CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

74803

ADMINISTRATIVE DOCUMENTS

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: August 2, 2001

FROM: Gary J. Buehler
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

/S/ 8/2/01

SUBJECT: ANDA 74-803
Fluoxetine Hydrochloride Capsules
Barr Laboratories, Inc.

TO: The Record Regarding U.S. Patent No. 6,258,853

July 10, 2001, U.S. Patent No. 6,258,853 (the '853 patent) was issued to Stowell, et.al. The abstract of the patent states" The present invention relates to novel pharmaceutical formulations and methods of using Form A of fluoxetine hydrochloride" .

On July 18, 2001, aai Pharma (aai) submitted a letter to the Agency under 21 C.F.R. 314.53(f) to advise the agency that the holder of NDA 18-936, Eli Lilly & Co. (Lilly) for Prozac® (fluoxetine hydrochloride) has failed to submit required patent information under 21 U.S.C. 355(c)(2) with respect to the '853 patent. aai claims that the patent meets all the legal requirements for listing and that Lilly must list the patent in Approved Drug Products with Therapeutic Equivalence Evaluations (the Orange Book). aai requested that FDA contact Lilly to confirm the correctness of Lilly's omission of information with respect to the '853 patent. aai also stated that FDA has an obligation to effect the Congressional intent of protecting patent owner rights whether or not the patent owner or licensee is an NDA applicant.

On July 23, 2001, the FDA issued a letter to Lilly asking Lilly to review the patent challenge submitted under 314.53(f) and to confirm whether the patent information for NDA 18-936 is correct.

On July 31, 2001, Lilly replied to the FDA's July 23, 2001, letter and stated they reviewed the challenge and that the patent information contained in the Orange Book is correct. Lilly stated

that no changes need to be made to the patent and exclusivity information addendum of the Orange Book.

On August 2, 2001, the Agency fully approved applications for fluoxetine hydrochloride that were otherwise ready for approval. All scientific and regulatory issues had been resolved. All patent and exclusivity information currently listed in the Orange Book had been addressed.

The statute 21 U.S.C. 355(c)(2) states that the holder of an approved application shall file with the Secretary, the patent number and the expiration date of any patent which claims the drug for which the application was submitted, or which claims a method of using such drug, and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner engaged in the manufacture, use, or sale of the drug. Because the NDA holder, Lilly, declined to list the '853 patent, the Agency did not list the patent. The Agency's ministerial role in the patent listing process is limited. The statute requires the Agency to publish the patent after it is submitted to the Agency by the applicant. The Agency does not independently list patents, which are not submitted to it by the applicant for listing. The Agency fulfilled its ministerial role by forwarding the patent challenge submitted under 21 C.F.R. 314.53(f) for the '853 patent to the NDA applicant, Lilly.

REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: **74-803** Date of Submission: **June 15, 1998**

Applicant's Name: **Barr Laboratories, Inc.**

Established Name: **Fluoxetine Capsules USP, 10 mg and 20 mg**

Labeling Deficiencies:

1. GENERAL COMMENTS

   a. Revisions related to you previously via fax dated July 14, 1998 are preceded by an asterisk (*).

   b. Section 126 of Title I of the FDA Modernization Act of 1997, amends Section 503(b)(4) of the Federal Food, Drug, and Cosmetic Act to require, at a minimum, that prior to dispensing, the label of prescription products contain the symbol "Rx only". A GUIDANCE FOR INDUSTRY entitled "Implementation of Section 126 of the Food and Drug Administration Modernization Act of 1997 Elimination of Certain Labeling Requirements", was revised July 1998 and posted at Internet site: **http://www.fda.gov/cder/guidance/index.htm.** Please note that Section IV, "Frequently Asked Questions" offers guidance on placement of the symbol on all labels and labeling.

2. CONTAINER (100s) 10 mg and 20 mg

   See GENERAL COMMENTS above.

3. INSERT

   a. GENERAL COMMENTS

      i. See GENERAL COMMENTS above.

*ii. Due to recent revision of the insert labeling of the reference listed drug, Prozac® (Fluoxetine) Capsules (NDA 18-936 -- Approved March 13, 1998; Revised January 1998), please make the following changes:

iii. We recognize your intent to market this product before the patent expiration dates of the listed drug. Please note, however, that after November 21, 1999, the information regarding bulimia must be included in your labeling.

iv. Delete "hydrochloride" throughout the text of the insert except in the following locations:

A). The chemical name.

B). The last sentence of the first paragraph.

C). The second paragraph.

D). The first sentence of the third paragraph.

b. CLINICAL PHARMACOLOGY

Absorption, Distribution, Metabolism, and Excretion

i. Systemic Bioavailability, Second paragraph, first sentence - The capsule and oral solution dosage forms of fluoxetine are bioequivalent.

ii. Renal Disease, last sentence - under **PRECAUTIONS** and **DOSAGE AND ADMINISTRATION**). [delete bold print from word "and").

c. INDICATIONS AND USAGE

Depression, third paragraph - The second sentence (The efficacy of ...) Begins a new paragraph.

d. PRECAUTIONS

i. General

A). Anxiety and Insomnia, last paragraph -

... with discontinuation (incidence at least twice that for placebo and at least 1% for fluoxetine in clinical trials collecting only a primary event associated with

discontinuation) in U.S. ... were anxiety (2% in OCD), insomnia (1% in combined indications), and nervousness (1% in depression) (see Table 3, below).

B). Altered Appetite and Weight, Last paragraph - Replace the last sentence with the following:

Patients treated with fluoxetine, 60 mg, on average lost 0.45 kg compared with a gain of .16 kg by patients treated with placebo in the 16-week double-blind trial. Weight change should be monitored throughout therapy.

C). Seizures -- First paragraph, first sentence - ... fluoxetine and 0.2% of patients treated ... ("0.2%" rather than "2%").

ii. Carcinogenesis, Mutagenesis, Impairment of Fertility -- Second paragraph, last sentence - ... recommended human dose (MRHD) ...

e. ADVERSE REACTIONS

i. Incidence in US Placebo-Controlled Clinical Trials (excluding data from extensions of trials), Table 2 - Indent the word "insomnia".

*ii. Associated with Discontinuation in U.S. Placebo-Controlled Clinical Trials (excluding data from extensions of trials), Table 3

A). Place **(N=1108)** beneath title of first column.

B). Place **(N=392)** beneath title of second column.

C). Place **(N=266)** beneath title of third column.

D). Delete "Nervousness (1%)" from first column.

E). Delete "Insomnia (1%)" and "Nausea (1%)" from second column.

F). Revise "Rash (3%)" to read "Rash (1%)" in third column.

iii. Other Events Observed in All US Clinical Trials.

A). Cardiovascular System -- Rare - ... embolism,

cerebral ischemia, cerebrovascular ...

B). Digestive System -- Rare - "biliary" rather than "bilary".

C). Nervous System -- Frequent - "lability" rather than "liability".

D). Skin and Appendages -- Infrequent - "eczema" rather than ecxema".

E). Last sentence - ... disorder is the COSTART ... ("is" rather than "in").

iv. Postintroduction Reports - ... epidermal necrolysis, erythema nodosum, exfoliative dermatitis, ...

f. DOSAGE AND ADMINISTRATION

Switching Patients to a Tricyclic Antidepressant (TCA): -- Last sentence - under **PRECAUTIONS, Drug Interactions**).

g. HOW SUPPLIED

Indicate that capsules contain fluoxetine present as 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.

/S/

Jerry Phillips
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research