

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
21-299

CORRESPONDENCE



NDA 21-299

Synthon Pharmaceuticals Ltd.
Attention: Susan W. Harts
Vice President of Regulatory Affairs
6330 Quadrangle Drive, Suite 305
Chapel Hill, NC 27514

Dear Ms. Harts:

We acknowledge receipt on September 20, 2001 of your September 19, 2001 resubmission to your new drug application (NDA) for Paroxetine mesylate 10 mg, 20 mg, 30 mg, and 40 mg Tablets.

This resubmission contains additional clinical, chemistry, manufacturing, and controls (CMC), and clinical pharmacology and biopharmaceutics information submitted in response to our May 25, 2001 action letter.

We consider this a complete class 2 response to our action letter. Therefore, the user fee goal date is March 20, 2002.

If you have any questions, call Paul David, R.Ph., Regulatory Project Manager, at (301) 594-5530.

Sincerely,

{See appended electronic signature page}

Russell Katz, M.D.
Director
Division of Neuropharmacological Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Russell Katz
9/25/01 08:58:50 AM



NDA 21-299

DISCIPLINE REVIEW LETTER

Synthon Pharmaceuticals Ltd.
Attention: Susan W. Harts
Vice President of Regulatory Affairs
6330 Quadrangle Drive, Suite 305
Chapel Hill, NC 27514

Dear Ms. Harts:

Please refer to your new drug application (NDA) dated July 26, 2000, received July 26, 2000, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Paroxetine mesylate 10 mg, 20 mg, 30 mg, and 40 mg Tablets.

Reference is also made to an Agency approvable letter dated May 25, 2001.

We acknowledge receipt of your amendment dated June 7, 2001, providing for a response to only the chemistry, manufacturing, and controls deficiencies of our May 25, 2001 approvable letter.

Please note that we do not consider this a complete response to our action letter. Therefore, the review clock will not be started until we have received a complete response.

However, we have completed our review of your June 7, 2001 response, and we have identified the following deficiencies:

DEFICIENCIES PERTAINING TO DRUG SUBSTANCE:

- Please recalculate the RRFs for the impurities in _____ Paroxetine mesylate drug substance and Paroxetine (as mesylate) Tablets using the same absorbance wavelength for the impurity and Reference Standard. Please recalculate the impurity content in _____ Paroxetine mesylate drug substance and Paroxetine (as mesylate) Tablets batches reported in NDA 21-299 using the recalculated RRFs and provide the FDA with the analysis results.

DEFICIENCIES PERTAINING TO THE DRUG PRODUCT:

- Please provide the FDA with a copy of the validated methods for testing the enantiomeric purity of Paroxetine (as mesylate) Tablets 10 mg, 20 mg, 30 mg, 40 mg.

We are providing these comments to you prior to your formal resubmission to give you preliminary notice of issues that we have identified. In conformance with the prescription drug user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and subject to change as we finalize our review of

your application. In addition, we may identify other information that must be provided before we can approve this application. If you respond to these issues during this review cycle, depending on the timing of your response, and in conformance with the user fee reauthorization agreements, we may not be able to consider your response before we take an action on your application during this review cycle.

If you have any questions, call Paul David, R.Ph., Senior Regulatory Project Manager, at (301) 594-5530.

Sincerely,

{See appended electronic signature page}

Russell Katz, M.D.
Director
Division of Neuropharmacological Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Russell Katz
7/17/01 12:48:54 PM

5 Page(s) Withheld



VIA FEDERAL EXPRESS

NEW CORRESP

DUPLICATE

N-C

CENTER FOR DRUG EVALUATION
AND RESEARCH

MAR 20 2001

RECEIVED HFD-120

March 19, 2001

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Neuropharmacological Drug
Products, HFD-120
Attention: Division Document Room 4008
1451 Rockville Pike
Rockville, Maryland 20852-1420

**Re: NDA No. 21-299 (Paroxetine (as mesylate) tablets) -
Amendment 012 --Documentation of receipt of patent notice**

Dear Sir or Madam:

We have enclosed one original and two copies of Amendment 012 to Synthon Pharmaceuticals, Ltd. (Synthon's) new drug application (NDA) for paroxetine mesylate oral tablets (NDA No. 21-299). The amendment is being submitted pursuant to 21 C.F.R. § 314.52(e) and includes documentation of the receipt by the appropriate NDA holder and the U.S. agent of the patent owner of Synthon's notice of patent invalidity or noninfringement for patents added to Synthon's paragraph IV certification pursuant to Synthon's NDA Amendment 010.

In accordance with 21 C.F.R. § 314.52(a) and the Agency's July 13, 2000 letter authorizing the use of Federal Express for the delivery of Synthon's paragraph IV notice, Synthon has delivered the notice via Federal Express to the following addresses:

1. SmithKline Beecham Corporation
Corporate Intellectual Property Group
King of Prussia, Pennsylvania
(U.S. Agent for patent owner)
2. SmithKline Beecham Pharmaceuticals
Legal Department
Collegeville, Pennsylvania
(NDA holder)

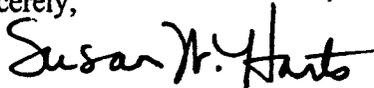
March 19, 2001

The addressees received the notice on March 19, 2001. Therefore, in accordance with FDA's regulations, 21 C.F.R. § 314.52(f), March 20, 2001 is the first day of the 45-day period provided for in Section 505 (c)(3)(C) of the Act.

Documentation confirming receipt of the notice by the aforementioned addressees is included in the enclosed amendment in the form of copies of the Federal Express air bills and proof of delivery documentation for each air bill. A completed Form FDA 356h is also included in the amendment.

Should you have any questions concerning this amendment or any other aspect of Synthon's application, please contact me at 919-493-6006.

Sincerely,



Susan W. Harts, RN, RAC
Vice President of Regulatory Affairs

Enclosure(s)

Cc: Paul David (FDA)

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

APPLICATION TO MARKET A NEW DRUG, BIOLOGIC,
OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations, 314 & 601)

Form Approved: OMB No. 0910-0338
Expiration Date: March 31, 2003
See OMB Statement on page 2.

FOR FDA USE ONLY

APPLICATION NUMBER

APPLICANT INFORMATION

NAME OF APPLICANT Synthon Pharmaceuticals Ltd.	DATE OF SUBMISSION March 19, 2001
TELEPHONE NO. (Include Area Code) 919-493-6006	FACSIMILE (FAX) Number (Include Area Code) 919-493-6104
APPLICANT ADDRESS (Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued): 6330 Quadrangle Drive Suite 305 Chapel Hill, NC 27514	AUTHORIZED U.S. AGENT NAME & ADDRESS (Number, Street, City, State, ZIP Code, telephone & FAX number) IF APPLICABLE NA

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER (if previously issued) NA

ESTABLISHED NAME (e.g., Proper name, USP/USAN name) Paroxetine Mesylate	PROPRIETARY NAME (trade name) IF ANY NA
CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME (if any) NA	CODE NAME (if any) NA

DOSAGE FORM: Tablet STRENGTHS: 10 mg, 20 mg, 30 mg, 40 mg ROUTE OF ADMINISTRATION: oral

(PROPOSED) INDICATION(S) FOR USE: Depressive illness, obsessive compulsive disorder, panic disorder

APPLICATION INFORMATION

APPLICATION TYPE (check one) NEW DRUG APPLICATION (21 CFR 314.50) ABBREVIATED NEW DRUG APPLICATION (ANDA, 21 CFR 314.94)
 BIOLOGICS LICENSE APPLICATION (21 CFR part 601)

IF AN NDA, IDENTIFY THE APPROPRIATE TYPE 505 (b)(1) 505 (b)(2)

IF AN ANDA, or 505(b)(2), IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION
Name of Drug Paxil Holder of Approved Application SmithKline Beecham

TYPE OF SUBMISSION (check one) ORIGINAL APPLICATION AMENDMENT TO A PENDING APPLICATION RESUBMISSION
 PRESUBMISSION ANNUAL REPORT ESTABLISHMENT DESCRIPTION SUPPLEMENT EFFICACY SUPPLEMENT
 LABELING SUPPLEMENT CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT OTHER

IF A SUBMISSION OR PARTIAL APPLICATION, PROVIDE LETTER DATE OF AGREEMENT TO PARTIAL SUBMISSION: NA

IF A SUPPLEMENT, IDENTIFY THE APPROPRIATE CATEGORY CBE CBE-30 Prior Approval (PA)

REASON FOR SUBMISSION Amendment to provide documentation of receipt of patent notice

PROPOSED MARKETING STATUS (check one) PRESCRIPTION PRODUCT (Rx) OVER THE COUNTER PRODUCT (OTC)

NUMBER OF VOLUMES SUBMITTED 1 THIS APPLICATION IS PAPER PAPER AND ELECTRONIC ELECTRONIC

ESTABLISHMENT INFORMATION (Full establishment information should be provided in the body of the Application.)
Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g., Final dosage form, Stability/testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.

See originally filed Form 356h

Cross References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMFs referenced in the current application)

See originally filed Form 356h

This application contains the following items: (Check all that apply)

- 1. Index
- 2. Labeling (check one) Draft Labeling Final Printed Labeling
- 3. Summary (21 CFR 314.50(c))
- 4. Chemistry section
 - A. Chemistry, manufacturing, and controls information (e.g., 21 CFR 314.50(d)(1); 21 CFR 601.2)
 - B. Samples (21 CFR 314.50(e)(1); 21 CFR 601.2 (a)) (Submit only upon FDA's request)
 - C. Methods validation package (e.g., 21 CFR 314.50(e)(2)(i); 21 CFR 601.2)
- 5. Nonclinical pharmacology and toxicology section (e.g., 21 CFR 314.50(d)(2); 21 CFR 601.2)
- 6. Human pharmacokinetics and bioavailability section (e.g., 21 CFR 314.50(d)(3); 21 CFR 601.2)
- 7. Clinical Microbiology (e.g., 21 CFR 314.50(d)(4))
- 8. Clinical data section (e.g., 21 CFR 314.50(d)(5); 21 CFR 601.2)
- 9. Safety update report (e.g., 21 CFR 314.50(d)(5)(vi)(b); 21 CFR 601.2)
- 10. Statistical section (e.g., 21 CFR 314.50(d)(6); 21 CFR 601.2)
- 11. Case report tabulations (e.g., 21 CFR 314.50(f)(1); 21 CFR 601.2)
- 12. Case report forms (e.g., 21 CFR 314.50(f)(2); 21 CFR 601.2)
- 13. Patent information on any patent which claims the drug (21 U.S.C. 355(b) or (c))
- 14. A patent certification with respect to any patent which claims the drug (21 U.S.C. 355(b)(2) or (j)(2)(A))
- 15. Establishment description (21 CFR Part 600, if applicable)
- 16. Debarment certification (FD&C Act 306(k)(1))
- 17. Field copy certification (21 CFR 314.50(k)(3))
- 18. User Fee Cover Sheet (Form FDA 3397)
- 19. Financial Information (21 CFR Part 54)
- 20. OTHER (Specify) Amendment to provide documentation of receipt of patent notice

CERTIFICATION

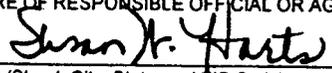
I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including, but not limited to the following:

1. Good manufacturing practice regulations in 21 CFR Parts 210, 211 or applicable regulations, Parts 606, and/or 820.
2. Biological establishment standards in 21 CFR Part 600.
3. Labeling regulations in 21 CFR Parts 201, 606, 610, 660 and/or 809.
4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR 202.
5. Regulations on making changes in application in FD&C Act Section 506A, 21 CFR 314.71, 314.72, 314.97, 314.99, and 601.12.
6. Regulations on Reports in 21 CFR 314.80, 314.81, 600.80 and 600.81.
7. Local, state and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act, I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.

The data and information in this submission have been reviewed and, to the best of my knowledge are certified to be true and accurate.

Warning: A willfully false statement is a criminal offense, U.S. Code, title 18, section 1001.

SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT 	TYPED NAME AND TITLE Susan W. Harts Vice President of Regulatory Affairs	DATE March 19, 2001
ADDRESS (Street, City, State, and ZIP Code) 6330 Quadrangle Drive, Suite 305 Chapel Hill, NC 27514		TELEPHONE NUMBER 919-493-6006

Public reporting burden for this collection of information is estimated to average 24 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Department of Health and Human Services
Food and Drug Administration
CBER, HFM-99
1401 Rockville Pike
Rockville, MD 20852-1448

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.



March 16, 2001

VIA HAND DELIVERY

Russell Katz, M.D.
Food and Drug Administration
Office of Drug Evaluation I
Div. of Neuropharmacological Drug Products (HFD-120)
Woodmont II
1451 Rockville Pike
Rockville, Maryland 20852-1420

**Re: NDA No. 21-299 - Amendment 010 (Paroxetine (as mesylate) Tablets) -
Synthon Pharmaceuticals, Ltd.**

Dear Dr. Katz:

Enclosed please find the original and two copies of Amendment 010 to NDA number 21-299. The purpose of the amendment is to amend Synthon's paragraph IV patent certification and statement to include patents that were listed in the Orange Book subsequent to the filing of Synthon's 505(b)(2) application. The patents are identified in the Orange Book as claiming the Paxil® (paroxetine hydrochloride) drug product that is referenced in Synthon's application.

The amendment consists of the following documents:

- A completed Form FDA 356h;
- An amended paragraph IV patent certification (page 18 of the original NDA submission); and
- An amended paragraph IV statement (page 19 of the original NDA submission).

Should you have any questions concerning this submission, please contact me at (919) 493-6006.

Sincerely,

A handwritten signature in black ink that reads "Susan Harts". The signature is written in a cursive style with a long horizontal stroke at the end.

Susan W. Harts, RN, RAC
Vice President of Regulatory Affairs

Enclosure(s)
cc: Mr. Paul David

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

APPLICATION TO MARKET A NEW DRUG, BIOLOGIC,
OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations, 314 & 601)

Form Approved: OMB No. 0910-0338
Expiration Date: March 31, 2003
See OMB Statement on page 2.
FOR FDA USE ONLY
APPLICATION NUMBER

APPLICANT INFORMATION

NAME OF APPLICANT Synthon Pharmaceuticals Ltd.	DATE OF SUBMISSION March 16, 2001
TELEPHONE NO. (Include Area Code) 919-493-6006	FACSIMILE (FAX) Number (Include Area Code) 919-493-6104
APPLICANT ADDRESS (Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued): 6330 Quadrangle Drive Suite 305 Chapel Hill, NC 27514	AUTHORIZED U.S. AGENT NAME & ADDRESS (Number, Street, City, State, ZIP Code, telephone & FAX number) IF APPLICABLE NA

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER (if previously issued) NA		
ESTABLISHED NAME (e.g., Proper name, USP/USAN name) Paroxetine Mesylate	PROPRIETARY NAME (trade name) IF ANY NA	
CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME (if any) NA	CODE NAME (if any) NA	
DOSAGE FORM: Tablet	STRENGTHS: 10 mg, 20 mg, 30 mg, 40 mg	ROUTE OF ADMINISTRATION: oral
(PROPOSED) INDICATION(S) FOR USE: Depressive illness, obsessive compulsive disorder, panic disorder		

APPLICATION INFORMATION

APPLICATION TYPE (check one) <input checked="" type="checkbox"/> NEW DRUG APPLICATION (21 CFR 314.50) <input type="checkbox"/> BIOLOGICS LICENSE APPLICATION (21 CFR part 601) <input type="checkbox"/> ABBREVIATED NEW DRUG APPLICATION (ANDA, 21 CFR 314.94)
IF AN NDA, IDENTIFY THE APPROPRIATE TYPE <input type="checkbox"/> 505 (b)(1) <input checked="" type="checkbox"/> 505 (b)(2)
IF AN ANDA, or 505(b)(2), IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION Name of Drug Paxil Holder of Approved Application Smithkline Beecham
TYPE OF SUBMISSION (check one) <input type="checkbox"/> ORIGINAL APPLICATION <input checked="" type="checkbox"/> AMENDMENT TO A PENDING APPLICATION <input type="checkbox"/> RESUBMISSION <input type="checkbox"/> PRESUBMISSION <input type="checkbox"/> ANNUAL REPORT <input type="checkbox"/> ESTABLISHMENT DESCRIPTION SUPPLEMENT <input type="checkbox"/> EFFICACY SUPPLEMENT <input type="checkbox"/> LABELING SUPPLEMENT <input type="checkbox"/> CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT <input type="checkbox"/> OTHER
IF A SUBMISSION OR PARTIAL APPLICATION, PROVIDE LETTER DATE OF AGREEMENT TO PARTIAL SUBMISSION: NA
IF A SUPPLEMENT, IDENTIFY THE APPROPRIATE CATEGORY <input type="checkbox"/> CBE <input type="checkbox"/> CBE-30 <input type="checkbox"/> Prior Approval (PA)
REASON FOR SUBMISSION Amendment of patent certification and statement to reflect patents that were issued subsequent to the original filing of the application.
PROPOSED MARKETING STATUS (check one) <input checked="" type="checkbox"/> PRESCRIPTION PRODUCT (Rx) <input type="checkbox"/> OVER THE COUNTER PRODUCT (OTC)
NUMBER OF VOLUMES SUBMITTED <u>1</u> THIS APPLICATION IS <input checked="" type="checkbox"/> PAPER <input type="checkbox"/> PAPER AND ELECTRONIC <input type="checkbox"/> ELECTRONIC

ESTABLISHMENT INFORMATION (Full establishment information should be provided in the body of the Application.)
Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g., Final dosage form, Stability/testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.

See originally filed Form FDA 356h

Cross References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMFs referenced in the current application)

See originally filed Form FDA 356h

This application contains the following items: (Check all that apply)

- 1. Index
- 2. Labeling (check one) Draft Labeling Final Printed Labeling
- 3. Summary (21 CFR 314.50(c))
- 4. Chemistry section
 - A. Chemistry, manufacturing, and controls information (e.g., 21 CFR 314.50(d)(1); 21 CFR 601.2)
 - B. Samples (21 CFR 314.50(e)(1); 21 CFR 601.2 (a)) (Submit only upon FDA's request)
 - C. Methods validation package (e.g., 21 CFR 314.50(e)(2)(i); 21 CFR 601.2)
- 5. Nonclinical pharmacology and toxicology section (e.g., 21 CFR 314.50(d)(2); 21 CFR 601.2)
- 6. Human pharmacokinetics and bioavailability section (e.g., 21 CFR 314.50(d)(3); 21 CFR 601.2)
- 7. Clinical Microbiology (e.g., 21 CFR 314.50(d)(4))
- 8. Clinical data section (e.g., 21 CFR 314.50(d)(5); 21 CFR 601.2)
- 9. Safety update report (e.g., 21 CFR 314.50(d)(5)(vi)(b); 21 CFR 601.2)
- 10. Statistical section (e.g., 21 CFR 314.50(d)(6); 21 CFR 601.2)
- 11. Case report tabulations (e.g., 21 CFR 314.50(f)(1); 21 CFR 601.2)
- 12. Case report forms (e.g., 21 CFR 314.50(f)(2); 21 CFR 601.2)
- 13. Patent information on any patent which claims the drug (21 U.S.C. 355(b) or (c))
- 14. A patent certification with respect to any patent which claims the drug (21 U.S.C. 355(b)(2) or (j)(2)(A))
- 15. Establishment description (21 CFR Part 600, if applicable)
- 16. Debarment certification (FD&C Act 306(k)(1))
- 17. Field copy certification (21 CFR 314.50(k)(3))
- 18. User Fee Cover Sheet (Form FDA 3397)
- 19. Financial Information (21 CFR Part 54)
- 20. OTHER (Specify)

CERTIFICATION

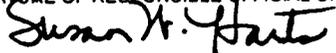
I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including, but not limited to the following:

1. Good manufacturing practice regulations in 21 CFR Parts 210, 211 or applicable regulations, Parts 606, and/or 820.
2. Biological establishment standards in 21 CFR Part 600.
3. Labeling regulations in 21 CFR Parts 201, 606, 610, 660 and/or 809.
4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR 202.
5. Regulations on making changes in application in FD&C Act Section 506A, 21 CFR 314.71, 314.72, 314.97, 314.99, and 601.12.
6. Regulations on Reports in 21 CFR 314.80, 314.81, 600.80 and 600.81.
7. Local, state and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act, I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.

The data and information in this submission have been reviewed and, to the best of my knowledge are certified to be true and accurate.

Warning: A willfully false statement is a criminal offense, U.S. Code, title 18, section 1001.

SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT 	TYPED NAME AND TITLE Susan W. Harts Vice President of Regulatory Affairs	DATE March 16, 2001
ADDRESS (Street, City, State, and ZIP Code) 6330 Quadrangle Drive, Suite 305 Chapel Hill, NC 27514		TELEPHONE NUMBER 919-493-6006

Public reporting burden for this collection of information is estimated to average 24 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Department of Health and Human Services
 Food and Drug Administration
 CBER, HFM-99
 1401 Rockville Pike
 Rockville, MD 20852-1448

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

Paragraph IV Patent Certification

Synthon Pharmaceuticals Ltd. has caused all of the following actions to be taken with respect to the following patent certification concerning its paroxetine (as mesylate) tablets, 10 mg, 20 mg, 30 mg, and 40 mg:

1. The publication entitled "Approved Drug Products with Therapeutic Equivalence Evaluations" (Orange Book), 20th Edition, 2000, and Cumulative Supplement 12 to the 20th Edition (February 2001) have been examined for patent entries related to the listed drug (Paxil® tablets).
2. The U.S. Patent and Trademark Office's ("PTO's") February 13, 2001 list of Patent Terms Extended Under 35 U.S.C. § 156 (Waxman-Hatch extensions) has been examined for entries related to the listed drug.
3. The February 13, 2001 list entered in FDA's Docket Number 95S-0117 concerning information on "PATENT TERM EXTENSION AND NEW PATENTS" has been examined for entries related to the listed drug.

Based upon the above-identified actions, Synthon Pharmaceuticals Ltd. certifies that, in its opinion and to the best of its knowledge:

Paragraph IV

The following patents are invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the paroxetine (as mesylate) tablets for which this application is submitted:

<u>Patent Number</u>	<u>Inventor</u>	<u>Issue Date</u>	<u>Expiration Date</u>
4,721,723	Barnes et al.	Jan. 26, 1988	Dec. 29, 2006
5,789,449	Norden	Aug. 4, 1998	Jan. 6, 2009
5,872,132	Ward et al.	Feb. 16, 1999	May 19, 2015
5,900,423	Ward et al.	May 4, 1999	May 19, 2015
6,063,927	Craig et al.	May 16, 2000	Apr. 23, 2019
6,080,759	Ward et al.	June 27, 2000	May 19, 2015
6,113,944	Pathak et al.	Sept. 5, 2000	Dec. 14, 2014
6,121,291	Gleason	Sept. 19, 2000	Mar. 17, 2017
6,133,289	Ward et al.	Oct. 17, 2000	May 19, 2015
6,172,233	Ward et al.	Jan. 9, 2001	Jan. 15, 2018

Synthon Pharmaceuticals Ltd.



Dr. William J. Taylor
President

Paragraph IV Statement

Synthon Pharmaceuticals Ltd. hereby states, in accordance with Section 505(b)(3)(A) of the Federal Food, Drug, and Cosmetic Act ("the Act") and 21 C.F.R. § 314.50(i)(1)(i)(A)(4), that it has given or is giving on even date herewith notices containing the information required by Section 505(b)(3)(B) of the Act and 21 C.F.R. § 314.52(c) to the following persons by Federal Express with receipt verification:

1. The owner(s) of each of the following patent numbers:
4,721,723; 5,789,449; 5,872,132; 5,900,423; 6,063,927; 6,080,759; 6,113,944;
6,121,291; 6,133,289; and 6,172,233, or the representative of each owner
designated to receive the notice; and
2. The holder of approved NDA number 20-031 or the representative of the holder
designated to receive the notice.



January 26, 2001

VIA FEDERAL EXPRESS

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Neuropharmacological Drug
Products (HFD-120)
Attention: Division Document Room 4008
1451 Rockville Pike
Rockville, MD 20852-1420

**Re: New Drug Application
Paroxetine (as mesylate) tablets
NDA No. 21-299
Amendment 009**

Dear Sir or Madam:

We have enclosed two copies of an amendment to Synthon Pharmaceuticals, Ltd. new drug application (NDA) for paroxetine (as mesylate) oral tablets (NDA No. 21-299). The amendment consists of responses raised during the chemistry review of the application. The responses were previously submitted informally to the Food and Drug Administration (FDA) on January 16, 2001.

Should you have any additional questions, please do not hesitate to contact me at (919) 493-6006.

Sincerely,

A handwritten signature in black ink that reads "Susan W. Harts". The signature is written in a cursive, flowing style.

Susan W. Harts, RN, RAC
Vice President of Regulatory Affairs

Enclosures

CC: Mr. Paul David (w/Form 356h, w/o binder)
Mr. Lorenzo Rocca (w/Form 356h, w/o binder)

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

APPLICATION TO MARKET A NEW DRUG, BIOLOGIC,
OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations, 314 & 601)

Form Approved: OMB No. 0910-0338
Expiration Date: March 31, 2003
See OMB Statement on page 2.

FOR FDA USE ONLY

APPLICATION NUMBER

APPLICANT INFORMATION

NAME OF APPLICANT
Synthon Pharmaceuticals Ltd.

DATE OF SUBMISSION
January 26, 2001

TELEPHONE NO. (Include Area Code)
919-493-6006

FACSIMILE (FAX) Number (Include Area Code)
919-493-6104

APPLICANT ADDRESS (Number, Street, City, State, Country, ZIP Code or Mail Code,
and U.S. License number if previously issued):
6330 Quadrangle Drive
Suite 305
Chapel Hill, NC 27514

AUTHORIZED U.S. AGENT NAME & ADDRESS (Number, Street, City, State,
ZIP Code, telephone & FAX number) IF APPLICABLE
NA

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER (If previously issued) 21-299

ESTABLISHED NAME (e.g., Proper name, USP/USAN name)
Paroxetine Mesylate

PROPRIETARY NAME (trade name) IF ANY NA

CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME (If any) NA

CODE NAME (If any) NA

DOSAGE FORM: Tablet

STRENGTHS: 10 mg, 20 mg, 30 mg, 40 mg

ROUTE OF ADMINISTRATION: oral

(PROPOSED) INDICATION(S) FOR USE: Depressive illness, obsessive compulsive disorder, panic disorder

APPLICATION INFORMATION

APPLICATION TYPE
(check one) NEW DRUG APPLICATION (21 CFR 314.50) ABBREVIATED NEW DRUG APPLICATION (ANDA, 21 CFR 314.94)
 BIOLOGICS LICENSE APPLICATION (21 CFR part 601)

IF AN NDA, IDENTIFY THE APPROPRIATE TYPE 505 (b)(1) 505 (b)(2)

IF AN ANDA, or 505(b)(2), IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION
Name of Drug Paxil Holder of Approved Application SmithKline Beecham

TYPE OF SUBMISSION (check one) ORIGINAL APPLICATION AMENDMENT TO A PENDING APPLICATION RESUBMISSION
 PRESUBMISSION ANNUAL REPORT ESTABLISHMENT DESCRIPTION SUPPLEMENT EFFICACY SUPPLEMENT
 LABELING SUPPLEMENT CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT OTHER

IF A SUBMISSION OR PARTIAL APPLICATION, PROVIDE LETTER DATE OF AGREEMENT TO PARTIAL SUBMISSION: NA

IF A SUPPLEMENT, IDENTIFY THE APPROPRIATE CATEGORY CBE CBE-30 Prior Approval (PA)

REASON FOR SUBMISSION Amendment to clarify the structure and identity of impurity

PROPOSED MARKETING STATUS (check one) PRESCRIPTION PRODUCT (Rx) OVER THE COUNTER PRODUCT (OTC)

NUMBER OF VOLUMES SUBMITTED 1 THIS APPLICATION IS PAPER PAPER AND ELECTRONIC ELECTRONIC

ESTABLISHMENT INFORMATION (Full establishment information should be provided in the body of the Application.)
Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g., Final dosage form, Stability/testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.

See originally filed Form 356h

Cross References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMFs referenced in the current application)

See originally filed Form 356h

This application contains the following items: (Check all that apply)

<input type="checkbox"/>	1. Index	<input type="checkbox"/>	Draft Labeling	<input type="checkbox"/>	Final Printed Labeling
<input type="checkbox"/>	2. Labeling (check one)				
<input type="checkbox"/>	3. Summary (21 CFR 314.50(c))				
<input type="checkbox"/>	4. Chemistry section				
<input checked="" type="checkbox"/>	A. Chemistry, manufacturing, and controls information (e.g., 21 CFR 314.50(d)(1); 21 CFR 601.2)				
<input type="checkbox"/>	B. Samples (21 CFR 314.50(e)(1); 21 CFR 601.2 (a)) (Submit only upon FDA's request)				
<input type="checkbox"/>	C. Methods validation package (e.g., 21 CFR 314.50(e)(2)(i); 21 CFR 601.2)				
<input type="checkbox"/>	5. Nonclinical pharmacology and toxicology section (e.g., 21 CFR 314.50(d)(2); 21 CFR 601.2)				
<input type="checkbox"/>	6. Human pharmacokinetics and bioavailability section (e.g., 21 CFR 314.50(d)(3); 21 CFR 601.2)				
<input type="checkbox"/>	7. Clinical Microbiology (e.g., 21 CFR 314.50(d)(4))				
<input type="checkbox"/>	8. Clinical data section (e.g., 21 CFR 314.50(d)(5); 21 CFR 601.2)				
<input type="checkbox"/>	9. Safety update report (e.g., 21 CFR 314.50(d)(5)(vi)(b); 21 CFR 601.2)				
<input type="checkbox"/>	10. Statistical section (e.g., 21 CFR 314.50(d)(6); 21 CFR 601.2)				
<input type="checkbox"/>	11. Case report tabulations (e.g., 21 CFR 314.50(f)(1); 21 CFR 601.2)				
<input type="checkbox"/>	12. Case report forms (e.g., 21 CFR 314.50(f)(2); 21 CFR 601.2)				
<input type="checkbox"/>	13. Patent information on any patent which claims the drug (21 U.S.C. 355(b) or (c))				
<input type="checkbox"/>	14. A patent certification with respect to any patent which claims the drug (21 U.S.C.355(b)(2) or (j)(2)(A))				
<input type="checkbox"/>	15. Establishment description (21 CFR Part 600, if applicable)				
<input type="checkbox"/>	16. Debarment certification (FD&C Act 306(k)(1))				
<input type="checkbox"/>	17. Field copy certification (21 CFR 314.50(k)(3))				
<input type="checkbox"/>	18. User Fee Cover Sheet (Form FDA 3397)				
<input type="checkbox"/>	19. Financial Information (21 CFR Part 54)				
<input type="checkbox"/>	20. OTHER (Specify)				

CERTIFICATION

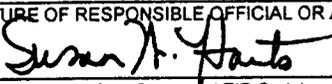
I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including, but not limited to the following:

1. Good manufacturing practice regulations in 21 CFR Parts 210, 211 or applicable regulations, Parts 606, and/or 820.
2. Biological establishment standards in 21 CFR Part 600.
3. Labeling regulations in 21 CFR Parts 201, 606, 610, 660 and/or 809.
4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR 202.
5. Regulations on making changes in application in FD&C Act Section 506A, 21 CFR 314.71, 314.72, 314.97, 314.99, and 601.12.
6. Regulations on Reports in 21 CFR 314.80, 314.81, 600.80 and 600.81.
7. Local, state and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act, I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.

The data and information in this submission have been reviewed and, to the best of my knowledge are certified to be true and accurate.

Warning: A willfully false statement is a criminal offense, U.S. Code, title 18, section 1001.

SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT 		TYPED NAME AND TITLE Susan W. Harts, RN, RAC Vice President of Regulatory Affairs	DATE January 26, 2001
ADDRESS (Street, City, State, and ZIP Code) 6330 Quadrangle Drive, Suite 305 Chapel Hill, NC 27514		TELEPHONE NUMBER 919-493-6006	

Public reporting burden for this collection of information is estimated to average 24 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Department of Health and Human Services
Food and Drug Administration
CBER, HFM-99
1401 Rockville Pike
Rockville, MD 20852-1448

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.



Synthon
Pharmaceuticals Ltd.

6330 Quadrangle Dr. Suite 305
Chapel Hill, NC 27514
USA

Tel: +1-919-493-6006
Fax: +1-919-493-6104
Email: sharts@synthon-usa.com

To: Mr. Lorenzo Rocca
FDA Reviewer
Fax No: 301-594-2859
From: Susan Harts, RN, RAC
Number of Pages (including this page): 4

Date: January 16, 2001

Regarding: NDA 21-299 - INFORMATION AMENDMENT

Dear Mr. Rocca:

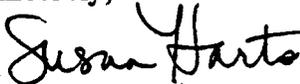
In response to your question on the identity and structure of impurity _____ found on the chromatogram on page 280 of NDA 21-299, a copy of page 758 of the NDA is attached to this fax. The identity and structure of impurity _____ is described on this page from the drug product section.

As additional explanation, this impurity is a _____

However, since very similar HPLC methods are used for testing the identity and purity of both the active drug substance and finished drug product, the same system suitability mix is used for both analyses. (Please refer to NDA page 1023 and 1034, which are also attached to this fax.)

If you have additional questions, please contact me at 919-493-6006.

Sincerely,


Susan W. Harts, RN, RAC
Vice President of Regulatory Affairs

Cc: Paul David, Project Manager

3 Page(s) Withheld

McKenna & Cuneo, L.L.P.

Attorneys at Law

Los Angeles

San Francisco

San Diego

1900 K Street, N.W. ■ Washington, D.C. 20006-1108
202-496-7500 ■ Fax: 202-496-7756
www.mckennacuneo.com

Denver

Dallas

Brussels

January 9, 2001

VIA FEDERAL EXPRESS

Gary L. Yingling

202-496-7645

gary_yingling@mckennacuneo.com

Russell Katz, M.D.
Food and Drug Administration
Office of Drug Evaluation I
Div. of Neuropharmacological Drug Products (HFD-120)
Woodmont II
1451 Rockville Pike
Rockville, Maryland 20852-1420

Re: NDA No. 21-299 – Amendment 008 (Paroxetine (as mesylate) Tablets) – Synthon Pharmaceuticals, Ltd.

Dear Dr. Katz:

Enclosed please find the original and two copies of this cover letter and a signed Form FDA 356h for Amendment 008 to NDA number 21-299 that we are submitting on behalf of our client, Synthon Pharmaceuticals, Ltd. ("Synthon"). The purpose of the amendment is to notify the Food and Drug Administration ("FDA") that SmithKline Beecham ("SmithKline") (the holder of the NDA cited in Synthon's 505(b)(2) application) has not brought an action of infringement against Synthon with respect to patent numbers 6,121,291 and 6,133,289. These two patents were added to Synthon's original paragraph IV certification on November 15, 2000 (see NDA Amendment No. 004) and SmithKline received notice of the amended certification on November 16, 2000 (see NDA Amendment No. 005).

Because a court action has not been brought concerning patent numbers 6,121,291 and 6,133,289 within the requisite 45-day period, issues concerning these two patents no longer bar the approval of Synthon's NDA.

McKenna & Cuneo, L.L.P.

Attorneys at Law

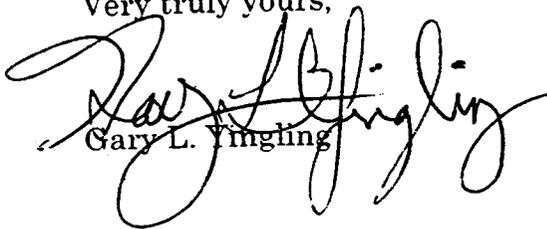
Russell Katz, M.D.

January 9, 2001

Page 2

Should you have any questions concerning this amendment, please do not hesitate to contact me at (202) 496-7645.

Very truly yours,



Gary L. Yingling

GLY/mhh

Enclosure(s)

cc: Mr. Paul David

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

APPLICATION TO MARKET A NEW DRUG, BIOLOGIC,
OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations, 314 & 601)

Form Approved: OMB No. 0910-0338
Expiration Date: March 31, 2003
See OMB Statement on page 2.

FOR FDA USE ONLY
APPLICATION NUMBER

APPLICANT INFORMATION

NAME OF APPLICANT
Synthon Pharmaceuticals Ltd.

DATE OF SUBMISSION
1/09/2001

TELEPHONE NO. (Include Area Code)
919-493-6006

FACSIMILE (FAX) Number (Include Area Code)
919-493-6104

APPLICANT ADDRESS (Number, Street, City, State, Country, ZIP Code or Mail Code,
and U.S. License number if previously issued):
6330 Quadrangle Drive
Suite 305
Chapel Hill, NC 27514

AUTHORIZED U.S. AGENT NAME & ADDRESS (Number, Street, City, State,
ZIP Code, telephone & FAX number) IF APPLICABLE
NA

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER (If previously issued) NA

ESTABLISHED NAME (e.g., Proper name, USP/USAN name)
Paroxetine Mesylate

PROPRIETARY NAME (trade name) IF ANY NA

CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME (If any) NA

CODE NAME (If any) NA

DOSAGE FORM: Tablet

STRENGTHS: 10 mg, 20 mg, 30 mg, 40 mg

ROUTE OF ADMINISTRATION: oral

(PROPOSED) INDICATION(S) FOR USE: Depressive illness, obsessive compulsive disorder, panic disorder

APPLICATION INFORMATION

(check one) NEW DRUG APPLICATION (21 CFR 314.50) ABBREVIATED NEW DRUG APPLICATION (ANDA, 21 CFR 314.94)
 BIOLOGICS LICENSE APPLICATION (21 CFR part 601)

IF AN NDA, IDENTIFY THE APPROPRIATE TYPE 505 (b)(1) 505 (b)(2)

IF AN ANDA, or 505(b)(2), IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION
Name of Drug Paxil Holder of Approved Application Smithkline Beecham

TYPE OF SUBMISSION (check one) ORIGINAL APPLICATION AMENDMENT TO A PENDING APPLICATION RESUBMISSION
 PRESUBMISSION ANNUAL REPORT ESTABLISHMENT DESCRIPTION SUPPLEMENT EFFICACY SUPPLEMENT
 LABELING SUPPLEMENT CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT OTHER

IF A SUBMISSION OR PARTIAL APPLICATION, PROVIDE LETTER DATE OF AGREEMENT TO PARTIAL SUBMISSION: NA

IF A SUPPLEMENT, IDENTIFY THE APPROPRIATE CATEGORY CBE CBE-30 Prior Approval (PA)

REASON FOR SUBMISSION Amendment to provide notification concerning expiration of the 45-day period for the filing of patent litigation

PROPOSED MARKETING STATUS (check one) PRESCRIPTION PRODUCT (Rx) OVER THE COUNTER PRODUCT (OTC)

NUMBER OF VOLUMES SUBMITTED 1 THIS APPLICATION IS PAPER PAPER AND ELECTRONIC ELECTRONIC

ESTABLISHMENT INFORMATION (Full establishment information should be provided in the body of the Application.)
Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g., Final dosage form, Stability/testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.

See originally filed Form FDA 356h

Cross References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMFs referenced in the current application)

See originally filed Form FDA 356h

This application contains the following items: (Check all that apply)

- 1. Index Draft Labeling Final Printed Labeling
- 2. Labeling (check one)
- 3. Summary (21 CFR 314.50(c))
- 4. Chemistry section
 - A. Chemistry, manufacturing, and controls information (e.g., 21 CFR 314.50(d)(1); 21 CFR 601.2)
 - B. Samples (21 CFR 314.50(e)(1); 21 CFR 601.2 (a)) (Submit only upon FDA's request)
 - C. Methods validation package (e.g., 21 CFR 314.50(e)(2)(i); 21 CFR 601.2)
- 5. Nonclinical pharmacology and toxicology section (e.g., 21 CFR 314.50(d)(2); 21 CFR 601.2)
- 6. Human pharmacokinetics and bioavailability section (e.g., 21 CFR 314.50(d)(3); 21 CFR 601.2)
- 7. Clinical Microbiology (e.g., 21 CFR 314.50(d)(4))
- 8. Clinical data section (e.g., 21 CFR 314.50(d)(5); 21 CFR 601.2)
- 9. Safety update report (e.g., 21 CFR 314.50(d)(5)(vi)(b); 21 CFR 601.2)
- 10. Statistical section (e.g., 21 CFR 314.50(d)(6); 21 CFR 601.2)
- 11. Case report tabulations (e.g., 21 CFR 314.50(f)(1); 21 CFR 601.2)
- 12. Case report forms (e.g., 21 CFR 314.50(f)(2); 21 CFR 601.2)
- 13. Patent information on any patent which claims the drug (21 U.S.C. 355(b) or (c))
- 14. A patent certification with respect to any patent which claims the drug (21 U.S.C.355(b)(2) or (j)(2)(A))
- 15. Establishment description (21 CFR Part 600, if applicable)
- 16. Debarment certification (FD&C Act 306(k)(1))
- 17. Field copy certification (21 CFR 314.50(k)(3))
- 18. User Fee Cover Sheet (Form FDA 3397)
- 19. Financial Information (21 CFR Part 54)
- 20. OTHER (Specify) Notification of the expiration of the 45-day patent litigation filing period.

CERTIFICATION

I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including, but not limited to the following:

1. Good manufacturing practice regulations in 21 CFR Parts 210, 211 or applicable regulations, Parts 606, and/or 820.
2. Biological establishment standards in 21 CFR Part 600.
3. Labeling regulations in 21 CFR Parts 201, 606, 610, 660 and/or 809.
4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR 202.
5. Regulations on making changes in application in FD&C Act Section 506A, 21 CFR 314.71, 314.72, 314.97, 314.99, and 601.12.
6. Regulations on Reports in 21 CFR 314.80, 314.81, 600.80 and 600.81.
7. Local, state and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act, I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.
The data and information in this submission have been reviewed and, to the best of my knowledge are certified to be true and accurate.

Warning: A willfully false statement is a criminal offense, U.S. Code, title 18, section 1001.

SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT <i>Susan W. Harts</i> by <i>nmh</i>	TYPED NAME AND TITLE Susan W. Harts Vice President of Regulatory Affairs	DATE 1/09/2001
ADDRESS (Street, City, State, and ZIP Code) 6330 Quadrangle Drive, Suite 305 Chapel Hill, NC 27514		TELEPHONE NUMBER 919-493-6006

Public reporting burden for this collection of information is estimated to average 24 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Department of Health and Human Services
Food and Drug Administration
CBER, HFM-99
1401 Rockville Pike

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

McKenna & Cuneo, L.L.P.

Attorneys at Law

Los Angeles
San Francisco
San Diego

1900 K Street, N.W. ■ Washington, D.C. 20006-1108
202-496-7500 ■ Fax: 202-496-7756
www.mckennacuneo.com

Denver
Dallas
Brussels

November 30, 2000

VIA HAND DELIVERY

Gary L. Yingling
202-496-7645
gary_yingling@mckennacuneo.com

Russell Katz, M.D.
Food and Drug Administration
Office of Drug Evaluation I
Div. of Neuropharmacological Drug Products (HFD-120)
Woodmont II
1451 Rockville Pike
Rockville, Maryland 20852-1420

Re: NDA No. 21-299 – Amendment 006 (Paroxetine (as mesylate) Tablets) – Synthron Pharmaceuticals, Ltd.

Dear Dr. Katz:

Enclosed please find the original and two copies of Amendment 006 to NDA number 21-299 that we are submitting on behalf of our client, Synthron Pharmaceuticals, Ltd. ("Synthron"). The purpose of the amendment is to provide documentation of the initiation of an infringement action by SmithKline Beecham Corporation ("SmithKline") against Synthron concerning three of the seven patents listed in Synthron's original paragraph IV certification. The action was brought in the U.S. District Court for the Middle District of North Carolina on November 22, 2000. The amendment consists of the following documents:

- A completed Form 356h
- A date-stamped copy of the complaint filed by SmithKline

SmithKline did not bring an action of infringement against Synthron with respect to the following patents that were included on Synthron's paragraph IV certification and the notification received by SmithKline on October 9, 2000:

5,789,449
5,872,132
5,900,423
6,080,759

McKenna & Cuneo, L.L.P.

Attorneys at Law

Russell Katz, M.D.
November 30, 2000
Page 2

Therefore, the 45-day period in which a court action must be brought in order to trigger the 30 month stay of FDA approval has run for these patents. Therefore, the approval of Synthon's NDA is not delayed by these four patents.

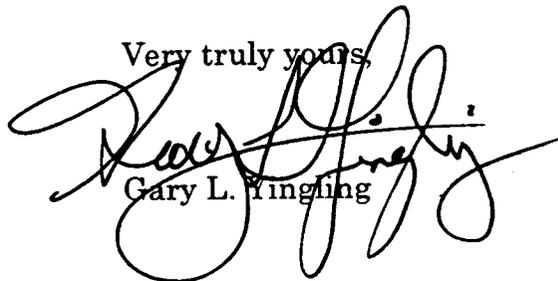
However, SmithKline has brought an infringement action with respect to the following three patents:

4,721,723
6,063,927
6,113,944

As the enclosed copy of the complaint indicates, this action was brought within the 45-day period that commenced upon SmithKline's receipt of Synthon's patent notification. Therefore, this action triggers the 30-month period described in section 505(c)(3)(C) of the Federal Food, Drug, and Cosmetic Act (the "FDCA"). That period commenced on October 10, 2000 and will terminate on April 9, 2003. FDA will be authorized to approve Synthon's NDA on or after April 10, 2003 unless, prior to that date, the court issues a preliminary injunction prohibiting Synthon from manufacturing or selling the product, or the court decides that any of the three patents are valid, enforceable and infringed by Synthon. See FDCA §§ 505(c)(3)(C)(ii), (iii); see also 21 C.F.R. §§ 314.107(b)(3)(i)(A), (b)(3)(iii), (b)(3)(iv). FDA could approve Synthon's NDA before April 10, 2003 if the court decides that all three patents are invalid, not infringed, or unenforceable, or if the court orders that the 30 month period be shortened. See FDCA § 505(c)(3)(C) and (c)(3)(C)(i); see also 21 C.F.R. §§ 314.107(b)(3)(i)(A); (b)(3)(ii).

Should you have any questions concerning this amendment, please do not hesitate to contact me at (202) 496-7645.

Very truly yours,



Gary L. Kingling

GLY/mhh
Enclosure(s)
cc: Mr. Paul David

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

APPLICATION TO MARKET A NEW DRUG, BIOLOGIC,
OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations, 314 & 601)

Form Approved: OMB No. 0910-0338
Expiration Date: March 31, 2003
See OMB Statement on page 2.

FOR FDA USE ONLY

APPLICATION NUMBER

APPLICANT INFORMATION

NAME OF APPLICANT Synthon Pharmaceuticals Ltd.	DATE OF SUBMISSION 11/30/2000
TELEPHONE NO. (Include Area Code) 919-493-6006	FACSIMILE (FAX) Number (Include Area Code) 919-493-6104
APPLICANT ADDRESS (Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued): 6330 Quadrangle Drive Suite 305 Chapel Hill, NC 27514	AUTHORIZED U.S. AGENT NAME & ADDRESS (Number, Street, City, State, ZIP Code, telephone & FAX number) IF APPLICABLE NA

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER (If previously issued) NA		
ESTABLISHED NAME (e.g., Proper name, USP/USAN name) Paroxetine Mesylate	PROPRIETARY NAME (trade name) IF ANY NA	
CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME (If any) NA		CODE NAME (If any) NA
DOSAGE FORM: Tablet	STRENGTHS: 10 mg, 20 mg, 30 mg, 40 mg	ROUTE OF ADMINISTRATION: oral
(PROPOSED) INDICATION(S) FOR USE: Depressive illness, obsessive compulsive disorder, panic disorder		

APPLICATION INFORMATION

(check one) NEW DRUG APPLICATION (21 CFR 314.50) ABBREVIATED NEW DRUG APPLICATION (ANDA, 21 CFR 314.94)
 BIOLOGICS LICENSE APPLICATION (21 CFR part 601)

IF AN NDA, IDENTIFY THE APPROPRIATE TYPE 505 (b)(1) 505 (b)(2)

IF AN ANDA, or 505(b)(2), IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION
Name of Drug Paxil Holder of Approved Application Smithkline Beecham

TYPE OF SUBMISSION (check one) ORIGINAL APPLICATION AMENDMENT TO A PENDING APPLICATION RESUBMISSION
 PRESUBMISSION ANNUAL REPORT ESTABLISHMENT DESCRIPTION SUPPLEMENT EFFICACY SUPPLEMENT
 LABELING SUPPLEMENT CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT OTHER

IF A SUBMISSION OR PARTIAL APPLICATION, PROVIDE LETTER DATE OF AGREEMENT TO PARTIAL SUBMISSION: NA

IF A SUPPLEMENT, IDENTIFY THE APPROPRIATE CATEGORY CBE CBE-30 Prior Approval (PA)

REASON FOR SUBMISSION Amendment to provide documentation of the filing of patent litigation

PROPOSED MARKETING STATUS (check one) PRESCRIPTION PRODUCT (Rx) OVER THE COUNTER PRODUCT (OTC)

NUMBER OF VOLUMES SUBMITTED 1 THIS APPLICATION IS PAPER PAPER AND ELECTRONIC ELECTRONIC

ESTABLISHMENT INFORMATION (Full establishment information should be provided in the body of the Application.)
Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g., Final dosage form, Stability/testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.

See originally filed Form FDA 356h

Cross References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMFs referenced in the current application)

See originally filed Form FDA 356h

This application contains the following items: (Check all that apply)

- 1. Index
- 2. Labeling (check one) Draft Labeling Final Printed Labeling
- 3. Summary (21 CFR 314.50(c))
- 4. Chemistry section
 - A. Chemistry, manufacturing, and controls information (e.g., 21 CFR 314.50(d)(1); 21 CFR 601.2)
 - B. Samples (21 CFR 314.50(e)(1); 21 CFR 601.2 (a)) (Submit only upon FDA's request)
 - C. Methods validation package (e.g., 21 CFR 314.50(e)(2)(i); 21 CFR 601.2)
- 5. Nonclinical pharmacology and toxicology section (e.g., 21 CFR 314.50(d)(2); 21 CFR 601.2)
- 6. Human pharmacokinetics and bioavailability section (e.g., 21 CFR 314.50(d)(3); 21 CFR 601.2)
- 7. Clinical Microbiology (e.g., 21 CFR 314.50(d)(4))
- 8. Clinical data section (e.g., 21 CFR 314.50(d)(5); 21 CFR 601.2)
- 9. Safety update report (e.g., 21 CFR 314.50(d)(5)(vi)(b); 21 CFR 601.2)
- 10. Statistical section (e.g., 21 CFR 314.50(d)(6); 21 CFR 601.2)
- 11. Case report tabulations (e.g., 21 CFR 314.50(f)(1); 21 CFR 601.2)
- 12. Case report forms (e.g., 21 CFR 314.50(f)(2); 21 CFR 601.2)
- 13. Patent information on any patent which claims the drug (21 U.S.C. 355(b) or (c))
- 14. A patent certification with respect to any patent which claims the drug (21 U.S.C.355(b)(2) or (j)(2)(A))
- 15. Establishment description (21 CFR Part 600, if applicable)
- 16. Debarment certification (FD&C Act 306(k)(1))
- 17. Field copy certification (21 CFR 314.50(k)(3))
- 18. User Fee Cover Sheet (Form FDA 3397)
- 19. Financial Information (21 CFR Part 54)
- 20. OTHER (Specify) Documentation of filing of patent litigation

CERTIFICATION

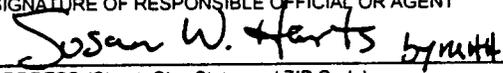
I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including, but not limited to the following:

1. Good manufacturing practice regulations in 21 CFR Parts 210, 211 or applicable regulations, Parts 606, and/or 820.
2. Biological establishment standards in 21 CFR Part 600.
3. Labeling regulations in 21 CFR Parts 201, 606, 610, 660 and/or 809.
4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR 202.
5. Regulations on making changes in application in FD&C Act Section 506A, 21 CFR 314.71, 314.72, 314.97, 314.99, and 601.12.
6. Regulations on Reports in 21 CFR 314.80, 314.81, 600.80 and 600.81.
7. Local, state and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act, I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.

The data and information in this submission have been reviewed and, to the best of my knowledge are certified to be true and accurate.

Warning: A willfully false statement is a criminal offense, U.S. Code, title 18, section 1001.

SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT 	TYPED NAME AND TITLE Susan W. Harts Vice President of Regulatory Affairs	DATE 11/30/2000
ADDRESS (Street, City, State, and ZIP Code) 6330 Quadrangle Drive, Suite 305 Chapel Hill, NC 27514		TELEPHONE NUMBER 919-493-6006

Public reporting burden for this collection of information is estimated to average 24 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Department of Health and Human Services
 Food and Drug Administration
 CBER, HFM-99
 1401 Rockville Pike
 Rockville, MD 20852-1448

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

IN THE UNITED STATES DISTRICT COURT
FOR THE MIDDLE DISTRICT OF
NORTH CAROLINA



2000 NOV 22 2:08

SMITHKLINE BEECHAM CORPORATION,
SMITHKLINE BEECHAM, P.L.C.,
and BEECHAM GROUP, P.L.C.,

Plaintiffs,

v.

SYNTHON PHARMACEUTICALS, LTD.
and SYNTHON B.V.,

Defendants.

FILED
U.S. DISTRICT COURT
GREENSBORO, NC

CIVIL ACTION NO. _____

JURY TRIAL DEMANDED

1:00CV01179

COMPLAINT

Plaintiffs SmithKline Beecham Corporation ("SB"), SmithKline Beecham p.l.c. ("SB p.l.c."), and Beecham Group p.l.c. ("Beecham"), bring this action for patent infringement against Defendants Synthon Pharmaceuticals, Ltd. ("Synthon") and Synthon B.V., and aver as follows:

NATURE OF ACTION

This action for patent infringement relates to SB's, SB p.l.c.'s, and Beecham's patents covering paroxetine methanesulfonate, paroxetine hydrochloride hemihydrate, and pharmaceutical products in tablet form containing paroxetine.

JURISDICTION AND VENUE

1. This action for patent infringement arises under the United States patent laws, Title 35, United States Code, including 35 U.S.C. §§ 271(b), 271(e), and 281-283.

2. This Court has subject matter jurisdiction under 28 U.S.C. §§ 1331, 1332(a), and 1338(a). The amount in controversy exceeds \$75,000, exclusive of interest and costs. Venue is proper in this judicial district under 28 U.S.C. §§ 1391(b), (c), and (d), and 1400(b).

THE PARTIES

3. SB, SB p.l.c., Beecham, and related entities are engaged in the business of research, development, manufacture, and sale of pharmaceutical products throughout the world. They manufacture crystalline paroxetine hydrochloride hemihydrate in bulk form in the United Kingdom, and then tablet and sell that product in the United States under the trademark Paxil[®]. Paxil[®] is used to treat depression, panic disorder, obsessive compulsive disorder, and social phobia, and is one of the most widely prescribed prescription drugs in the United States.

4. SB is a corporation organized and existing under the laws of the Commonwealth of Pennsylvania, with its principal place of business in Philadelphia, Pennsylvania. SB was owner of United States Letters Patent No. 4,721,723, granted on January 26, 1988, for an invention entitled "Anti-Depressant Crystalline Paroxetine Hydrochloride Hemihydrate" (the '723 patent). A copy of the '723 patent is attached as Exhibit A. The '723 patent claims, *inter alia*, crystalline paroxetine hydrochloride hemihydrate and its use in treating depression.

5. Beecham is a corporation organized and existing under the laws of England, with its principal place of business in Brentford, Middlesex, England. The '723 patent, as issued, was assigned to Beecham. This assignment was recorded in the U.S. Patent and Trademark Office ("PTO") on February 12, 1987, at Reel 4689, Frame 508. On November 1, 1995, Beecham assigned the '723 patent to SB. This assignment was recorded in the PTO on January 22, 1996, at Reel 7613, Frame 0400. On April 27, 2000, SB reassigned the '723 patent to Beecham. This assignment was recorded in the PTO on May 1, 2000, at Reel 010785, Frame 0931.

6. SB p.l.c. is a corporation organized and existing under the laws of England, with its principal place of business in Brentford, Middlesex, England. SB p.l.c. is the current owner of United States Letters Patent No. 6,063,927, granted on May 16, 2000, for an invention entitled "Paroxetine Derivatives" (the '927 patent). The '927 patent, as issued, is assigned to SB p.l.c. This assignment was recorded in the PTO on February 4, 2000, at Reel 10590, Frame 0254. A copy of the '927 patent is attached as Exhibit B. The '927 patent claims, *inter alia*, paroxetine methanesulfonate (paroxetine mesylate) and a method for making paroxetine hydrochloride by conversion of paroxetine methanesulfonate.

7. On May 25, 2000, SB, on behalf of SB p.l.c., filed a Request for Certificate of Correction in the PTO to correct errors in the '927 patent claims and errors in inventorship. A copy of this Request is attached as Exhibit C.

8. SB p.l.c. is the current owner of United States Letters Patent No. 6,113,944,

granted on September 5, 2000, for an invention entitled "Paroxetine Tablets and Process to Prepare Them" (the '944 patent). The '944 patent, as issued, is assigned to SB p.l.c. This assignment was recorded in the PTO on November 19, 1999, at Reel 10434, Frame 0045. A copy of the '944 patent is attached as Exhibit D. The '944 patent claims, *inter alia*, a pharmaceutical composition in tablet form containing paroxetine hydrochloride, produced on a commercial scale by a defined process.

9. On September 7, 2000, SB, on behalf of SB p.l.c., filed a Request for Certificate of Correction in the PTO to correct errors in the '944 patent claims. The '944 patent, as printed, did not include the allowed claims. The PTO approved the Request and so notified SB in a letter dated November 2, 2000. The Certificate of Correction was published by the PTO on Tuesday, November 21, 2000. A copy of the Certificate of Correction is attached as Exhibit E.

10. Upon information and belief, Defendant Synthon is a corporation organized under the laws of North Carolina, with its principal place of business at 6330 Quadrangle Drive, Chapel Hill, N.C. 27514. Upon further information and belief, Synthon is in the business of manufacturing and marketing pharmaceutical compounds in the United States. Upon further information and belief, Synthon conducts substantial business throughout the United States and in this district.

11. Upon information and belief, Defendant Synthon B.V. is a corporation organized

under the laws of the Netherlands, with its principal place of business at Microweg 22 6545 CM Nijmegen, Netherlands. Upon further information and belief, Synthon B.V. is in the business of manufacturing and marketing pharmaceutical compounds and conducts substantial business in this district and throughout the United States. Upon further information and belief, Synthon is a subsidiary of Synthon B.V., and Synthon B.V. owns and controls Synthon.

FIRST COUNT FOR PATENT INFRINGEMENT

12. Upon information and belief, Defendant Synthon filed with the United States Food and Drug Administration (FDA) a New Drug Application (NDA) No. 21-299, for paroxetine methanesulfonate tablets, under 21 U.S.C. § 355(b)(2), together with a purported certification under 21 U.S.C. § 355(b)(3)(B).

13. On October 9, 2000, SB received a letter from Synthon sent by certified mail, purporting to be a Notice of Certification under 21 U.S.C. § 355(b)(3)(B) (section 505(b)(3)(B) of the Federal Food, Drug, and Cosmetic Act). This letter is attached as Exhibit F. This letter alleges that the product for which Synthon seeks approval is paroxetine methanesulfonate tablets. This letter further alleges, *inter alia*, that the Synthon paroxetine methanesulfonate tablets do not infringe the '723 or '927 patents, and that the '927 and '944 patents are invalid.

14. Upon information and belief, the product that Defendant Synthon intends to market will infringe the '723 patent.

15. Under 35 U.S.C. § 271(e)(2)(A), Defendant Synthon infringed the '723 patent by submitting and/or causing to be submitted to the FDA a NDA seeking approval for the commercial marketing of paroxetine methanesulfonate tablets before the expiration date of the '723 patent, a product, manufacture, use, import, offer for sale, or sale of which will infringe claims of the '723 patent.

16. Upon information and belief, Defendant Synthon B.V. participated in, encouraged, and induced the acts of infringement by Defendant Synthon as alleged in paragraphs 12-15 above, and therefore infringed the '723 patent.

SECOND COUNT FOR PATENT INFRINGEMENT

17. Plaintiffs incorporate by reference paragraphs 1-13 of this Complaint as if fully set forth herein.

18. Upon information and belief, the product that Defendant Synthon intends to market will infringe the '927 patent.

19. Under 35 U.S.C. § 271(e)(2)(A), Defendant Synthon infringed the '927 patent by submitting and/or causing to be submitted to the FDA a NDA seeking approval for the commercial marketing of paroxetine methanesulfonate tablets before the expiration date of the '927 patent, a product, manufacture, use, import, offer for sale, or sale of which will infringe claims of the '927 patent.

20. Upon information and belief, Defendant Synthon B.V. participated in, encouraged, and induced the acts of infringement by Defendant Synthon as alleged in paragraphs 17-19 above, and therefore infringed the '927 patent.

THIRD COUNT FOR PATENT INFRINGEMENT

21. Plaintiffs incorporate by reference paragraphs 1-13 of this Complaint as if fully set forth herein.

22. Upon information and belief, the product that Defendant Synthon intends to market will infringe the '944 patent.

23. Under 35 U.S.C. § 271(e)(2)(A), Defendant Synthon infringed the '944 patent by submitting and/or causing to be submitted to the FDA a NDA seeking approval for the commercial marketing of paroxetine methanesulfonate tablets before the expiration date of the '944 patent, a product, manufacture, use, import, offer for sale, or sale of which will infringe claims of the '944 patent.

24. Upon information and belief, Defendant Synthon B.V. participated in, encouraged, and induced the acts of infringement by Defendant Synthon as alleged in paragraphs 21-23 above, and therefore infringed the '944 patent.

PRAYER FOR RELIEF

WHEREFORE, Plaintiffs SB, SB p.l.c., and Beecham demand judgment against Defendants Synthon and Synthon B.V., and respectfully request that this Court enter Orders:

- a. as to Count I, prohibiting any approval by the FDA of Synthon's and/or Synthon B.V.'s paroxetine methanesulfonate tablets on any effective date prior to the expiration of the '723 patent, or such later date as the Court may determine;
- b. as to Count I, enjoining Synthon and Synthon B.V. from the commercial manufacture, use, import, offer for sale, or sale of paroxetine methanesulfonate tablets until the expiration of the '723 patent, or such later date as the Court may determine;
- c. as to Count II, prohibiting any approval by the FDA of Synthon's and/or Synthon B.V.'s paroxetine methanesulfonate tablets on any effective date prior to the expiration of the '927 patent, or such later date as the Court may determine;
- d. as to Count II, enjoining Synthon and Synthon B.V. from the commercial manufacture, use, import, offer for sale, or sale of paroxetine methanesulfonate tablets until the expiration of the '927 patent, or such later date as the Court may determine;
- e. as to Count III, prohibiting any approval by the FDA of Synthon's and/or Synthon B.V.'s paroxetine methanesulfonate tablets on any effective date

- prior to the expiration of the '944 patent, or such later date as the Court may determine;
- f. as to Count III, enjoining Synthon and Synthon B.V. from the commercial manufacture, use, import, offer for sale, or sale of paroxetine methanesulfonate tablets until the expiration of the '944 patent, or such later date as the Court may determine;
- g. as to all Counts, awarding SB, SB p.l.c., and Beecham such further and additional relief as this Court deems just and proper.

Dated this 2nd day of November, 2000.

By:

Allison K. Overbay

James L. Gale
State Bar No. 6160
SMITH HELMS MULLISS & MOORE, L.L.P.
2800 Two Hannover Square
Raleigh, N.C. 27601
Telephone: (919) 755-8700
Facsimile: (919) 755-8800

Allison K. Overbay
State Bar No. 23430
SMITH HELMS MULLISS & MOORE, L.L.P.
300 N. Greene St., Suite 1400
Greensboro, N.C. 27401
Telephone: (336) 378-5200
Facsimile: (336) 378-5400

Of Counsel:

Ford F. Farabow
Robert D. Bajefsky
Richard B. Racine
Joann M. Neth
FINNEGAN, HENDERSON, FARABOW,
GARRETT & DUNNER
1300 I Street, N.W., Suite 700
Washington, D.C. 20005-3315
Telephone: 202-408-4000
Facsimile: 202-408-4400

Attorneys for Plaintiffs SmithKline Beecham
Corporation, SmithKline Beecham p.l.c., and
Beecham Group, p.l.c.



October 12, 2000

VIA HAND DELIVERY

Russell Katz, M.D.
Food and Drug Administration
Office of Drug Evaluation I
Division of Neuropharmacological Drug Products (HFD-120)
Center for Drug Evaluation and Research
Woodmont II
1451 Rockville Pike
Rockville, Maryland 20852-1420

**Re: Synthon Pharmaceuticals, Ltd. – NDA No. 21-299
(Paroxetine (as mesylate) tablets)**

Dear Dr. Katz:

This letter authorizes Gary Yingling and Michael Hinckle of McKenna and Cuneo, L.L.P., regulatory counsel for Synthon Pharmaceuticals, Ltd. ("Synthon"), to make submissions to the firm's NDA number 21-299, and to communicate with the FDA on Synthon's behalf.

Sincerely,

A handwritten signature in cursive script that reads "Susan W. Harts".

Susan W. Harts
Vice President of Regulatory Affairs

McKenna & Cuneo, L.L.P.

Attorneys at Law

Los Angeles

San Francisco

San Diego

1900 K Street, N.W. ■ Washington, D.C. 20006-1108
202-496-7500 ■ Fax: 202-496-7756
www.mckennacuneo.com

CENTER FOR DRUG EVALUATION
AND RESEARCH

Denver

Delhi

Brussels

OCT 12 2000

RECEIVED HFD-120

October 12, 2000

VIA HAND DELIVERY

Gary L. Yingling

202-496-7645

gary_yingling@mckennacuneo.com

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Neuropharmacological Drug
Products, HFD-120
Attention: Division Document Room 4008
1451 Rockville Pike
Rockville, Maryland 20852-1420

ORIG AMENDMENT

N-X2

Re: NDA No. 21-299 (Synthon Pharmaceuticals, Ltd.) –
Amendment to provide documentation of receipt of
patent notice

Dear Sir or Madam:

We have enclosed, on behalf of our client, Synthon Pharmaceuticals, Ltd., one original and two copies of an amendment to Synthon's new drug application (NDA) for paroxetine mesylate oral tablets (NDA No. 21-299) (see attached authorization letter). The amendment is being submitted pursuant to 21 C.F.R. § 314.52(e) and includes documentation of the receipt by the appropriate patent owners and NDA holder of Synthon's notice of patent invalidity or noninfringement under section 505(b)(3) of the Federal Food, Drug, and Cosmetic Act (the "Act").

In accordance with the paragraph IV certification submitted in Synthon's NDA, and the agency's July 13, 2000 letter authorizing the use of Federal Express for the delivery of Synthon's paragraph IV notice, Synthon has delivered the notice via Federal Express to the following addressees:

1. SmithKline Beecham P.L.C.
Brentford, United Kingdom

Food and Drug Administration
October 12, 2000
Page 2

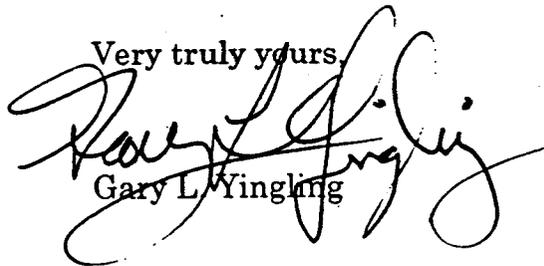
2. SmithKline Beecham Corporation
Corporate Intellectual Property Group
King of Prussia, Pennsylvania
3. SmithKline Beecham Pharmaceuticals
Legal Department
Collegeville, Pennsylvania
4. Mr. Michael J. Norden
c/o Mr. Jeffery B. Oster
Davis, Wright, and Tremaine, L.L.P.
Seattle, Washington

All four of the addressees received the notice on October 9, 2000. Therefore, in accordance with FDA's regulations, 21 C.F.R. § 314.52(f), October 10, 2000 was the first day of the 45-day period provided for in Section 505(c)(3)(C) of the Act.

Documentation confirming receipt of the notice by the aforementioned addressees is included in the enclosed amendment in the form of copies of the Federal Express airbills and proof of delivery documentation for each airbill. A completed Form FDA 356h is also included in the amendment.

Should you have any questions concerning this amendment or any other aspect of Synthon's application, please contact me or the Synthon representative identified on the Form 356h, Susan W. Harts.

Very truly yours,



Gary L. Yingling

GLY/mhh

Enclosure(s)

cc: ✓ Paul David (FDA)

Synthon Pharmaceuticals, Ltd.

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

**APPLICATION TO MARKET A NEW DRUG, BIOLOGIC,
OR AN ANTIBIOTIC DRUG FOR HUMAN USE**

(Title 21, Code of Federal Regulations, 314 & 601)

Form Approved: OMB No. 0910-0338
Expiration Date: March 31, 2003
See OMB Statement on page 2.

FOR FDA USE ONLY
APPLICATION NUMBER

APPLICANT INFORMATION

NAME OF APPLICANT Synthon Pharmaceuticals Ltd.	DATE OF SUBMISSION 10/12/2000
TELEPHONE NO. (Include Area Code) 919-493-6006	FACSIMILE (FAX) Number (Include Area Code) 919-493-6104
APPLICANT ADDRESS (Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued): 6330 Quadrangle Drive Suite 305 Chapel Hill, NC 27514	AUTHORIZED U.S. AGENT NAME & ADDRESS (Number, Street, City, State, ZIP Code, telephone & FAX number) IF APPLICABLE NA

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER (If previously issued) NA		
ESTABLISHED NAME (e.g., Proper name, USP/USAN name) Paroxetine Mesylate	PROPRIETARY NAME (trade name) IF ANY NA	
CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME (If any) NA		CODE NAME (If any) NA
DOSAGE FORM: Tablet	STRENGTHS: 10 mg, 20 mg, 30 mg, 40 mg	ROUTE OF ADMINISTRATION: oral

(PROPOSED) INDICATION(S) FOR USE: Depressive illness, obsessive compulsive disorder, panic disorder

APPLICATION INFORMATION

(check one) <input checked="" type="checkbox"/> NEW DRUG APPLICATION (21 CFR 314.50) <input type="checkbox"/> ABBREVIATED NEW DRUG APPLICATION (ANDA, 21 CFR 314.94) <input type="checkbox"/> BIOLOGICS LICENSE APPLICATION (21 CFR part 601)		
IF AN NDA, IDENTIFY THE APPROPRIATE TYPE <input type="checkbox"/> 505 (b)(1) <input checked="" type="checkbox"/> 505 (b)(2)		
IF AN ANDA, or 505(b)(2), IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION Name of Drug Paxil Holder of Approved Application Smithkline Beecham		
TYPE OF SUBMISSION (check one) <input type="checkbox"/> ORIGINAL APPLICATION <input checked="" type="checkbox"/> AMENDMENT TO A PENDING APPLICATION <input type="checkbox"/> RESUBMISSION <input type="checkbox"/> PRESUBMISSION <input type="checkbox"/> ANNUAL REPORT <input type="checkbox"/> ESTABLISHMENT DESCRIPTION SUPPLEMENT <input type="checkbox"/> EFFICACY SUPPLEMENT <input type="checkbox"/> LABELING SUPPLEMENT <input type="checkbox"/> CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT <input type="checkbox"/> OTHER		
IF A SUBMISSION OR PARTIAL APPLICATION, PROVIDE LETTER DATE OF AGREEMENT TO PARTIAL SUBMISSION: NA		
IF A SUPPLEMENT, IDENTIFY THE APPROPRIATE CATEGORY <input type="checkbox"/> CBE <input type="checkbox"/> CBE-30 <input type="checkbox"/> Prior Approval (PA)		
REASON FOR SUBMISSION Amendment to provide documentation of receipt of notice in accordance with 21 C.F.R. 314.52(e).		
PROPOSED MARKETING STATUS (check one) <input checked="" type="checkbox"/> PRESCRIPTION PRODUCT (Rx) <input type="checkbox"/> OVER THE COUNTER PRODUCT (OTC)		

NUMBER OF VOLUMES SUBMITTED <u>1</u>	THIS APPLICATION IS <input checked="" type="checkbox"/> PAPER <input type="checkbox"/> PAPER AND ELECTRONIC <input type="checkbox"/> ELECTRONIC
--------------------------------------	---

ESTABLISHMENT INFORMATION (Full establishment information should be provided in the body of the Application.)
Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g., Final dosage form, Stability/testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.

See originally filed Form FDA 356h

Cross References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMFs referenced in the current application)

See originally filed Form FDA 356h

his application contains the following items: (Check all that apply)

- 1. Index
- 2. Labeling (check one) Draft Labeling Final Printed Labeling
- 3. Summary (21 CFR 314.50(c))
- 4. Chemistry section
 - A. Chemistry, manufacturing, and controls information (e.g., 21 CFR 314.50(d)(1); 21 CFR 601.2)
 - B. Samples (21 CFR 314.50(e)(1); 21 CFR 601.2 (a)) (Submit only upon FDA's request)
 - C. Methods validation package (e.g., 21 CFR 314.50(e)(2)(i); 21 CFR 601.2)
- 5. Nonclinical pharmacology and toxicology section (e.g., 21 CFR 314.50(d)(2); 21 CFR 601.2)
- 6. Human pharmacokinetics and bioavailability section (e.g., 21 CFR 314.50(d)(3); 21 CFR 601.2)
- 7. Clinical Microbiology (e.g., 21 CFR 314.50(d)(4))
- 8. Clinical data section (e.g., 21 CFR 314.50(d)(5); 21 CFR 601.2)
- 9. Safety update report (e.g., 21 CFR 314.50(d)(5)(vi)(b); 21 CFR 601.2)
- 10. Statistical section (e.g., 21 CFR 314.50(d)(6); 21 CFR 601.2)
- 11. Case report tabulations (e.g., 21 CFR 314.50(f)(1); 21 CFR 601.2)
- 12. Case report forms (e.g., 21 CFR 314.50(f)(2); 21 CFR 601.2)
- 13. Patent information on any patent which claims the drug (21 U.S.C. 355(b) or (c))
- 14. A patent certification with respect to any patent which claims the drug (21 U.S.C.355(b)(2) or (j)(2)(A))
- 15. Establishment description (21 CFR Part 600, if applicable)
- 16. Debarment certification (FD&C Act 306(k)(1))
- 17. Field copy certification (21 CFR 314.50(k)(3))
- 18. User Fee Cover Sheet (Form FDA 3397)
- 19. Financial Information (21 CFR Part 54)
- 20. OTHER (Specify) Documentation of receipt of notice of certification of patent invalidity or noninfringement

CERTIFICATION

I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including, but not limited to the following:

1. Good manufacturing practice regulations in 21 CFR Parts 210, 211 or applicable regulations, Parts 606, and/or 820.
2. Biological establishment standards in 21 CFR Part 600.
3. Labeling regulations in 21 CFR Parts 201, 606, 610, 660 and/or 809.
4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR 202.
5. Regulations on making changes in application in FD&C Act Section 506A, 21 CFR 314.71, 314.72, 314.97, 314.99, and 601.12.
6. Regulations on Reports in 21 CFR 314.80, 314.81, 600.80 and 600.81.
7. Local, state and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act, I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.

The data and information in this submission have been review and, to the best of my knowledge are certified to be true and accurate.

Warning: A willfully false statement is a criminal offense, U.S. Code, title 18, section 1001.

SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT <i>Susan W. Harts</i> by <i>edhd</i>	TYPED NAME AND TITLE Susan W. Harts Vice President of Regulatory Affairs	DATE 10/12/2000
ADDRESS (Street, City, State, and ZIP Code) 6330 Quadrangle Drive, Suite 305 Chapel Hill, NC 27514		TELEPHONE NUMBER 919-493-6006

Public reporting burden for this collection of information is estimated to average 24 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Department of Health and Human Services
Food and Drug Administration
CBER, HFM-99
1401 Rockville Pike
Rockville, MD 20852-1448

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.



GENERIC DRUG ENFORCEMENT ACT OF 1992-CERTIFICATION STATEMENT

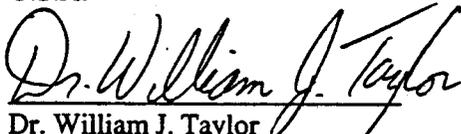
Certification about the use of a debarred person

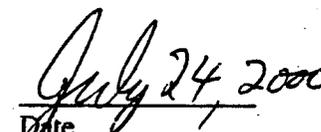
Synthon Pharmaceuticals Ltd. hereby certifies that it did not and will not use in any capacity, the services of any person debarred under subsection (a) or (b) of the Federal Food, Drug and Cosmetic Act (section 306 (a) or 306 (b)), in connection with this application for "Paroxetine 10, 20, 30, 40 mg (as mesylate) tablets."

Conviction Information Requirements

Pursuant to 306(k)(2) of the Act, Synthon Pharmaceuticals, Ltd. certifies that neither the applicant nor any affiliated persons responsible for the development or submission of this application have been convicted of crimes as described in subsections (a) and (b) {section 306(a) and (b)} within the previous 5 years. Therefore, no list of convictions is provided.

Synthon Pharmaceuticals Ltd.
6330 Quadrangle Drive, Suite 305
Chapel Hill, NC 27514
U.S.A.


Dr. William J. Taylor
President


Date

Synthon Pharmaceuticals Ltd..
6330 Quadrangle Dr Suite 305
Chapel Hill
NC 27514

USA

Date
30.06.2000

**GENERIC DRUG ENFORCEMENT ACT OF 1992 IN CONNECTION WITH THE APPLICATION FOR
"PAROXETINE 40 MG (AS MESYLATE) TABLETS"**

_____ certifies, that it is not
debarred under Section 306 (a) or (b) of the Federal Food, Drug and Cosmetic Act. Furthermore,
_____ certifies, that we did not use and will not use in any capacity the services of any person
who was debarred under Section 306 (a) or (b) of the Food, Drug and Cosmetic Act.

30.05.00

Date

30.05.2000

Date

New Drug Application
Paroxetine (as mesylate)
tablets

Synthon Pharmaceuticals Ltd.
6330 Quadrangle Drive
Suite 305
Chapel Hill, NC 27514
USA

Signed debarment statement of Synthon BV



Synthon BV

GENERIC DRUG ENFORCEMENT ACT OF 1992- CERTIFICATION STATEMENT

1 Certification about the use of a debarred person

Synthon BV certifies that it did not and will not use in any capacity, the services of any person debarred under subsection (a) or (b) of the Federal Food, Drug and Cosmetic Act [section 306(a) or 306(b)], in connection with this application for "Paroxetine 10 mg (as mesylate) tablets".

Synthon BV
Microweg 22
6545 CM Nijmegen
The Netherlands

Dr. J.M. Lemmens
President

18-02-1999
Date

[REDACTED]

**GENERIC DRUG ENFORCEMENT ACT OF 1992 IN CONNECTION WITH THE APPLICATION
FOR "PAROXETINE MESYLATE"**

[REDACTED] certifies, that it is not debarred
under Section 306 (a) or (b) of the Federal Food, Drug and Cosmetic Act. Furthermore
certifies, that it did not use and will not use in any capacity the services of any person
who was debarred under Section 306 (a) or (b) of the Food, Drug and Cosmetic Act.

[REDACTED]

Synthon Pharmaceuticals Ltd.
6330 Quadrangle Dr Suite 305
Chapel Hill
NC 27514
USA

July 15th, 1999

**GENERIC DRUGS ENFORCEMENT ACT OF 1992 IN CONNECTION WITH THE
APPLICATION FOR "PAROXETINE MESYLATE"**

_____ certifies, that it is not de-
barred under Section 306 (a) or (b) of the Federal Food, Drug and
Cosmetic Act. Furthermore _____ certifies, that we did not
use and will use any capacity the services of any person who was
debarred under Section 306 (a) or (b) of the Federal Food, Drug
and Cosmetic Act.

[Redacted]

Synthon Pharmaceuticals Ltd
6330 Quadrangle Dr Suite 305
Chapel Hill
NC 27514

USA

**GENERIC DRUG ENFORCEMENT ACT OF 1992 IN CONNECTION WITH THE
APPLICATION FOR „PAROXETINE MESYLATE“**

[Redacted], certifies, that it is not debarred under
Section 306 (a) or (b) of the Federal Food, Drug and Cosmetic Act. Furthermore
certifies, that it did not use and will not use any capacity of the services of any person who was
debarred under Section 306 (a) or (b) of the Food, Drug and Cosmetic Act.

[Redacted]

[Redacted]

[Redacted]

Signed Debarment Statement of _____

Certification about the use of a debarred person

_____ hereby certifies that it did not and will not use in any capacity, the services of any person debarred under subsection (a) or (b) of the Federal Food, Drug and Cosmetic Act (section 306 (a) or 306 (b)), in connection with this application for "Paroxetine 10, 20, 30, 40 mg (as mesylate) tablets."

Date 10/22/00

June 22, 2000

Debarment statement in connection with Paroxetine (as mesylate) tablets

_____ certifies,
that it is not debarred under Section 306 (a) or (b) of the Federal Food, Drug and Cosmetic Act.
Furthermore _____ certifies, that it did not use and will not use in any capacity
the services of any person who was debarred under Section 306 (a) or (b) of the Federal Food,
Drug and Cosmetic Act.

DEBARMENT CERTIFICATION In accordance with the requirements of the Federal Food, Drug and Cosmetic Act, _____ certifies that to the best of their knowledge, _____ not and will not be using any person debarred under 21 USC section 306 subsection (a) or (b) in any capacity in connection with the performance of this study or studies.

_____ also certifies that to the best of their knowledge, _____ is not and will not be using any person or affiliate person/firm for whom convictions subject to debarment have occurred in the last five (5) years in any capacity in connection with the performance of this study or studies.

If at any time after execution of this Agreement, _____ becomes aware that _____ or any person employed thereby or any affiliate person/firm is in the process of being debarred, _____ hereby certifies that they will so notify Sponsor at once.

08/Apr/99
Date

New Drug Application
Paroxetine (as mesylate)
tablets

Synthon Pharmaceuticals Ltd.
6330 Quadrangle Dr. Suite 305
Chapel Hill, NC 27514
USA

C TECHNICAL DATA SECTION
Nonclinical Pharmacology and Toxicology Section
Additional Information

2.6.1 Debarment Statement from

GENERIC DRUG ENFORCEMENT ACT OF 1992 - CERTIFICATION STATEMENT

1 Certification about the use of a debarred person

— certifies that, to the best of its knowledge, it did not and will not use in any capacity, the services of any person debarred under subsection (a) or (b) of the Federal Food, Drug and Cosmetic Act (section 306(a) of 306(b)), in connection with this application for "Paroxetine (as mesylate) tablets".

2 List of relevant convictions for persons debarred or not debarred

— certifies that no individual employed by — and no individual from any partnership, corporation or association responsible for the development or submission of records or data used to support approval of this application for "Paroxetine (as mesylate)" and/or related to the manufacturing, processing, or testing of the active ingredient or the finished dosage form, have been convicted in the last five years of crimes that are described in the Act as grounds for mandatory or permissive debarment (section 306(a) of 306(b)).

Date

18 07 98



October 6, 2000

VIA HAND DELIVERY

Russell Katz, M.D.
Food and Drug Administration
Office of Drug Evaluation I
Div. of Neuropharmacological Drug Products (HFD-120)
Woodmont II
1451 Rockville Pike
Rockville, Maryland 20852-1420

**Re: Synthon Pharmaceuticals, Ltd. Amendment to
NDA No. 21-299 (Paroxetine (as mesylate) Tablets)**

Dear Dr. Katz:

Enclosed please find the original and two copies of an amendment to Synthon Pharmaceuticals, Ltd.'s ("Synthon's") NDA number 21-299. The purpose of the amendment is to amend Synthon's paragraph IV patent certification and statement to include patents that were listed in the Orange Book subsequent to the filing of Synthon's 505(b)(2) application. The patents are identified in the Orange Book as claiming the Paxil® (paroxetine hydrochloride) drug product that is referenced in Synthon's application.

The amendment consists of the following documents:

- A completed Form FDA 356h;
- An amended paragraph IV patent certification (page 18 of the original NDA submission); and

Russell Katz, M.D.

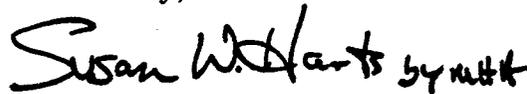
October 6, 2000

Page 2

- An amended paragraph IV statement (page 19 of the original NDA submission).

Should you have any questions concerning this submission, please contact me at (919) 493-6006, or the Synthon's legal counsel, Gary Yingling, at (202) 496-7645.

Sincerely,

A handwritten signature in black ink that reads "Susan W. Harts by mhh". The signature is written in a cursive, somewhat stylized font.

Susan W. Harts

Vice President of Regulatory Affairs

SWH/mhh

Enclosure(s)

cc: Mr. Paul David

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

**APPLICATION TO MARKET A NEW DRUG, BIOLOGIC,
OR AN ANTIBIOTIC DRUG FOR HUMAN USE**

(Title 21, Code of Federal Regulations, 314 & 601)

Form Approved: OMB No. 0910-0338
Expiration Date: March 31, 2003
See OMB Statement on page 2.

FOR FDA USE ONLY
APPLICATION NUMBER

APPLICANT INFORMATION

NAME OF APPLICANT Synthon Pharmaceuticals Ltd.	DATE OF SUBMISSION 10/06/2000
TELEPHONE NO. (Include Area Code) 919-493-6006	FACSIMILE (FAX) Number (Include Area Code) 919-493-6104
APPLICANT ADDRESS (Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued): 6330 Quadrangle Drive Suite 305 Chapel Hill, NC 27514	AUTHORIZED U.S. AGENT NAME & ADDRESS (Number, Street, City, State, ZIP Code, telephone & FAX number) IF APPLICABLE NA

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER (if previously issued) NA		
ESTABLISHED NAME (e.g., Proper name, USP/USAN name) Paroxetine Mesylate	PROPRIETARY NAME (trade name) IF ANY NA	
CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME (if any) NA		CODE NAME (if any) NA
DOSAGE FORM: Tablet	STRENGTHS: 10 mg, 20 mg, 30 mg, 40 mg	ROUTE OF ADMINISTRATION: oral
(PROPOSED) INDICATION(S) FOR USE: Depressive illness, obsessive compulsive disorder, panic disorder		

APPLICATION INFORMATION

(check one) NEW DRUG APPLICATION (21 CFR 314.50) ABBREVIATED NEW DRUG APPLICATION (ANDA, 21 CFR 314.94)
 BIOLOGICS LICENSE APPLICATION (21 CFR part 601)

IF AN NDA, IDENTIFY THE APPROPRIATE TYPE 505 (b)(1) 505 (b)(2)

IF AN ANDA, or 505(b)(2), IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION
Name of Drug Paxil Holder of Approved Application Smithkline Beecham

TYPE OF SUBMISSION (check one) ORIGINAL APPLICATION AMENDMENT TO A PENDING APPLICATION RESUBMISSION
 PRESUBMISSION ANNUAL REPORT ESTABLISHMENT DESCRIPTION SUPPLEMENT EFFICACY SUPPLEMENT
 LABELING SUPPLEMENT CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT OTHER

IF A SUBMISSION OR PARTIAL APPLICATION, PROVIDE LETTER DATE OF AGREEMENT TO PARTIAL SUBMISSION: NA

IF A SUPPLEMENT, IDENTIFY THE APPROPRIATE CATEGORY CBE CBE-30 Prior Approval (PA)

REASON FOR SUBMISSION Amendment of patent certification and statement to reflect patents that were issued subsequent to the original filing of the application.

PROPOSED MARKETING STATUS (check one) PRESCRIPTION PRODUCT (Rx) OVER THE COUNTER PRODUCT (OTC)

NUMBER OF VOLUMES SUBMITTED <u>1</u>	THIS APPLICATION IS <input checked="" type="checkbox"/> PAPER <input type="checkbox"/> PAPER AND ELECTRONIC <input type="checkbox"/> ELECTRONIC
ESTABLISHMENT INFORMATION (Full establishment information should be provided in the body of the Application.) Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g., Final dosage form, Stability/testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.	
See originally filed Form FDA 356h	

Cross References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMFs referenced in the current application)

See originally filed Form FDA 356h

This application contains the following items: (Check all that apply)

- 1. Index
- 2. Labeling (check one) Draft Labeling Final Printed Labeling
- 3. Summary (21 CFR 314.50(c))
- 4. Chemistry section
 - A. Chemistry, manufacturing, and controls information (e.g., 21 CFR 314.50(d)(1); 21 CFR 601.2)
 - B. Samples (21 CFR 314.50(e)(1); 21 CFR 601.2 (a)) (Submit only upon FDA's request)
 - C. Methods validation package (e.g., 21 CFR 314.50(e)(2)(i); 21 CFR 601.2)
- 5. Nonclinical pharmacology and toxicology section (e.g., 21 CFR 314.50(d)(2); 21 CFR 601.2)
- 6. Human pharmacokinetics and bioavailability section (e.g., 21 CFR 314.50(d)(3); 21 CFR 601.2)
- 7. Clinical Microbiology (e.g., 21 CFR 314.50(d)(4))
- 8. Clinical data section (e.g., 21 CFR 314.50(d)(5); 21 CFR 601.2)
- 9. Safety update report (e.g., 21 CFR 314.50(d)(5)(vi)(b); 21 CFR 601.2)
- 10. Statistical section (e.g., 21 CFR 314.50(d)(6); 21 CFR 601.2)
- 11. Case report tabulations (e.g., 21 CFR 314.50(f)(1); 21 CFR 601.2)
- 12. Case report forms (e.g., 21 CFR 314.50(f)(2); 21 CFR 601.2)
- 13. Patent information on any patent which claims the drug (21 U.S.C. 355(b) or (c))
- 14. A patent certification with respect to any patent which claims the drug (21 U.S.C.355(b)(2) or (j)(2)(A))
- 15. Establishment description (21 CFR Part 600, if applicable)
- 16. Debarment certification (FD&C Act 306(k)(1))
- 17. Field copy certification (21 CFR 314.50(k)(3))
- 18. User Fee Cover Sheet (Form FDA 3397)
- 19. Financial Information (21 CFR Part 54)
- 20. OTHER (Specify)

CERTIFICATION

I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including, but not limited to the following:

1. Good manufacturing practice regulations in 21 CFR Parts 210, 211 or applicable regulations, Parts 606, and/or 820.
2. Biological establishment standards in 21 CFR Part 600.
3. Labeling regulations in 21 CFR Parts 201, 606, 610, 660 and/or 809.
4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR 202.
5. Regulations on making changes in application in FD&C Act Section 506A, 21 CFR 314.71, 314.72, 314.97, 314.99, and 601.12.
6. Regulations on Reports in 21 CFR 314.80, 314.81, 600.80 and 600.81.
7. Local, state and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act, I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.

The data and information in this submission have been review and, to the best of my knowledge are certified to be true and accurate.

Warning: A willfully false statement is a criminal offense, U.S. Code, title 18, section 1001.

SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT 	TYPED NAME AND TITLE Susan W. Harts Vice President of Regulatory Affairs	DATE 10/6/00
ADDRESS (Street, City, State, and ZIP Code) 6330 Quadrangle Drive, Suite 305 Chapel Hill, NC 27514		TELEPHONE NUMBER 919-493-6006

Public reporting burden for this collection of information is estimated to average 24 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Department of Health and Human Services
 Food and Drug Administration
 CBER, HFM-99
 1401 Rockville Pike
 Rockville, MD 20852-1448

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

Paragraph IV Patent Certification

Synthon Pharmaceuticals Ltd. has caused all of the following actions to be taken with respect to the following patent certification concerning its paroxetine (as mesylate) tablets, 10 mg, 20 mg, 30 mg, and 40 mg:

1. The publication entitled "Approved Drug Products with Therapeutic Equivalence Evaluations" (Orange Book), 20th Edition, 2000, and Cumulative Supplement 7 to the 20th Edition (July 2000) have been examined for patent entries related to the listed drug (Paxil® tablets).
2. The U.S. Patent and Trademark Office's ("PTO's") June 6, 2000 list of Patent Terms Extended Under 35 U.S.C. § 156 (Waxman-Hatch extensions) has been examined for entries related to the listed drug.
3. The August 23, 2000 list entered in FDA's Docket Number 95S-0117 concerning information on "PATENT TERM EXTENSION AND NEW PATENTS" has been examined for entries related to the listed drug.

Based upon the above-identified actions, Synthon Pharmaceuticals Ltd. certifies that, in its opinion and to the best of its knowledge:

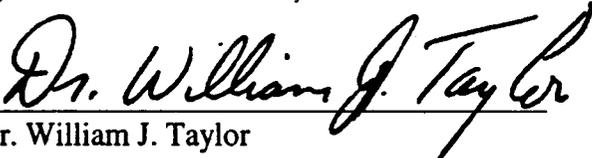
Paragraph IV

The following patents are invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the paroxetine (as mesylate) tablets for which this application is submitted:

<u>Patent Number</u>	<u>Inventor</u>	<u>Issue Date</u>	<u>Expiration Date</u>
4,721,723	Barnes et al.	Jan. 26, 1988	Sept. 25, 2008*
5,789,449	Norden	Aug. 4, 1998	Jan. 6, 2009
5,872,132	Ward et al.	Feb. 16, 1999	May 19, 2015
5,900,423	Ward et al.	May 4, 1999	May 19, 2015
6,063,927	Craig et al.	May 16, 2000	Apr. 23, 2019
6,080,759	Ward et al.	June 27, 2000	May 19, 2015
6,113,944	Pathak et al.	Sept. 5, 2000	December 14, 2014

* The expiration date of this patent is erroneously listed in the Orange Book as December 29, 2006.

Synthon Pharmaceuticals Ltd.


Dr. William J. Taylor
President

Paragraph IV Statement

Synthon Pharmaceuticals Ltd. hereby states, in accordance with Section 505(b)(3)(A) of the Federal Food, Drug, and Cosmetic Act ("the Act") and 21 C.F.R. § 314.50(i)(1)(i)(A)(4), that, upon receipt from FDA of an acknowledgement letter stating that this new drug application is sufficiently complete to permit a substantive review, it will give notices containing the information required by Section 505(b)(3)(B) of the Act and 21 C.F.R. § 314.52(c) to the following persons by Federal Express with receipt verification:

1. The owner(s) of each of the following patent numbers:
4,721,723; 5,789,449; 5,872,132; 5,900,423; 6,063,927; 6,080,759; and 6,113,944
or the representative of each owner designated to receive the notice;
and
2. The holder of approved NDA number 20-031 or the representative of the holder designated to receive the notice.



NDA 21-299

AUG 9 2000

Synthon Pharmaceuticals Ltd.
Attention: Susan W. Harts
Vice President of Regulatory Affairs
6330 Quadrangle Drive, Suite 305
Chapel Hill, NC 27514

Dear Ms. Harts:

We have received your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: Paroxetine mesylate Tablets

Review Priority Classification: Standard (S)

Date of Application: July 26, 2000

Date of Receipt: July 26, 2000

Our Reference Number: NDA 21-299

Unless we notify you within 60 days of our receipt date that the application is not sufficiently complete to permit a substantive review, this application will be filed under section 505(b) of the Act on September 24, 2000 in accordance with 21 CFR 314.101(a). If the application is filed, the primary user fee goal date will be May 26, 2001 and the secondary user fee goal date will be July 26, 2001.

Please cite the NDA number listed above at the top of the first page of any communications concerning this application. All communications concerning this NDA should be addressed as follows:

U.S. Postal Service:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Neuropharmacological Drug
Products, HFD-120
Attention: Division Document Room 4008
5600 Fishers Lane
Rockville, Maryland 20857

Courier/Overnight Mail:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Neuropharmacological Drug
Products, HFD-120
Attention: Division Document Room 4008
1451 Rockville Pike
Rockville, Maryland 20852-1420

If you have any questions, call Paul David, R.Ph., Regulatory Project Manager, at (301) 594-5530.

Sincerely,



Russell Katz, M.D.
Director
Division of Neuropharmacological Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

NDA 21-299

Page 3

cc:

Archival NDA 21-299

HFD-120/Div. Files

HFD-120/P.David

HFD-120/R.Katz/T.Laughren

HFD-120/G.Fitzgerald/R.Seevers

HFD-860/R.Baweja

DISTRICT OFFICE

151

filename: Paroxetine Mesylate\N21299\ORIGINAL NDA ACKNOWLEDGEMENT LETTER.DOC

ACKNOWLEDGEMENT (AC)



David

DEC 10 1999
DEC

IND 57,407

Synthon Pharmaceuticals Ltd.
Attn: William J. Taylor, Pharm.D.
President, Synthon Pharmaceuticals
6330 Quadrangle Drive, Suite 305
Chapel Hill, North Carolina 27514

Dear Dr. Taylor:

Please refer to your Investigational New Drug Application (IND) submitted pursuant to section 505(i) of the Federal Food, Drug, and Cosmetic Act for paroxetine mesylate.

We additionally refer to the Pre-NDA meeting between representatives of your firm and FDA held on October 21, 1999.

We acknowledge receipt of your version of meeting minutes dated November 2, 1999.

A copy of our minutes of that meeting is enclosed. These minutes are the official minutes of the meeting. You are responsible for notifying us of any significant differences in understanding you have regarding the meeting outcomes.

We wish to emphasize the following points made at the October 21, 1999 meeting:

1. You should perform a separate study to explore the multiple dose pharmacokinetics of your drug product in accordance with 21 CFR 320.25(e). You would not need to perform a comparative multiple dose pK study relative to the referenced Paxil product. Instead, you could perform a historical comparison using data submitted to the NDA of the referenced drug product.
2. The  speed used in dissolution testing  may be too fast to discriminate product quality. You may wish to try using surfactants with lower  speeds as per the *in vitro* dissolution guidance for industry.
3. In the NDA submission, you should submit the qualitative and quantitative compositions for all products used in the bioavailability studies.
4. Regarding dissolution testing, your product should be tested in three pH ranging media from which one medium will be selected as a common medium for all tablet strengths for future testing.

IND 57,407

Page 2

If you have any questions concerning this IND, please contact Mr. Paul David, Regulatory Project Manager, at (301) 594-5530.

Sincerely yours,

RSI

Russell Katz M.D.
Director
Division of Neuropharmacological Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Enclosure