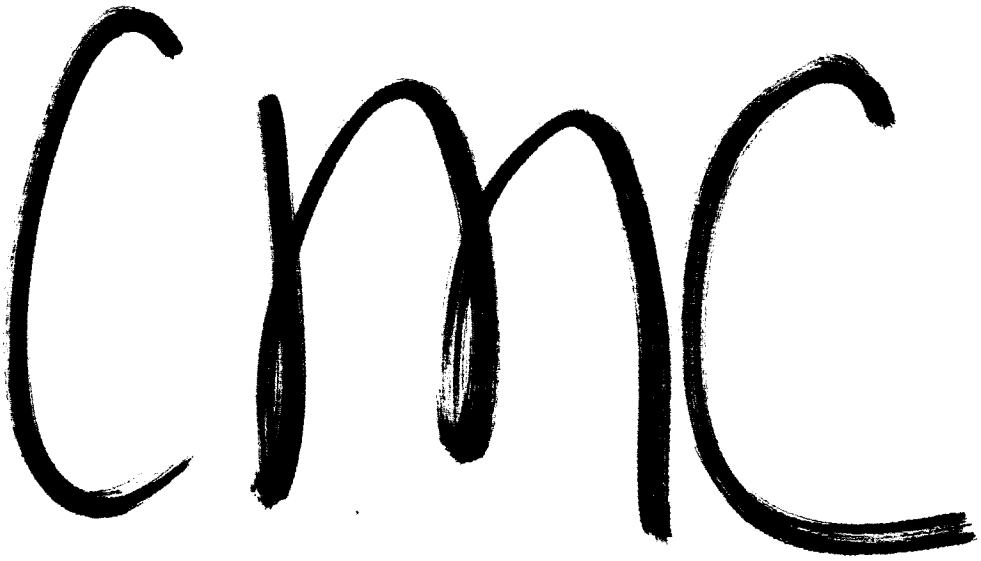

CMC

David

FEB 9 1999

DIVISION OF NEUROPHARMACOLOGICAL DRUG PRODUCTS, HFD-120
REVIEW OF CHEMISTRY, MANUFACTURING, AND CONTROLS

NDA 20-990 **CHEM REVIEW: #1** **REVIEW DATE:** 2/8/99

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
ORIGINAL	4/15/98	4/16/98	4/24/98
N(C) Amendment	8/13/98	8/14/98	8/18/98
N(BC)C Amendment	8/13/98	8/14/98	8/18/98
N(BC) Amendment	8/13/98	8/14/98	8/18/98
N(BC) Amendment	10/21/98	10/22/98	10/28/98
N(BC) Amendment	11/18/98	11/19/98	11/23/98

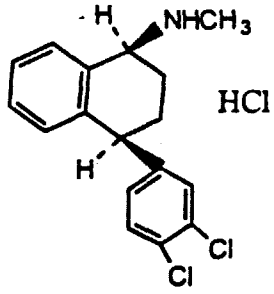
NAME AND ADDRESS OF APPLICANT
Pfizer Inc.
235 East 42nd Street
New York, New York 10017

DRUG PRODUCT NAME
Proprietary: Zoloft®
Non proprietary/USAN: sertraline hydrochloride
Code Name/Number: None provided
Chem. Type/Ther. Class: 3S

PHARMACOLOGICAL CATEGORY/INDICATION:
DOSAGE FORM: Concentrate
STRENGTH: 20mg/mL of sertraline hydrochloride
ROUTE OF ADMINISTRATION: Oral
DISPENSED: x RX ___OTC

SPECIAL PRODUCTS: _Yes x No

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA
CA Name: 1-naphthalenamine,4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-*N*-methyl-,hydrochloride,(1S-*cis*)-
USAN Name: sertraline hydrochloride
Chemical Formula: $C_{17}H_{17}NCl_2 \cdot HCl$
Molecular Weight: 342.70
CAS Registry Number: CAS-79559-97-0



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the requested microbiology specification.

OTHER REQUESTS:

Establishment Evaluation Request

[redacted]

Methods Validation	Pending	The following test methods will be submitted to the FDA laboratories after the review issues are resolved: E11.2; S146.0; I2.482; and S146.2.

RELATED REVIEWS

Clinical Pharmacology and Biopharmaceutics	Final review: 12/30/98; The pivotal BE study failed to demonstrate bioequivalence between the oral sertraline solution and the marketed sertraline tablet. Statistical analysis indicated that the oral solution did not pass the bioequivalence cruteria for Cmax. The clinical significance of the slightly increased Cmax observed following the oral solution compared to that following the tablet will be determined by the medical officer.

REMARKS/COMMENTS:

1. Refer to the respective CMC sections for the evaluation. The following CMC sections of the submission are acceptable: Drug Substance; Drug Product: components/composition; manufacturer; in-process controls & tests: Investigational Formulations; Environmental Assessment; Establishment Inspection. The S146.2 analytical method was found unacceptable. Refer to the deficiency in Section 6. Once the deficiency has been adequately addressed, I will review the S146.2 validation data and conclude if the **Individual Unspecified Degradants and Total Unspecified Degradants** proposed specifications are acceptable.
2. On 7/14/98 – 7/17/98 I accompanied the [redacted]
3. It should be noted that in the 11/18/98 amendment, Pfizer reduced the proposed expiration date from 36

months to 24 months. On 2/5/99 Pfizer confirmed the proposed 24 month expiration dating period with me.

4. On 2/5/99 I rechecked the EES system for the current status of the four establishment sites. All four sites are **acceptable**.
5. The stability data submitted to support the use of the following diluents demonstrates that the drug product's strength and purity are not compromised: tap water; refrigerated tap water; orange juice; ginger ale; lemon-lime soda; and lemonade. The pH range that the drug product was exposed was 2.5 through 7.2. On page 63 in Volume 1.2, Pfizer states that the drug substance is stable to acidic and basic challenge conditions. However, the drug product concentrate wasn't exposed to either acidic or basic degradation studies. I believe that Pfizer should have surveyed the different types of the following diluents to understand the range of pH that the drug product would be exposed at the time of adminstration: orange juice; ginger ale; lemon-lime soda; and lemonade. I also believe that Pfizer should have conducted acidic or basic degradation studies on the drug product concentrate. Because Pfizer has not conducted acidic and basic degradation studies on the drug product and not submitted a survey of the four different diluents, the use of either orange juice, ginger ale, lemon-lime soda, or lemonade is not acceptable. In addition, because Pfizer has not conducted both an acidic and basic degradation study on the drug product, the use of water as a diluent is not acceptable.
6. Pfizer has noted that the drug product degrades when in contact with stainless steel. The Agency is concerned about this degradation because some patients will use stainless steel spoons to stir the drug product with the diluent. One of the stability deficiencies states that Pfizer must demonstrate that the drug product's identity, strength, quality, and purity are not compromised by this interaction.

CONCLUSIONS & RECOMMENDATIONS: Approvable, see the draft deficiency letter.

1. Based on the 24 month 25°C/60%RH primary stability data submitted, the proposed 24 month expiration period is acceptable. This applies to the drug product in the modified bottle with the child resistant closure. However, Pfizer must demonstrate that the dropper assembly is compatible with the Zoloft® Oral Concentrate for at least 96 days.

/S/ 2/8/99

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

APPEARS THIS WAY
ON ORIGINAL

/S/ 2/8/99

Robert Seevers, Ph.D.
Chemistry Team Leader, HFD-120

cc:
Orig. NDA 20-990
HFD-120/Division File
HFD-810/CHoiberg
HFD-810/JSimmons
HFD-120/DKlein
HFD-120/RSeevers
HFD-120/AMosholder
HFR-NE150/JLiubicich
HFD-120/PDavid
File: C:\hfd120\N20990\N20990Review

APPEARS THIS WAY
ON ORIGINAL

DIVISION OF NEUROPHARMACOLOGICAL DRUG PRODUCTS, HFD-120
REVIEW OF CHEMISTRY, MANUFACTURING, AND CONTROLS

NDA 20-990 **CHEM REVIEW: #2** **REVIEW DATE:** 3/18/99

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
ORIGINAL	4/15/98	4/16/98	4/24/98
N(C) Amendment	8/13/98	8/14/98	8/18/98
N(BC)C Amendment	8/13/98	8/14/98	8/18/98
N(BC) Amendment	8/13/98	8/14/98	8/18/98
N(BC) Amendment	10/21/98	10/22/98	10/28/98
N(BC) Amendment	11/18/98	11/19/98	11/23/98
N(BZ) Amendment	3/8/99	3/9/99	3/11/99
N(BC) Amendment	3/12/99	3/15/98	3/17/99

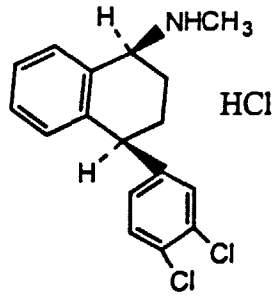
NAME AND ADDRESS OF APPLICANT
Pfizer Inc.
235 East 42nd Street
New York, New York 10017

DRUG PRODUCT NAME
Proprietary: Zoloft®
Non proprietary/USAN: sertraline hydrochloride
Code Name/Number: None provided
Chem. Type/Ther. Class: 3S

PHARMACOLOGICAL CATEGORY/INDICATION:
DOSAGE FORM: Concentrate
STRENGTH: 20mg/mL of sertraline hydrochloride
ROUTE OP ADMINISTRATION: Oral
DISPENSED: x RX ___OTC

SPECIAL PRODUCTS: _Yes x No

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA
CA Name: 1-naphthalenamine,4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-*N*-methyl-,hydrochloride,(1S-*cis*)-
USAN Name: sertraline hydrochloride
Chemical Formula: $C_{17}H_{17}NCl_2 \cdot HCl$
Molecular Weight: 342.70
CAS Registry Number: CAS-79559-97-0



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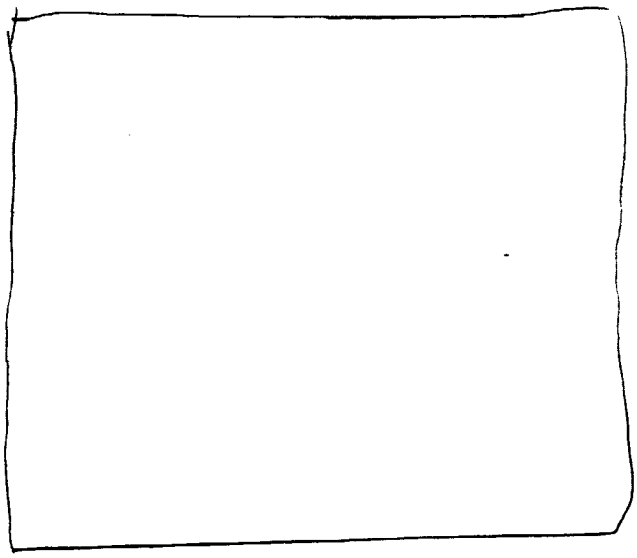
CONSULTS:

Microbiology		Submitted on 8/14/98 by Don Klein; The micro. consult was completed on 11/19/98 by Dr. Uratani. One deficiency faxed to Pfizer on 12/4/98. Dr. Uratani stated that N20-990 is approvable pending the resolution of the microbiological issues. On 2/5/99 Pfizer informed me that they will be adding the requested microbiology specification. On 3/12/99 I faxed Pfizer's micro. response to Dr. Uratani. On 3/16/99 Dr. Uratani recommended approval for the issue concerning micro.

OTHER REQUESTS:

Establishment Evaluation Request		
Methods Validation	Pending	The following test methods will be submitted to the FDA laboratories after the review issues are resolved: E11.2; S146.0; I2.482; S146.2; and S32.631.

RELATED REVIEWS

Clinical Pharmacology and Biopharmaceutics	Final review: 12/30/98; The pivotal BE study failed to demonstrate bioequivalence between the oral sertraline solution and the marketed sertraline tablet. Statistical analysis indicated that the oral solution did not pass the bioequivalence criteria for Cmax. The clinical significance of the slightly increased Cmax observed following the oral solution compared to that following the tablet will be determined by the medical officer.
Clinical	1. This NDA may be approved from a clinical standpoint.

The differences in pharmacokinetic parameters between the concentrate and the tablet formulations, while beyond the limits for bioequivalence, are not likely to have a clinical impact. **2.** The labeling should state that the alcohol content is 12% not only under Dosage and Administration, but also under Description and How Supplied. **3.** The labeling should indicate that Antabuse is contraindicated with Zoloft concentrate. This should be under Contraindications and also under Dosage and Administration.

REMARKS/COMMENTS:

1. I have evaluated Pfizer's responses to the CMC deficiencies from CMC review #1 and information requested on 1/28/99
2. In the 3/8/99 amendment, Pfizer confirmed that the drug product expiration date is 24 months. A copy of the revised stability protocol is attached to this review. The microbial limits and testing have been added.
3. In the 3/12/99 amendment, Pfizer stated that they will not be using the
4. In regards to the revised package insert and labeling, Pfizer has adequately addressed the three CMC deficiencies from chemistry review # 1.

CONCLUSIONS & RECOMMENDATIONS: Recommend Approvable

/S/ 3/18/99

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

/S/ 3/17/99

Robert Seevers, Ph.D.
Chemistry Team Leader, HFD-120

DIVISION OF NEUROPHARMACOLOGICAL DRUG PRODUCTS, HFD-120
REVIEW OF CHEMISTRY, MANUFACTURING, AND CONTROLS

NDA 20-990 **CHEM REVIEW:** #3 **REVIEW DATE:** 11/8/99

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
ORIGINAL	4/15/98	4/16/98	4/24/98
N(C) Amendment	8/13/98	8/14/98	8/18/98
N(BC)C Amendment	8/13/98	8/14/98	8/18/98
N(BC) Amendment	8/13/98	8/14/98	8/18/98
N(BC) Amendment	10/21/98	10/22/98	10/28/98
N(BC) Amendment	11/18/98	11/19/98	11/23/98
N(BZ) Amendment	3/8/99	3/9/99	3/11/99
N(BC) Amendment	3/12/99	3/15/98	3/17/99
N(AZ) Amendment	6/4/99	6/7/99	6/9/99
N(BC) Amendment	10/28/99	10/29/99	11/1/99

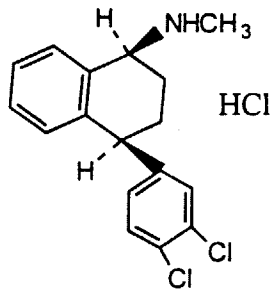
NAME AND ADDRESS OF APPLICANT
Pfizer Inc.
235 East 42nd Street
New York, New York 10017

DRUG PRODUCT NAME
Proprietary: Zoloft®
Non proprietary/USAN: sertraline hydrochloride
Code Name/Number: None provided
Chem. Type/Ther. Class: 3S

PHARMACOLOGICAL CATEGORY/INDICATION:
DOSAGE FORM: Concentrate
STRENGTH: 20mg/mL of sertraline hydrochloride
ROUTE OP ADMINISTRATION: Oral
DISPENSED: x RX ___OTC

SPECIAL PRODUCTS: _Yes x No

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA
CA Name: 1-naphthalenamine,4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-*N*-methyl-,hydrochloride,(1S-*cis*)-
USAN Name: sertraline hydrochloride
Chemical Formula: $C_{17}H_{17}NCl_2 \cdot HCl$
Molecular Weight: 342.70
CAS Registry Number: CAS-79559-97-0



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RELATED REVIEWS

Clinical Pharmacology and Biopharmaceutics	Final review: 12/30/98; The pivotal BE study failed to demonstrate bioequivalence between the oral sertraline solution and the marketed sertraline tablet. Statistical analysis indicated that the oral solution did not pass the bioequivalence criteria for Cmax The clinical significance of the slightly increased Cmax observed following the oral solution compared to that following the tablet will be determined by the medical officer.
Clinical	**1.** This NDA may be approved from a clinical standpoint. The differences in pharmacokinetic parameters between the concentrate and the tablet formulations, while beyond the limits for bioequivalence, are not likely to have a clinical impact. **2.** The labeling should state that the alcohol content is 12% not only under Dosage and Administration, but also under Description and How Supplied. **3.** The labeling should indicate that Antabuse is contraindicated with Zoloft concentrate. This should be under Contraindications and also under Dosage and Administration.

REMARKS/COMMENTS:

1. I have evaluated Pfizer's responses to the CMC deficiencies from CMC review #2.
2. The following changes were made to the drug product specifications as compared to the original 4/15/99 submission:
   a. Microbial Limit Tests
   b. Enantiomeric Identity
3. I have updated the container closure system information in Table 4.
4. The for the drug product is **acceptable**. The method is adequately described in the 3/12/99 amendment.
5.

CONCLUSIONS & RECOMMENDATIONS: Recommend Approval for the CMC section of this submission.

/S/ 11/8/99
Donald N. Klein, Ph.D.
Reviewing Chemist, HFD-120

/S/ 11/10/99
Robert Seevers, Ph.D.
Chemistry Team Leader, HFD-120

MICRO

REVIEW FOR HFD-120
OFFICE OF NEW DRUG CHEMISTRY
MICROBIOLOGY STAFF HFD-805

Microbiologist's Review #1 of NDA 20-990
November 18, 1998

A. 1. APPLICATION NUMBER: 20-990

APPLICANT: Pfizer Pharmaceuticals
235 East 42nd Street
New York, NY 10017-5755

2. PRODUCT NAMES: Zoloft (sertraline hydrochloride) Oral Concentrate

3. DOSAGE FORM AND ROUTE OF ADMINISTRATION: 20 mg/ml of sertraline. It is packaged in a 60 ml amber glass bottle (60 ml fill volume) with an accompanying calibrated dropper. The drug product is diluted with approximately 120 ml of diluent (water, gingerale, lemon/lime soda or orange juice) prior to oral administration.

4. METHOD(S) OF STERILIZATION:

5. PHARMACOLOGICAL CATEGORY: Zoloft is indicated for treatment of depression.

B. 1. DATE OF INITIAL SUBMISSION: April 15, 1998

2. AMENDMENT: none

3. RELATED DOCUMENTS:

4. ASSIGNED FOR REVIEW: August 17, 1998

5. DATE OF CONSULT REQUEST: August 14, 1998

C. REMARKS:

Zoloft was originally approved in December of 1991 for the treatment of depression. The original approval covered a tablet formulation. This submission requests approval of a new formulation of sertraline, the oral liquid concentrate.

D. CONCLUSIONS:

The application is approvable pending resolution of microbiology issues.

/S/ 11/18/98

Brenda Uratani, Ph.D.
Review Microbiologist

/S/ 11/19/98

cc:

NDA 20-990
HFD-120/ Div. File
HFD-805/ Uratani
HFD-120/Klein
drafted by: Brenda Uratani, 11/18/98
R/D initialed by P. Cooney, 11/18/98