CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:
NDA 20-031/S-027

Name:	Paxil Tablets (paroxetine hydrochloride)
Sponsor:	SmithKline Beecham Pharmaceuticals
Approval Date:	September 20, 2000

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-031/S-027

CONTENTS

Reviews / Information Included in this Review	
Approval Letter	X
Approvable Letter(s)	
Final Printed Labeling	
Medical Review(s)	
Chemistry Review(s)	X
EA/FONSI	
Pharmacology Review(s)	
Statistical Review(s)	
Microbiology Review(s)	
Clinical Pharmacology/Biopharmaceutics Review(s)	X
Administrative Document(s)	X
Correspondence Document(s)	X

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-031/S-027

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville MD 20857

NDA 20-031/S-027

SmithKline Beecham Pharmaceuticals
Attention: Deborah E. Zuber, R.Ph.
Assistant Director, Regulatory Affairs
1250 S. Collegeville Road, P.O. Box 5089
Collegeville, PA 19426-0989

SEP 20 2000

Dear Ms. Zuber:

Please refer to your supplemental new drug application dated May 25, received May 31, 2000, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Paxil (paroxetine hydrochloride) 10 mg, 20 mg, 30 mg, and 40 mg Tablets.

This supplemental new drug application provides for the addition of a score line in the 10 mg tablet.

We have completed the review of this supplemental application, and it is approved.

Additionally, we remind you that the first commercial batch of scored 10 mg tablet drug product should be placed on stability as per SUPAC-IR.

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

cc:
Archival NDA 20-031
HFD-120/Div. File
HFD-120/P.David
HFD-120/R.Katz/T.Laughren/G.Dubitsky
HFD-120/R.Seevers/R.Lostritto
HFD-860/R.Baweja/H.Zhao
HFD-095/DDMS-IMT
HFD-093/DDMS-IST (with labeling)
HFD-810/DNDC Division Director
DISTRICT OFFICE

09/18/00pd
filename:PAXIL/NDA/20031/SCM-027 APPROVAL LETTER.DOC

APPROVED (AP)

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-031/S-027

CHEMISTRY REVIEW(S)

11311

SEP 14 2000

CHEMIST'S REVIEW

1. ORGANIZATION HFD-120 DNDP	2. NDA NUMBER 20-031
3. NAME AND ADDRESS OF APPLICANT *(City and State)* SmithKline Beecham Pharmaceuticals, Collegeville, PA	4. AF NUMBER SEP 15 2000
	5. SUPPLEMENT (S) NUMBER(S) DATES(S) SCM-027 5/31/00 (CDER Date) (subject of this review)
6. NAME OF DRUG Paxil® Tablets	7. NONPROPRIETARY NAME paroxetine hydrochloride
8. SUPPLEMENT PROVIDES FOR: a score in the 10 mg tablet strength only. There are NO formulation, process, site or other changes.	9. AMENDMENTS DATES SEP 15 2000
10. PHARMACOLOGICAL CATEGORY treatment of depression	11. HOW DISPENSED RX X OTC _____
12. RELATED IND/NDA/DMF SEP 14 2000	
13. DOSAGE FORM(S) film coated IR tablets	14. POTENCY. 10 mg, 20 mg, 30 mg and 40 mg tablets
15. CHEMICAL NAME AND STRUCTURE see 1996 USAN page	16. RECORDS AND REPORTS CURRENT YES_____NO_____ REVIEWED YES_____NO_____

17. COMMENTS

cc:
Orig. NDA # 20-031
HFD-120/Div. File
HFD-120/RLostritto
HFD-120/RSeevers
HFD-120/PDavid
R/D Init. by: RTL 9/15/00
F/T by: RTLostritto
doc # n20031.s27

18. CONCLUSIONS AND RECOMMENDATIONS. It is recommended that this supplement be **APPROVED.** The applicant has provided adequate release and comparative dissolution data (F2) which indicate that addition of a score to the 10 mg tablet is without substantive impact on this drug product. This conclusion is in accord with that reached by the Biopharm Review dated 7/27/00. **See attached draft review comment which reminds the applicant to put their first commercial batch of scored 10 mg tablet drug product on stability as per SUPAC-IR.**

19. REVIEWER

NAME	SIGNATURE	DATE COMPLETED
Richard T. Lostritto, Ph.D.	RTL 9/14/00	9/14/00

DISTRIBUTION ORIGINAL JACKET ___ DIVISION FILE ___ REVIEWER ___ CSO ___ TEAM LEADER ___

Redacted 3 page(s)

of trade secret and/or

confidential commercial

information from

Chemistry Review

S-027

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-031/S-027

CLINICAL PHARMACOLOGY/ BIOPHARMACEUTICS REVIEW(S)

111 1631

COMPLETED JUL 27 2000

JUL 25 2000

OFFICE OF CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

Submission Dates: 5/25/2000

NDA:	20-031/SCM-027
Name of Drug:	Paxil (Paroxetine HCl, Hemihydrate) 10 mg Scored Tablets
Indication of Drug:	Depression
Type of Submission:	CMC Manufacturing Supplement
Sponsor:	SmithKline Beecham, Collegeville, PA
Reviewer:	Hong Zhao, Ph.D.

Introduction

This is a manufacturing supplement that provides for the scoring of the Paxil 10 mg tablet strength. The sponsor has provided comparative dissolution data for review.

Dissolution Data Review

Comparative dissolution profiles were generated between three Paxil 10mg Scored Tablet lots and a NDA validation lot (non score) using the currently approved FDA method and specification. The analyses were done on whole and half tablets. See Attachment I for individual dissolution profile data for 12 halves derived from a separate whole tablet, for whole scored tablet, and for whole non scored tablet. The mean dissolution data with ranges are summarized in the following table:

		Mean (Range) Dissolved (%, N=12)			
Time (min)		15	30	45	60
Lot X21-9B10	*Half*	75 (⊏ ⊐)	93 (⊏ ⊐)	94 (⊏ ⊐)	94 (⊏ ⊐)
	Whole	71 (⊏ ⊐)	92 (⊏ ⊐)	96 (⊏ ⊐)	97 (⊏ ⊐)
Lot X22-9B10	*Half*	75 (⊏ ⊐)	93 (⊏ ⊐)	94 (⊏ ⊐)	94 (⊏ ⊐)
	Whole	75 (⊏ ⊐)	93 (⊏ ⊐)	95 (⊏ ⊐)	95 (⊏ ⊐)
Lot X23-9B10	*Half*	76 (⊏ ⊐)	93 (⊏ ⊐)	93 (⊏ ⊐)	93 (⊏ ⊐)
	Whole	69 (⊏ ⊐)	93 (⊏ ⊐)	98 (⊏ ⊐)	98 (⊏ ⊐)
Lot X8-6B10 (Non Scored)	Whole	85 (⊏ ⊐)	100 (⊏ ⊐)	103 (⊏ ⊐)	101 (⊏ ⊐)
	Specification		**Q=⊏⊐% in 60 minutes**		

Also see Attachment II for Content uniformity for whole scored tablets and for halve scored tablets. Greater than ⊏⊐% of the drug was dissolved in 30 minutes for all batches tested including scored, unscored and non scored tablets. Every testing set has met the specification for Paxil® Tablet. Content uniformity for whole scored tablets and halves of scored tablets is with the limits of 85.0-115.0%.

Comment

Based on these data, the scored Paxil® 10 mg tablet is shown to be equivalent to a whole unscored tablet of the same strength. OCPB finds that the scoring Paxil 10 mg tablet strength is acceptable.

Hong Zhao, Ph.D. Hong Zhao 7/24/2000

RD/FT Initialed by Raman Baweja, Ph.D. R. Baweja 7/25/00

cc: NDA 20-031/SCM-027 (Paxil, Paroxetine HCl, Hemihydrate Tablets), HFD-120, HFD-860 (Zhao, Baweja, Mehta), Central Documents Room (CDR-Biopharm)

Attachment I
1 of 7

Table II
Individual Tablet Weight and Dissolution Profile of Twelve (12) Half Tablets

Lot X21-9B10

		Half Tablets			
		Dissolution Data - Spec = Q[ ]% in 30 min			
Sample	weight (mg)	15 min	30 min	45 min	60 min
1	[redacted]				
2					
3					
4					
5					
6					
7					
8					
9					
10					
11					
12					
Average	89.10	75	93	94	94
Max	[redacted]				
Min					
RSD	3.7	10.0	4.6	4.2	4.3

Table III
Individual Tablet Weight and Dissolution Profile of Twelve (12) Half Tablets

Lot X22-9B10

		Half Tablets			
		Dissolution Data - Spec = Q□% in 30 min			
Sample	weight (mg)	15 min	30 min	45 min	60 min
1					
2					
3					
4					
5					
6					
7					
8					
9					
10					
11					
12					
Average	88.46	75	93	94	94
Max					
Min					
RSD	2.6	8.1	3.7	3.8	3.7

Table IV
Individual Tablet Weight and Dissolution Profile of Twelve (12) Half Tablets

Lot X23-9B10

		Half Tablets			
		Dissolution Data - Spec = Q[illegible]% in 30 min			
Sample	weight (mg)	15 min	30 min	45 min	60 min
1	[illegible]				
2					
3					
4					
5					
6					
7					
8					
9					
10					
11					
12					
Average	87.80	76	93	93	93
Max	[illegible]				
Min					
RSD	2.9	8.3	4.7	5.0	4.8

Table V
Individual Table Weight and Dissolution Data for the Whole Scored Paxil 10 mg Tablets
Lot # X21-9B10

		Dissolution Data (spec. = Q[ ]% in 60 min)			
Sample	weight (mg)	15 min	30 min	45 min	60 min
1					
2					
3					
4					
5					
6					
7					
8					
9					
10					
11					
12					
Average	178	71	92	96	97
Max					
Min					
RSD	1.2	7.3	5.2	3.6	3.3

Table VI
Individual Table Weight and Dissolution Data for the Whole Scored Paxil 10 mg Tablets

Lot # X22-9B10

		Dissolution Data (spec. = Q[ ]% in 60 min)			
Sample	weight (mg)	15 min	30 min	45 min	60 min
1					
2					
3					
4					
5					
6					
7					
8					
9					
10					
11					
12					
Average	178	75	93	95	95
Max					
Min					
RSD	0.9	6.6	3.6	3.3	3.2

Table VII
Individual Table Weight and Dissolution Data for the Whole Scored Paxil 10 mg Tablets

Lot X23-9B10

		Dissolution Data (spec. = Q[ ]% in 60 min)			
Sample	weight (mg)	15 min	30 min	45 min	60 min
1	[redacted]				
2					
3					
4					
5					
6					
7					
8					
9					
10					
11					
12					
Average	177.58	69	93	98	98
Max	[redacted]				
Min					
RSD	0.9	8.1	3.7	2.8	2.5

Table VIII
Individual Dissolution Tablet Data for Lot # X8-6B10
Controlled Non-scored Paxil 10 mg Tablet

Sample	Weight(mg)	15 min % Diss.	30min % Diss.	45 min % Diss.	60 min % Diss.
1					
2					
3					
4					
5					
6					
7					
8					
9					
10					
11					
12					
Average	177.12	85	100	103	101
Max					
Min					
RSD	2.6	8.3	5.4	3.8	4.0

Attachment II

1 of 2

Table 1 Content Uniformity for Whole Tablets
Paxil 10 mg Scored Tablets

	Lot X21-9B10		X22-9B10		X23-9B10	
Sample	Sample Weight	% Claim	Sample Weight	% Claim	Sample Weight	% Claim
1						
2						
3						
4						
5						
6						
7						
8						
9						
10						
Average		99.7		98.5		101.4
Ave. RSD	3.2%		3.7%		5.0%	
Limits	85.0-115.0% RSD:NMT 6%		85.0-115.0% RSD:NMT 6%		85.0-115.0% RSD:NMT 6%	

000031

Attachment 11
2 of 2

Table 2 Content Uniformity for Halve Tablets
Paxil 10 mg Scored Tablets

	Lot X21-9B10				X22-9B10				X23-9B10			
	Sample Weight		% Claim		Sample Weight		% Claim		Sample Weight		% Claim	
Sample	Pan 758	Pan 759	Pan 758	Pan 759	Pan 758	Pan 759	Pan 758	Pan 759	Pan 758	Pan 759	Pan 758	Pan 759
1												
2												
3												
4												
5												
6												
7												
8												
9												
10												
Average			101.3	97.5			103.4	99.5			100.9	99.7
Ave. RSD			4.7	5.4			2.7	4.1			2.4	5.0
Limits			85.0-115.0% RSD:NMT 6%				85.0-115.0% RSD:NMT 6%				85.0-115.0% RSD:NMT 6%	

COMPLETED SEP 2 3 199

P 70829

SEP 2 2 1999

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

Paroxetine Hydrochloride (Paxil®)
10 mg Tablets
NDA #**20-031**
Reviewer: Z. Wahba, Ph.D.

SmithKline Beecham
Collegeville, PA
Submission Date:
August 19, 1999

REVIEW OF AN NDA Correspondence

BACKGROUND

Paroxetine hydrochloride is indicated for the treatment of depression.

The sponsor is adding a score line to its current marketed product, paroxetine Hydrochloride 10 mg tablets (Scored Paxil® 10 mg tablets) (see Attachment 1). In this NDA correspondence, the sponsor is seeking the Agency's comments on a "Change Being Effected" supplement for the scoring of paroxetine HCl 10 mg tablets.

COMMENT

The sponsor is requested to submit dissolution profiles comparing whole tablets of the currently marketed drug (Paxil® 10 mg tablets) to half-tablets of the same strength of the drug. Twelve individual units of whole tablets and half-tablets should be tested. Dissolution testing should be conducted according to the currently approved FDA method and specification of the drug. The sponsor should provide F2 comparisons for the dissolution data obtained. It should be noted that each individual half-tablet used in the dissolution testing should be derived from a separate whole tablet. In addition, please provide the weights of all half-tablets that were used in the dissolution comparison. Finally, the sponsor should clearly indicate that there were no changes made to the currently approved formulation of the 10 mg tablet.

RECOMMENDATION

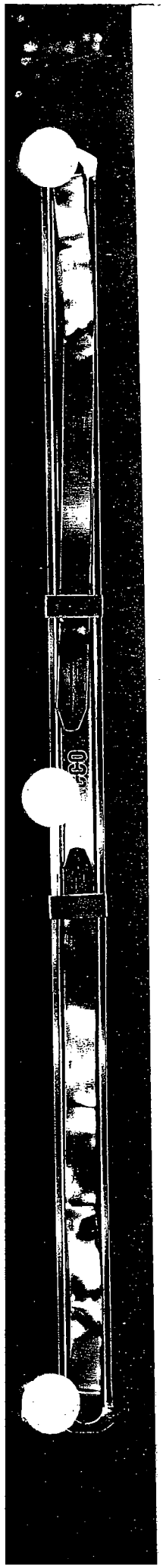
Please forward the above Comment to the sponsor.

Zakaria Z. Wahba, Ph.D. Zakaria Z. Wahba 9/22/99
Division of Pharmaceutical Evaluation I

RD/FT initialed by Raman Baweja, Ph.D. R. Baweja 9/24/99.

cc: NDA #20-031, HFD-120, HFD-860 (Wahba, Baweja, Mehta),
Central Documents Room

Attachment 1



SmithKline Beecham
Pharmaceuticals

NEW CORRESP

DUPLICATE NC

August 19, 1999

NDA 20-031
Paxil® (paroxetine hydrochloride, hemihydrate)Tablets

Russel Katz, M.D., Acting Director
Division of Neuropharmacologic
Drug Products (HFN-120, Room 10B-45)
Center for Drug Evaluation and Research
Office of Drug Evaluation I
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

CENTER FOR DRUG EVALUATION AND RESEARCH

AUG 23 1999

RECEIVED HFD-120

RE: NDA Correspondence: Request for FDA Guidance
Scored Paxil® 10 mg Tablet

Dear Dr. Katz:

Reference is made to NDA 20-031 for Paxil (paroxetine hydrochloride, hemihydrate) tablets, 10 mg, 20 mg, 30 mg, and 40 mg. This submission requests FDA concurrence on the type of Chemistry Supplement that will be required at submission to seek approval of adding a score line to the current Paxil® 10 mg tablet.

SmithKline Beecham proposes to provide a "Changes Being Effected" Supplement containing the following data and documents:

- Tablet drawing demonstrating the addition of the score line to the 10 mg tablet
- Batch analysis data on three (3) validation batches of scored 10 mg tablets manufactured at the Cidra , P.R., facility.
- Comparative dissolution profile data of the scored 10 mg tablet versus the non-scored currently marketed 10 mg tablet on one validation batch. Also comparative dissolution profile data on both halves of the scored 10 mg tablet. The f2 value will be calculated for all dissolution data to demonstrate "similar" tablets.
- Revised draft drug product labeling describing the addition of the score line to the 10 mg tablet.

1250 S. Collegeville Road, PO Box 5089, Collegeville, PA 19426-0989. Telephone (610) 917 7000. Fax (610) 917 7707.

Attachment 1 (continued)

- Revised drug product specification for the 10 mg scored tablet
- Commitment to place these batches on stability in accordance with the validation stability protocol in the NDA. Stability results will be reported in future annual reports.

The Draft FDA Stability Guidelines propose a "Prior Approval" Supplement be provided for the addition of a score line. However, since this guidance document is currently draft and being evaluated by both FDA and industry, SmithKline Beecham is seeking FDA agreement on a "Changes Being Effected" Supplement with a 30 day implementation date.

The score line is being added to the Paxil® 10 mg tablet for ease of smoother dose titration.

If you should have any additional questions regarding this proposal, please do not hesitate to contact me at (610) 917-6884.

Sincerely,

Deborah E. Zuber

Deborah E. Zuber, R.Ph.
Assistant Director
Regulatory Affairs, North America

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-031/S-027

ADMINISTRATIVE

M E M O R A N D U M

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

DATE: September 19, 2000

FROM: Thomas P. Laughren, M.D.
Team Leader, Psychiatric Drug Products
Division of Neuropharmacological Drug Products
HFD-120

SUBJECT: Recommendation for Approval Action for CMC Changes for Paxil 10, 20, 30, and 40 mg strength tablets

TO: File NDA 20-031/S-027
[Note: This memo should be filed with the 5-25-00 original submission.]

Paxil is an approved drug product, for the treatment of depression and several other psychiatric disorders, currently available in 10, 20, 30, and 40 mg strength tablets. This supplement provides for scoring for the 10 mg strength. The sponsor provided comparative dissolution data in support of S-027.

There was no requirement for in vivo bioequivalence data for this supplement. The dissolution data provided were reviewed by Dr. Hong Zhao from Biopharmaceutics. She concluded that the supplement can be approved.

The CMC data provided in this supplement were reviewed by Dr. Richard Lostritto from Chemistry. He also concluded that the supplement can be approved.

There are no clinical issues requiring review. The ability to divide the 10 mg strength may provide for more refined dosing in certain patient groups, e.g., the elderly and patients with panic disorder.

Recommendation

I agree with the recommendations of both reviewers that this supplement can be approved.

Appears This Way
On Original

cc:
Orig NDA 20-031/S-027
HFD-120/DivFile
HFD-120/TLaughren/RKatz/PDavid

DOC: NDA20031.027

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-031/S-027

CORRESPONDENCE

113-1 SC/1 6.1

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-031/S-027

JUN - 6 2000

SmithKline Beecham Pharmaceuticals
1250 South Collegeville Road
P.O. Box 5089
Collegeville, PA 19426-0989

Attention: Deborah E. Zuber. R.Ph.

Dear Ms Zuber:

We acknowledge receipt of your supplemental application for the following:

Name of Drug: Paxil Tablets

NDA Number: 20-031

Supplement Number: S-027

Date of Supplement: May 25, 2000

Date of Receipt: May 31, 2000

Unless we find the application not acceptable for filing, this application will be filed under Section 505(b)(1) of the Act on July 30, 2000 in accordance with 21 CFR 314.101(a).

All communications concerning this NDA should be addressed as follows:

Center for Drug Evaluation and Research
Division of Neuropharmacological Drug Products, HFD-120
Office of Drug Evaluation I
Attention: Document Control Room 4008
5600 Fishers Lane
Rockville, MD 20857

Sincerely,

John S. Purvis
Chief, Project Management Staff
Division of Neuropharmacological Drug Products, HFD-120
Office of Drug Evaluation I
Center for Drug Evaluation and Research

cc:
Original NDA 20-031/S-027
HFD-120/Div. Files
HFD-120/CSO/David

filename: C:\WPWIN61\TEMPLATE\FDA\20031S27.WPD

SUPPLEMENT ACKNOWLEDGEMENT

SmithKline Beecham
Pharmaceuticals

ORIGINAL

May 25, 2000

NDA 20-031
Paxil® (paroxetine hydrochloride, hemihydrate) Tablets

CENTER FOR DRUG EVALUATION AND RESEARCH

MAY 31 2000

RECEIVED HFD-120

NDA NO 20-031 REF NO. 027
NDA SUPPL FOR SCM

Russell Katz, M.D., Acting Director
Division of Neuropharmacologic
Food and Drug Administration
Division of Neuropharmacological Drug Products
Room 54049, HFD 120
1451 Rockville Pike
Rockville, Maryland 20852

Re: Prior Approval Supplement – Chemistry
Addition of a Score-Line to the Paxil® 10 mg Tablet

Dear Dr. Katz:

Reference is made to NDA 20-031 for Paxil (paroxetine hydrochloride, hemihydrate) Tablets and to the FDA letter dated October 19, 1999. SmithKline Beecham had requested Agency concurrence on the proposal submitted to the FDA on August 19, 1999, to support a chemistry supplement providing for the addition of a score-line in the Paxil® 10 mg tablet strength. The October 10, 1999 FDA letter described the data to be included in the Prior Approval Supplement.

This submission provides data on three full-scale validation lots. There were no changes made to the currently approved formulation for the 10 mg tablet. During manufacture of these batches, tablets were compressed with a score-line. The following data are provided in this supplement.

- Batch analysis data (tested according to the currently approved specification).
- Comparative dissolution profile data (12 tablets) of whole and half tablets generated via the currently approved dissolution method.
- Content uniformity data.
- Calculation of f2 comparisons for the dissolution data.
- Weight of all half-tablets and whole tablets used in the dissolution comparison.
- Copy of the revised manufacturing order.

CC0001

1250 S. Collegeville Road, PO Box 5089, Collegeville, PA 19426-0989. Telephone (610) 917 7000. Fax (610) 917 7707.

- Revised drug product specification and drug product stability testing specification and protocol.
- Revised draft labeling.
- Copies of tablet drawings.

All data conclude equivalency between the currently approved Paxil® 10 mg whole tablet and the proposed scored-Paxil® 10 mg tablet.

If you should have any additional questions regarding this proposal, please do not hesitate to contact me at (610) 917-6884.

Sincerely,

Deborah E. Zuber

Deborah E. Zuber, R.Ph.
Assistant Director
Regulatory Affairs, North America