

COOR

MEMO OF TELEPHONE CALL

Date: November 30, 1999
NDA: 20-990
NDA: 19-839/SE1-026
Subject: Final labeling for Pending NDA
Drug: Zoloft (sertraline hydrochloride) tablets (19-839) and oral concentrate (20-990)
Indication: OCD/Depression/Panic Disorder/PTSD
Firm: Pfizer
Contact: Martha Brumfield, Ph.D
Phone #: (212) 573-5406

At the request of Dr. Laughren, I contacted Dr. Brumfield in reference to their faxed labeling counterproposal dated 11-19-99, responding to the labeling proposal faxed by the Agency on 11-2-99. The labeling revisions reflected changes to the labeling to provide for the new oral concentrate formulation, additional safety related changes previously requested by the Agency or in pending supplemental applications, and corrections to Table 3 in the Adverse Reactions section of labeling. The attempt of these faxes was to secure labeling agreement at the Team leader level.

I informed Dr. Brumfield that the Agency was willing to accept some of Pfizer's proposed changes (see attached e-mail from Dr. Mosholder). Dr. Brumfield was additionally informed that the Agency wished to have a tabular format in lieu of a narrative format for the Adverse Reactions-Sexual Dysfunction section of labeling. Dr. Brumfield replied that Pfizer was willing to accept all of these changes.

I also noted that the PTSD efficacy supplement, 19-839/SE1-026, was to be acted on at the same time as the oral concentrate application, NDA 20-990. Pfizer had previously informed me that they did not wish to have the oral concentrate labeling and the PTSD labeling together for the following reasons: 1) their detail people need to be trained on the appropriate use of the concentrate and the new indication of PTSD, and 2) they are not able to commercially distribute the concentrate until 3/2000.

I informed her that the Agency would be willing to provide separate labeling for the PTSD and the oral concentrate (with the understanding that Pfizer would combine the labeling once the FPL for the oral concentrate was submitted). However, all of the safety related changes in our agreed upon labeling (attached) would also be incorporated into the PTSD labeling so that these changes would be in the marketplace as soon as possible. Dr. Brumfield agreed with this approach.

APPEAR THIS WAY
ON ORIGINAL

/S/

Paul A. David, R.Ph.
Regulatory Project Manager

NDA 20-990
NDA 19-839/SE1-026
NDA:DIV FILES
HFD-120/TLaughren/AMosholder
/PDavid/AMHomonnay
ATTACHMENTS (2)

MEMORANDUM OF TELEPHONE CONVERSATION

NDA#: 20-990
PRODUCT NAME: Zoloft Oral Concentrate
DATE: June 2 & 4, 1998
CONVERSATION WITH: Ms. Kuskin, Regulatory Affairs
FIRM NAME: Pfizer
SUBJECT: Follow-up to request for container/closure system
PHONE#: (212)733-3527

11:55AM, (6/2/98): Ms. Kuskin called and told me that Pfizer would be shipping to me the complete container-closure system.

6/4/98: Received the [redacted] from Ms. Kuskin by priority mail.

3:53PM-3:56PM, (6/4/98): I called Ms. Kuskin and told her that I received the [redacted] today. Ms. Kuskin told me that she would be faxing to me this afternoon the information pertaining to the updated stability data that I had previously requested.

6/4/98: Received the fax pertaining to the update of stability information. The fax states that in October, 1998 an updated stability amendment will be submitted to the NDA. Fax attached.

[redacted] 6/4/98
Donald N. Klein, Ph.D.
Review Chemist
HFD-120

cc:
NDA 20-990
HFD-120/Division File
HFD-120/DKlein
HFD-120/PDavid
File: C:\hfd120\n20990\n20990TC#3

APPROVED FOR SIGNATURE
DATE: 6/4/98

Pfizer Pharmaceuticals

To: Dr. Donald Klein, DNPDP

From: Ms. Mary H. Kuskin

Date: June 4, 1998

RE: Zoloft (sertraline) oral concentrate
NDA # 20-990
Update of stability information

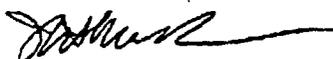
Further to my telephone conversation with Mr. Paul David on May 26, 1998, and the questions regarding the submission of additional stability data to the sertraline hydrochloride oral concentrate NDA, updated stability data will be submitted as an amendment to the NDA in October, 1998. A summary of the stability amendment that will be prepared is described below:

- Accelerated and 3 month 25°C/60%RH stability results for the confirmatory batch (N8023C, N8023D) stored in the inverted, sideways and upright positions as requested by FDA.
- Accelerated and 6 month 25°C/60%RH stability results for batch N7137B stored upright and sideways in which initial results were filed in the original application. Three month data are currently available if requested
- Additional long term stability data for batches N5223A and N5224A (24 months at 25°C/60%RH) will also be provided.

In addition, the question regarding the status of the 150mg and 200mg strength tablets, which are approved, I have confirmed that we currently have no plans for marketing this dosage form.

Please let me know if I can be of further assistance in this matter.

Sincerely,



Mary H. Kuskin, R.Ph.
MK/mk
stabrepl

cc: Paul David

6/5/98

Paul,

FYI.

/S/

Regulatory Affairs Division
Pfizer Pharmaceuticals Group
Pfizer Inc
235 East 42nd Street
New York, NY 10017-5755
Tel 212 573 5991 Fax 212 573 1563
Email claira@pfizer.com

DESK COPY



Pfizer Pharmaceuticals

Andrew G. Clair, PhD
Director
Regulatory Affairs

October 1, 1999

Russell Katz, M.D., Director
Division of Neuropharmacological Drug Products (HFD-120)
Center for Drug Evaluation and Research
Office of Drug Evaluation I
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

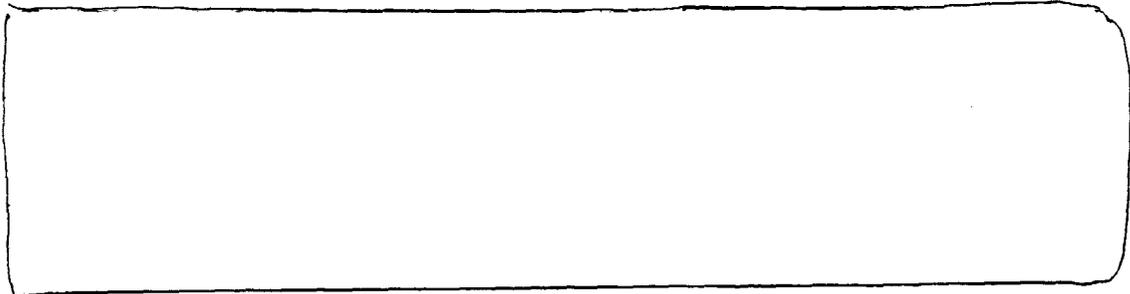
**RE: Zoloft® (sertraline hydrochloride) Oral Concentrate
NDA 20-990
New Draft Labeling**

Dear Dr. Katz:

Reference is made to our June 4, 1999 correspondence that provided chemistry, manufacturing and control information and draft product labeling for Zoloft® Oral Concentrate. Reference is further made to a September 21, 1999 telephone communication with Paul David.

During the September 21st conversation, we discussed a proposal to incorporate language into the draft product label in **CLINICAL PHARMACOLOGY (Pharmacokinetics [under] Systemic Bioavailability)** to more adequately describe the outcome of the sertraline oral solution versus tablet pharmacokinetic study.

The proposed wording is as follows:



Russell Katz, M.D., Director
Page 2

We are resubmitting the enclosed revised labeling in its entirety and respectfully request this is considered our official draft labeling for the subject file. Please note that only the **Pharmacokinetics** subsection under **CLINICAL PHARMACOLOGY**, as described above, has been revised and the proposed modification is underlined and in bolded text. Based upon the revision, we have deleted the bioequivalence statement as presented in our June 4th amendment. All other labeling sections are identical with what was previously submitted in our June 4, 1999 amendment.

If there are any further comments or questions, please contact me.

Sincerely,

A handwritten signature in cursive script that reads "Andrew G. Clair".

Andrew G. Clair, Ph.D.

Desk Copy:

Paul David (faxed revised page 3 of draft labeling)

APPEARS THIS WAY
ON ORIGINAL

MEMORANDUM

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

DATE: March 23, 1999

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

SUBJECT: Recommendation for Approvable Action for Zoloft (sertraline) Oral Solution (20 mg/ml)

TO: File NDA 20-990
[Note: This memo should be filed with the 4-15-98 original submission.]

Zoloft is an SSRI approved for the treatment of depression, OCD, and panic disorder and is available as 25, 50, & 100 mg immediate release tablets. This NDA provides support for a sertraline solution for oral administration at a concentration of 20 mg/mL. It will be available in 60 mL bottles containing 1200 mg of sertraline. The solution contains 12% ethanol and is to be diluted in some suitable beverage before administration.

The application has been reviewed by Donald Klein, Ph.D. from the chemistry group, Vanitha Sekar, Ph.D. from the biopharm group, and Andrew Mosholder, M.D. from the clinical group. All 3 reviewers have concluded that the application is approvable.

Several issues require comment:

-In 2 bioequivalence trials, sertraline solution was slightly more available than the tablet (both C_{max} and AUC), and in fact the upper bound of the 90% CI was slightly above the threshold for declaring the 2 formulations bioequivalent. Dr. Mosholder has argued that the difference is not likely to be of any clinical importance, given the already wide inter-individual variability in PK and the wide therapeutic index for this drug, and I agree. Therefore, I agree that the solution is approvable and also that no dosage adjustment is needed for the solution.

-As noted the solution contains 12% ethanol, and Dr. Mosholder has recommended its contraindication with disulfiram (Antabuse). I agree, and appropriate changes to labeling regarding this potential interaction have been made.

-In addition, we have made other labeling changes based on various requests made of the sponsor in recent years that have not yet been implemented, as follows:

-A potential for an interaction between SSRIs and sumatriptan

-Standard language for sexual dysfunction with SSRIs

APPEARS THIS WAY
ON ORIGINAL

-Revisions to the Overdosage Section

-We have not incorporated language regarding a potential interaction with several drugs that are 3A4 substrates (see 12-21-98 letter), since this is a controversial change and needs more discussion before it can be resolved.

-The approvable letter contains a listing of several chemistry issues that need resolution prior to final approval.

In conclusion, I agree that this NDA is approvable, and I recommend that we issue the attached approvable letter with our proposed labeling.

APPEARS THIS WAY
ON ORIGINAL

cc:

Orig NDA 20-990

HFD-120/DivFile

HFD-120/TLaughren/RKatz/PDavid

DOC: NDA20990.01

David

MEMORANDUM OF TELEPHONE CONVERSATION

NDA#: 20-990
PRODUCT NAME: Zoloft Oral Concentrate
DATE: April 26, 1999
CONVERSATION WITH: Ms. Kuskin, Regulatory Affairs
FIRM NAME: Pfizer
SUBJECT: NDA 20-990
PHONE#: (212) 733-3527

(10:48AM, 4/26/99): Ms. Kuskin called to tell me that she would be sending me a fax. Fax attached.

(11:17AM, 4/26/99): I called Ms. Kuskin to tell her that I received the fax. I also asked her Pfizer's policy on using e-mail communication for non-confidential communication like a fax is being sent or received. Ms. Kuskin will be checking into my question and I told her that I will be following-up with my supervisor.

(4/26/99, 11:46AM): I left a phone message with Ms. Kuskin: Please call me back to discuss the use of e-mail communication. My supervisor informed me that CDER can use e-mail for non-confidential communication. I told her that there are other points I would like to discuss regarding e-mail communication.

(4/26/99, 12:20 and 1:11): Ms. Kuskin and I tried to contact one another.

(4/26/99, 2:00): Ms. Kuskin called and I told her the following:
1. I can communicate by e-mail with industry regarding non-confidential information; 2. I cannot communicate by e-mail with industry regarding confidential information; 3. Industry can submit information by the Internet but all submissions are conducted at the companies risk. I told her that I have wordperfect and word programs, specifically, Office 97. Therefore, she could submit by the attachments; 4. I told her that CDER and Pfizer are investigating the submission of information(confidential) via the Internet.

Ms. Kuskin told me that she is still discussing this with Pfizers' staff, but her supervisor told her that e-mail(non-confidential) communication with CDER is acceptable.

APPEARS THIS WAY
ON ORIGINAL

/S/

Donald N. Klein, Ph.D.
Review Chemist
HFD-120

5/18/99

cc:
NDA 20-990
HFD-120/Division File
HFD-120/DKlein
HFD-120/PDavid
File: C:\hfd120\N20990\N20990TC#15.doc

APPEARS THIS WAY
ON ORIGINAL

Pfizer Pharmaceuticals Group
PPC Regulatory Affairs
Pfizer Inc
235 East 42nd Street
New York, NY 10017-5755
Tel 212 733 3527 Fax 212 573-1563

Pfizer Pharmaceuticals

April 26, 1999

Dr. Donald Klein
Division of Neuropharmacological
Drug Products (HFD-120)
Center for Drug Evaluation & Research
1451 Rockville Pike
Rockville, Maryland 20857

RE: Zoloft (sertraline) oral concentrate
NDA # 20-990
Response to Agency comments Dated 15, 1999

APPROVED BY

Dear Dr. Klein:

Further to your comments on March 15, 1999 and the letter from the Division dated April 15, 1999, please find the attached facsimile response regarding [redacted] of sertraline hydrochloride. This also addresses your comment to the statement in the March 12, 1999, response number 15.

This will be included our amendment to the NDA which will address all of the deficiencies listed in the Approvable letter dated April 15, 1999. If you have any further questions please call me at (212) 733-3527.

Sincerely,



Mary H. Kuskin, R.Ph.
Director, Regulatory Affairs

APPROVED THIS WAY
ON ORIGINAL

**ZOLOFT® (sertraline) Oral Concentrate
NDA-20-990**

Response to FDA Comments

Dated 15 March 1999

APPROVED FOR
ORIGINAL

FDA Comment to Response #8

- a. What is the [redacted] discussed in the response?
- b. In comparison to the [redacted] for the Zoloft Tablet, why didn't you set a [redacted] for the Zoloft Oral Concentrate?

Pfizer Response:

[Redacted response area]

(1) Welch, W.M. Kraska, A R, Sarges, R. Koe. B K, J Med Chem., 1984, 27(11), 1508-1515

NOT FOR DISTRIBUTION
ORIGINAL



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

JUN 15 1999

DAVID

NDA 20-990

Pfizer Pharmaceuticals
Attention: Mary H. Kuskin, R.Ph.
Director, Drug Regulatory Affairs
235 East 42nd Street
New York, New York 10017-5755

Dear Ms. Kuskin:

We acknowledge receipt on June 7, 1999 of your June 4, 1999 resubmission to your new drug application (NDA) for Zoloft (sertraline hydrochloride) 20 mg/ml oral concentrate.

This resubmission contains additional chemistry, manufacturing, and controls (CMC) and labeling information submitted in response to our April 15, 1999 action letter.

We consider this a complete class 2 response to our action letter. Therefore, the user fee goal date is December 7, 1999.

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

Sincerely,

 6/14/99

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

David

MEMORANDUM OF TELEPHONE CONVERSATION

NDA#: 20-990
PRODUCT NAME: Zoloft Oral Concentrate
DATE: June 25 and 28, 1999
CONVERSATION WITH: Dr. Mike Ganey, Regulatory Affairs
Ms. Mary Kuskin, Director, Regulatory Affairs
Mr. Andrew Clare, Regulatory Affairs (works
with Ms. Kuskin)
FIRM NAME: Pfizer
SUBJECT: NDA 20-990
PHONE#: (212) 733-3527: Dr. Ganey
(212) 733-3527: Ms. Kuskin

1:45PM, 6/25/99: Dr. Ganey called and left a phone message: Is there any CMC information you need in regards to the review of NDA 20-990?

2:57PM, 6/28/99: I called Ms. Kuskin and got her phone mail and the second time I called I was connected to her secretary with whom I left the following message: I had a question regarding NDA 20-990.

About 3PM, 6/28/99: I received a call from Mr. Clare and I asked him to whom at Pfizer I should contact regarding NSA 20-990 CMC questions. I explained that Ms. Kuskin's name is listed in the NDA 20-990 but I received a call from Dr. Ganey on 6/25/99. Mr. Clare explained that all questions should be directed to Ms. Kuskin.



Donald N. Kleih, Ph.D.
Review Chemist
HFD-120

7/16/99

cc:
NDA 20-990
HFD-120/Division File
HFD-120/DKlein
HFD-120/PDavid
File: C:\hfd120\N20990\N20990TC#17.doc

APPEARS THIS WAY
ON ORIGINAL



NDA 20-990

OCT 12 1999

INFORMATION REQUEST LETTER

DAVID

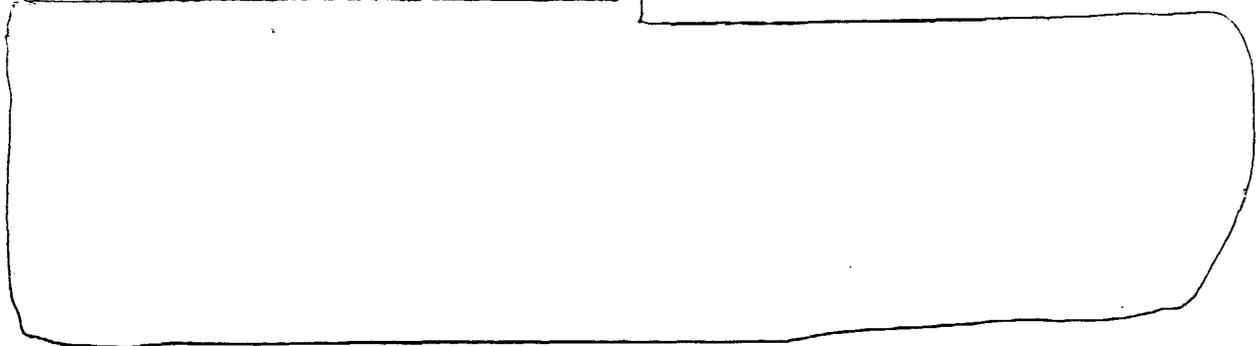
Pfizer Pharmaceuticals
Attention: Ms. Mary H. Kuskin, R.Ph.
Director, Regulatory Affairs
235 East 42nd Street
New York, NY 10017-5755

Dear Ms. Kuskin:

Please refer to your June 4, 1999 new drug application for Zoloft [®](sertraline hydrochloride) Oral Concentrate.

We are reviewing the Chemistry section of your submissions and have the following comments and information requests. We need your prompt written response to continue our evaluation of your NDA.

1. Please provide the complete description, *e.g.*, reference to a Drug Master File, of the



If you have any questions, contact Donald N. Klein, Ph.D., Review Chemist, at (301)594-5537.

Sincerely,

RS/

10/8/99

Robert H. SeEVERS, Ph.D.
Chemistry Team Leader, Psychiatric Drugs for the
Division of Neuropharmacological Drug Products,
(HFD-120)
DNDC I, Office of New Drug Chemistry
Center for Drug Evaluation and Research

NDA 20-990

Pfizer Pharmaceuticals
Attention: Martha Brumfield, Ph.D.
Drug Regulatory Affairs
235 East 42nd Street
New York, New York 10017-3184

FEB 11 1999

Dear Dr. Brumfield:

Please refer to your pending new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Zoloft (sertraline hydrochloride) 20 mg/ml Oral Concentrate.

We have completed our review of the CMC section(s) of your submission and have the following comments and information requests:

DEFICIENCIES PERTAINING TO THE DRUG PRODUCT:

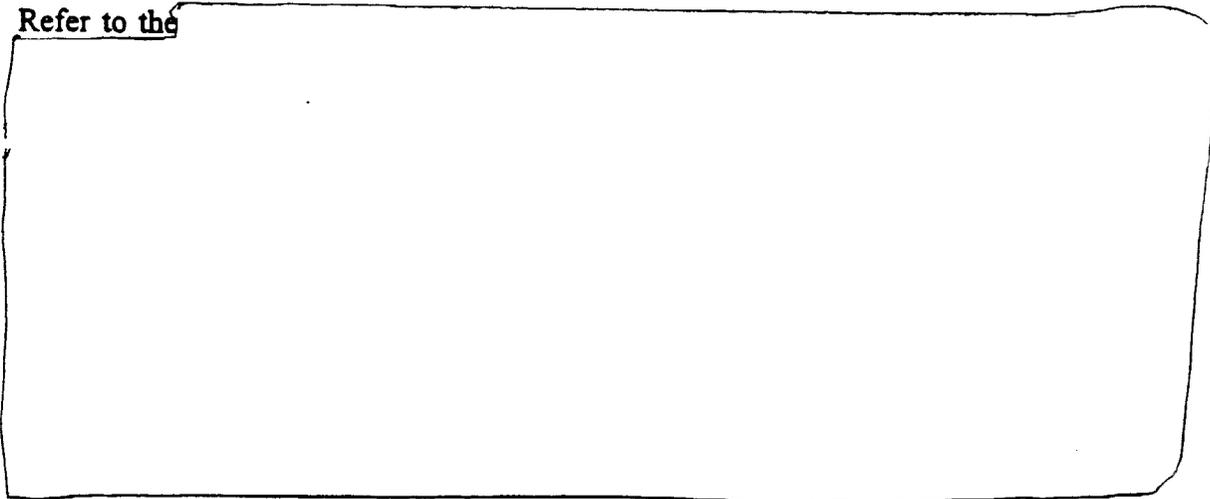
1. Refer to the following statement on page 11 in Volume 1.2. "Periodically, all of the USP/NF tests are performed to verify the information contained in the vendor's certificate of analysis." Please define "periodically".
2. As required by 21 CFR 314.50(d) (1)(ii)(a), please provide a list of equipment that is used in the manufacturing of the drug product.
3. Clarification: Refer to the following statement on page 243 in Volume 1.2. Batch record for lot N5224{

The results of this investigation should be submitted to the N20-990 Annual Report. Also, please forward a desk copy of this investigation to the review chemist, Donald N. Klein, Ph.D.

4. Please provide a batch analysis for the following primary stability batches: N7137B-QC2367; N8023C-QC2367; and N8023D-QC2367. Refer to the table on page 39 in Volume 1.2.
5. Refer to Section 4, Manufacturing Process, in Volume 1.2. Is there [redacted] of the drug product?

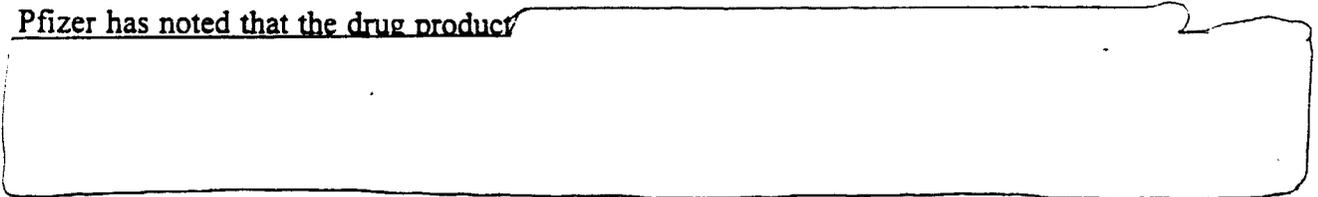
6. Refer to the chromatograms on pages 207 and 208 in Volume 1.2 and the last paragraph on page 65 in Volume 1.2. How are the following [redacted]
7. In establishing the specifications for the drug product, were the response factors of each of the known [redacted] taken into consideration?
8. Refer to the proposed specifications on page 30 in Volume 1.2. According to the Methods and Specification section of the May 1, 1992 FDA's Policy Statement for the Development of New Stereoisomeric Drugs, a [redacted] product should include a identity test and/or a [redacted] assay method. The [redacted] test is one of the Zoloft Tablet specifications. Please add the appropriate test or justify its absence.
9. Refer to the proposed specifications on page 30 in Volume 1.2. According to the Guideline for Submitting Supporting Documentation in Drug Applications for the Manufacture of Drug Products, February 1987, [redacted] should be one of specifications for a drug product that is a solution. Please add the appropriate test or justify its absence.
10. Is the [redacted] in the [redacted]
11. Refer to the [redacted] section of the table on page 40 in Volume 1.2. Are both [redacted]
12. Refer to the footnote page in the November 18, 1998 amendment. Please provide a description of the [redacted]. How is [redacted] defined? Have the different [redacted] been qualitatively defined?
13. Refer to Tables 45 and 46 in the November 18, 1998 amendment. Have you conducted these in-use compatibility studies using the [redacted]?
14. Refer to page 71, Table 45, and Table 46 in Volume 1.2. Also, refer to Tables 45 and 46 in the November 18, 1998 amendment. Which is the correct timepoint in the compatibility studies: 18 days or 14 days? Please revise the tables such that the timepoints are consistent.
15. According to the Stability section of the May 1, 1992 FDA's Policy Statement for the Development of New Stereoisomeric Drugs, a [redacted] product stability protocol should include a [redacted]. Please add the appropriate test or justify its absence.
16. According to the Guideline for Submitting Supporting Documentation for the Stability of Human Drugs and Biologics, February 1987, pH determination should be a stability specification for a drug product that is a solution. Please add the appropriate test or justify its absence.

17. Refer to the

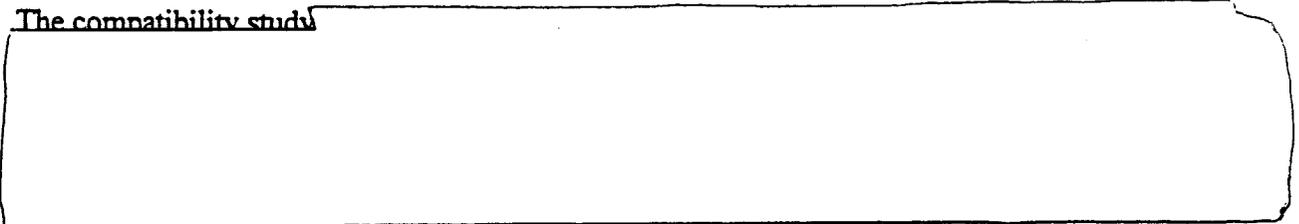


18. Please provide the information as stated in 21 CFR 314.50(d)(1)(ii)(b) for each primary stability batch, the drug product batch used in the bioequivalence studies 050-027 and 050-028, and the drug product batch used in the bioavailability study 050-029.

19. Pfizer has noted that the drug product



20. The compatibility study



LABELING:

1. Refer to the "HOW SUPPLIED" section of the package insert. Since the Zoloft Tablets and the Zoloft Oral Concentrate will have the same package insert, the Zoloft Oral Concentrate storage statement should be the following:

"Store at controlled room temperature, 59° to 86°F(15° to 30°C)"

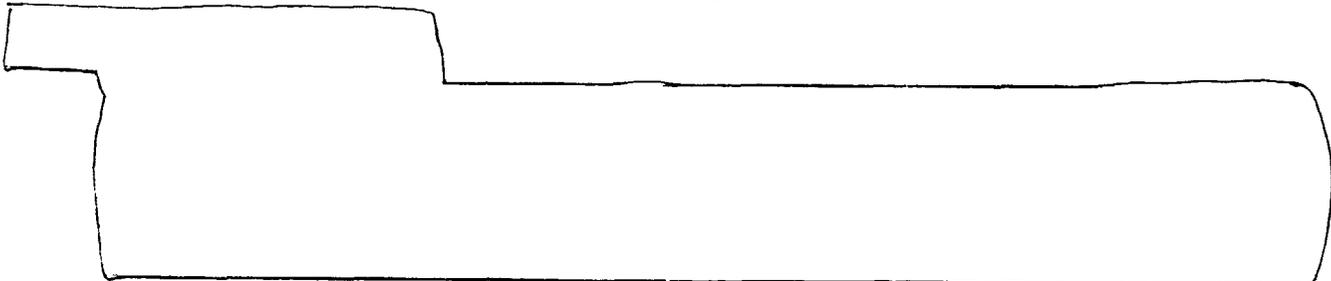
2. The storage statement on the label should be the following:

"Store at controlled room temperature, 59° to 86°F(15° to 30°C)"

3. The following sentence in the "Information for Patients" section of the package insert should

be corrected to the following:

"At times, a slight haze may appear after mixing; this is normal."



We would appreciate your prompt written response so we can continue our evaluation of your NDA.

These comments are being provided to you prior to completion of our review of the application to give you preliminary notice of issues that have been identified. Per the 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 are subject to change as the review of your application is finalized. In addition, we may identify other information that must be provided prior to approval of this application. If you choose to respond to the issues raised in this letter during this review cycle, depending on the timing of your response, as per the user fee reauthorization agreements, we may or may not be able to consider your response prior to taking an action on your application during this review cycle.

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

Sincerely yours,

2/11/95

Robert H. Seevers, Ph.D.
Chemistry Team Leader, Psychiatric Drugs
Division of Neuropharmacological
Drug Products, (HFD-120)
DNDC I, Office of New Drug Chemistry
Center for Drug Evaluation and Research

APPEARS THIS WAY
ON ORIGINAL

David

NDA 20-990

APR 29 1998

Pfizer Pharmaceuticals
Attention: Martha Brumfield, Ph.D.
Drug Regulatory Affairs
235 East 42nd Street
New York, New York 10017-3184

Dear Dr. Brumfield:

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: Zoloft (sertraline hydrochloride) 20 mg/ml Oral Concentrate

Therapeutic Classification: Standard

Date of Application: April 15, 1998

Date of Receipt: April 16, 1998

Our Reference Number: 20-990

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 June 15, 1998 in accordance with 21 CFR 314.101(a).

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

Please cite the NDA number listed above at the top of the first page of any communications concerning this application.

Sincerely yours,



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

David

MEMORANDUM OF TELEPHONE CONVERSATION

NDA#: 20-990
PRODUCT NAME: Zoloft Oral Concentrate
DATE: February 9, 19, and March 2, 11, 12, 1999
CONVERSATION WITH: Ms. Kuskin, Regulatory Affairs; Mr. Mike Ganey, Regulatory Affairs
FIRM NAME: - Pfizer
SUBJECT: NDA 20-990
PHONE#: (212)733-3527

(11:45AM, 2/9/99): Ms. Kuskin called and asked if there were any labeling changes. I told her that I had recommended that labeling be consistent in regards to the storage statement, but my supervisor has yet to comment on my conclusions in my review. I told Ms. Kuskin that if she hasn't heard from me by Friday, 2/12/99, to call me.

(about 4:20, 2/9/99): I called Ms. Kuskin and told her the labeling deficiencies since Dr. SeEVERS has signed off on the CMC review. Paul David will probably be faxing up the deficiencies on 2/10/99. I told Ms. Kuskin that Pfizer can contact me if they have questions about the CMC deficiencies.

(about 4:00PM, 2/19/99): Mr. Mike Ganey, Regulatory Affairs, called me and requested clarification and discussion regarding the following chemistry review #1 deficiencies: 3, 5, 8, 9, 12, 15, 17, 18, 19, and 20. Mr. Ganey stated that Pfizer will be removing the [redacted] on the [redacted]. Also, Pfizer has decided not to use the [redacted]. In response to Mr. Ganey's question, I stated that I would like the responses to all the CMC deficiencies by March 15, 1999. In regards to the following deficiencies I have summarized my discussion with Mr. Ganey.

- a. #17: Mr. Ganey explained that the [redacted] should not be [redacted] and this [redacted] will be removed. Mr. Ganey also explained why the 60mL volume of the drug product will only last for 28 days.
- b. #18: Mr. Ganey requested clarification regarding deficiency #18. In reference to the table on page 246 in Volume 1.2, I told Mr. Ganey that the response should contain identification of each of the components used in the primary stability batches, the drug product batch used in the bioequivalence studies, and the drug product batch used in the bioavailability study. Also, the identification of the container closure components used in the primary stability batches, the bioequivalence batch, and the bioavailability batch. I told Mr. Ganey that it was not necessary to submit any additional actual batch records in the response. Also, I told Mr. Ganey that it wasn't necessary to submit any additional certificate of analyses for components of the above described batches.
- c. #20: Mr. Ganey requested clarification about deficiency #20. I told him that because of the [redacted]

[redacted] Specifically, this was a safety concern to ensure that the drug product's quality is not [redacted] by the [redacted]. I also told him that using [redacted] was acceptable.

(About 4:30PM, 3/2/99): Mr. Mike Ganey called and discussed the situation of the sertraline oral concentrate [redacted] which then [redacted]. I told him that answers the question of the stability of the drug product in [redacted].

(3/11/99 and 3/12/99): I requested from Ms. Kuskin, Pfizer, the revised

(3/12/99): 40 page fax received.

/S/ 3/15/99

Donald N. Klein, Ph.D.
Review Chemist
HFD-120

APPEARS THIS WAY
ON ORIGINAL

cc:
NDA 20-990
HFD-120/Division File
HFD-120/DKlein
HFD-120/PDavid
File: C:\hfd120\N20990\N20990TC#12.doc

APPEARS THIS WAY
ON ORIGINAL

Memorandum to file, NDA 20-990

DATE: November 23, 1998

**From: Donald N. Klein, Ph.D.
Review Chemist, HFD-120**



11/23/98

SUBJECT: Microbiologist Review #1: NDA 20-990, Zoloft® (sertraline hydrochloride) Oral Concentrate.

On 11/20/98 I received the microbiologist review #1 for NDA 20-990, Zoloft® (sertraline hydrochloride) Oral Concentrate. I had submitted this consult on 8/14/98. Brenda Uratani, Ph.D., microbiologist, concluded that this application is approvable pending resolution of the microbiology issues.

cc:
NDA 20-990
HFD-120/Division File
HFD-120/DKlein
HFD-120/PDavid
File: C:\hfd120\20990\micromemo.doc

APPROVED TO MAY
ON ORIGINAL

MEMORANDUM OF TELEPHONE CONVERSATION

NDA#: 20-990
PRODUCT NAME: Zolofit Oral Concentrate
DATE: November 6 & 13, 1998
CONVERSATION WITH: Mr. Mike Ganey, Regulatory Affairs
FIRM NAME: Pfizer
SUBJECT: Stability data to be submitted

Approx. 12:50PM, (11/6/98): Mike Ganey left the following phone message: The updated stability data and the legible copies of the [redacted] for NDA 20-990 will be sent by mid-November. He stated he will call back later today to discuss this upcoming amendment.

11:15-11:22AM, (11/13/98): Mike Ganey called to tell me that the NDA 20-990 amendment containing the stability data should be received by 11/18/98. He briefly discussed some of the data that is in this amendment.

/S/

11/23/98

Donald N. Klein, Ph.D.
Review Chemist
HFD-120

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cc:
NDA 20-990
HFD-120/Division File
HFD-120/DKlein
HFD-120/PDavid
File: C:\hfd120\N20990\N20990TC#10.doc

APPEARS THIS WAY
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MEMORANDUM OF TELEPHONE CONVERSATION

NDA#: 20-990
PRODUCT NAME: Zoloft Oral Concentrate
DATE: November 2 & 3, 1998
CONVERSATION WITH: Ms. Kuskin, Regulatory Affairs
FIRM NAME: Pfizer
SUBJECT: Stability data to be submitted; CMC request
PHONE#: (212)733-3527

11/2/98: On Friday, 10/30/98, Paul David, Project Manager, received a phone message from Ms. Kuskin. She stated that the additional stability data that was to be submitted by the end of October would be delayed. The stability data would be submitted by mid-November 1998. I received this phone message from Mr. David on 11/2/98.

11/3/98: I faxed a request for legible copies of spectra in Volume 1.3. Fax attached.

1:00PM, (11/3/98): Ms. Kuskin's assistant, Christine, called and left the following phone message: The fax was received. Ms. Kuskin's new fax number is (212)573-1563.

15/
Donald N. Klein, Ph.D.
Review Chemist
HFD-120

11/4/98

cc:
NDA 20-990
HFD-120/Division File
HFD-120/DKlein
HFD-120/PDavid
File: C:\hfd120\N20990\N20990TC#9.doc

MEMORANDUM OF TELEPHONE CONVERSATION

NDA#: 20-990
PRODUCT NAME: Zoloft Oral Concentrate
DATE: July 22 & 23, 1998
CONVERSATION WITH: Ms. Kuskin, Regulatory Affairs
FIRM NAME: Pfizer
SUBJECT: Request for the Pre-Approval Inspection Document
PHONE#: (212)733-3527
FAX#: (212)883-4856

5:22PM-5:24PM, (7/22/98): I called Ms. Kuskin and left the following phonemail message: I will be faxing a request today and will call tomorrow to discuss this request. Fax attached.

9:31AM-9:37AM, (7/23/98): I called Ms. Kuskin to follow-up on the 7/22/98 fax. I explained to her that the FDA inspector and I had reviewed the Product Development Report (Pre-Approval Inspection Document) during the inspection last week (7/14-7/17/98) of Pfizer's [redacted] site. I told her that if a copy of the Product Development Report is provided that it should be submitted as an amendment to NDA 20-990.

Ms. Kuskin stated that Dr. Taylor (Assistant Director, Analytical Research & Development, Pfizer) was retrieving the information I had requested on 7/21/98 regarding stability testing conducted by [redacted]. Ms. Kuskin would be faxing me this stability testing information next week.

APPEAR THIS WAY

[redacted signature]

Donald N. Klein, Ph.D.
Review Chemist
HFD-120

7/23/98

cc:
NDA 20-990
HFD-120/Division File
HFD-120/DKlein
HFD-120/PDavid
HFR-NE150/JLiubicich
File: C:\hfd120\n20990\n20990TC#6

APPEAR THIS WAY
ON ORIGINAL

MEMORANDUM OF TELEPHONE CONVERSATION

NDA#: 20-990
PRODUCT NAME: Zoloft Oral Concentrate
DATE: July 27, 28, & 29, 1998
CONVERSATION WITH: Ms. Kuskin, Regulatory Affairs
FIRM NAME: Pfizer
SUBJECT: Follow-up to discussions during the week of 7/20/98
PHONE#: (212)733-3527
FAX#: (212)573-1563

10:00AM, (7/27/98): Ms. Kuskin left a phone message: Follow-up to discussions during the week of 7/20/98.

9:35AM-9:45AM, (7/28/98): Ms. Kuskin called to inform me that she would be faxing to me today Pfizer's response to my 7/21/98 request regarding [redacted]. Ms. Kuskin also stated that they would not be providing a copy of the Pre-Approval Inspection Document (Product Development Report) to me. I told Ms. Kuskin that in the course of my review of the NDA if I have follow-up questions related to the Product Development Report information that I had read I will refer to the Product Development Report accordingly.

7/28/98 and 7/29/98: I received the attached fax from Pfizer on 7/28/98. On 7/29/98 I received a copy [redacted] of the 7/28/98 fax by Fed-Ex. Pfizer states that they will be submitting this response as an amendment to the NDA.

[redacted] /S/ 7/30/98
Donald N. Klein, Ph.D.
Review Chemist
HFD-120

APPEARS THIS WAY
ON ORIGINAL

CC:
NDA 20-990
HFD-120/Division File
HFD-120/DKlein
HFD-120/PDavid
HFR-NE150/JLiubicich
File: C:\hfd120\n20990\n20990TC#7

14. Patent Certification

14. PATENT CERTIFICATION

Pfizer certifies that patent numbers 4,536,518 (expires December 30, 2005) 4,962,128 (expires November 2, 2009) and 5,248,699 (expires August 13, 2012), which are listed in section 13 of this application, claim, respectively, the drug sertraline, a method of treating anxiety related disorders using sertraline, and a crystalline polymorphic form of sertraline hydrochloride, and that sertraline is the subject of this application for approval under section 505 of the Federal Food, Drug, and Cosmetic Act.

APPEARS THIS WAY
ON ORIGINAL

EXCLUSIVITY SUMMARY for NDA # 20-990 SUPPL # _____

Trade Name Zoloft Generic Name sertraline HCL 20 mg/ml oral concentrate

Applicant Name Pfizer Pharmaceuticals HFD-120
Approval Date _____

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete Parts II and III of this Exclusivity Summary only if you answer "YES" to one or more of the following questions about the submission.

a) Is it an original NDA? YES /X/ NO /___/

b) Is it an effectiveness supplement? YES /___/ NO /X/

If yes, what type(SE1, SE2, etc.)? _____

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "NO.")

YES /___/ NO /X/

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

Bioavailability study to establish bioequivalence between the oral concentrate to the approved immediate release tablet formulation.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

d) Did the applicant request exclusivity?

YES /X/ NO /___/

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

THREE YEARS

e) Has pediatric exclusivity been granted for this Active Moiety?

YES /___/ NO /X/

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule previously been approved by FDA for the same use?

YES /___/ NO /X/

If yes, NDA # _____ Drug Name _____

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

3. Is this drug product or indication a DESI upgrade?

YES /___/ NO /X/

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES
(Answer either #1 or #2, as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES /X/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA # 19-839 Zoloft (sertraline HCL) Immediate Release 25, 50, and 100 mg Tablets

NDA # _____

NDA # _____

2. Combination product.

If the product contains more than one active moiety (as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES /___/ NO /X/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA # _____

NDA # _____

NDA # _____

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9. IF "YES," GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2, was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES /_X_/ NO /___/

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would

have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

For the purposes of this section, studies comparing two products with the same ingredient(s) are considered to be bioavailability studies.

- (a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES /___/ NO /X___/

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval **AND GO DIRECTLY TO SIGNATURE BLOCK ON Page 9:**

Efficacy has already been established using the immediate release formulation. This NDA is a vehicle to solely obtain a liquid formulation on the market place.

- (b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES /___/ NO /___/

- (1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES /___/ NO /___/

If yes, explain: _____

- (2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES /___/ NO /_X_/

If yes, explain: _____

© If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Investigation #1, Study # _____

Investigation #2, Study # _____

Investigation #3, Study # _____

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES /___/ NO /___/

Investigation #2 YES /___/ NO /___/

Investigation #3 YES /___/ NO /___/

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

NDA # _____ Study # _____
NDA # _____ Study # _____
NDA # _____ Study # _____

b) For each investigation identified as "essential to the approval," does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES /___/ NO /___/
Investigation #2 YES /___/ NO /___/
Investigation #3 YES /___/ NO /___/

If you have answered "yes" for one or more investigations, identify the NDA in which a similar investigation was relied on:

NDA # _____ Study # _____
NDA # _____ Study # _____
NDA # _____ Study # _____

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

Investigation #_, Study # _____
Investigation #_, Study # _____
Investigation #__, Study # _____

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND,

was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1
IND # _____ YES /___/ ! NO /___/ Explain: _____

Investigation #2
IND # _____ YES /___/ ! NO /___/ Explain: _____

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?
N/A

Investigation #1
YES /___/ Explain _____ ! NO /___/ Explain _____

Investigation #2
YES /___/ Explain _____ ! NO /___/ Explain _____

Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be

credited with having "conducted or sponsored" the study?
(Purchased studies may not be used as the basis for exclusivity.
However, if all rights to the drug are purchased (not just
studies on the drug), the applicant may be considered to have
sponsored or conducted the studies sponsored or conducted by its
predecessor in interest.)

YES /___/ NO /___/

If yes, explain: _____

/S/ _____

Signature of preparer
Title: Project Manager

3-19-99
Date

Signature of Division Director

Date

cc:
Archival NDA 20-990
HFD-120/Division File
HFD-120/PDavid
HFD-92/Mary Ann Holovac

APPROVED
BY: _____

Form OGD-011347
Revised 8/7/95; edited 8/8/95; revised 8/25/98

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ON ORIGINAL

