CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 18-936/S-054

ADMINISTRATIVE/CORRESPONDENCE DOCUMENTS

M E M O R A N D U M

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

DATE: May 17, 1999

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

SUBJECT: Recommendation for Approval Action for Prozac capsules (40 & 60 mg strengths)

TO: File NDA 18-936/S-054
[Note: This memo should be filed with the 6-17-98 original submission.]

Prozac is an SSRI approved for the treatment of depression, OCD, and bulimia. It is available as 10 & 20 mg immediate release capsules and in a solution. This supplement provides support for 2 higher strength immediate release capsules, i.e., 40 & 60 mg.

A Not Approvable letter was issued on 12-16-98, on the basis of the application's failure to meet the requirements for a waiver of an in vivo study to show bioequivalence between the higher and lower strength capsules.

We met with the sponsor on 2-5-99 to discuss options, and agreed that they needed to either conduct an in vivo study for the 60 mg strength, or provide data from an earlier study (38) that might meet the requirements for an in vivo bioequivalence study.

They chose the latter option, and submitted data from study 38 in submissions dated 2-17-99 & 4-5-99. These data were reviewed by Rae Yuan, Ph.D., in a 4-21-99 review, and she concluded, with concurrence of supervisory staff, that the 60 mg capsule can be reasonable considered bioequivalent to the 20 mg capsule. Although bioequivalnce was demonstrated only for fluoxetine, and not for norfluoxetine, OCPB nevertheless considered this a sufficient demonstration of bioequivalence in this specific situation. The 40 mg strength can then be considered bioequivalent on the basis of compositional proportionality and comparable dissolution profiles for the 40 & 60 mg strengths.

I refer to Dr. Yuan's 4-21-99 review and to a brief clinical review by Dr. Mosholder (4-28-99) for more details regarding this supplement.

In conclusion, I agree that this supplement can be approved, and I recommend that we issue the attached approval letter.

cc:
Orig NDA 18-936/S-054
HFD-120/DivFile
HFD-120/TLaughren/RKatz/PDavid

DOC: NDA18936.11

160

RECORD OF TELEPHONE CONVERSATION/MEETING

Date: 3/11/1999

Ms. Torres had called to ask about the status o[redacted] regard to this supplement. There has been some confusion as to the status of this DMF as it is a Type I DMF, but is being referenced to support specific closures by the DMF holder and this applicant. I told Ms. Torres that the DMF as presently constituted is inadequate because it is missing certain information. I told her that the following information must be available to the agency for review, whether in this DMF, in an amendment to the application, or in a new DMF:

[redacted]

151

NDA #: 18-936/S-054

Telecon/Meeting initiated by:

● Applicant/Sponsor
OFDA
By: Telephone

Product Name: Prozac

Firm Name: Lilly

Name and Title of Person with whom conversation was held: Lorraine Torres

Phone: 787-257-5579

Name: Robert H. Seevers **HFD-120**

cc
Division File NDA 18-936
HFD-120/R Seevers
HFD-120/P David
HFD-180/A Shaw

MEETING MINUTES
NDA 18-936/S-054

Date: February 5, 1999; 11:00 - 12:30 PM
Location: Conference Room E; WOC2
Firm: Eli Lilly
Type: Face-to-Face
Drug: Prozac (fluoxetine hydrochloride) 40 and 60 mg Capsules
Participants:
FDA:
Drs. Temple, Laughren, Mosholder, Katz, Lesko, Mehta, Sahajwalla, Yuan, Seevers, and Mr. David

Lilly:

Dr. Gary Tollefson	President, Neuroscience Products
Dr. Richard Bergstrom	Senior Research Scientist, Pharmacokinetics
Dr. William Barr	Professor, Virginia Commonwealth University, Consultant
Dr. Greg Brophy	Director, US Regulatory Affairs
Dr. Ben Cerimele	Senior Research Scientist, Statistics
Dr. Dave Miner	CM&C Scientist
Dr. Reed Tarwater	Regulatory Research Scientist
Mr. Tom Van Abeele	CMC Project Management

Purpose

Lilly requested a Type A meeting to discuss the Agency's not approvable letter dated December 16, 1998 for supplemental application S-054. This application provided for two new dosage strengths, 40 mg and 60 mg, based upon *in vitro* data. The sponsor had requested a waiver of the *in vivo* data requirements, and this waiver was rejected by the Agency.

Discussion

- Lilly contends that these new strengths should be approved for the following reasons (Agency response follows):

  1) Prozac meets all the criteria for a BCS Case 1 drug, i.e., high solubility and high permeability.

     The Agency believes that Lilly has not adequately made a case of the high solubility of Prozac. Regardless, the BCS classification guidance is under preparation and further, this application does not fall under the SUPAC IR guidelines which are changes to an approved product. The regulatory guidelines used in deciding these two new unapproved strengths may be found in 320.22. This regulation states that the drug must exhibit compositional proportionality to the approved formulations in order for a bio waiver to be granted.

2) The sponsor has clinical data (Protocols 38 and 58) using 40 mg and 60 mg strengths.

The clinical data derived from Protocol 38 (N=4 patients) may be useful since the sponsor used deuterium labeled fluoxetine which could provide for more sensitive assay results.

3) The sponsor has clinical data using the unapproved ———— ———— This formulation was similar to their proposed formulation.

The extrapolation of clinical data for this supplement from studies used to support an unapproved indication and dosage form would not be beneficial.

4) Dissolution data of the 40 and 60 mg formulation in 0.1N HCL.

The regulatory dissolution specifications for Prozac is in water, and the dissolution profiles of 40 and 60 mg are shown to be different from those of 10 and 20 mg. The sponsor should not use this supplement as a means of changing the regulatory dissolution specifications.

Conclusions

- The Agency concluded by informing Lilly that, unless they derive acceptable additional data on Protocol 38, they will need to conduct an *in vivo* study in order to get these strengths approved. This could be a truncated study measuring only the parent drug. Alternatively, Lilly could provide the Agency with any additional clinical data which might be available to support these new strengths.

/S/

Minutes Preparer: _____
Paul A. David , R.Ph.
Project Manager, DNDP

/S/ 2/22/99

Chair Concurrence: _____
(or designated signatory)

cc:
NDA ORIG 18-936/S-054
IND: DIV FILE
HFD-100RTemple
HFD-120/RKatz/TLaughren/AMosholder
HFD-120/PDavid
HFD-860/LLesko/MMehta/CSahajwalla/RYuan/
rd:02/09/99pd;
rev:02/09/99ry;cs;tl
ft:02/12/99pd
DOC #PROZAC\NDA\02-05-99.MM
MEETING MINUTES

C
160

Meeting Minutes
Teleconference: CMC Issues from Not Approvable Letter
NDA 18-936/S-054, PROZAC® (fluoxetine) Pulvules, 40 and 60 mg
Eli Lilly and Company, Inc.

Date/Time/Site: 14 January 1999, WOC II 4030 (P. David's Office)

Participants: Applicant: Jim Edelman, Global Packaging Technology and Development; Reed Tarwater, U.S. Regulatory Affairs; Lorraine Torres, Regulatory Affairs (Site Manufacturing, Lilly Puerto Rico); Tom Van Abeele, Development Projects Management
120: Bob Seevers, Chemistry Team Leader; Doris Bates, Regulatory Project Manager (Meeting Recorder for Paul David *in absentia*)
Draft: 22 January, 1999
Final:

Background: A Not Approvable (NA) action letter was issued to this supplemental NDA on 16 December 1998. The letter also included CMC deficiencies which were not the basis for the NA action. Lilly contacted the Division and a teleconference was arranged in order to discuss means of resolving these deficiencies.

Discussion: Only the CMC issues were discussed. These are summarized below.

Following this discussion Dr. Seevers summarized all topics and agreements, and the telecon concluded cordially.

/S/

Doris J. Bates, Ph.D., RPM
(for Paul David)

/S/

Robert H. Seevers, Ph.D.

CC:
HFD-120/Original NDA 18-936/S-054
HFD-120/Division File
/Katz
/Seevers
/David/BATES

Lilly

NDA SUPP AMEND

(FA) / (FA)
SCF-054 / SLR-059

Lilly Research Laboratories
A Division of Eli Lilly and Company

Lilly Corporate Center
Indianapolis, Indiana 46285
317 276.2000

July 21, 1999

CENTER FOR DRUG EVALUATION AND RES...

JUL 23 1999

RECEIVED ... :20

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Neuropharmacological
Drug Products
5600 Fishers Lane
Rockville MD 20857-1706

ORIGINAL

Re: NDA 18-936, Prozac® (fluoxetine hydrochloride) - Pulvules
(FPL for Approved Supplement NDA 18-936/S-054 and S-059)
NDA 20-101, Prozac® (fluoxetine hydrochloride) - Liquid
NDA 20-974, Prozac®(fluoxetine hydrochloride) – Tablets

In response to the FDA letter dated June 15, 1999 approving NDA 18-936/S-054, enclosed are 20 copies of the final printed labeling (FPL) with 10 copies mounted on heavyweight paper.

This labeling also includes revisions made to the description of major depressive episode under the **Indications and Usage** section to more closely resemble the current criteria for major depressive episode as listed in DSM-IV. This is in response to the FDA letter of approval for NDA 18-936/S-059 dated June 16, 1999.

At this time Eli Lilly has made the business decision not to market the 60-mg capsule. Accordingly this FPL only refers to the 40 mg capsule.

Please contact either Dr. Reed Tarwater at (317) 276-4952 or me at (317) 277-3799 if you have questions. Thank you for your continued cooperation and assistance.

Sincerely,

ELI LILLY AND COMPANY

Gregory D Enas

for Gregory T. Brophy, Ph.D.
Director
US Regulatory Affairs

cc: Mr. Paul David (FDA)

8/2/99
From a clinical standpoint this FPL is acceptable. To be reviewed by project manager

/S/
Medical Officer

Lilly

ORIGINAL

Lilly Research Laboratories
A Division of Eli Lilly and Company

Lilly Corporate Center
Indianapolis, Indiana 46285
317.276.2000

NDA SUPP/AMEND
SCF-054 (BB)
1

April 5, 1999

CENTER FOR DRUG EVALUATION AND RESEARCH

APR 06 1999

RECEIVED HFD-120

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Neuropharmacological
Drug Products
5600 Fishers Lane
Rockville MD 20857-1706

Re: NDA 18,936, Prozac® fluoxetine hydrochloride, S-054

Attached is our response to the questions discussed on March 26 and March 29, 1999 by Mr. Paul David of the FDA and Dr. Gregory Brophy of Eli Lilly and Company.

Please contact either Dr. Reed Tarwater at (317) 276-4952 or me at (317) 277-3799 if you have questions. Thank you for your continued cooperation and assistance.

Sincerely,

ELI LILLY AND COMPANY

Gregory T. Brophy, Ph.D.
Director
US Regulatory Affairs

cc: Mr. Paul David (FDA)

Lilly

Eli Lilly and Company

Lilly Corporate Center
Indianapolis, Indiana 46285
317.276.2000

ORIGINAL

March 12, 1999

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

SUPPLEMENT AMENDMENT

NDA SUPP AMEND
SCF-054
BC

Re: NDA 18-936, Prozac® Pulvules® (Fluoxetine Capsules, USP), S-054

Reference is made to the correspondence from Paul Leber, Director, Division of Neuropharmacological Drug Products, CDER, received on December 16, 1998 related to our supplemental application S-054 providing for the addition of two new capsule strengths, 40 mg and 60 mg, submitted to NDA 18-936, Prozac Pulvules.

This correspondence contained Biopharmaceutics and Chemistry, Manufacturing and Controls observations found during the review of the supplemental application. The application was found to be non-approvable under section 505(d) of the FD&C Act and CFR 314.125(b).

In addition, reference is made to our January 14, 1999 telephone conversation between Ms. Doris Bates and Dr. Robert Seevers FDA, and Mr. Thomas Van Abeele, Ms. Lorraine Torres, Mr. Jim Edelman and Mr. Reed Tarwater to discuss the Chemistry, Manufacturing and Control observations.

We are providing herewith written responses to the Chemistry, Manufacturing and Controls deficiencies. The Biopharmaceutics responses will be addressed in a separate amendment.

Please call Ms. Lorraine Torres, Regulatory Team Leader at (787) 257-5579 or Dr. David Miner, Director, US Regulatory Affairs (CM&C) at (317) 276-4509 if we can be of assistance.

Sincerely,

ELI LILLY AND COMPANY

for Greg Brophy, Ph.D.
Director
U.S. Regulatory Affairs

Lilly

Lilly Research Laboratories
A Division of Eli Lilly and Company

Lilly Corporate Center
Indianapolis, Indiana 46285
(317) 276-2000

ORIGINAL

February 17, 1999

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Neuropharmacological Drug Products, HFD-120
Attn: Division Document Room
5600 Fishers Lane

SCF-054
(SE) AB
NDA SUPP AMEND

Re: NDA 18-936, Prozac® Pulvules® (Fluoxetine Capsules USP), Supplement S-054.

The attached report is submitted in response to the meeting held on 5 February 1999 between representatives of the FDA and Eli Lilly and Company.

Please call me at (317) 277-3799, or Dr. Reed Tarwater at (317) 276-4952 if you have any questions. Thank you for your continued cooperation and assistance.

Sincerely,

ELI LILLY AND COMPANY

Gregory T. Brophy, Ph.D.
Director
US Regulatory Affairs

cc: Mr. Paul David, R.Ph.
Project Manager, FDA.

NDA 18-936/S-054

DEC 1 1998

Lilly Research Laboratories
Attention: Gregory T. Brophy, Ph.D.
Director, U.S. Regulatory Affairs
Lilly Corporate Center
Indianapolis, Indiana 46285

Dear Dr. Brophy:

Please refer to your supplemental New Drug Application dated June 17, 1998, for Prozac (fluoxetine hydrochloride) pulvules providing for two new capsule strengths, 40 mg and 60 mg.

Reference is also made to a meeting between the Agency and representatives from Lilly dated October 23, 1998, to discuss the biopharmaceutic data submitted to this application.

We acknowledge receipt of your submission dated October 30, 1998, providing for your version of meeting minutes from the aforementioned meeting

We have completed our review of your meeting minutes, and we have the following comments:

1. We would like to clarify that this application can not be considered a SUPAC-IR change since SUPAC-IR pertains to only approved products. Since this supplemental application provides for the addition of two new unapproved strengths of Prozac, your request for a waiver of *in vivo* bioavailability must be reviewed using the criteria outlined under 21 CFR 320.22.

2. The meeting minutes should additionally reflect that Lilly should use 3 different dissolution media at different pHs including purified water since this is the approved dissolution medium.

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

Sincerely yours,

/S/

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

cc:
NDA ORIG 18-936/S-054
HFD-120/DIV File
HFD-120/PLeber/TLaughren/AMosholder/PLavid
HFD-120/RSeevers
HFD-860/CSahajwalla/RYuan
11/06/98pd
DOC #: PROZAC\SCM40-60\10-30-98.LTR
ADVICE LETTER

Lilly

ORIGINAL

Lilly Research Laboratories
A Division of Eli Lilly and Company

Lilly Corporate Center
Indianapolis, Indiana 46285
(317) 276-2000

November 13, 1998

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Neuropharmacological Drug Products, HFD-120
Attn.: Division Document Room
5600 Fishers Lane
Rockville, MD 20857-1706

NDA SUPP AMEND
SCF-054
(BB)

Re: NDA 18-936, Prozac® Pulvules® (Fluoxetine Capsules, USP) Amendment to Supplement S-054 (CM&C)

This amendment to supplement S-054 is submitted in response to a request from Dr. R. Yuan of FDA made in phone calls on October 20 and October 23, 1998, to perform f_2 calculations to compare the dissolution profiles of the 40 mg and 60 mg Prozac® Pulvules® to the dissolution profiles of the 10 mg and 20 mg Prozac Pulvules. We are submitting herein such comparisons among the four formulations.

We are also submitting a rationale for granting a waiver of bioequivalence, which is based on the extensive history with fluoxetine and its biopharmaceutical properties.

Based on this information, we are requesting the granting of this waiver for the two new 40 mg and 60 mg dosage sizes.

Please call me at (317) 276-4509 or Dr. Reed Tarwater at (317) 276-4952 if you require any additional information or if there are any questions. Thank you for your continued cooperation and assistance.

Sincerely,

ELI LILLY AND COMPANY

David J. Miner, Ph.D.
Director, US Regulatory Affairs
(CMC - Marketed Products)

DJM:at

Lilly

Lilly Research Laboratories
A Division of Eli Lilly and Company

Lilly Corporate Center
Indianapolis, Indiana 46285
(317) 276-2000

October 30, 1998

Food and Drug Administration
Center for Drug Evaluation and Research
HFD-860
Attention: Dr. Ruihua Yuan
Woodmont Building No II
1451 Rockville Pike
Rockville, MD 208521448

Re: NDA 18-936 – Prozac® (fluoxetine hydrochloride)

Attached are our minutes of the 23 October 1998 phone call between Drs. Yuan and Sahajwalla of the FDA and Drs. Bergstrom and Tarwater, Ms. Garing, and Mr. Van Abeele of Lilly.

Please contact either Dr. Reed Tarwater at (317) 276-4952, or me at (317) 277-3799 if you have questions. Thank you for your continued cooperation and assistance.

Sincerely,
ELI LILLY AND COMPANY

Gregory T. Brophy, Ph.D.
Director
U.S. Regulatory Affairs,

cc: Mr. Paul David, (FDA)

Kae - see if you agree + the following - plus is there anything else that is missing from mine? Thanks - Isl

Paul,

2 points are missing.

1. We pointed out this is not a SUPAC change, this is a request for Bio waiver for unapproved strength. SUPAC does to point out ~~that~~ how they should calculate F2 and 12 units be used.
2. We indicated that they should use dissolution in 3 media & one of which should be the ~~the~~ approved dissolution method

MINUTES
23 OCTOBER 1998 PHONE CALL REGARDING 40 & 60 MG FLUOXETINE TABLETS BETWEEN THE FDA AND ELI LILL AND COMPANY

Background:
On Tuesday, October 20th, Dr. Reed Tarwater received a call from Dr. Ruihua Yuan, the Biopharm reviewer of the Prozac 40 mg and 60 mg supplement for FDA. Dr. Yuan asked if Lilly had performed an F2 calculation to compare the dissolution profiles of the 40 mg and 60 mg capsule strengths to the 10 mg and 20 mg capsule strengths. Dr. Tarwater indicated that he would obtain information from the technical experts and update Dr. Yuan.

Ms. Barbara Garing prepared a plot that showed dissolution profiles (sample collection at 10, 20 and 30 minutes) for 10 mg, 20 mg, 40 mg, and 60 mg capsule strengths. Dr. Tarwater faxed the plot to Dr. Yuan on October 21st and set up a conference call with Dr. Yuan for Friday, October 23rd. The dissolution plot is attached for reference.

Participants in the Conference Call:
Lilly: Dr. Rich Bergstrom (Pharmacokinetics and Bioavailability); Ms. Barbara Garing (Dry Products Technical Services); Dr. Reed Tarwater (U. S. Regulatory Affairs); and Mr. Tom Van Abeele (Development Projects Management)
FDA: Dr. Ruihua Yuan (Biopharm reviewer); and Dr. Chadra Sahajwalla (Biopharm team leader)

Main points of the Conference Call:
Dr. Tarwater started the meeting with introductions of the participants. He then asked Dr. Yuan to reiterate her question for the group. Dr. Yuan asked if Lilly had performed an F2 calculation for the dissolution profile data to compare the dosage forms in the supplemental application (40 mg and 60 mg capsules) to the approved 10 mg and 20 mg capsules.

Ms. Garing stated that Lilly's policy has been to use the F2 calculation to compare dissolution profiles for the same dosage strengths for changes covered in SUPAC-IR. She further mentioned that we would expect the dissolution profiles of different dosage strengths to be somewhat different at the earlier sample collection times, especially at 10 minutes. As the dissolution plot shows, the rate of release at 10 minutes is somewhat slower for the 40 mg and 60 mg capsules compared to the 10 mg or 20 mg capsule strengths. Since the 40 mg and 60 mg dosage strengths are in larger capsules (size 2 capsule and size 1 capsule respectively) compared to the 10 mg and 20 mg dosage forms (size 3 capsules), this could be due to the break-up of the capsule itself in the medium. However, the percent released at both 20 minutes and 30 minutes is comparable across all dosage strengths. The proposed specification for the 40 mg and 60 mg capsules is the same as the approved specification for the 10 mg and 20 mg capsules, which is Q= ——————— . . . Therefore, the percent released at the proposed specification time point ——— 's comparable across dosage strengths.

Dr. Yuan pointed out that FDA must have confidence that dissolution is adequately controlled in order to grant a waiver of bioequivalence work.

Dr. Bergstrom explained the absorption characteristics of fluoxetine. The main points were that dissolution *in vivo* was not the rate limiting step in the absorption of fluoxetine and fluoxetine is considered highly soluble and highly permeable. As an example, Dr. Bergstrom pointed out that the bioavailability of fluoxetine in an enteric-coated formulation is equivalent to the bioavailability of fluoxetine in an immediate release formulation and that the absorption of an oral solution reaches a peak plasma concentration value 4 to 8 hours after administration of the dose.

Drs. Yuan and Sahajwalla stated that, for a bioequivalence waiver for a higher dosage strength when a lower dosage strength is approved, the dissolution profiles need to be similar (not just similar dissolution results at ——— . Furthermore, it was pointed out that dissolution data must use a sample size of 12 (i.e., n=12) as opposed to n=6. Dr. Yuan also stated that, according to SUPAC-IR, if a higher dosage strength was approved, the F2 calculation should be used to compare the dissolution profiles of the lower and higher strengths for approval of the lower strength. Although this situation is the opposite scenario in terms of the dosage strengths (current application is for higher dosage strengths, with lower dosage strengths being approved), Dr. Yuan maintained that this interpretation is applicable to the approval of higher dosage strengths.

It was also pointed out that this is not a SUPAC change.

Post Meeting Note: Lilly does not agree with this interpretation of SUPAC-IR. Our interpretation is that the F2 calculation should only be used to compare dissolution profiles for formulae of the same dosage strength.

All participants agreed that fluoxetine can be classified as a highly soluble, highly permeable drug according to the Biopharmaceutics Classification System (BCS Case 1).

Ms. Garing referenced SUPAC-IR and mentioned that dissolution profiles should be compared using 0.1N HCl as the dissolution medium for a "Case A" (i.e., highly soluble, highly permeable) drug. Dr. Sahajwalla pointed out that we should use purified water as the dissolution medium for comparing dissolution profiles of the various strengths since this is the medium that is used in our approved dissolution method. Mr. Van Abeele questioned the use of water as the dissolution medium for generating dissolution profiles based on the BPCS, SUPAC-IR and our *in vitro-in vivo* experience with fluoxetine. Regardless of the approved dissolution method for fluoxetine, Lilly would recommend following SUPAC-IR and perform dissolution testing using Q=, ——— minutes if ——————— support the application. However, Dr. Sahajwalla reiterated that purified water should be used since it is the medium used in the FDA-approved method.

use 3 dissolution media of different pH including

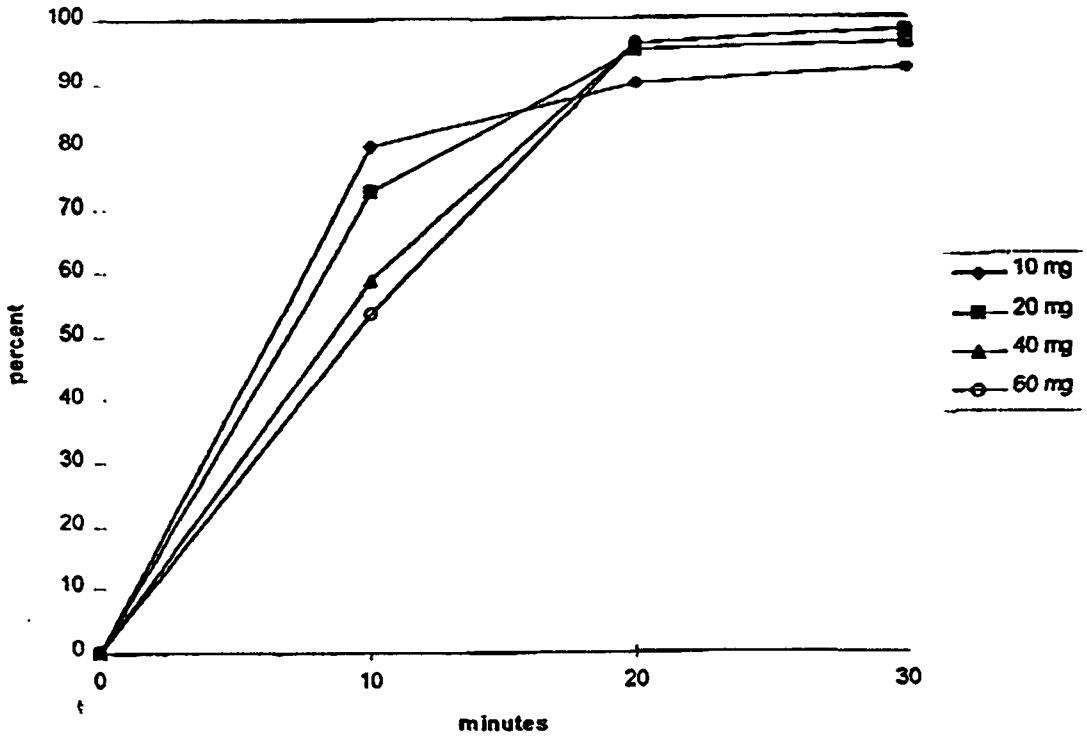
(3 media including)

Ms. Garing also asked about the number of lots required of each dosage strength for collecting the dissolution profile data. Dr. Sahajwalla stated that, using a sample size of n=12, one lot of each dosage strength would be sufficient.

Dr. Tarwater requested that FDA send written correspondence to Lilly regarding this issue, and this was agreed.

Dr. Tarwater also agreed to send minutes of this conference call to the FDA participants.

Prozac Dissolution Profiles



10 mg data represents average of lot no. 2AE60
20 mg data represents average of lot no. 2MA21
40 mg data represents average of lot nos. D20655, D20656, D20657
60 mg data represents average of lot nos. 8AN84, 8AN85, 8AN86

Lilly

Lilly Research Laboratories
A Division of Eli Lilly and Company

Lilly Corporate Center
Indianapolis, Indiana 46285
(317) 276-2000

ORIGINAL

October 30, 1998

Food and Drug Administration
Center for Drug Evaluation and Research
HFD-860
Attention: Dr. Ruihua Yuan
Woodmont Building No II
1451 Rockville Pike
Rockville, MD 208521448

Re: NDA 18-936 – Prozac® (fluoxetine hydrochloride)

Attached are our minutes of the 23 October 1998 phone call between Drs. Yuan and Sahajwalla of the FDA and Drs. Bergstrom and Tarwater, Ms. Garing, and Mr. Van Abeele of Lilly.

Please contact either Dr. Reed Tarwater at (317) 276-4952, or me at (317) 277-3799 if you have questions. Thank you for your continued cooperation and assistance.

Sincerely,
ELI LILLY AND COMPANY

Gregory T. Brophy, Ph.D.
Director
U.S. Regulatory Affairs,

cc: Mr. Paul David, (FDA)

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 18-936/S-054

Eli Lilly & Co.
Lilly Corporate Center
Indianapolis, IN 46285

JUN 23 1998

Attention: Gregory T. Brophy, Director

Dear Dr. Brophy:

We acknowledge receipt of your supplemental application for the following:

Name of Drug: Prozac Pulvule

NDA Number: 18-936

Supplement Number: S-054

Date of Supplement: June 17, 1998

Date of Receipt: June 18, 1998

Unless we find the application not acceptable for filing, this application will be filed under Section 505(b)(1) of the Act on August 17, 1998 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,

/S/

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

cc:
Original NDA 18-936/054
HFD-120/Div. Files
HFD-120/CSO/David

filename: C:\WPWIN61\TEMPLATE\FDA\18-936.054

SUPPLEMENT ACKNOWLEDGEMENT

Lilly Research Laboratories
A Division of Eli Lilly and Company

Lilly Corporate Center
Indianapolis, Indiana 46285
(317) 276-2000

ORIGINAL

June 17, 1998

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Neuropharmacological
Drug Products, HFD-120
5600 Fishers Lane
Rockville, MD 20857-1706

Re: NDA 18-936 – Prozac® (fluoxetine hydrochloride) Pulvule®

Enclosed is a supplement to NDA 18-936 which requests approval for marketing of 40 mg and 60 mg Pulvules. We would appreciate your prompt review of this supplement.

NDA 18-936 supports the use of Prozac doses up to 80 mg/day. The 40 mg and 60 mg formulae will be marketed to expand dosage form options.

Please contact either Dr. Reed Tarwater at (317) 276-4952, or me at (317) 277-3799 if you have questions. Thank you for your continued cooperation and assistance.

Sincerely,

ELI LILLY AND COMPANY

Gregory T. Brophy

for Gregory T. Brophy, Ph.D.
Director
U.S. Regulatory Affairs,

cc: Mr. Paul David (FDA)

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Application: **NDA 18936/054**
Priority: **1P** Org Code: **120**
Stamp: **18-JUN-1998** Regulatory Due: **18-DEC-1998**
Action Goal: District Goal: **13-SEP-1998**
Applicant: **LILLY RES LABS**
LILLY CORPORATE CENTER
307 EAST MCCARTY ST
INDIANAPOLIS, IN 46285
Brand Name: **PROZAC (FLUOXETINE HCL) CAPSULES**
Established Name:
Generic Name: **FLUOXETINE HYDROCHLORIDE**
Dosage Form: **CAP (CAPSULE)**
Strength: **10MG, 20MG**

FDA Contacts:

P. DAVID	**(HFD-120)**	**301-594-2850**	**, Project Manager**
R. SEEVERS	**(HFD-120)**	**301-594-2850**	**, Review Chemist**
R. SEEVERS	**(HFD-120)**	**301-594-2850**	**, Team Leader**

Overall Recommendation:

ACCEPTABLE on 08-JUL-1998 by J. D AMBROGIO (HFD-324) 301-827-0062

Establishment: **1819470**
ELI LILLY AND CO
LILLY CORP CTR/WHITE RIVER PK
INDIANAPOLIS, IN 46200
DMF No:
AADA No:

Profile: **CHG** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Milestone Date **08-JUL-1998**
Decision: **ACCEPTABLE**
Reason: **DISTRICT RECOMMENDATION**
Responsibilities: **FINISHED DOSAGE MANUFACTURER**
FINISHED DOSAGE PACKAGER
FINISHED DOSAGE RELEASE TESTER

Establishment: **2619243**
ELI LILLY INDUSTRIES INC
12.6 KM 65TH INFANTRY RD
CAROLINA, PR 00985
DMF No:
AADA No:

Profile: **CHG** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Milestone Date **29-JUN-1998**
Decision: **ACCEPTABLE**
Reason: **DISTRICT RECOMMENDATION**
Responsibilities: **FINISHED DOSAGE MANUFACTURER**
FINISHED DOSAGE PACKAGER
FINISHED DOSAGE RELEASE TESTER

Establishment: [redacted]
DMF No:
AADA No:

Profile: **CHG** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Milestone Date **24-JUN-1998**
Responsibilities: [redacted]

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Decision: **ACCEPTABLE**
Reason: **BASED ON FILE REVIEW**
BASED ON PROFILE

Establishment [redacted]

DMF No:
AADA No:

Profile: **CHG** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Milestone Date **24-JUN-1998**
Decision: **ACCEPTABLE**
Reason: **BASED ON PROFILE**

Responsibilities: [redacted]
