

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*  
**75049**

**CORRESPONDENCE**

Min. Jan 4-1

ANDA 75-049

MAR 16 2001

Geneva Pharmaceuticals, Inc.  
Attention: Beth Brannan  
2555 W. Midway Blvd.  
Broomfield, CO 80038-0446

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, 28<sup>th</sup> 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,

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

*for 3/16/2001*

JUL 11 1997

*11' P. Hennig*

Geneva Pharmaceuticals, Inc.  
Attention: Beth Brannan  
2555 W. Midway Blvd.  
Post Office Box 446  
Broomfield CO 80038-0446  
|||||

Dear Madam:

Reference is made to the Abbreviated New Drug Application submitted on December 31, 1996, for Fluoxetine Hydrochloride Capsules, 10 mg and 20 mg.

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

1. As some samples in the non-fasting study were stored for 185 days before analysis, it will be necessary to document the stability of both fluoxetine and norfluoxetine, in frozen plasma samples during this time period.
2. Food study: Samples from subject #23 were run on two separate days; period I and II on Oct. 16, 1996 and period III samples were run on Nov. 8, 1996. Please note for future studies that all samples from one subject should be run on the same day.
3. None of the samples analyzed during the study had either fluoxetine or norfluoxetine plasma concentrations higher than 33.43 ng/mL. Most of the samples were between                    ng/mL for fluoxetine, and between                    ng/mL for norfluoxetine. The laboratory used the standard curve of 0.50-100 ng/mL, and the following QC sample concentrations: low                    ng/mL, medium 40 ng/mL, and high                    ng/mL. In the future, the concentrations of the quality control samples should be chosen within and/or much closer to the concentration range of the actual plasma concentrations of the drug.
4. The waiver request for the 10 mg capsule cannot be granted at this time. A response to item 1 is required. Please resubmit the waiver request for the 10 mg capsule along with the response to deficiency #1 above.

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 Lizzie Sanchez, Pharm.D., Project Manager, at (301) 827-5847. In future correspondence regarding this issue, please include a copy of this letter.

Sincerely yours,

NS

Nicholas Fleischer, Ph.D.  
Director, Division of Bioequivalence  
Office of Generic Drugs  
Center for Drug Evaluation and Research

ANDA 75-049

Geneva Pharmaceuticals, Inc.  
Attention: Beth Brannan  
2555 W. Midway Blvd.  
Broomfield, CO 80038-0446  
|||||

FEB 24 1997

Dear Madam:

We acknowledge the receipt of your abbreviated new drug application submitted pursuant to Section 505(j) of the Federal Food, Drug and Cosmetic Act.

NAME OF DRUG: Fluoxetine Hydrochloride Capsules, 10 mg (base) and 20 mg (base)

DATE OF APPLICATION: December 31, 1996

DATE OF RECEIPT: January 2, 1997

We will correspond with you further after we have had the opportunity to review the application.

Please identify any communications concerning this application with the ANDA number shown above.

Should you have questions concerning this application, contact:

Tim Ames

---

Project Manager  
(301) 594-0305

Sincerely yours,

*JS*  
Jerry Phillips *2/24/97*  
Director  
Division of Labeling and Program Support  
Office of Generic Drugs  
Center for Drug Evaluation and Research



Beth Brannan, Director  
Drug Regulatory Affairs

Geneva Pharmaceuticals, Inc.  
2655 W. Midway Blvd.  
P.O. Box 446  
Broomfield, CO 80038-0446

Tel +1 303 438-4237  
Fax +1 303 438-4600  
Internet:  
Beth.Brannan@gx.novartis.com

~~FEDERAL EXPRESS~~

Gary Buehler, Acting Director  
Office of Generic Drugs  
Center for Drug Evaluation and Research  
Metro Park North 2, Room 150  
7500 Standish Place  
Rockville, MD 20855

MINOR AMENDMENT  
(LABELING)

U/AF

ORIG AMENDMENT

JUL 31 2001

RE: ANDA 75-049 Fluoxetine Capsules USP, 10 and 20 mg  
Minor Amendment - Labeling

Dear Mr. Buehler:

Geneva Pharmaceuticals, Inc. is hereby submitting a minor amendment to our tentatively approved Abbreviated New Drug Application for Fluoxetine Capsules USP, 10 and 20 mg in accord with Section 505 (j) of the Federal Food, Drug, and Cosmetic Act and with 21 CFR Part 314.96.

Reference is made to a phone conversation on July 30, 2001 between Peter Rickman, FDA and Beth Brannan, Geneva.

As requested, enclosed are twelve copies of insert labeling revised to delete reference to the 20 mg capsule product in the Description and How Supplied section. No other changes were made to the labeling previously submitted on May 18, 2001.

This information is submitted for your review and approval. Please acknowledge receipt of this document by signing and dating the enclosed copy of the cover letter and returning it in the self-addressed stamped envelope.

Sincerely,

GENEVA PHARMACEUTICALS, INC.

*Beth Brannan*  
Beth Brannan, Director  
Drug Regulatory Affairs

Enclosures  
BB/jw





FEDERAL EXPRESS

MINOR AMENDMENT  
(PATENT)

Gary Buehler, Acting Director  
Office of Generic Drugs  
Center for Drug Evaluation and Research  
Metro Park North 2, Room 150  
7500 Standish Place  
Rockville, MD 20855

NEW CORRESP

July 30, 2001

RE: ANDA 75-049 Fluoxetine Capsules USP, 10 and 20 mg  
Court Decision concerning Patents

Dear Mr. Buehler:

Geneva Pharmaceuticals, Inc. is hereby submitting a minor amendment to our tentatively approved Abbreviated New Drug Application 75-049 for Fluoxetine Capsules USP, 10 and 20 mg in accord with Section 505 (j) of the Federal Food, Drug, and Cosmetic Act and with 21 CFR Part 314.96.

Reference is made to the tentative approval letter from FDA dated April 30, 2001. Please also reference our amendments dated June 5, 2001 and June 8, 2001 concerning patent information.

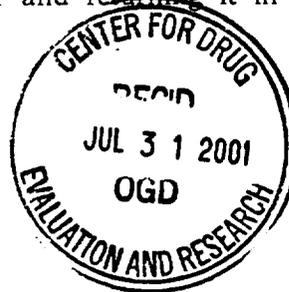
Enclosed is a copy of the final judgment entered by the U.S. Court of Appeals for the Federal Circuit on July 27, 2001. The court has found that U.S. Patent No. 4,626,549 (549' patent) was invalid. Therefore, based on this July 27, 2001 decision on the 549' patent and since Geneva was successful in our litigation, we are anticipating approval of our 10 mg fluoxetine capsule product on August 2, 2001 upon expiration of the 4,314, 081 patent.

This information is submitted for your review. Please acknowledge receipt of this document by signing and dating the enclosed copy of the cover letter and returning it in the self-addressed stamped envelope.

Sincerely,

GENEVA PHARMACEUTICALS, INC.

  
Beth Brannan, Director  
Drug Regulatory Affairs



Enclosures  
BB/jw



FEDERAL EXPRESS

TELEPHONE AMENDMENT

*MOU 549*

Gary Buehler, Acting Director  
Office of Generic Drugs  
Center for Drug Evaluation and Research  
Metro Park North 2, Room 150  
7500 Standish Place  
Rockville, MD 20855

NEW CORRESP

NC

*Emily M...*  
*NHS*  
*6/21/01*

June 8, 2001

RE: ANDA 75-049 Fluoxetine Capsules USP, 10 and 20 mg  
Telephone Amendment – Patent Information

Dear Mr. Buehler:

Geneva Pharmaceuticals, Inc. is hereby submitting a telephone amendment to our unapproved Abbreviated New Drug Application for ANDA 75-049 Fluoxetine Capsules USP, 10 and 20 mg in accordance with Section 505 (j) of the Federal Food, Drug, and Cosmetic Act and with 21 CFR Part 314.96.

Reference is made to the tentative approval letter from FDA dated April 30, 2001. Please also refer to our minor amendment dated May 18, 2001, a paragraph IV patent certification submitted May 21, 1997, and a telephone conversation of June 8, 2001 between Greg Davis, Jeen Min, and Adolph Vezza of FDA and Beth Brannan of Geneva.

As requested, we are now amending our ANDA with a statement concerning a Method of Use for United States Patent No. 4,626,549 (549' patent). Geneva does not claim the method of use for treating animals suffering from an appetite disorder for Fluoxetine Capsules USP, 10 and 20 mg. The required statement is enclosed.

This information is submitted for your review and approval. Please acknowledge receipt of this document by signing and dating the enclosed copy of the cover letter and returning it in the self-addressed stamped envelope.

Sincerely,

GENEVA PHARMACEUTICALS, INC.

*Beth Brannan*

Beth Brannan, Director  
Drug Regulatory Affairs



Enclosures  
BB/jw



Labeling review  
drafted 6/11/01  
A. Vezina

FEDERAL EXPRESS

MINOR (90 DAY) AMENDMENT

Gary Buehler, Acting Director  
Office of Generic Drugs  
Center for Drug Evaluation and Research  
Metro Park North 2, Room 150  
7500 Standish Place  
Rockville, MD 20855



FPL  
ORIG AMENDMENT  
jm

MAY 18 2001

RE: ANDA 75-049 Fluoxetine Capsules USP, 10 and 20 mg  
Minor Amendment – Chemistry, Manufacturing, and Controls; Labeling

Dear Mr. Buehler:

Geneva Pharmaceuticals, Inc. is hereby submitting a minor 90-day amendment to our unapproved Abbreviated New Drug Application for ANDA 75-049 Fluoxetine Capsules USP, 10 and 20 mg in accord with Section 505 (j) of the Federal Food, Drug, and Cosmetic Act and with 21 CFR Part 314.96.

Reference is made to the tentative approval letter from FDA dated April 30, 2001. We are now amending our ANDA with the required updated information prior to full approval.

**ATTACHMENT 1 – REVISED LABELING**

- Twelve copies of final printed inserts are provided. The changes made to our final printed insert last submitted on March 20, 2001 are highlighted on the first page in Attachment 1. Reference is made to FDA's letter dated March 16, 2001. Statements related to "appetite disorders" have been removed from Geneva's proposed insert labeling.
- Twelve copies of final printed container labels for a 30 count and 1000 count bottle for the 20 mg product are provided. These new package sizes are fully described in Attachment 5.

**ATTACHMENT 2 – ACTIVE AND INACTIVE INGREDIENTS**

**1815 Fluoxetine HCl (Active)**

- Per FDA's telephone request dated December 27, 2000 and Geneva's commitment dated January 5, 2001, the Heavy Metals specification for the provided by has been reduced from NMT % to NMT %. An updated Raw Material Specification and Data Sheet for the (Code 1815) is provided in Attachment 2.

7-

10/22/01  
5/22/01  
m/w

1822 Fluoxetine HCl ( Active - )

- The Assay Method has been revised to include a note regarding stability of the standard and sample preparation. Additionally, the calculation section was corrected by adding "x 100", changing "%" to "decimal form" for P in the potency of standard, and adding "100 is the conversion factor for percent". There has been no change to the procedure, however. (The last page of all methods provided in this section includes a history of the changes made.)
- The Related Compounds Method has been revised. The note to not use PEEK tubing has been removed since the amount of THF in the mobile phase will not degrade PEEK tubing. A paragraph was added concerning column care and the calculation section was corrected as noted above for the Assay method. There has been no change to the procedure, however.
- The Residual Solvent Method has been revised to add a note concerning solvents that need not be added to the Standard if a manufacturer's letter is available certifying the absence of the OVI solvents. There has been no change to the procedure, however.

5843 #3 White Capsule, Imprinted GG575, Green Ink Bands (10 mg product)

5844 #3 White Capsule, Imprinted GG550, Black Ink Bands (20 mg product)

- Geneva is adding a Microbial Limits specification and associated analytical test methods to our gelatin capsule raw material testing. This specification for microbial limits is based on the manufacturer's specification and the NF monograph for Gelatin NF. This change provides for additional characterization of the gelatin capsules and therefore increased assurance that the drug product will have the characteristics of strength, purity, and quality that it purports to possess. The following table summarizes the proposed microbial limits specification:

Proposed Microbial Limits Test	
Method	Specification
M-20, M-26	Total Aerobic Microbial Count : NMT 1000 cfu/g Total Combined Molds and Yeasts Count: NMT100 cfu/g Staphylococcus aureus: Negative Pseudomonas aeruginosa: Negative Escherichia coli: Negative Salmonella sp.: Negative

The updated specification and data sheet for each capsule shell and the methods for gelatin capsules microbial limits (M-20 and M-26) are provided in Attachment 2. Method M-20 has previously been submitted to this application but is provided again for ease of reference.

### General

- Geneva's Foreign Matter by Visual Inspection Method has been revised to clarify the procedure in Section I. Step has been split into Steps which clarifies removing container.

### ATTACHMENT 3 – FINISHED PRODUCT SPECIFICATIONS, FINISHED PRODUCT AND STABILITY METHODS

- Per FDA's FAX correspondence dated February 8, 2001, the USP 24, Supplement 1 dissolution specification has been incorporated into our quality control and stability programs. Therefore, the specification has been revised from NLT % to NLT % as requested. Revised finished product specifications are provided in Attachment 3.
- The Related Compounds Method has been redeveloped from a . Please note that the method and validation also refers to a 40 mg product. However, we are not currently seeking approval of the 40 mg product. The method was developed in anticipation of a future submission for this strength.
- Specificity Report for Related Compounds Method Please note that the Specificity Report and Validation Report both reference the number for the Related Compounds method. This method is the same as the method provided in Attachment 3. The difference in the numbering relates to internal control of the documents.
- Analytical method validation for the Related Compounds Method (Refer to Section 4 of the Report Number: Addendum 2 for the Related Compounds method validation.)

### ATTACHMENT 4 – PACKAGING SPECIFICATIONS

- The Master Packaging Specifications (MPS) provided in Attachment 4 for the 20 mg product have been revised to reflect the addition of a 30 count (60cc) and 1000 count (750cc) package size. Supporting documentation for the bottles and closures is provided in Attachment 4. The bottles are manufactured with the same resin as previously submitted to this application . The resin for the 53 mm plastic screw cap and inner portion of the 33 mm plastic child resistant closure is the same as previously submitted . Information pertaining to the resins used for the outer (overcap) portion of the child resistant closure, which is not in contact with the product, is provided in Attachment 4. The closure liners for both the 33 mm PCR and 53 mm PSC are the same as previously submitted.
- Accelerated and room-temperature stability data to support the two new package sizes for the 20 mg product are provided.

- The Master Packaging Specifications for unit dose packaging have been revised. The foil code number was ~~change~~ from \_\_\_\_\_, and the film code from \_\_\_\_\_. The new code numbers reflect adjustments to the starting dimensions of these components for use with Geneva's new unit dose packaging equipment. The materials from which the foil and film are made and the finished blister dimensions remain unchanged. Specifications for the unit dose packaging components with revised code numbers are provided in Attachment 4. The analytical methods for packaging components are the same as previously submitted. Additionally, the package code for the unit dose box (Code 7823) is now included on the MPS. The blister packs are packaged 10 strips per box; however the box code number was previously not provided on the MPS.

#### ATTACHMENT 5 - STABILITY PROTOCOLS

- Per FDA's FAX correspondence dated February 8, 2001, the USP 24, Supplement 1 dissolution specification has been incorporated into our quality control and stability programs. Therefore, the specification has been revised from NLT 1% to NLT % as requested. Revised stability protocols are provided in Attachment 5. The protocols provided represent different submissions made to this ANDA, e.g. the original ANDA, an alternate API source, and the addition of package sizes for the 20 mg product. Protocols will be combined following full approval of the ANDA but are maintained as separate documents until then in the event of non-approval of an amendment. All information will be incorporated into the final protocols which will be submitted in the first Annual Report. There will be no changes made to testing requirements, however.

#### STABILITY DATA

- Room temperature stability data for bottles and unit dose packaging through the proposed expiration period were previously submitted to this application.
- Stability data to support the addition of a \_\_\_\_\_ count and \_\_\_\_\_ count package size for the 20 mg product is provided in Attachment 4.

This information is submitted for your review and approval. Please acknowledge receipt of this document by signing and dating the enclosed copy of the cover letter and returning it in the self-addressed stamped envelope.

Sincerely,

GENEVA PHARMACEUTICALS, INC.

*Beth Brannan*

Beth Brannan, Director  
Drug Regulatory Affairs

Enclosures

BB/jw



Beth Brannan, Director  
Drug Regulatory Affairs

Geneva Pharmaceuticals, Inc.  
2655 W. Midway Blvd.  
P.O. Box 446  
Broomfield, CO 80038-0446

Tel +1 303 438-4237  
Fax +1 303 438-4600  
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Beth.Brannan@gx.novartis.com

FEDERAL EXPRESS

Gary Buehler, Acting Director  
Office of Generic Drugs  
Center for Drug Evaluation and Research  
Metro Park North 2, Room 150  
7500 Standish Place  
Rockville, MD 20855

NEW BIOEQUIVALENCE  
CORRESPONDENCE

ANDA ORIS AMENDMENT

JAN 05 2001

RE: ANDA 75-049 Fluoxetine Capsules USP, 10 and 20 mg  
Bioequivalence Waiver Information Request for New 40 mg Strength of Fluoxetine  
Capsules

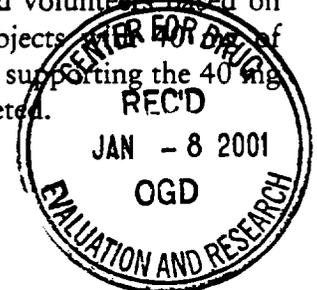
Dear Mr. Buehler:

Geneva Pharmaceuticals, Inc. is hereby submitting a New Bioequivalence Correspondence to our tentatively approved Abbreviated New Drug Application for Fluoxetine Capsules USP, 10 and 20 mg. This correspondence is a request for information pertaining to the requirements for inclusion of a new 40 mg Fluoxetine Capsule product in this Abbreviated New Drug Application.

Geneva's ANDA 75-049 for the 10 and 20 mg Fluoxetine Capsules was submitted on December 31, 1996. At that time, the Reference Listed Drug (RLD) identified in The Orange Book, 16<sup>th</sup> Edition was Prozac<sup>®</sup> capsules, 20 mg. Geneva's ANDA was tentatively approved on June 1, 1999. The innovator's 40 mg Prozac<sup>®</sup> capsules were subsequently approved on June 15, 1999.

Now that the 40 mg Prozac<sup>®</sup> product is available as a reference, Geneva has manufactured a supportive batch of Fluoxetine 40 mg capsules. The proposed 40 mg capsule formulation is proportionally similar to our tentatively approved 10 and 20 mg capsule formulation and the proposed manufacturing process is the same for all strengths. Refer to the component and composition table and manufacturing summary enclosed. A Certificate of Analysis for Geneva's 40 mg product (Lot # D 00041) is also provided.

In support of the tentative approval of our 10 and 20 mg capsules, Geneva successfully completed a two-way randomized crossover bioequivalency study in fasted volunteers based on our 20 mg capsules. The study design included dosing each of 41 subjects with either 40 mg of Fluoxetine manufactured by Geneva (2 X 20 mg) or Prozac<sup>®</sup>. A new study supporting the 40 mg capsules would essentially be the same as the study we have already completed.



Additionally, we have performed dissolution studies in 4 media, 0.1N HCl, pH 4.5 Acetate Buffer, pH 6.8 Phosphate Buffer, and water. These studies indicate that the dissolution profiles of Geneva's 40 mg capsules versus Prozac® 40 mg are very similar in each media. The dissolution profiles are enclosed.

We would like to receive Agency comments regarding the possibility of a bio waiver request being granted for our 40 mg capsules based on the following:

- We have successfully completed a 20 mg bioequivalence study of basically the same design indicated for the 40 mg capsules (fasting subjects, 2 X 20 mg capsules).
- The formulations for the 10, 20 and 40 mg capsules are proportionally similar and the manufacturing process is the same.
- Dissolution data in 4 media support that Geneva's 40 mg capsules dissolve very similarly to Prozac® 40 mg. Please note that according to the October 2000 Guidance "Bioavailability and Bioequivalence Studies for Orally Administered Drug Products – General Considerations", Section V.C.2.a, the  $t_2$  approach is not suitable for rapidly dissolving drug products (e.g. % dissolved in 15 minutes or less). At the 15 minute time point, Geneva's 40 mg product was % dissolved in water, the media to be used for release testing according to our tentatively approved ANDA for the 10 and 20 mg product.
- Stability studies are ongoing to support the 40 mg product. We acknowledge that any waiver granted would be contingent on acceptable stability results as well as submission and approval of other ANDA supporting documentation for the 40 mg product.

We believe there is substantial information indicating that an additional biostudy should not be required to support the addition of the 40 mg capsules. We look forward to receiving your comments in regard to this issue.

Please acknowledge receipt of this document by signing and dating the enclosed copy of the cover letter and returning it in the self-addressed, stamped envelope provided.

Sincerely,

GENEVA PHARMACEUTICALS, INC.



Beth Brannan, Director  
Drug Regulatory Affairs

Enclosures  
BB/jw



Beth Brannan, Director  
Drug Regulatory Affairs

Geneva Pharmaceuticals, Inc.  
2655 W. Midway Blvd.  
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~~FEDERAL EXPRESS~~

Gary Buehler, Acting Director  
Office of Generic Drugs  
Center for Drug Evaluation and Research  
Metro Park North 2, Room 150  
7500 Standish Place  
Rockville, MD 20855

ORIG AMENDMENT  
N/A

TELEPHONE  
AMENDMENT

JAN 05 2001

RE: ANDA 75-049 Fluoxetine Capsules USP, 10 and 20 mg  
Telephone Amendment to Alternate Source Amendment dated November 14, 2000

Dear Mr. Buehler:

Geneva Pharmaceuticals, Inc. is hereby submitting a telephone amendment to our November 14, 2000 alternate source amendment for our tentatively approved Abbreviated New Drug Application for Fluoxetine Capsules USP, 10 and 20 mg. This submission is in accordance with Section 505 (j) of the Federal Food, Drug, and Cosmetic Act and with 21 CFR Part 314.96.

Reference is made to Geneva's original amendment dated November 14, 2000 and to the December 27, 2000 telephone conversation between Edwin Ramos (FDA) and Beth Brannan (Geneva).

Certificates of Analysis are enclosed that provide comparison of physical characteristics for the Fluoxetine HCl active drug substance from our original ANDA source and our recently submitted alternate source. The tests requested include, IR (without using the recrystallization step as allowed for in USP), melting range and optical rotation. The X-ray diffraction scans for both sources are also provided, as requested.

As clarification of data previously submitted, Geneva did not originally provide analytical results for melting range for the or optical rotation for the since these are not USP test parameters and the manufacturers did not provide specifications on their Certificates of Analysis. We are now providing this data. The IR scans previously submitted for the Identification A test parameter for both sources were generated *without* the recrystallization step as allowed for in USP, as requested. However, we are again providing the scans for your reference.

Although the USP specification for Heavy Metals is NMT %, Geneva agrees and commits to revise the specification for the alternate source to NMT % to be consistent



with the specification. Geneva has determined that the will pass the  
tighter specification.

This information is submitted for your review and approval.

Please acknowledge receipt of this document by signing and dating the enclosed copy of the  
cover letter and returning it in the self-addressed stamped envelope.

Sincerely,

GENEVA PHARMACEUTICALS, INC.



Beth Brannan, Director  
Drug Regulatory Affairs

Enclosures  
BB/jw

31

Beth Brannan  
Director, Drug Regulatory Affairs

Geneva Pharmaceuticals, Inc.  
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**Geneva**  
pharmaceuticals, inc.

~~FEDERAL EXPRESS~~

AMENDMENT

Gary Buehler, Acting Director  
Office of Generic Drug  
Center for Drug Evaluation and Research  
Metro Park North 2, Room 150  
7500 Standish Place  
Rockville, MD 20855

**ORIG AMENDMENT**

*N/A*

**NOV 14 2000**

RE: ANDA 75-049 Fluoxetine Capsules USP, 10 and 20 mg  
Amendment – Chemistry, Manufacturing, and Controls: Alternate Source of

Dear Director:

Geneva Pharmaceuticals, Inc. is hereby submitting an amendment to our tentatively approved Abbreviated New Drug Application for Fluoxetine Capsules USP, 10 and 20 mg in accordance with Section 505(j) of the Federal Food, Drug, and Cosmetic Act and 21 CFR Part 314.96.

This supplement provides for an alternate source of the active drug substance Fluoxetine Hydrochloride USP. The following information is provided in support of the alternate source.

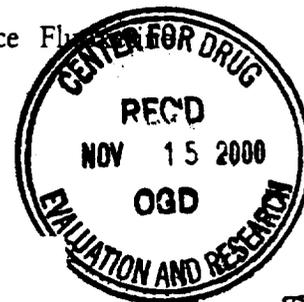
**ATTACHMENT 4 – DMF INFORMATION**

The proposed manufacturer and supplier of the active drug substance Fluoxetine Hydrochloride USP are:

Manufacturer

Supplier

(DMF)



*NW*  
*11-2000*

A Drug Master File authorization letter from \_\_\_\_\_ in Attachment 1.

\_\_\_\_\_ for DMF \_\_\_\_\_ is provided

**ATTACHMENT 2 – ACTIVE INGREDIENT SPECIFICATIONS, ANALYTICAL DATA, METHODS, AND REPORTS**

- \_\_\_\_\_ manufacturer's \_\_\_\_\_ Certificate of Analysis for the alternate source
- \_\_\_\_\_ updated \_\_\_\_\_ specifications
- Two letters from the \_\_\_\_\_ manufacturer \_\_\_\_\_ concerning manufacturing solvents used and benzene
- Geneva's proposed Specifications and Data Sheet for the alternate source
- Geneva Certificate of Analysis for the alternate source
- Copies of representative spectra and chromatograms for Geneva \_\_\_\_\_ used in the manufacture of the alternate source supportive batch
- Specification Justification Report
- Geneva's analytical methods for the alternate source \_\_\_\_\_ Methods previously submitted to this application are not provided.
- Analytical Method Development Summary Report
- Analytical Method Validation Report

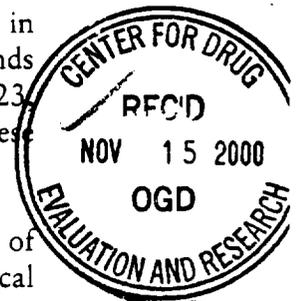
**ATTACHMENT 3 – EXECUTED BATCH RECORDS**

- Executed batch record for Batch # 6498026 of Fluoxetine Capsules USP, 20 mg manufactured with \_\_\_\_\_ (Batch 97H124). ✓  
Note: The proposed scale-up Master Manufacturing Forms (MMF) for the 20 mg tablets \_\_\_\_\_ and 10 mg tablets \_\_\_\_\_ were previously submitted to this application in an amendment dated November 3, 2000.

**ATTACHMENT 4 – FINISHED PRODUCT DATA**

- Certificate of Analysis for 20 mg alternate source Batch 6498026
- Finished Product Specifications  
The Finished Product Specifications have been revised since testing of Batch 6498026. Geneva submitted revised Related Compounds specifications in an amendment dated August 12, 1998. The specification for Any Individual Unknown was tightened from NMT \_\_\_\_\_ % to NMT \_\_\_\_\_ % as requested in FDA's communication dated March 16, 1998. The Total Related Compounds specification was tightened from NMT \_\_\_\_\_ % to NMT \_\_\_\_\_ % per USP 23 Supplement 7. The analytical results for Batch 6498026 still meet these current, tentatively approved specifications.

Additionally, the dissolution method number referenced on the Certificate of Analysis for Batch 6498026 provided in Attachment 4 contains a typographical error. The method number should be \_\_\_\_\_ rather than \_\_\_\_\_. However, the dissolution data for Batch 6498026 was generated according to \_\_\_\_\_



our current, tentatively approved dissolution parameters as stated on the Certificate of Analysis. ✓

#### ATTACHMENT 5 – STABILITY COMMITMENT, PROTOCOLS, AND DATA

- Stability commitment ✓
- Stability protocols including proposed expiration dating ✓
- Accelerated stability data (bottles and unit dose) for alternate source Batch 6498026 (20 mg) ✓
- Currently available room-temperature stability data for alternate source Batch 6498026 (20 mg) ✓
- Key to Stability Report Header Fields and Container Closure System Abbreviations ✓

#### ATTACHMENT 6 – BIO WAIVER REQUEST

- Bio waiver request
- Comparative dissolution profiles for:
  - Geneva's Batch 6498026 manufactured with product (Batch 1AP65A) vs. the innovator
  - Geneva Batch 6498026 manufactured with primary source of the (Batch 6496022) vs. Geneva's
- $f_1$  and  $f_2$  calculations for:
  - Alternate source (Batch 6498026) vs. the innovator (Batch 1AP65A)
  - Alternate source (Batch 6498026) vs. the primary source (Batch 6496022)

The supportive data provided in this amendment demonstrates that the alternate source of the active drug substance produces product that is equivalent in quality, purity, and stability to that produced with Geneva's primary source of active drug substance. Based upon this data, the alternate and primary sources can be used interchangeably. ✓

This information is submitted for your review and approval.

Please acknowledge receipt of this document by signing and dating the enclosed copy of the cover letter and returning it in the self-addressed stamped envelope.

Sincerely,

GENEVA PHARMACEUTICALS, INC.



Beth Brannan, Director  
Drug Regulatory Affairs

Enclosures  
BB/jw



**Geneva**  
pharmaceuticals, inc.

*Labeling review  
drafted 11/14/00  
A. Uezza*

**FEDERAL EXPRESS**

Gary Buehler, Acting Director  
Office of Generic Drugs  
Center for Drug Evaluation and Research  
Metro Park North 2, Room 150  
7500 Standish Place  
Rockville, MD 20855

**MINOR (90 DAY) AMENDMENT**

**NDA ORIG AMENDMENT**  
*N/AM*

**NOV 03 2000**

RE: ANDA 75-049 Fluoxetine Capsules USP, 10 and 20 mg  
Minor Amendment – Chemistry, Manufacturing, and Controls; Labeling

Dear Mr. Buehler:

Geneva Pharmaceuticals, Inc. is hereby submitting an amendment to our unapproved Abbreviated New Drug Application for ANDA 75-049 Fluoxetine Capsules USP, 10 and 20 mg in accord with Section 505 (j) of the Federal Food, Drug, and Cosmetic Act and with 21 CFR Part 314.96.

Tentative approval for this application was received on June 15, 1999. We are now amending our ANDA with the required updated information prior to full approval.

**ATTACHMENT 1 - LABELING**

- Twelve copies of final printed insert labeling are provided in Attachment 1. Revisions requested in FDA communications dated January 6, 2000, November 10, 1999, and July 28, 1999 have been incorporated into the revised labeling and are more fully described in Attachment 1.

**ATTACHMENT 2 - ACTIVE AND INACTIVE INGREDIENTS**

**1822 Fluoxetine HCl (Active)**

- Geneva hereby informs you that there has been a change in the Manufacturing and Laboratory sites in the DMF for Fluoxetine Drug Substance referenced in our ANDA. The DMF is held by The relevant amendment to the DMF has been submitted for review. The new site of manufacture is listed below:



*AW  
11/14/00*

This information has been compiled according to recommendations of FDA-OGD representatives. The recommendations are summarized in minutes of a meeting held July 26, 1999 and provided in Attachment 2.

Accordingly, we hereby amend our ANDA with an updated Letter of Access. The new authorization letter for DMF is provided in Attachment 2 together with the manufacturer's and Geneva's Certificates of Analysis for a lot of Fluoxetine HCl drug substance manufactured at the new site. Geneva has been informed that the new site inspection was completed in November 1999.

Geneva Pharmaceuticals, Inc. commits to put the first production batch of each strength of Fluoxetine 10 and 20 mg capsules manufactured, utilizing material from the new site, into our long term stability program. Each batch will be tested according to our annual stability batch requirements referenced on our current stability protocol. The results of these tests will be reported in our annual report as they become available. Copies of the current stability protocols for Fluoxetine Tablets USP, 10 and 20 mg are provided in Attachment 5.

- An updated Raw Material Specification and Data Sheet for the active ingredient is provided. See "General" comments below as well as the following information for changes.
- Geneva Tapped Density method has been revised to comply with current USP. Additionally the method has been updated to Geneva's current format for analytical methods and sieving and a visual inspection were added as the first step of the procedure. If no particles greater than 1 mm are observed, no sieving is necessary. This will minimize the analyst's exposure to hazardous raw materials during the sieving process and will also minimize the effects of static charge on the tapped density.
- Although "Manufacturer's Check", Method is now referenced on the Specification and Data Sheet, this method is not provided since it is only administrative in nature.

#### General

- The Raw Material Specification and Data Sheets provided in Attachment 2 for active and inactive ingredients have been updated to Geneva's current format and to reflect "Current NF" or "Current USP", as appropriate, in the method column. By using this statement, Geneva will automatically test using the most current version of the compendia for the identified parameter.
- Geneva's Foreign Matter by Visual Inspection Method has been revised to provide additional detail, improve foreign matter recovery, and clarify testing of the different types of raw materials. The title has been changed to "Foreign Matter Check". A screening step has been added for further examination of all solid and liquid raw materials, with noted exceptions. Due to the nature of the following items, hazardous compounds, colors, flavors, intermediates, capsules, and packaging components are further examined by a visual inspection. Provisions have been added for tightening the sampling plan for receipts of raw materials following a rejected lot. The acceptance criteria for active ingredients have been revised to clarify the calculation and more accurately reflect the requirements in MIL STD

105E. Additionally the acceptance criteria has been revised to specify rejection of material containing any metallic foreign matter greater than 0.8mm in any dimension.

- The method has been updated to Geneva's current format and to reference "current" USP. There has been no change to the procedure, however.

#### 2072 Pregelatinized Starch NF

- An alternate method for the detection of *Salmonella sp.* has been added to the microbial limits parameter. The alternate method, M-21, allows for the detection of *Salmonella sp.* using an immunological assay. This assay uses media containing *Salmonella*-specific antibodies which form a visible band in the presence of *Salmonella sp.* The alternate method has been validated and shown to detect *Salmonella sp.* at an equivalent level to the USP method <61>. The new method, M-21, 1-2 Test for *Salmonella* species (Dilution A), is provided.
- The Particle Size method has been renumbered from due to administrative changes only. There has been no change in the procedure.

#### 2035 Magnesium Stearate NF

- Geneva method M-16 for Magnesium Stearate Microbial Limits Testing has been rewritten to provide a more detailed method for the analysts. USP 23, General Chapter <61> was used as a reference. The new method clarifies the procedure, equipment, and supplies necessary for each test, identifies steps to be performed in the biosafety cabinet, and provides an easy to follow format for each individual test. References to *S. aureus* and *Ps. aeruginosa* have been deleted since these tests are no longer compendial requirements.

All references to the use of blender equipment have been eliminated from the initial sample preparation. The use of this equipment greatly increases the chance of microbial contamination, and does not yield a homogeneous suspension. The new materials and apparatus listed in I.A.1 through 5 and II.A.1 through 5 reduce the chance of microbial contamination and allow the analyst to bring the initial sample preparation to specific volume as directed in USP 23, General Chapter <61>.

- The Surface Area method has been revised. The weighing step under "Preparing Samples for Analysis" has been removed since the final weight is obtained after the sample is fully outgassed. "Weighing container" was replaced by "sample tube" since sample is transferred directly into the sample tube. Under "Preparing Samples for Analysis", the weight requirement of NLT grams was removed. The density of the material often does not allow the method requirement of NLT grams and NMT the tube volume to both be met. The critical parameter for the analysis is the tube volume.

#### 2040 Corn Starch NF

- Physical testing parameters for Particle Size and Tapped Density have been added for corn starch. Although previously not filed, Geneva has been testing and releasing the ingredients by these physical tests for other Geneva products and are now being provided to bring this application up to Geneva's current standards.

is provided following the Specification and Data sheet for corn starch. was previously provided following the active ingredient Specification and Data sheet.

5843 #3 White Capsule, imprinted GG 575, green ink bands

5844 #3 White Capsule, imprinted GG 550, black ink bands

- Method Capsules Loss on Drying, has been revised to which is not currently in use. Testing will be performed using the oven.
- Empty Capsule Evaluation method has been revised. Policy statements have been removed since they are more appropriately described in SOPs. Wording was clarified for non-listed observations to be documented on the appropriate form. The supervisor disposition was changed to a second check. Disposition of the form is not necessary since it is documented on the analytical. A trained analyst performs the second check.

ATTACHMENT 3 – MASTER MANUFACTURING FORMS (MMFs)

- The proposed commercial batch size for the 10 mg product has been increased from to capsules which is less than 10 times the original ANDA batch size of capsules. The proposed MMFs are provided in Attachment 3 and changes are described.
- The proposed commercial Master Manufacturing Form for the 20 mg product has been revised and is provided in Attachment 3 and changes described. The batch size remains the same as previously submitted (i.e. capsules).

ATTACHMENT 4 – PACKAGING SPECIFICATIONS AND METHODS

- The Master Packaging Specifications (MPS) provided in Attachment 4 have been revised to reflect a change in bottle code from (100 cc) and a change in closure (cap) code from (PSC/HIS 38 mm). These changes reflect a change from one HDPE resin to another HDPE resin for both the bottle and closure. Supportive documentation and a more detailed description of the bottle and closure resin changes are provided in Attachment 4.
- The description of the product has been revised on the MPS to more clearly describe the imprinting with “Ink Bands” rather than just the color of the ink.
- the laboratory that performs resin testing for our bottles, has changed their name to This is a name change only. Correspondence from is provided as the last page of Attachment 4.

ATTACHMENT 5 - STABILITY PROTOCOLS AND METHODS

- The stability protocols have been revised to indicate a method number change for the Appearance parameter from Effective October 27, 1999, analytical method *Appearance Check of Stability Samples*, was revised to more clearly identify our intent as it relates to checking stability samples for appearance. The revisions to method do not reflect a fundamental change in the way the check is performed. They are intended to clearly define the purpose of the method which is to identify any characteristic or uncharacteristic change in a product's physical appearance and to trigger a management review of any noted change(s).



ATTACHMENT 6 - ROOM TEMPERATURE STABILITY DATA

- Currently available room temperature stability data for bottles and unit dose packaging are provided in Attachment 6.



This information is submitted for your review and approval.

Please acknowledge receipt of this document by signing and dating the enclosed copy of the cover letter and returning it in the self-addressed stamped envelope.

Sincerely,

GENEVA PHARMACEUTICALS, INC.

A handwritten signature in cursive script that reads "Beth Brannan".

Beth Brannan, Director  
Drug Regulatory Affairs

Enclosures  
BB/jw



**Geneva**  
pharmaceuticals, inc.

Beth Brannan, Director  
Drug Regulatory Affairs

Geneva Pharmaceuticals, Inc.  
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Tel +1 303 438-4237  
Fax +1 303 438-4600  
Internet:  
Beth.Brannan@gx.novartis.com

*Labeling Review  
drafted 5/27/99  
avezza*

**FEDERAL EXPRESS**

Douglas Sporn, Director  
Office of Generic Drugs  
Center for Drug Evaluation and Research  
Metro Park North 2, Room 150  
7500 Standish Place  
Rockville, MD 20855

**AMENDMENT**

**NDA ORIG AMENDMENT**

*N/AF*

May 25, 1999

RE: ANDA 75-049 Fluoxetine Capsules USP, 10 and 20 mg  
Amendment -Labeling

Dear Sir:

Geneva Pharmaceuticals, Inc. is hereby submitting an amendment to our unapproved Abbreviated New Drug Application ANDA 75-049 for Fluoxetine Capsules USP, 10 and 20 mg in accordance with Section 505 (j) of the Federal Food, Drug, and Cosmetic Act and with 21 CFR Part 314.96.

Per the telephone request of Adolph Vezza, FDA, to Beth Brannan, Geneva Pharmaceuticals, we have revised our insert labeling for Fluoxetine Capsules. In the **ADVERSE REACTION** section, Subsection **Postintroduction Reports**, "erythema nodosum" has been added after "epidermal necrolysis". No other changes were made. Twelve copies of final printed inserts are provided in the review copy and the archival copy.

This information is submitted for your review and approval.

Please acknowledge receipt of this document by signing and dating the enclosed copy of the cover letter and returning it in the self-addressed stamped envelope.

Sincerely,

GENEVA PHARMACEUTICALS, INC.

*Beth Brannan*

Beth Brannan, Director  
Drug Regulatory Affairs

Enclosures  
BB/jw





**Geneva**  
pharmaceuticals, inc.

Beth Brannan, Director  
Drug Regulatory Affairs

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Beth.Brannan@gx.novartis.com

FAX and ~~FEDERAL~~ EXPRESS

March 23, 1999

FACSIMILE AMENDMENT

Douglas Sporn, Director  
Office of Generic Drugs  
Center for Drug Evaluation and Research  
Metro Park North 2, Room 150  
7500 Standish Place  
Rockville, MD 20855

NEW CORRESPONDENCE

NC

RE: ANDA 75-049 Fluoxetine Capsules USP, 10 mg and 20 mg  
Facsimile Amendment - Chemistry, Manufacturing, and Controls

Dear Sir:

Geneva Pharmaceuticals, Inc. is hereby submitting a facsimile amendment to our unapproved Abbreviated New Drug Application for Fluoxetine Capsules USP, 10 mg and 20 mg in accordance with Section 505 (j) of the Federal Food, Drug, and Cosmetic Act and with 21 CFR Part 314.96.

Reference is made to your communication dated March 17, 1999.

1. The limit for any individual unknown impurity has been revised from NMT % to NMT % as requested. This change has been reflected on the revised finished product release specifications and stability protocols provided in Attachment 1. ✓
2. The in-process blend uniformity acceptance criteria of % (mean of individual test results) with an RSD of %" has been incorporated into Geneva's in-process testing. The revised in-process specifications and blend uniformity method which replaces our previously submitted blend uniformity method , are provided in Attachment 2 and reflect the new acceptance criteria. Blend uniformity data previously submitted are also provided in Attachment 2. Since the data were generated prior to the new acceptance criteria, the specification listed on the blend uniformity report still indicates our previous specification. However, the data demonstrate that the blend does meet the new acceptance criteria of % (mean of individual test results) with an RSD of %". ✓

RECEIVED

MAR 25 1999

GENERIC DRUGS

3. Unit dose packaging consisted of 51 boxes of 100 dosage units each for the 10 mg product and 62 boxes of 100 dosage units each for the 20 mg product. Complete packaging records for the 10 mg and 20 mg ANDA batches, which include documentation of unit dose packaging, are provided in Attachment 3. ✓
4. \_\_\_\_\_ film is a component of the laminated \_\_\_\_\_ film used in unit dose packaging. Refer to page 52 of our August 12, 1998 amendment where \_\_\_\_\_ is identified as the product contact layer of the \_\_\_\_\_ film. This film was previously supplied to \_\_\_\_\_ by \_\_\_\_\_. However, as of March 14, 1997, \_\_\_\_\_ was acquired by VPI Mirrex Corp. We are therefore providing a letter describing the company name change as well as an updated product sheet for the \_\_\_\_\_ film (formerly \_\_\_\_\_ film). Refer to Attachment 4.

This information is submitted for your review and approval.

Please acknowledge receipt of this document by signing and dating the enclosed copy of the cover letter and returning it in the self-addressed stamped envelope.

Sincerely,

GENEVA PHARMACEUTICALS, INC.

  
Beth Brannan, Director for  
Drug Regulatory Affairs

Enclosures  
BB/jw

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

1300 I STREET, N. W.  
WASHINGTON, DC 20005-3315

202 • 408 • 4000  
FACSIMILE 202 • 408 • 4400

WRITER'S DIRECT DIAL NUMBER:

(202) 408-4068

January 28, 1999

ATLANTA  
404 • 653 • 6400  
PALO ALTO  
650 • 849 • 6600

TOKYO  
011 • 813 • 3431 • 6943  
BRUSSELS  
011 • 322 • 646 • 0353

*NAC 2/10/99*  
*Presley*  
*Judgment / Injunction*  
*no fee*

**NEW CORRESP**  
*NC*

**VIA FEDERAL EXPRESS**

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

**RECEIVED**  
JAN 29 1999  
**GENERIC DRUGS**

Re: Fluoxetine Hydrochloride Capsules, 10 mg and 20 mg  
Abbreviated New Drug Application No. 75-049  
Notification of Injunction Prohibiting Approval of ANDA

Dear Sir or Madam:

We represent Eli Lilly and Company ("Lilly"), owner of U.S. Patent Nos. 4,314,081 ("the '081 patent") and 4,626,549 ("the '549 patent"). We are sending you this letter on behalf of our client under 21 C.F.R. § 314.107(b)(3)(iii) to notify you of the following:

On July 3, 1997, we notified you, pursuant to 21 C.F.R. § 314.107(f)(2), that Eli Lilly and Company ("Lilly") had filed a patent infringement action against Geneva Pharmaceuticals, Inc. ("Geneva"), pursuant to 35 U.S.C. § 271(e)(2), based on Geneva's filing of its Abbreviated New Drug Application ("ANDA") No. 75-049 regarding fluoxetine hydrochloride capsules. Lilly commenced the infringement action within 45 days after receiving a Notice of Paragraph IV Certification indicating that Geneva was contesting the validity and enforceability of Lilly's '081 and '549 patents. Lilly alleged, among other things, that under 35 U.S.C. § 271(e)(2)(A), Geneva's submission to the FDA of an ANDA to obtain approval for the commercial manufacture, use, or sale of fluoxetine hydrochloride before the expiration of the '081 and '549 patents was an act that infringes claim 5 of the '081 patent and claim 7 of the '549 patent.

On January 25, 1999, the United States District Court for the Southern District of Indiana (Civil Action No. IP96-0491 C B/S) entered a Final Judgment and Injunction in that case. A copy of the Final Judgment and Injunction is attached. The Court held that the '081 and the '549 patents had not been proven to be either invalid or unenforceable and that Geneva infringed the '081 and '549 patents by filing ANDA No. 75-049. (Final Judgment and Injunction at paras. 2 and 3.) The Court prohibited the FDA from approving any ANDA that is subject to the

*Andria*  
*2-4-99*

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

Food & Drug Administration

January 28, 1999

Page 2

injunction of paragraph 4, which includes Geneva's ANDA No. 75-049.<sup>1</sup> (*Id.* at para. 5.)  
Therefore the approval of ANDA No. 75-049 shall not be made effective until the expiration of  
U.S. Patent No. 4,626,549 on December 2, 2003, subject to any further rulings by the courts.

Sincerely,



David S. Forman

DSF/mrm  
Enclosure

cc: Richard S. Clark, Esq.

---

<sup>1</sup> Also covered by the injunction is ANDA No. 74-803 that was filed by Barr  
Laboratories, Inc.

FEDERAL EXPRESS

SEP 22 1998

*Labeling revision  
drafted 9/28/98  
A. Vega*

AMENDMENT

Douglas Sporn, Director  
Office of Generic Drugs  
Center for Drug Evaluation and Research  
Metro Park North 2, Room 150  
7500 Standish Place  
Rockville, MD 20855

**AMENDMENT**  
*N/AF*

RE: ANDA 75-049 Fluoxetine Capsules USP, 10 and 20 mg  
Amendment - Labeling

Dear Sir:

Geneva Pharmaceuticals, Inc. is hereby submitting an amendment to our unapproved Abbreviated New Drug Application for Fluoxetine Capsules USP, 10 and 20 mg in accordance with Section 505 (j) of the Federal Food, Drug, and Cosmetic Act and with 21 CFR Part 314.96.

Reference is made to your communication of August 20, 1998 requesting labeling revisions.

Labeling Deficiencies:

1. Unit dose blister labels have been revised to read "Capsule" rather than "Capsules". We have also changed the statement "Dist. By..." to "Mfg. By...".
2. Unit dose carton labels have been revised to include the statement "This unit-dose package is not child-resistant". The optional second sentence concerning dispensing for outpatient use has not been included.
3. Geneva anticipates receiving tentative ANDA approval prior to the November 21, 1999 expiration of the exclusivity for the bulimia indication. We acknowledge that to receive full ANDA approval and to market Fluoxetine Capsules before November 21, 1999, we must remove the bulimia indication from the labeling and submit it to this application for review and approval.

Revised final printed unit dose blister labels and unit dose carton labels are enclosed.

This information is submitted for your review and approval.

Please acknowledge receipt of this document by signing and dating the enclosed copy of the cover letter and returning it in the self-addressed stamped envelope.

Sincerely,

GENEVA PHARMACEUTICALS, INC.

*Beth Brannan*

Beth Brannan, Director  
Drug Regulatory Affairs

Enclosures  
BB/jw



**RECEIVED**

**SEP 24 1998**

**GENERIC DRUGS**

FEDERAL EXPRESS

(303) 466-2400

*Labeling review  
drafted 8/17/98  
A. V. 380*

**MINOR AMENDMENT**

Douglas Sporn, Director  
Office of Generic Drugs  
Center for Drug Evaluation and Research  
Metro Park North 2, Room 150  
7500 Standish Place  
Rockville, MD 20855

AUG 12 1998

*FPL*

**NDA ORIG AMENDMENT**

*N/AC*

RE: ANDA 75-049 Fluoxetine Capsules USP, 10 mg and 20 mg  
Minor Amendment – Chemistry, Manufacturing, and Controls; Unit Dose Packaging;  
Labeling

Dear Director:

Geneva Pharmaceuticals, Inc. is hereby submitting a minor amendment to our unapproved Abbreviated New Drug Application for Fluoxetine Capsules USP, 10 mg and 20 mg in accordance with Section 505 (j) of the Federal Food, Drug, and Cosmetic Act and with 21 CFR Part 314.96 (a).

Reference is made to your communications dated March 16, 1998 and July 14, 1998. The response to your comments and an index are provided.

**A. Deficiencies (March 16, 1998 FDA letter):**

1. The Chromatographic Purity limit for "Any Individual Unknown" has been revised to NMT % for the 10 mg and 20 mg tablet release and stability testing. The limit for "Total Related Compounds" in the finished product was also reduced from NMT % to NMT % per USP 23, Supplement 7. Revised finished product specifications and stability protocols reflecting these changes are provided in Attachment 1.
2. We have been notified by \_\_\_\_\_ that \_\_\_\_\_ manufacturer of the active ingredient, has responded to deficiencies in their DMF \_\_\_\_\_ Refer to \_\_\_\_\_ letter provided in Attachment 2 that identifies the dates of their communications.

**B. Dissolution Acknowledgment (March 16, 1998 FDA letter):**

1. At the request of the Division of Bioequivalence, we acknowledge that the following dissolution testing has been incorporated into our stability and quality control programs:

The dissolution testing will be conducted in 900 mL of water, at 37°C using Apparatus II (paddles) at 50 rpm. The specifications are NLT % (Q) of the labeled amount of the drug in the dosage form is dissolved in 30 minutes.

**RECEIVED**

AUG 13 1998



**GENERIC DRUGS**

Finished product specifications and stability protocols have been revised accordingly. Please note that for dissolution method previously submitted on page 509 of Geneva's original application dated December 31, 1996, the wording of Step of the ~~Stock Standard~~ Solution Preparation has been changed. This step now reads

There are no other changes to the method. Refer to Attachment 1 for revised finished product specifications, stability protocols, and dissolution method

#### **C. Labeling (March 16, 1998 and July 14, 1998 FDA letters)**

All labeling comments from the March 16, 1998 and July 14, 1998 communications have been incorporated into final printed labeling provided in Attachment 3. A side-by-side comparison with container labels and the insert previously submitted on October 6, 1997 is also enclosed with changes highlighted.

The addition of unit dose packaging is reflected in the "How Supplied" section of the revised insert. Unit dose carton and blister pack labels are provided in Attachment 3. A side-by-side annotated comparison of Geneva's unit dose carton labels with the 20 mg innovator unit dose carton label is also provided.

#### **D. Unit Dose Package**

Geneva is adding unit dose packaging for Fluoxetine Capsules USP, 10 mg and 20 mg. In support of this packaging configuration, Attachment 4 contains Master Packaging Specifications, Summary of the Unit Dose System, technical information, unit dose stability protocols, and accelerated and room temperature stability data for the finished product packaged in the unit dose system. Labeling is provided in Attachment 3 as referenced above. Geneva proposes an 18-month expiration period for the unit dose package.

#### **E. Active Pharmaceutical Ingredient (API)**

Fluoxetine Capsules became an official USP product on November 15, 1997 per USP 23, Supplement 7. Geneva intends to use the USP designation for this product and has updated documentation accordingly. Geneva acknowledges that in the event of a dispute, the USB methods are the official regulatory methods. Updated API Specifications and Methods are provided in Attachment 5.

#### **OVI**

The USP Organic Volatile Impurities test parameter and specifications have been added to the Residual Solvent Method previously developed and validated to test for the five USP OVIs as well as dimethylacetamide, ethylacetate, and toluene, was provided in our submission dated October 6, 1997. Method has been added as an additional OVI method. is a general purpose method that eliminates unnecessary OVI testing if the manufacturer provides assurance that there is no potential for any of the five USP organic volatile impurities to be present. Refer to Attachment 5 for OVI Method

### Related Compounds

Related Compounds Method has been re-developed from an isocratic to a method to better separate the Amino Alcohol ( $\alpha$ -[2-(methylamino)ethyl]-benzenemethanol) impurity from the solvent front. The new Related Compounds Method and validation report are provided in Attachment 5.

Additionally, the parameter name for related compound N-methyl-3-phenyl-2-propene-1-amine was changed to Fluoxetine Related Compound B to be consistent with USP 23, Supplement 8. The N-methyl-3-phenyl-2-propene-1-amine compound is an unsaturated analogue of Fluoxetine Related Compound B. The former compound was previously designated as Fluoxetine Related Compound B while the method was in the Pharmacopeial Forum. Thus, this compound was included in the active ingredient specifications originally. Fluoxetine Related Compound B designation changed to N-methylbenzene propanamine. The new Related Compounds Method includes a relative retention time for the new Related Compound B. Therefore, the active ingredient specifications reflect this change. (This also applies to the Finished Product Specifications and finished product Related Compounds Method)

The limit for Total Related Compounds for the active ingredient has been tightened from the NMT % USP specification to NMT % to be consistent with the specification for the finished product.

### Particle Size

A typographical error on Particle Size Method has been corrected and the revised method provided in Attachment 5. On page 2 of this method, corrections were made to Steps of the PROCEDURE by changing ' There were no other changes to the method.

### Identification C

Identification C has been updated to USP 23, Supplement 7. The "alkaloidal" term was removed from the General Chapter < 191 > for Identification of Chlorides. The general test for hydrochlorides proves to be acceptable for this parameter and will continue to be used for Identification C testing.

## F. Finished Product Methods and Stability Protocols

All USP test parameters and specifications have been incorporated into finished product and stability testing at limits that are the same as or tighter than USP specifications. Geneva acknowledges that in the event of a dispute, the USP methods are the official regulatory methods. Refer to Attachment 1 for finished product specifications, Dissolution Method, and stability protocols for bottles. Unit dose stability protocols are provided in Attachment 4.

### Related Compounds

Related Compounds Method has been re-developed from an isocratic to a method to better separate the Amino Alcohol ( $\alpha$ -[2-(methylamino)ethyl]-benzenemethanol) impurity from the solvent front. The new Related Compounds Method

is provided in Attachment 6 and the validation is provided in Attachment 5. Several stability samples for ANDA Lots 6496034 (10 mg) and 6496022 (20 mg) have been re-analyzed for related compounds by the new method. These data, which support the new method and lower specification of NMT % for Any Individual Unknown, are provided in Attachment 6. (Refer to information provided under E. Related Compounds concerning the name change of Related Compound B.)

Upon reviewing all stability data generated to date, it appeared that two samples would not pass the new specification of NMT % Any Individual Unknown when tested by the old Related Compounds method. However, these samples did pass the % specification that was in place when they were originally analyzed. The two samples in question were the 10 mg (Lot 6496034) 6-month room temperature HDPE bottle sample with a result of % and the 20 mg (Lot 6496022) 4-week 40°/75% RH unit dose sample with a result of %.

Further examination of the original chromatogram for the 10 mg, 6-month RT sample, revealed that the peak labeled as the % Unknown was eluding in the solvent front and could be solvent or placebo. Furthermore, this same peak in the 9-month and 12-month sample chromatograms was not integrated, and was labeled as solvent front. This inconsistency of identifying peaks as unknowns or placebo, along with the Amino Alcohol peak eluding too close to the solvent front, were the main reasons why the related compound method was re-developed. To confirm the peaks being quantitated were actually placebo, the related compound placebo chromatogram from specificity report (Fluoxetine) was analyzed. The placebo chromatogram showed peaks being detected at the same retention times as the peaks in the 6, 9, and 12 month sample chromatograms that were being identified as related compounds. The chemist was inconsistent in labeling and reporting these peaks as placebo or related compounds. Continuing, the 10 mg 12-week sample (100cc 40°/75% RH) and the 24-month sample (100cc RT) were re-tested using the new method and all peaks detected were below the reporting limit of %. This further indicates that if the peak detected in the 6-month RT sample was an actual degradant, it should also have been detected in the 40°/75% RH samples analyzed by the new method since these conditions are the most stressful. It is therefore concluded that the % result originally reported for the 10 mg, 6-month RT sample was not a degradant.

Further examination of the original chromatogram for the 20 mg, 4-week 40°/75% RH unit dose sample revealed that the peak quantitated at % by the old method was also eluding in the solvent front. This peak was identified as the known related compound N-methyl-3-phenyl-2-propene-1-amine since its relative retention time corresponded to the relative retention time that was stated in the method for that known related compound. This peak was also identified as the N-methyl-3-phenyl-2-propene-1-amine in the 12-week 40°/75% RH unit dose sample chromatogram. This peak was incorrectly identified as a known related compound instead of being labeled as a placebo peak. The 12-week sample was tested by the new related compounds method which does separate all known impurities and unknowns from the placebo and solvent front. The results show no individual or total related compounds above the reporting limit of %. Once again, if this was an actual degradant, it would have been detected by the re-developed method. This new data

supports the conclusion that peaks being identified as related compounds with results of % were actually placebo peaks eluding in the solvent front.

Original chromatograms for the two samples referenced above (10 mg (Lot 6496034) 6-month room temperature HDPE bottle sample with a result of % and the 20 mg (Lot 6496022) 4-week 40°/75% RH unit dose sample with a result of %) and the placebo analyzed by the old related compounds method are provided in Attachment 6. For comparison, chromatograms of the twelve-week accelerated stability samples for the two samples in question analyzed by the new related compounds method are also provided which support Geneva's position that the results previously reported for these two samples were in error and were not impurities.

### **G. Updated Excipient Specifications and Methods**

Excipient specifications and methods updated since our previous submission are provided in Attachment 7. The changes are itemized as follows:

1. **2072 Pregelatinized Starch NF**  
**2040 Corn Starch NF**  
**2035 Magnesium Stearate NF**

Microbial Method M-20 has been added for these excipients as clarification of compendial methodology. The method provides additional instruction to the analyst concerning receipt of samples, documentation procedures, and initial preparation of samples.

2. **2035 Magnesium Stearate NF**

Particle Size Method has been renumbered as part of Geneva's method reengineering project. Sieve screen cleaning instructions have also been clarified. No other changes have been made.

Surface Area Method has been renumbered as part of Geneva's method reengineering project. The method was also revised in Section III, Analyzing the Samples. A note was added concerning the correlation coefficient from USP as acceptance criteria for the data. No other changes have been made.

3. **5843 #3 White Capsule, Imprinted GG 575, Green Ink Bands**  
**5844 #3 White Capsule, Imprinted GG 550, Black Ink Bands**

Capsule Loss on Drying Method has been revised to versus the drying oven.

No other changes were made.

**H. Room Temperature Stability Data**

Available room temperature stability data (HDPE bottles) for ANDA supportive Lots 6496034 (10 mg) and 6496022 (20 mg) are provided in Attachment 8. Refer to Attachment 4 for 18-month unit dose stability data.

This information is submitted for your review and approval.

Please acknowledge receipt of this document by signing and dating the enclosed copy of the cover letter and returning it in the self-addressed stamped envelope.

Sincerely,

GENEVA PHARMACEUTICALS, INC.



Beth Brannan, Director  
Drug Regulatory Affairs

Enclosures  
BB/jw

*NAI*

FEDERAL EXPRESS

(303) 466-2400

Douglas Sporn, Director  
Office of Generic Drugs  
Center for Drug Evaluation and Research  
Metro Park North 2, Room 150  
7500 Standish Place  
Rockville, MD 20855

AMENDMENT

APR 13 1998

*Proof of Notification  
and copy of civil  
NEW CORRESP*

*no  
action  
\* 5/5/98*

RE: ANDA 75-049 Fluoxetine Capsules, 10 and 20 mg  
Amendment - Patent (Documentation of Receipt of Notice)

Dear Director:

Geneva Pharmaceuticals, Inc. is hereby submitting an amendment to our unapproved Abbreviated New Drug Application for ANDA 75-049 Fluoxetine Capsules, 10 and 20 mg in accordance with Section 505 (j) of the Federal Food, Drug, and Cosmetic Act and with 21 CFR Parts 314.95 and 314.107.

A "Patent Certification Notice" was sent to Lilly Research Labs on May 21, 1997 for U.S. Patent No.(s) 4,314,081 and 4,626,549 as required by 21 CFR 314.95. Enclosed are copies of that notification and the return receipt as documentation of receipt of the notice on May 28, 1997 by Lilly Research Labs. The 45-day time period provided for in Section 505 (j)(4)(B)(iii) of the Federal Food, Drug, and Cosmetic Act expired July 14, 1997.

Geneva was notified of Lilly Research Labs' intent to sue for patent infringement filed on June 23, 1997 with the U.S. District Court, Southern District of Indiana, Indianapolis Division. A copy of that Civil Action number IP97-1029 C is enclosed.

Please incorporate this information into ANDA # 75-049 and acknowledge receipt of this document by signing and dating the enclosed copy of the cover letter and returning it in the self-addressed stamped envelope.

Sincerely,

GENEVA PHARMACEUTICALS, INC.

*Beth Brannan*

Beth Brannan, Director  
Drug Regulatory Affairs

Enclosures  
BB/jw

RECEIVED  
APR 14 1998  
GENERIC DRUGS

*Madden  
4-21-98*



*Labels + labeling  
satisfactory for approval  
-labeling review drafted  
2/11/98 abeja*

**FEDERAL EXPRESS**

(303) 466-2400

**MAJOR AMENDMENT**

Douglas Sporn, Director  
Office of Generic Drugs  
Center for Drug Evaluation and Research  
Metro Park North 2, Room 150  
7500 Standish Place  
Rockville, Maryland 20855

**OCT 06 1997**

**ORIG AMENDMENT**

*N/A C w/ FPL*

RE: ANDA 75-049 Fluoxetine Capsules 10 mg and 20 mg  
Major Amendment - Chemistry, Labeling and Manufacturing Controls

Dear Director:

We are submitting an amendment to our unapproved Abbreviated New Drug Application for Fluoxetine Capsules, 10 mg and 20 mg in accordance with Section 505(j) of the Federal Food, Drug and Cosmetic Act and 21 CFR Part 314.96(a).

Reference is made to your written communication of July 30, 1997. Response to your comments is provided in the order of appearance in your communication.

**A. Chemistry Deficiencies:**

1. The information contained in Geneva's components and composition statement does indicate an empty capsule shell weight of 50 mg. This is an approximate weight determined during development. However, it is understood to be a theoretical weight which is necessary to prepare the Master Manufacturing Form (batch record). Upon manufacturing a batch the encapsulation page of the batch record provides the space to record the actual average empty capsule shell weight. The average empty capsule shell weight is determined by taking an average weight of 40 capsules. This capsule weight is used to calculate the quantity to be weighed out for the batch. It is also used to determine the gross running weight for each batch (see comment #8).

2. The Identification Specification has been revised to include a "positive test result for chromatographic retention" to the existing IR Identification, and ID Specification of positive test result for alkaloidal chloride. A copy of the revised Active Raw Material Specifications and Methods Sheet and the Raw Material Method are provided in Attachment 1.

3. The drug substance specification for Heavy Metals has been revised to meet the manufacturer's specification of NMT % . A copy of the revised Active Raw Material Specifications and Methods Sheet is provided in Attachment 1.



**RECEIVED**

**OCT 07 1997**

**GENERIC DRUGS**  
GP097

4. The peak observed at a retention time of 6.659 min in the USP Organic Volatile Impurity (OVI) Method has been identified as ethyl acetate by comparison with an ethyl acetate standard and spiked samples. The drug substance manufacturer has confirmed the presence of low levels of ethyl acetate residual solvent. Additionally, toluene and dimethylacetamide have been identified as potential residual solvents by the drug substance manufacturer. Geneva has validated a GC method to quantitate these three residual solvents in addition to the five USP OVI solvents and has set limits for the bulk drug substance which are below recommended ICH guidelines (FR Vol. 62, No. 85, May 2, 1997, pg. 24302-24309). A copy of the revised Raw Material Specifications and Methods Sheet can be found in Attachment 1. Provided in Attachment 2 is a copy of the Residual Solvent Method

5. The drug substance manufacturer has certified that the three lots of fluoxetine hydrochloride including the lot used for the ANDA batch have been tested for polymorphism using Differential Scanning Calorimetry (DSC) and X-Ray Diffraction. The results demonstrate no evidence of polymorphism. Geneva has also confirmed these results by DSC analysis. The presence of a single endotherm at the same temperature for all four lots is direct evidence of a single crystal structure (polymorph). Results of Geneva's confirmation testing are provided in Attachment 3. Finally, to the best of our knowledge, there is no evidence of polymorphism in fluoxetine hydrochloride in the literature. Therefore, Geneva does not feel that it is necessary to test for polymorphs in the fluoxetine drug substance.

6. Laser diffraction particle size analyzers produce frequency distribution graphs of the data generated (see Attachment 4). For specification reporting it is easier to pick one or more points on the graph and report the values. The particle size data is reported as the size beneath which a specific percentage of the distribution falls. [d(x) values ( $d_{10}$ ,  $d_{50}$  and  $d_{90}$ ) are commonly used nomenclature, meaning the percent less than (x). The percentages 10, 50 and 90 were chosen because all laser diffraction instruments report these values and serve to describe the distribution by picking one point near the center of the curve, and two points near the ends].

7. The upper and lower control limits reported for the ANDA batches are values statistically derived from overall variation of data collected throughout the encapsulation run. Upper and lower control limits are for informational use only and do not reflect specifications for capsule weight. Control limits at Geneva are used by the operators to determine when machine adjustments are necessary. These control limits are drawn at approximately  $\pm 3$  standard deviations from the central line on the average portion of the chart. The value outside the lower control limit represents the need for a machine adjustment to maintain the target weight, and does not reflect failing weights.

This information is normally collected by Geneva and used with past and future data collected to set upper and lower control limits for production and commercial batches.

8. The capsule fill weight is based on the formula. A gross running weight for each batch is calculated by adding the fill weight to the average empty capsule weight. The encapsulation Standard Operating Procedure lists a specification for individual capsule weights within  $\pm 10\%$  of the gross running weight. Also per Standard Operating Procedures, individual capsule weight determinations are performed and recorded in-process periodically. If any individual measurement is out-of-specification the following procedure is followed:

- a. Discard all product back to the last acceptable measurement.
- b. Find and record root cause, if possible.
- c. Make a machine adjustment, if necessary.
- d. If machine adjustments do not correct the problem, notify supervisor.

9. We have added a test and methodology for in-process blend uniformity testing. Copies of revised In-Process Specifications and Methods Sheet and Method GP-1 are provided in Attachment 5.

10. Chromatographic purity specifications listing each known impurity and establishing limits for individual known, unknown and total impurities have been revised for the raw material, finished product and stability. A copy of the revised Raw Material Specifications and Methods Sheet can be found in Attachment #1. Copies of the revised Finished Product Specification Sheets, Finished Product Method, and Stability Protocols are provided in Attachment 6.

dec 1-22-98

11. A review of the chromatographic data for the dissolution testing shows a baseline disturbance where the sample solvent (void volume) elutes. Positive and negative perturbations are present after the void volume. The perturbations are caused by the dissolution medium which is acidified water (either 0.1N HCl or water acidified with HCl). The mobile phase, which contains water, acetonitrile and diethylamine, provides a certain amount of background absorbance. When the dissolution sample is injected into the system, a change in absorbance is observed at the column void volume. The change in absorbance is due to several factors: a difference in the absorbance of the sample solvent injected, a difference in the refractive index of the sample solvent, and/or an analyte associated with the buffer or excipients that absorbs at that wavelength. At a low UV wavelength, chloride is known to absorb light. Therefore, as the chloride ion elutes off the column and in the void volume a positive peak will be observed.

Since the sample solvent is different from the mobile phase, it is not unusual to observe this perturbation. Most importantly, these perturbations do not have any effect on the accurate quantitation of fluoxetine in the dissolution samples.

**B. Acknowledgments:**

1. Geneva has contacted the drug substance manufacturer and learned that the deficiencies found in DMF were responded to September 5, 1997.
2. We acknowledge that the final decision regarding the acceptability of the dissolution specification and test methods is the responsibility of the Division of Bioequivalence.
3. Geneva acknowledges that this product is compendial, however, the methods need to be "validated" in the FDA laboratory.

**C. Labeling Deficiencies:**

1. Container - 100s

Container labels for both the 10 mg and 20 mg strengths have been revised as requested.

2. Insert

Insert labeling has been revised as requested.

The general comment is acknowledged and an updated patent and exclusivity statement regarding treatment of bulimia is provided in Attachment 7.

Final printed container labeling and insert labeling are provided in Attachment 8.

This information is submitted for your review and approval.

Please acknowledge receipt of this document by signing and dating the enclosed copy of the cover letter and return it to the self-addressed stamped envelope.

Sincerely,

**GENEVA PHARMACEUTICALS, INC.**



Beth Brannan, Director

Drug Regulatory Affairs

Enclosures

BB:ap

**FEDERAL EXPRESS**

(303) 466-2400

May 21, 1997

*N/A  
6/2/97*

Douglas Sporn, Director  
Office of Generic Drugs  
Center for Drug Evaluation and Research  
Metro Park North 2, Room 150  
7500 Standish Place  
Rockville, MD 20855

**NEW CORRESP**  
**NC**

RE: ANDA 75-049 Fluoxetine Capsules, 10 and 20 mg  
Amendment - Patent Certification

Dear Director:

Geneva Pharmaceuticals, Inc. is hereby submitting an amendment to our unapproved Abbreviated New Drug Application for 75-049 Fluoxetine Capsules, 10 and 20 mg, in accord with Section 505 (j) of the Federal Food, Drug, and Cosmetic Act.

A revised patent certification for Fluoxetine U.S. Patent No.(s). 4,314,081 and 4,626,549 is being submitted.

This information is submitted toward the approval of ANDA 75-049.

Please acknowledge receipt of this document by signing and dating the enclosed copy of the cover letter and return it in the self-addressed stamped envelope.

Sincerely,

GENEVA PHARMACEUTICALS, INC.

*Beth Brannan*

Beth Brannan, Director  
Drug Regulatory Affairs

Enclosures

BB/slc



RECEIVED

MAY 22 1997

GENERIC DRUGS

*Madame  
5/27/97*

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

1300 I STREET, N.W.  
WASHINGTON, DC 20005-3315

202-408-4000  
FACSIMILE 202-408-4400

WRITER'S DIRECT DIAL NUMBER

(202) 408-4068

July 3, 1997

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FACSIMILE 011-322-646-2135

TOKYO OFFICE:  
TORANOMON NO. 45 MORI BUILDING  
1-5, TORANOMON 5-CHOME  
MINATO-KU, TOKYO 105, JAPAN  
TELEPHONE 011-813-3431-6943  
FACSIMILE 011-813-3431-6945

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

NEW CORRESP  
NC

VIA FEDERAL EXPRESS

Re: Fluoxetine Hydrochloride Capsules, 10 and 20 mg  
Abbreviated New Drug Application No. 75-049  
Notification of Filing of Legal Action for Patent Infringement

Dear Sir or Madam:

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 May 21, 1997, Ms. Beth Brannan, Director Drug Regulatory Affairs, of Geneva Pharmaceuticals, Inc. ("Geneva") sent a letter to Lilly by certified mail stating that Geneva 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 Geneva containing bioavailability or bioequivalence data or information with respect to fluoxetine hydrochloride 10 and 20 mg capsules.
  - (ii) The abbreviated new drug application number is 75-049.
  - (iii) The letter refers to the proposed drug product as fluoxetine capsules, 10 and 20 mg. (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 10 and 20 mg.)
  - (iv) The active ingredient, strength, and dosage form of the proposed drug product is fluoxetine hydrochloride 10 and 20 mg capsules for oral administration.

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GENERIC DRUGS

Food & Drug Administration

July 3, 1997

Page 2

- (v) The patent numbers and expiration dates, as known to Geneva, each claim of which is alleged to be either invalid 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 May 28, 1997.

Certification

We hereby certify that on June 23, 1997, Lilly filed an action for patent infringement against Geneva in the United States District Court for the Southern District of Indiana (Case Number IP97-1029 C B/S). Lilly alleges, among other things, that under 35 U.S.C. § 271(e)(2)(A) Geneva'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 Geneva'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

DSF/mco

cc: Beth Brannan, Director, Drug Regulatory Affairs  
Geneva Pharmaceuticals, Inc.

508 (12) (14)  
OK  
Clause

(303) 466-2400 FAX (303) 438-4600

FEDERAL EXPRESS

2/19/97

December 31, 1996

Douglas Sporn, Director  
Office of Generic Drugs  
Center for Drug Evaluation and Research  
Metro Park North 2, Room 150  
7500 Standish Place  
Rockville, MD 20855

RE: Fluoxetine Capsules, 10 mg and 20 mg

Dear Director:

Geneva Pharmaceuticals, Inc. is hereby submitting an Abbreviated New Drug Application for Fluoxetine Capsules, 10 mg and 20 mg as required by Section 505 (j) of the Federal Food, Drug, and Cosmetic Act, and in accordance with 21 CFR Part 314.92 and 314.94.

A comprehensive table of contents is provided which shows the volume and page number of our submission's contents, as required by the regulations Part 314.94(a)(2).

The blue archival copy (13 volumes) contains the complete application. The Methods Validation packet is also provided in a blue archival binder; it contains triplicate copies of raw material and finished product specifications, methods and results.

The red review chemistry section review copy (2 volumes) contains the complete application Chemistry, Labeling, Manufacturing, and Controls sections. The orange pharmacokinetic section review copy (10 volumes) contains bioequivalence information.

This information is submitted for your review and approval.

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JAN 02 1997

**GENERIC DRUGS**



Please acknowledge receipt of this document by signing and dating the enclosed copy of the cover letter and returning it in the self-addressed stamped envelope.

Sincerely,

GENEVA PHARMACEUTICALS, INC.

A handwritten signature in cursive script that reads "Beth Brannan".

Beth Brannan, Director  
Drug Regulatory Affairs

Enclosures

BB/slc

**FEDERAL EXPRESS**

5Sep97

Director,  
Division of Bioequivalence - HFD-650,  
Office of Generic Drugs,  
Centre for Drug Evaluation and Research,  
Metro Park North 2,  
7500 Standish Place, Room 150  
Rockville, MD 20855

*msb*  
**BIOAVAILABILITY**  
**NEW CORRESP**  
**AMENDMENT**  
*NC/BIO*

RE: ANDA 75-049 Fluoxetine Hydrochloride Capsules, 10 mg and 20 mg  
Amendment - Bioequivalence Study

Dear Director:

We are submitting an amendment to our unapproved Abbreviated New Drug Application for Fluoxetine Hydrochloride Capsules, in accord with Section 505(j) of the Federal Food, Drug and Cosmetic Act.

Reference is made to your written communication of July 11, 1997.

- Stability for both fluoxetine and norfluoxetine has been established for 462 days. Stability quality control (Stab QC) samples were originally spiked on April 30, 1996 and stored at -22 °C until analysed on September 30, 1996 (150 days stability) and on August 6, 1997 (462 days). Long term stability tests were performed by

The percent deviation from nominal values were calculated for fluoxetine and norfluoxetine. The information for fluoxetine is provided in Tables S7.1a and S7.1b (Attachment 1) while the information for norfluoxetine is provided in tables S7.2a and S7.2b (Attachment 2). For convenience, the information from these tables is summarized below:

Summary of 150 day long-term stability for fluoxetine and norfluoxetine in human plasma at -22 °C.				
	Fluoxetine		Norfluoxetine	
	Stab QC A	Stab QC C	Stab QC A	Stab QC C
Number of QC samples	14 <sup>a</sup>	14	14	14
CV (%)	4.9	3.8	7.4	7.0
Accuracy or Bias (%)	-3.7	-3.8	-6.7	-4.4
Number of QCs with acceptable % deviation from nominal <sup>b</sup>	14 out of 14	14 out of 14	14 out of 14	14 out of 14

<sup>a</sup> one outlier result was not used in the statistics

<sup>b</sup> per SOP #AL-G-1506-12.A01, acceptable % deviations are ±15% for QC C and ±20% for QC A (SOP provided in Attachment 3)

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SEP 08 1997



**GENERIC DRUGS**

Summary of 462 day long-term stability for fluoxetine and norfluoxetine in human plasma at -22 °C.				
	Fluoxetine		Norfluoxetine	
	Stab QC A	Stab QC C	Stab QC A	Stab QC C
Number of QC samples	9 <sup>a</sup>	10	9	10
CV (%)	5.7	10.0	9.6	10.7
Accuracy or Bias (%)	- 1.5	3.5	- 7.6	-1.3
Number of QCs with acceptable % deviation from nominal <sup>b</sup>	9 out of 9	8 out of 10	9 out of 9	9 out of 10

<sup>a</sup> one outlier result was not used in the statistics

<sup>b</sup> per SOP #AL-G-1506-12.A01, acceptable % deviations are ±15 % for QC C and ± 20 % for QC A (SOP provided in Attachment 3)

Since more than % of the QC samples at each concentration yielded acceptable percent deviations from nominal values, it appears that fluoxetine and norfluoxetine are stable for 462 days when stored in human plasma at -22 °C.

2. acknowledges that for future studies, all samples from one subject should be run on the same day.
3. acknowledges that for future studies, QC samples should be chosen that are closer to the concentration range of the actual plasma concentrations of the drug.
4. A request for waiver of *in vivo* studies for Fluoxetine Capsules, 10 mg is provided in Attachment 4. Also provided in Attachment 4 are the formula compositions for the 10 and 20 mg strengths, summary of information regarding the test and and reference products for each strength of Geneva and brand product, and the finished product certificates of analysis.

This information is provided for your review and approval.

Please acknowledge receipt of this document by signing and dating the enclosed copy of the cover letter and return it in the self-addressed stamped envelope.

Sincerely,

GENEVA PHARMACEUTICALS, INC.



Beth Brannan, Director  
Drug Regulatory Affairs

bb/skp

Enclosures

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SEP 03 1997

**GENERIC DRUGS**