, strength, and dosage form of the proposed drug product is fluoxetine hydrochloride, 20 mg capsules for oral administration.

(v) The patent number and expiration date, as known to Barr, of each patent alleged to be invalid, unenforceable, or not infringed is as follows:

U.S. Patent No. 4,314,081, which expires February 2, 2001, and
U.S. Patent No. 4,626,549, which expires December 2, 2003.

(2) Lilly received the letter on or about March 4, 1996.

Certification

We hereby certify that on April 10, 1996, Lilly filed an action for patent infringement against Barr in the United States District Court for the Southern District of Indiana (Case Number IP96-0491 C). Lilly alleges, among other things, that under 35 U.S.C. § 271(e)(2)(A), Barr's submission to the FDA of an abbreviated new drug application to obtain approval for the commercial manufacture, use, or sale of fluoxetine hydrochloride before the expiration of United States Patent Nos. 4,314,081 and 4,626,549 was an act that infringes claim 5 of United States Patent No. 4,314,081 and claim 7 of United States Patent No. 4,626,549.

We therefore respectfully request that the approval of Barr's abbreviated new drug application shall not be made effective until at least the expiration of the thirty-month period as provided by 21 U.S.C. § 355(j)(4)(B)(iii), subject to an appropriate ruling by the court.

Yours sincerely,

FINNEGAN, HENDERSON, FARABOW,
GARRETT & DUNNER, L.L.P.

By David S. Forman
David S. Forman

SDR/dem

cc: Mark E. Waddell, Esq.
Jan M. Carroll, Esq.

Barr Laboratories, Inc.

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

June 6, 1997

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

NEW CORRESP
NC/BIO
BIOAVAILABILITY

BIOEQUIVALENCE INFORMATION

REFERENCE: **ANDA 74-803**
FLUOXETINE HYDROCHLORIDE CAPSULES, 20 mg
AMENDMENT TO A PENDING APPLICATION

Reference is made to our pending Abbreviated New Drug Application dated *December 9, 1995* submitted under Section 505(j) of the Federal Food, Drug and Cosmetic Act for **FLUOXETINE HYDROCHLORIDE CAPSULES, 20 mg.**

The following response is to your letter dated *June 10, 1996* in which the following is stated:

The Office of Generic Drugs has reviewed the bioequivalence data submitted and the following comments are provided for your consideration.

COMMENT:

1. Regarding the single dose fasting study, please provide the following information which was missing from the submission:

   a. Stability data regarding the effect of room temperature storage during handling of the samples.

RECEIVED
JUN 0 9 1997
GENERIC DRUGS

cont...

Nadine 6-19-97

RESPONSE:

Please note that although the original ANDA submission did contain stability data, the report did not include data regarding the effect of room temperature storage during handling of the samples. The requested data were not included in the original submission since, at the time of the study, the Agency did not require this information.

Room temperature stability was not an issue because the following in-process stability controls were included with each analytical run.

1. **Standards and controls were done for each analytical run and**
2. **All project samples, standards, and controls for each run were handled simultaneously and were processed simultaneously.**

currently includes room temperature stability as part of their validation procedures and revalidated the assay as of March 1997. Barr is submitting in this application the "Limited Food Effects Study of Fluoxetine Hydrochloride Capsules, 20 mg" at pages 1 to 2158. data regarding the effect of room temperature storage during handling of the samples for both the "Single Dose Fasting Study" and the "Limited Food Effects Study of Fluoxetine Hydrochloride Capsules, 20 mg" are found at pages 1582 to 1583. These stability data show that fluoxetine and norfluoxetine are stable for at least 4 hours in room temperature plasma. The data are included in Method Validation Report LC105.1 Revision 1 entitled: Analysis of Fluoxetine and Norfluoxetine in Human Plasma (Sodium Heparin") dated March 1997 found in Appendix C to the Final Analytical Report at pages 1556 to 1661 of this submission.

- **Table 7A Room Temperature Stability for Fluoxetine see page 1582**
- **Table 7B Room Temperature Stability for Norfluoxetine see page 1583**

b. The batch/lot size for the test product, the assay potency and content uniformity data for both the test and reference products. In addition, the date of manufacture of the test product should be included.

cont...

RESPONSE:

The biobatch size for Barr Laboratories, Inc. test product Fluoxetine Hydrochloride Capsules, 20 mg Batch # 5R88719 used in the bioequivalence study entitled: "Single Dose Fasting Study" (and also in the "Limited Food Effects Study of Fluoxetine Hydrochloride Capsules, 20 mg"; see response to Comment 4) was capsules (page 12-00003; Exhibit 1). The batch size information is also found on the Master Formula in the original application on pages 11-00015 (unexecuted) and 12-00004 (executed) and are included again for your convenience in Exhibit 1 (pages 11-00015 and 12-00004).

The assay potency and content uniformity data for both the test and reference products were also submitted in original ANDA pages 06-02589 to 06-02592 and are included again for your convenience in Exhibit 2. The assay potencies for Barr Fluoxetine Hydrochloride Capsules, 20 mg, Batch #5R87719 and Dista Prozac®, 20 mg Pulvule Lot # 8AM94A were 99.1% and 100.6%, respectively. The content uniformity data were: $\bar{x}$ = 99.0% (95.7% to 103.4%) RSD = 2.30% for same Barr, and $\bar{x}$ = 99.9% (98.3% to 101.5%) RSD = 0.85% for Dista, respectively. The date of manufacture of the test product was the date of mixing 6/28/95 (12-00006; Exhibit 2) while the encapsulation date was 7/6/95 to 7/7/95 (12-00009 to 12-00010; Exhibit 2).

COMMENT:

2. The Physician's Desk Reference (PDR), 49 Ed. (pages 943-947) report the following statements:

   - A dose of 20 mg/day, administered in the morning, is recommended as the initial dose.

   - Studies comparing fluoxetine 20, 30, 40 and 60 mg/day to placebo indicate that 20 mg/day is sufficient to obtain a satisfactory antidepressant response.

cont...

- 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.

In your study, three capsules of 20 mg fluoxetine were administered to each subject. Please explain the rationale for administering a dosage which is three times higher than the recommended starting dose.

RESPONSE:

Barr Laboratories, Inc. was aware of the recommended dosing for fluoxetine (a dose of 20 mg administered once or twice a day up to a maximum dose of 80 mg/day) included in the PDR (pages 943-947) 49 Ed (at pages 2159 to 2163 of this submission). The determination to dose three capsules of the Fluoxetine Hydrochloride Capsules, 20 mg, a dosage three times higher than the recommended starting dose, was selected after careful evaluation of the following considerations.

During preliminary consideration of the appropriate design and dose selection for the bioequivalence study, FDA input was solicited on 4/18/95 when Barr Laboratories, Inc. submitted a written request for a bioequivalence guidance for Fluoxetine Hydrochloride Capsules.

- **NOTE: BARR PROPOSED TO USE A SINGLE 60 MG DOSE (3 X 20 MG CAPSULES OF FLUOXETINE HYDROCHLORIDE in the 4/18/95 Fax Transmission from Herb Luther, Barr Laboratories, Inc. to Mr. Jason Gross, CSO, Division of Bioequivalence, OGD, FDA. The Fax page was a cover for the 4/18/95 Barr letter requesting FDA comments and recommendations for bioequivalence studies for which FDA has no published guidelines. Dr. Luther's communication was specifically directed to the drug product Fluoxetine Hydrochloride Capsules (Prozac®) (at pages 2164 to 2166).**

- **On 4/28/95 the FDA (at pages 2167 to 2168) responded to the 4/18/95 request for bioequivalence guidance for Fluoxetine Hydrochloride Capsules. The 4/28/96 FDA guidance Reference No. Bio 95-060 included the following points.**

cont...

- Reviewed the potential need for a long washout period, (i.e., a minimum of at least 7 half-lives for the most slowly eliminated analyte (M-1) which would correspond to 9.2 weeks using the sponsor's values.

- Confirmed the dosing regimen to be within federal requirements. After an appropriate interval doses above 20 mg/d may be administered on a once a day or twice a day schedule and should not exceed a maximum dose of 80 mg/day. No IND is required since the proposed dose of 60 mg does not exceed the maximum single total daily dose of 80 mg 21 CFR 320.31 (b)(i).

- Note: The 4/28/95 FDA bioequivalence guidance for Fluoxetine Hydrochloride Capsules failed to mention the need for a limited food effect study to be conducted.

- Barr Laboratories, Inc. reviewed data obtained from a previous study experience with the 60 mg single dose conducted by . (at pages 2169 to 2177). No significant deleterious adverse effects or any adverse effects of any general interest were noted (verbal communication).

  - Fluoxetine and Norfluoxetine plasma levels following administration of a single oral dose of fluoxetine Hydrochloride 60 mg, i.e., single dosing with three 20 mg capsules of Prozac® were compared with single dosing of three 20 mg capsules Apo-fluoxetine 20 mg capsules (pages 2169 to 2175).

  - In this study, the limit of detection for fluoxetine was established as below 1.0 ng/mL and the limit for norfluoxetine was established as between 1.0 and 2.0 ng/mL (page 2176). The lower limits of quantification were retrospectively set for fluoxetine and norfluoxetine at 2 and 5 ng/mL, respectively (page 2177).

- The 1995 PDR 49 ed (PDR pages 943 to 947; pages 2159 to 2163 this submission) and the AHFS 95 Drug Information (pages 1483 to 1494; pages 2178 to 2191 this submission) report a 40 mg dose of fluoxetine may provide a C-max of 15-55 ng/mL over a range of 1.5 to 12 hours after oral administration. The data, using a study design of a 60 mg single dose (at page 2169) also transmitted as a personal communication to reported a fluoxetine C-max of 40.96 +/-8.7 ng/mL and a

cont...

norfluoxetine C-max of 22.6 +/- 8.2 ng/mL after the single 60 mg oral dose. The analytical laboratory for the study reported their lower limit of quantitation (LLOQ) would *"probably"* be 1 ng/mL 6/20/96 letter at pages 2192 to 2193).

- **Both the Physicians Desk Reference (pages 2159 to 2163) and the AHFS, (pages 2178 to 2191) indicated that variable blood concentrations could be expected to occur after dosing with fluoxetine. Since the expected LLOQ was 1 ng/mL and the metabolite could very conceivably produce data which might not exceed peak levels of 10 ng/mL, a 40 mg dose was deemed unacceptable and the dose of 60 mg was selected. Barr Laboratories, Inc. and investigators, medical personnel and IRB all agreed to proceed with the 60 mg dose.**

- **Barr Laboratories also consulted with the selected to dose the bioequivalency study and shared all of the above data with them 6/20/96 letter at pages 2192 to 2193).**

- **The medical team working with had excellent previous experience working with this product within the full range of doses allowed under labeling. Neither the medical investigators, medical colleagues, clinical investigators, or IRB had any concerns with the 60 mg dose beyond potential drowsiness or dizziness. All usual and customary precautions were taken to monitor for either the drowsiness or dizziness response. 6/20/96 letter at pages 2192 to 2193).**

In summary, Barr Laboratories, Inc. and reviewed all of the data contained in the above paragraphs and in the FDA response to the protocol submitted to the FDA and concluded that administration of the single 60 mg dose of fluoxetine, using Fluoxetine Hydrochloride Capsules, 20 mg, fulfilled the FDA scientific and regulatory requirements.

COMMENT:

3. Provide a brief description on the analytical methodology procedure.

cont...

REFERENCE: ANDA 74-803 Page 7
FLUOXETINE HYDROCHLORIDE CAPSULES, 20 mg

RESPONSE:

The analytical methodology used for Barr's Fluoxetine 20 mg Capsule fasting study is entitled "LC105.1- Analysis of Fluoxetine and Norfluoxetine in Human Plasma." A brief summary of this follows. A 1.0 mL sample volume is required for analysis. The sample is kept frozen at -20°C prior to analysis. At the time of analysis fluoxetine, norfluoxetine and the internal standard protryptyline are extracted from basic, heparinized human plasma using hexane/isoamyl alcohol. The compounds are then acid back-extracted into % phosphoric acid. separation is achieved by reverse phase on a column. Fluorescence detection with an excitation wavelength of 230 nm and an emission wavelength of 305 nm is used to detect fluoxetine and norfluoxetine. This method is validated with a minimum quantifiable level of ng/mL for fluoxetine and ng/mL for norfluoxetine. The upper level is ng/mL for each analyte. A linear weighted (1/concentration squared) least squares regression analysis is used to quantitate unknown samples.

COMMENT:

4. Due to the fact that the labeling of the reference listed drug (RLD) indicates that the drug may be administered with or without food and also "food does not appear to affect the systemic bioavailability of the drug", a food study is required for this product to demonstrate that the generic formulation will behave similarly to the RLD formulation under both fasting and non-fasting conditions.

   The single-dose post-prandial bioequivalence study should use a three-way crossover design comparing equal doses of the test and reference products. The study should be conducted in a random, three-treatment (Treatments 1&2: the test and reference products should be dosed immediately after standard breakfast, Treatment 3: the test product should be dosed under fasting conditions), three-period, cross-over design using a minimum of 18 healthy subjects. An adequate wash-out period between periods 1, 2, and 3 dosing should be applied.

cont...

Note: The standard breakfast should be as follows:

one buttered English muffin
one fried egg
one slice of American cheese
one slice of Canadian bacon
one serving of hashed brown potatoes
eight fluid ounces (240 mL) of whole milk
six fluid ounces (180 mL) of orange juice

RESPONSE:

"A Limited Food Effects Study of Fluoxetine Hydrochloride Capsules, 20 mg" was conducted by Protocol # (at pages 1 to 2158). The study was a randomized, single dose, three-way crossover design involving 24 healthy male subjects under non-fasting conditions. The standard breakfast as described in Comment 4 above was administered to the test subjects. The study compared Fluoxetine Hydrochloride Capsules, 20 mg by Barr Laboratories, Inc. Lot # 5R87719, Expiration date none available, with Prozac ® 20 mg Pulvules ® by Dista Products Company, A Division of Eli Lilly Industries, Inc. (A subsidiary of Eli Lilly & Company) Lot # 8AM94A, Exp. date: Oct 1, 1997.

Please note that the same Barr Batch # 5R88719 and the same Dista Lot # 8AM94A, Exp. Date October 1, 1997, were also used to dose volunteer subjects enrolled in both bioequivalence studies, i.e., in the "Limited Food Effects Study of Fluoxetine Hydrochloride Capsules, 20 mg" (pages 1 to 2158) and in the "Single Dose Fasting Study" (original ANDA pages 06-00006 to 06-00030D, Exhibit 3; pages 2194 to 2195).

The study dates for the "Limited Food Effects Study of Fluoxetine Hydrochloride Capsules, 20 mg" were:

cont...

REFERENCE: ANDA 74-803
FLUOXETINE HYDROCHLORIDE CAPSULES, 20 mg

Period 1: August 10 through September 08, 1996
Period 2: October 12 through November 10, 1996 and
Period 3: January 04 through February 02, 1997.

An adequate washout period between periods 1 and 2 and 2 and 3 was applied as per the 4/28/95 FDA bioequivalence guidance for Fluoxetine Hydrochloride Capsules. The OGD recommended a minimum washout period of at least seven half lives for the most slowly eliminated analyte (M-1 in this case). This would correspond to 9.2 weeks using the sponsor's values (pages 2167 to 2168). The elapsed times between each dosing period are cited below.

- **Dosing Date Aug. 10, 1996 Period 1 and Dosing Date Oct. 12, 1996 Period 2 = elapsed time of 9 weeks**
- **Dosing Date Oct. 12, 1996 Period 2 and Dosing Date Jan 04, 1997 Period 3 = elapsed time of 12 weeks**

Thus, an adequate wash out period varying between 9 and 12 weeks existed between periods 1 and 2 and 2 and 3, respectively.

In conclusion, the data included in the present submission indicate that Barr Laboratories, Inc. Fluoxetine Hydrochloride Capsules, 20 mg, behaved similarly to the Dista Products Company Prozac® 20 mg Pulvules under both fasting (at original ANDA pages 06-00038 to 06-00039; Exhibit 4) and non-fasting conditions (at pages 5 and 6 of this submission; also included in Exhibit 4 for your convenience). Food did not appear to effect the systemic bioavailability of the drug and thus Barr Laboratories, Inc. drug may be administered with or without food. This fact is indicated in the labeling of our generic product and agrees with the labeling for the referenced listed drug.

COMMENT:

5. Please submit a comparative dissolution study for both the test and reference drug products, performed as part of the same experiment (within 8-10 working days). The dissolution data should include the number of capsules (not less than 12), type and volume of the medium, the method that has been used, and the date the testing was performed. The dissolution testing should be done on capsules from the same lot number

cont...

that was used in the *in vivo* bioequivalence study. The comparative dissolution profiles (in a side-by-side tabular format, if possible) should be submitted with raw dissolution data, the dissolution mean, the range (high, low), and the percentage of coefficient of variation (% C.V.), and date(s) of analysis.

RESPONSE:

The original ANDA submission contained the Analytical Research and Development In-Vitro Comparative Study for Barr Fluoxetine Hydrochloride Capsules, 20 mg Lot # 5R87719 (Pages 06-02589 to 06-02592, Exhibit 2). This report also includes the dissolution testing done on Dista Prozac® 20 mg Pulvules Lot # 8AM94A.

This report contains the comparative dissolution study for both the test and reference drug products performed as part of the same experiment (conducted on 7/11/95 for the test product and 6/3/95 and 6/27/95 for the reference product (page 06-02590; Exhibit 2). Barr Laboratories, Inc. acknowledges that the time between the comparative dissolution testing of the test and the reference products is more than 8 to 10 days; however, Barr has now instituted a new SOP requiring all dissolution testing to be done within the required 8 to 10 days.

The in-vitro comparative dissolution study indicates that 12 capsules were used from each product, describes the type and volume of the medium employed as 900 mL of O.1 N HCL, and indicates that the dissolution testing was performed using USP 23 Dissolution Applications II (paddles) following the procedure as described in Barr Method TM-419.

Both testing methods and the updated were included in the original submission. Since the original ANDA submission, Barr has revised the analytical method to at pages 2196 to 2218 in this submission.

The dissolution testing was done on capsules from the same lots that were used in the in vivo bioequivalence studies. This fact is documented in our response to Comment # 4.

cont...

This completes the present response to the Agency's letter dated June 10, 1996 and a copy is attached as per your instructions.

Sincerely,

BARR LABORATORIES, INC.

Claire M. Lathers, Ph.D., F.C.P.
Chief Scientific Officer

This Submission is comprised of **Pages 1 to 2218 and Exhibits 1 to 4.**

Barr Laboratories, Inc.

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

April 29, 1998

BIOAVAILABILITY

ORIG AMENDMENT

4/98

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

BIOEQUIVALECY AMENDMENT

REFERENCE: **ANDA 74-803**
FLUOXETINE CAPSULES, USP 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.

Reference is also made to Barr's bioequivalency data submitted on 6/6/97 and to your letter dated January 8, 1998 in which the following is stated:

COMMENT:

Your dissolution testing of the test product in 900 ml of 0.1N HCL, using USP 23, apparatus II (paddle), at 50 rpm is not acceptable.

Please conduct the dissolution testing in 900 ml of water, using USP 23, apparatus II (paddle), at 50 rpm with valid assay methodology.

The dissolution results should meet the following specifications: Not less than % of the labeled amount of the drug (Fluoxetine) in the dosage form is dissolved in 30 minutes.

Note: The dissolution should be conducted for both the test and reference products, performed simultaneously. The lot numbers of the samples undergoing dissolution testing should be identical to those used in the in-vivo study. The dissolution profile for the test and reference products should include dissolution time points below and above the specification time point (30 minutes).

RECEIVED

APR 30 1998

GENERIC DRUGS

RESPONSE:

Barr has conducted the dissolution testing for both test and reference products using water as the dissolution medium. The lot numbers of the samples undergoing dissolution testing are identical to those used in the in-vivo study. The dissolution profile time points were 10, 15, 30 and 45 minutes.

Enclosed please find a copy of the "In-Vitro Comparative Study Report RD 98-033 for Fluoxetine Capsules, USP 20 mg, Lot number 5R87719, Manufactured by Barr Laboratories, Inc. and PROZAC®, 20 mg Lot Number 8AM94A manufactured by DISTA PRODUCTS COMPANY" dated March 2, 1998. Also please find a copy of Barr's finished product test method, TM-419F which has been updated to conform to the dissolution method proposed in the Pharmacopeial Forum, volume 23, number 2, and in response to the Agency's request.

The "In-Vitro Comparative Report" contains dissolution profile, assay and content uniformity for Barr's Fluoxetine Capsules, USP by Barr and DISTA's Prozac. The results are summarized in the form of tables, and demonstrate that the two products compare favorably.

Also please find a copy of a letter from USP stating that the dissolution in Pharmacopeial Forum 23(2) was changed from % to %. The % value published in the Pharmacopeial Previews section of PF 21(4) was in error.

This completes Barr's response to the Agency's letter dated January 8, 1998. 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

/kdb
Enc.

This Submission is comprised of **Pages 01 through 38.**

Barr Laboratories, Inc.

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

June 15, 1998

ORIG AMENDMENT

labeling review N/AC
drafted 7/16/98
avg

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

MAJOR AMENDMENT

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

Reference is made to our pending Abbreviated New Drug Application dated December 9, 1995 submitted under Section 505(j) of the Federal Food, Drug and Cosmetic Act for **FLUOXETINE HYDROCHLORIDE CAPSULES, 20 MG**. Please note the name change to Fluoxetine Capsules, USP 20 mg in accordance with the USP 23, Seventh Supplement monograph for this product.

This Major Amendment is being sent in response to your letter dated July 9, 1996 and to Supplement the pending application with the additional strength of Fluoxetine Capsules, USP 10 mg.

Part I: Responses to comment letter dated July 9, 1996

REFERENCE: ANDA 74-803 Page 2
FLUOXETINE CAPSULES, USP 20 MG AND
SUPPLEMENTAL APPLICATION FLUOXETINE CAPSULES,
USP 10 MG

COMMENT:

1. CHEMISTRY DEFICIENCIES

A. REGARDING SYNTHESIS:

DMF HAS BEEN FOUND TO BE DEFICIENT. A LETTER HAS BEEN SENT TO THE HOLDER IDENTIFYING THESE ISSUES. ALL DEFICIENCIES MUST BE CORRECTED BEFORE THE APPROVAL OF THIS APPLICATION.

RESPONSE:

Barr Laboratories, Inc. has contacted the holder of DMF regarding this comment. On January 14, 1998, submitted their response to the Agency's July 31, 1997 deficiency letter on Fluoxetine HCl. This response also included a complete update to DMF which was prepared to meet current documentation standards. Attached on Pages 0002 through 0003 is a copy of the letters from explaining their DMF update as well as the cover page of their response to FDA.

COMMENT:

2. REGARDING RAW MATERIAL CONTROLS:

A. PLEASE REVISE YOUR SPECIFICATIONS FOR FLUOXETINE HYDROCHLORIDE TO REPLACE "REPORT RESULTS" FOR RELATED SUBSTANCES AND "SEE TEST RECORD FOR LIMITS" FOR PARTICLE SIZE WITH SPECIFICATIONS BASED ON DATA ACCRUED TO DATE.

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

RESPONSE:

Barr has revised its Related Compounds specifications for Fluoxetine Hydrochloride, USP to replace "Report Results" as follows:

Related Compounds Tests	Limits	
+/- 1-Phenyl-3-methylamino-1-propanol (methaminol) (Barr Impurity I)	NMT	%
1-Phenyl-3-methylamino-propane (methamine) (Barr Impurity II)	NMT	%
p-Triflouromethylphenol (Barr Impurity III)	NMT	%
4-Chlorobenzotriflouride (Barr Impurity IV)	NMT	%
Fluoxetine Related Compound A	NMT	%
Individual Unknown Impurities	NMT	%
Total Known and Unknown Impurities	NMT	%

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

Barr intends to continue to use its own validated test method for Barr Impurities I, Impurity II, Impurity III, Impurity IV, and Individual Unknown Impurities. Barr's method offers superior chromatography, yields comparable results to the USP 23, Supplement Seven method, and is capable of quantitating Barr Impurity I, Impurity II, Impurity III and Impurity IV. Barr's method of quantitation via external standardization for each impurity is more reliable than the USP method, which quantitates using area percent normalization. In addition, the USP method does not resolve Barr Impurity IV. However, Barr adopted the USP 23, Seventh Supplement Chromatographic Purity Test Method for Related Compound A since Barr's method does not resolve this compound. To calculate the Total Known and Unknown Impurities, Barr will total the impurities detected using the Barr method with the Related Compound A from the USP method. As supporting documentation for Barr's Related Compounds Tests, enclosed please find the memorandum dated 2/3/98, "Evaluation of Chromatographic purity test procedure from USP 23, Supp. 7 for Fluoxetine Hydrochloride" (Pages 0004 through 0007).

Please note that the specifications for Barr Impurity I (USP Impurity -[2-(methylamino)ethyl]-benzenemethanol) and Barr Impurity II (USP Impurity 1-Phenyl-3-methylamino-propane(methamine)) match the USP 23, Seventh Supplement specifications for these impurities. In addition, the specifications for Individual Unknown Impurities and Total Known and Unknown Impurities are identical to the USP 23, Seventh Supplement specifications.

Barr has petitioned USP to change the Fluoxetine Hydrochloride monograph specification for Total Known and Unknown Impurities from % (see attached letter to Dr. Todd Cecil, Scientist, USP dated June 10, 1998 and supporting documentation on Pages 0008 through 0038). If USP adopts the specification of % for Total Known and Unknown Impurities, Barr will update its method and specification test record accordingly and submit them in the Annual Report.

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

Regarding Particle Size, Barr has revised its specifications to the following based on data accrued to date:

Particle Size Test	Limits		
	D (90%)	NMT	µm
	D (50%)	NLT	µm

Enclosed please find Barr's current Acceptance Tests for Raw Materials for Fluoxetine Hydrochloride, USP (RM-318C) and corresponding QC Raw Material Specifications & Test Record (Barr Specification No.: 01-0305, Rev. 3). These have been updated to reflect the changes noted above and to agree with USP 23, Seventh Supplement monograph for Fluoxetine Hydrochloride, USP (see Pages 0039 through 0062). Also enclosed is the method validation report (RD97-137) concluding that Barr Laboratories, Inc. related compounds test method for Fluoxetine Hydrochloride, USP is equivalent to the USP 23, Supplement 7 method for detecting and quantitating Barr Impurities I, II, III and IV (see Pages 0063 through 0096).

Also enclosed on Pages 0097 through 0098 please find a copy of the executed QC Raw Material Specifications & Test Record for Lot H362 of Fluoxetine Hydrochloride used to manufacture Barr's submission batch. This test record was submitted as supplemental pages 08-00017 through 08-00018 in the original application. This lot of material meets the specifications for Related Compounds and Particle Size that are stated above.

COMMENT:

B. PLEASE REVISE YOUR SPECIFICATIONS FOR FLUOXETINE HYDROCHLORIDE TO INCLUDE TESTS FOR MELTING POINT AND MOISTURE.

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

RESPONSE:

Barr commits to testing Fluoxetine Hydrochloride, USP for moisture using Karl Fischer analysis with a specification of NMT %, which is consistent with the 1997 European Pharmacopoeia and USP 23, Seventh Supplement monographs. Barr revised the Acceptance Tests for Raw Materials for Fluoxetine Hydrochloride, USP (RM-318C) and corresponding QC Raw Material Specifications & Test Record (Barr Specification No.: 01-0305, Rev. 3) to include the moisture test and specification (see Pages 0039 through 0062).

The melting point test for Fluoxetine Hydrochloride, USP is currently not contained in USP 23, Seventh Supplement monograph or the 1997 European Pharmacopoeia monograph. Mr. Ashley, Manager of Technical Affairs, Barr Laboratories, Inc. contacted Dr. Cecil, Scientist, USP on November 26, 1996 regarding this matter. In response to questions posed by Mr. Ashley, Dr. Cecil stated that neither the original manufacturer nor FDA had requested USP to add a specification for melting point to the Fluoxetine Hydrochloride monograph. If FDA were to make this request, Mr. Cecil further stated that the test would probably be added to the "Description and Solubility Section", which is a non-binding section for non-required tests and is only used for informational purposes. Therefore, Barr is not adopting the melting point test at this time.

Attached please find a letter to USP from Barr dated January 8, 1997 requesting the USP to not adopt the melting point test for this monograph (see Pages 0099 through 0100) as well as an acknowledgment from USP dated February 11, 1997 documenting that Barr's proposal is under consideration (see Page 0101).

COMMENT:

C. SINCE THE DRUG SUBSTANCE EXISTS AS A RACEMIC MIXTURE, PLEASE REVISE YOU SPECIFICATIONS TO INCLUDE TESTING FOR OPTICAL ROTATION TO ENSURE THAT A RACEMIC MIXTURE IS USED.

REFERENCE: ANDA 74-803 Page 7
FLUOXETINE CAPSULES, USP 20 MG
AND SUPPLEMENTAL APPLICATION
FLUOXETINE CAPSULES, USP 10 MG

RESPONSE:

Optical Rotation is not a USP test in the Fluoxetine Hydrochloride, USP monograph. Barr will, however, add a test for Specific Rotation with limits of –2.500° to +2.500° in response to the Agency's request and to be consistent with the European Pharmacopoeia monograph. This test was run on Barr's submission batch, Lot H362, and the result was 0.00° (racemic mixture) (see Celsis Laboratory Group testing results dated 2/2/98 on Page 0102). Barr revised the Acceptance Tests for Raw Materials for Fluoxetine Hydrochloride, USP (RM-318C) and corresponding QC Raw Material Specifications & Test Record (Barr Specification No.: 01-0305, Rev. 3) to include the optical rotation test and specification (see Pages 0039 through 0062).

COMMENT:

D. YOUR ASSAY SPECIFICATION (%) IS NOT CONSISTENT WITH THE SUPPLIER'S SPECIFICATION OF %. PLEASE REVISE YOUR SPECIFICATION TO BE CONSISTENT WITH THE SUPPLIER OR SUBMIT JUSTIFICATION AND SUPPORTING DATA FOR THE WIDER SPECIFICATION.

RESPONSE:

Barr has revised its specification for Assay from %" to agree with USP 23, Seventh Supplement specification of ' %". Barr has also adopted the USP method for Assay testing. See Pages 0039 through 0062 for copies of Barr's Acceptance Tests for Raw Materials for Fluoxetine Hydrochloride, USP (RM-318C) and corresponding QC Raw Material Specifications & Test Record.

Please note that Barr submitted a petition to USP to adopt the Assay specification of %" (see attached letter to Dr. Todd Cecil, Scientist, USP dated June 10, 1998 and supporting documentation on Pages 0008 through 0038). If USP adopts this specification, Barr will update its method and specification test record accordingly, and submit them in the Annual Report.

REFERENCE: ANDA 74-803 Page 8
FLUOXETINE CAPSULES, USP 20 MG
AND SUPPLEMENTAL APPLICATION
FLUOXETINE CAPSULES, USP 10 MG

COMMENT:

E. REGARDING THE REFERENCE STANDARD FOR FLUOXETINE HYDROCHLORIDE AND RELATED COMPOUNDS:

II. PLEASE INDICATE THE SOURCE OF REFERENCE STANDARDS FOR FLUOXETINE HYDROCHLORIDE AS WELL AS ALL RELATED COMPOUNDS.

RESPONSE:

the bulk drug substance manufacturer, provided Barr with the following reference standards:

- **Fluoxetine Hydrochloride (Manufacturer's Lot 195, Barr Lot H220)**
- **Impurity (±) 1-phenyl-3-methylamine-1- propanol/ -[2-(methylamino)ethyl]-benzenemethanol (Barr Impurity I)**
- **Impurity 1-phenyl-3-methylamino-propane (Barr Impurity II)**
- **Impurity p-trifluoromethylphenol/4-Hydroxybenzotriflouride (Barr Impurity III)**
- **Impurity 4-Chlorobenzotrifluoride (Barr Impurity IV)**

Please note that Barr Impurity IV is now commercially available from Acros Janssen Pharmaceuticals. Barr is currently purchasing Impurity IV from this source.

COMMENT:

II. PLEASE DESCRIBE ANY IN-HOUSE QUALIFICATION PROCEDURES OR PURIFICATION STEPS USED FOR ALL REFERENCE STANDARDS PRIOR TO USE.

REFERENCE: ANDA 74-803 Page 9
FLUOXETINE CAPSULES, USP 20 MG
AND SUPPLEMENTAL APPLICATION
FLUOXETINE CAPSULES, USP 10 MG

RESPONSE:

Barr Laboratories, Inc. and Apotex, Inc. are partners in the patent litigation versus Eli Lilly & Co. At the time Barr manufactured the submission batch, Apotex Inc.'s subsidiary, was also developing the liquid Fluoxetine HCl dosage form. Therefore, provided Barr with a Fluoxetine HCl reference standard. The standard was accompanied with "Reference Standard Specification and Certificate of Analysis" records. When Barr manufactured the submission batch there was no USP reference standard. Therefore, certification was accepted. Subsequently, Barr qualified Lot #H220 as its in-house reference standard (see Pages 0103 through 0113) for the supporting report and documentation).

Barr has established standard operating procedures to govern the qualification of all in-house reference standards prior to use. In general, this procedure defines primary, secondary and impurity reference standards. Primary reference standards obtained from standard setting agencies may be used when accompanied by a Certificate of Conformance ("COC") and containing information on storage, expiration, and use. A Certificate of Analysis ("COA") must accompany secondary or in-house reference standards for each lot received. Barr only uses these reference standards for quantitation after full monograph testing has established their equivalence to the current USP/Barr monograph requirements. In addition, the material must have been tested against a primary reference standard as an in-house reference standard, if applicable. For non-USP impurity/related compounds, Barr obtains impurity/related compound primary reference standards from the manufacturer of the bulk chemical. A COA accompanies this material to certify its identity and purity, if available.

COMMENT:

III. PLEASE SUBMIT SUPPLIER AND IN-HOUSE (IF APPLICABLE) CERTIFICATE OF ANALYSIS FOR YOUR REFERENCE STANDARDS FOR FLUOXETINE HYDROCHLORIDE AS WELL AS ALL RELATED COMPOUNDS.

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

Attached please find the following Certification of Analyses and additional supporting documentation for the reference standards for Fluoxetine Hydrochloride and Related Compounds used to test the submission batch:

Fluoxetine Hydrochloride Reference Standard:

- Reference Standard Specification and Certification of Analysis ("COA") (Manufacturer's Lot 195) (see Pages 0103 through 0106).
- Final Report dated June 17, 1996 documenting the certification of Fluoxetine Hydrochloride secondary reference standard (Manufacturer's Lot 195) (see Pages 0107 through 0110).
- Barr's subsequent COA for in-house qualification of reference standard, Manufacturer's Lot 195 (see Pages 0111 through 0113).

Related Compounds Reference Standards:

- COAs for Barr Impurities I, III, and IV from (see Pages 0114 through 0116).
- COA for Barr Impurity IV from (see Page 0117). Please note that Impurity IV is now commercially available from Barr is currently purchasing Impurity IV from this source.
- Correspondences from (distributor for regarding their inability to provide a COA for Barr Impurity II, Lot No. ST 250 (see Pages 0118 through 0120) as well as a COA for Lot No. 6820, a subsequent Lot of Impurity II received from

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

COMMENT:

3. REGARDING MANUFACTURING AND PROCESSING:

A. PLEASE REVISE YOUR MASTER BATCH RECORD TO INCLUDE THE MANUFACTURER, MODEL, AND MODE OF OPERATION (VERTICAL OR HORIZONTAL) OF THE HIGH SHEAR MIXER.

RESPONSE:

Barr has revised its manufacturing master (master batch record) to include the manufacturer and model of the high shear mixer as follows:

Manufacturer:
Model: Gral 600

The mode of operation of the Gral 600 high shear mixer is vertical. Barr does not routinely include this information in its manufacturing masters.

Attached on Pages 0121 through 0131 is a copy of the updated manufacturing master, master control number 087701A3 (1/26/98) for Fluoxetine Hydrochloride Capsules, USP 20 mg. The following changes were made:

- Added "USP" to product name (active raw material and finished product) to agree with USP 23, Seventh Supplement monographs
- Changed recording of weights to four significant digits to ensure weighing within the capability of Barr's scales
- Updated ingredient names to be consistent with vendors' descriptions
- Updated format

- 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 manufacturing revision, the next alpha character signals if a minor change has been made in equipment (i.e., Annual Report submission), and the last numeric digit specifies the site of manufacture. For example,

  0873 = Product Code for Fluoxetine Capsules, USP 20 mg
  01 = Revision #1
  A = Identical Equipment
  2 =

- Tightened Accountability Range from %" to %" (step
- Clarified the identification of waste in step by adding "Identify Origin if Applicable"
- Added "Any change to the start-up encapsulation speed must be documented on the encapsulation monitoring record" and added a line to record the encapsulation speed (step
- Added a column to record the encapsulation speed on the encapsulation monitoring record
- Removed spaces throughout to record F.P. thickness, hardness and friability since this information is not applicable for a capsule product

COMMENT:

B. PLEASE REVISE YOUR MASTER BATCH RECORD TO INCLUDE OSCILLATOR/MESH SETTINGS FOR SCREENING THE GRANULATION.

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

RESPONSE:

The manufacturing master (master batch record), submitted in the original application on Pages 11-00014 through 11-00025, already specifies the oscillator/mesh settings used for screening the granulation. Specifically, steps state "...through an Oscillator fitted with a mesh screen (Equip. No.:)..." For your convenience enclosed please find a copy of Page 11-00017 containing steps

COMMENT:

C. PLEASE REVISE YOUR MASTER BATCH RECORD TO INCLUDE THE RATE OF ENCAPSULATION (NOMINAL OR RANGE IN CAPSULES/HOUR) AS WELL AS ANY LIMITS ON ENVIRONMENTAL CONDITIONS (E.G. TEMPERATURE, RELATIVE HUMIDITY) FOR THE ENCAPSULATION PROCESS.

RESPONSE:

Part of Barr's normal validation process includes validating the full range of the encapsulation speeds. Upon completion of the three full-scale process validation batches, the manufacturing master (master batch record) is updated to include the validated rate of encapsulation. Please note that the enclosed manufacturing master, MC# 087701A3 (Pages 0121 through 0131) has been updated to include a speed column on the encapsulation monitoring record, a place to record the encapsulation speed, and a note specifying that any change to the start-up encapsulation speed must be documented on the encapsulation monitoring record (step 15). Regarding the environmental conditions during the encapsulation process, Barr has a standard operating procedure for the manufacturing areas and manufacturing process concerning the environmental conditions. The procedure states that the temperature limit is 59°F – 86°F and that the humidity be not more than %. The temperature and humidity are monitored in all manufacturing areas.

REFERENCE: ANDA 74-803 Page 14
FLUOXETINE CAPSULES, USP 20 MG
AND SUPPLEMENTAL APPLICATION
FLUOXETINE CAPSULES, USP 10 MG

COMMENT:

4. REGARDING CONTAINER/CLOSURE SYSTEMS:

A. PLEASE SUBMIT USP <671> CONTAINERS-PERMEATION TESTING RESULTS FOR THE PROPOSED CONTAINER/CLOSURE SYSTEM.

RESPONSE:

Enclosed on Pages 0133 through 0134 please find USP 23 <671> water vapor permeation testing results conducted by on behalf of Barr Laboratories, Inc. for the following proposed container/closure system:

100: 60 cc container/ 33 mm metal cap

COMMENT:

A. WE STRONGLY SUGGEST THAT THE SMALLEST CONTAINER/CLOSURE SYSTEM INCLUDED IN THE APPLICATION BE EQUIPPED WITH A CHILD RESISTANT CLOSURE. PLEASE COMMENT.