

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**19-839/S-044**

**20-990/S-010**

**ADMINISTRATIVE and CORRESPONDENCE  
DOCUMENTS**

**EXCLUSIVITY SUMMARY for NDA # 19-839/SE5-044 & 20-990/SE5-010**  
**Trade Name Zoloft tablets (19-839) and oral concentrate (20-990)**

**Generic Name (sertraline hydrochloride)**

**Applicant Name Pfizer HFD-120**  
**Approval Date 9-16-03**

**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 /    / NO / X /

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

If yes, what type (SE1, SE2, etc.)? SE5

This supplement provides for controlled clinical data in pediatric patients with major depressive disorder (MDD) treated with Zoloft. The results from Pfizer's two studies, Protocols A0501001 and A0501017, failed to individually demonstrate the efficacy of Zoloft in pediatric patients with MDD. However, based upon our review of the safety data, we requested revisions in the labeling regarding pediatric growth velocity. This labeling was eventually negotiated with Pfizer, and the approval letter provides for labeling changes to reflect the additional safety information in the pediatric population.

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.

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/\_\_\_ \_/

The applicant requested pediatric exclusivity.

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

6 months

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

YES /X\_\_\_/ NO /\_\_\_ \_/

Pediatric exclusivity was granted, based upon this submission, on 2-1-02.

**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? (Rx to OTC Switches should be answered No - Please indicate as such).

YES /X\_\_\_/ NO /\_\_\_ \_/

If yes, NDA # 19-839\_ Drug Name Zoloft

**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 /\_\_\_ \_/

**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 /\_\_\_/ NO /\_\_\_/

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

NDA #

NDA #

NDA #

2. Combination product. N/A

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 /\_\_\_/

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 /\_\_\_/ 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 /\_\_\_/

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:**

\_\_\_\_\_  
\_\_\_\_\_

(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 /\_\_\_/

If yes, explain: \_\_\_\_\_  
\_\_\_\_\_

(c) 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



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

(c) 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: \_\_\_\_\_

\_\_\_\_\_  
Signature of Preparer  
Title: Regulatory Project Manager

\_\_\_\_\_  
Date

\_\_\_\_\_  
Signature of Office of Division Director  
Title: Division Director

\_\_\_\_\_  
Date

cc:  
Archival NDA 19-839/S-044  
20-990/S-010  
HFD-120/Division File  
HFD-120/P.David  
HFD-093/Mary Ann Holovac  
HFD-104/PEDS/T.Crescenzi

Form OGD-011347  
Revised 8/7/95; edited 8/8/95; revised 8/25/98, edited 3/6/00

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/s/

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Russell Katz  
10/16/03 03:47:57 PM

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# PEDIATRIC EXCLUSIVITY DETERMINATION CHECKLIST

## PART I - TO BE COMPLETED BY THE REVIEWING DIVISION.

Date of Written Request from FDA 4/28/99. Application Written Request was made to: NDA/IND#19-839  
 Timeframe Noted in Written Request for Submission of Studies 4/28/02  
 NDA# 19-839/SE5-044 & 20-990/SE5-010  
 Sponsor Pfizer Pharmaceuticals  
 Generic Name: sertraline hydrochloride Trade Name Zoloft  
 Strength 25 mg, 50 mg, & 100 mg tablets (NDA 19-839) & 20 mg/ml oral concentrate (NDA 20-990) Date of Submission of Reports of Studies 12/14/01.  
 Pediatric Exclusivity Determination Due Date (60 or 90 days from date of submission of studies) 3/17/02.

Was a formal Written Request made for the pediatric studies submitted?	Y <u>X</u>	N <u>  </u>
Were the studies submitted after the Written Request?	Y <u>X</u>	N <u>  </u>
Were the reports submitted as a supplement, amendment to an NDA, or NDA?	Y <u>X</u>	N <u>  </u>
Was the timeframe noted in the Written Request for submission of studies met?	Y <u>X</u>	N <u>  </u>
If there was a written agreement, were the studies conducted according to the written agreement?  OR If there was no written agreement, were the studies conducted in accord with good scientific principles?	Y <u>X</u>	N <u>  </u>
Did the studies fairly respond to the Written Request?	Y <u>X</u>	N <u>  </u>

SIGNED  DATE 1/30/02  
 (Reviewing Medical Officer)

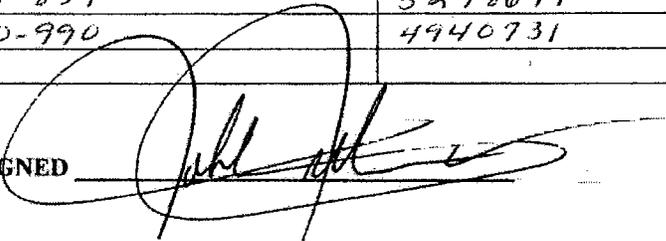
Do not enter in DES - FORWARD TO PEDIATRIC EXCLUSIVITY BOARD. HED-960.

## PART II - TO BE COMPLETED BY THE PEDIATRIC EXCLUSIVITY BOARD

Pediatric Exclusivity                       **Granted**                       **Denied**

Existing Patent or Exclusivity Protection:

NDA/Product #	Eligible Patents/Exclusivity	Current Expiration Date
19-839	I 279	7-DEC-2002
19-839, 20-990	M-11	6-AUG-2004
19-839, 20-990	4536518	30-DEC-2005
19-839	4962122	2-NOV-2009
19-839	5242699	13-AUG-2012
20-990	4940731	30-AUG-2009

SIGNED  DATE 2/1/02

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/s/

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Terrie Crescenzi  
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**REGULATORY PROJECT MANAGER  
LABELING REVIEW**

Date: September 12, 2003  
NDA: 19-839 (Tablets) & 20-990 (Oral Concentrate)  
DRUG: Zoloft (sertraline HCl) Tablets and Oral Concentrate  
Sponsor: Pfizer  
Indication: MDD/OCD/PD/PTSD/PMDD/SAD  
Supplements:

<b>NDA</b>	<b>Supplement</b>	<b>Dated</b>	<b>Action</b>
19-839	SE1-045	1-18-02	AP letter dated 2-7-03
20-990	SE1-011	1-18-02	AP letter dated 2-7-03
19-839	SE5-044	12-14-01	Open
20-990	SE5-010	12-14-01	Open

**Review:**

1. The last approved supplemental labeling applications, 19-839/SE1-045 & 20-990/SE1-011, providing for the new indication of social anxiety disorder were approved in an Agency letter dated 2-7-03. The approved labeling was attached to the 2-7-03 letter.
2. I secured labeling agreement with Pfizer on the pending supplements, 19-839/SE5-044 & 20-990/SE5-010, providing for additional safety data in the pediatric population in an electronic communication dated September 12, 2003 (see attached).
3. I compared the last approved labeling to the labeling which will be attached to the approval letter for the pediatric applications, and the only differences between these 2 labeling were the changes noted (using MS Word track changes) in the labeling.

**CONCLUSIONS**

- The labeling which will be attached to the final action letter on these open pediatric supplements is identical to the last approved labeling except where changes are noted in the labeling.

*{See appended electronic signature page}*

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Paul David. RPh  
Senior Regulatory Project Manager

Attachment

## MEMORANDUM

DATE: June 18, 2003

FROM: Director  
Division of Neuropharmacological Drug Products/HFD-120

TO: File, NDA 19-839/SE5-044 & NDA 20-990/SE5-010

SUBJECT: Action Memo for NDA 19-839/SE5-044 & NDA 20-990/SE5-010, Zolof (sertraline hydrochloride) Tablets and Oral Concentrate, respectively, for use in Pediatric Major Depressive Disorder (MDD)

NDA 19-839/SE5-044 & NDA 20-990/SE5-010, Zolof (sertraline hydrochloride) Tablets and Oral Concentrate, respectively, for use in Pediatric Major Depressive Disorder (MDD), were submitted by Pfizer Inc. on 12/14/01. This application was the subject of a Not Approvable letter dated 9/30/02, because the two controlled trials failed to distinguish drug from placebo. However, the letter requested labeling changes based on data generated in the trials. Specifically, the division had proposed that language be included in the Pediatric Use section of labeling describing weight loss associated with sertraline use in the controlled trials.

The sponsor responded to the NA letter in a submission dated 12/19/02. This submission contained analyses of weight data obtained in a 24 week open label extension study, which the sponsor believed documented that the patients achieved normal weight gain with prolonged treatment.

This submission was reviewed by Dr. Roberta Glass, medical reviewer in the division (review dated 4/24/03, signed by Dr. Paul Andreason, Psychiatric Drugs Team Leader, on 5/16/03). On the basis of this review of the weight data in the open label extension (which showed that there were no important differences between the patients randomized to sertraline or placebo in the controlled trial preceding the extension in the percentage of patients who experienced a weight loss of at least 7% of their body weight during the open extension), the review team proposed labeling changes describing the data. Specifically, they proposed a statement that said that there was no consistent pattern of weight change in the subset of patients who were treated in the open extension.

However, subsequent to this proposal, we became aware of data that suggested that, in fact, patients initially randomized to placebo did have a decrease in their weight gain during the open extension compared to patients previously treated with sertraline. Specifically, the sponsor performed an analysis in which they compared the patients' weight percentile at the beginning of the open label to their weight percentile at the end of the extension. The vast majority of patients randomized to placebo in the controlled trial ended the extension treatment in a

lower percentile than the one in which they started the extension phase; the results were the opposite for those patients who were originally randomized to sertraline in the controlled trial. In addition, our view is that it is inappropriate to assess weight changes over 24 weeks with the "7% of body weight loss" metric used in the short-term controlled trial; this is a far too stringent standard by which to judge weight changes in longer term exposure.

We discussed our view of the percentile-based analyses with the sponsor in a conversation on 6/18/03. We expressed the view that the statement about the lack of consistent pattern in weight change in the open label extension implied that there were no important changes on drug, but that the percentile-based analysis implied that for the 24 weeks after switching to sertraline in the previously placebo treated patients, there was a demonstrable weight effect, and that, therefore, the sentence should be removed; further, we discussed the need for additional analyses to address this question. We could not come to an agreement about the interpretation of the weight data in the extension study, and the sponsor strongly felt that the previously described statement should remain in labeling.

Because we could not come to an agreement on final labeling, we agreed that we would issue an Approvable letter, and the sponsor will submit additional analyses addressing the question of weight changes with long-term treatment. We agreed that the sponsor would submit the requested analyses (based on z-scores in relation to standardized norms for weight gain in pediatric patients) within one week of the receipt of the Approvable letter, so that final labeling could be agreed upon as quickly as possible.

#### **ACTION**

I will issue the attached Approvable letter (which includes our request for additional analyses of the long-term weight data), with attached draft labeling.

Russell Katz, M.D.

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/s/

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Russell Katz  
6/19/03 07:19:21 AM  
MEDICAL OFFICER

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NDA 19-839/S-044  
NDA 20-990/S-010

Pfizer Inc.  
Attention: Alan J. Dunbar  
Director, Worldwide Regulatory Strategy  
235 E. 42nd Street  
NY, NY 10017

Dear Mr. Dunbar:

We acknowledge receipt on July 21, 2003, of your July 18, 2003 resubmission to your supplemental new drug applications for Zoloft (sertraline hydrochloride) tablets (NDA 19-839) and oral concentrate (NDA 20-990).

We consider this a complete, class 1 response to our June 19, 2003 action letter. Therefore, the primary user fee goal date is September 21, 2003, and the secondary user fee goal date is January 21, 2004.

If you have any questions, call me at (301) 594-5530.

Sincerely,

*{See appended electronic signature page}*

Paul David, R.Ph.  
Senior Regulatory Project Manager  
Division of Neuropharmacological Drug Products  
Office of Drug Evaluation I  
Center for Drug Evaluation and Research

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**David, Paul A**

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**From:** Dunbar, Alan [Alan.Dunbar@pfizer.com]  
**Sent:** Friday, September 12, 2003 7:34 AM  
**To:** 'David, Paul A'  
**Subject:** RE: Zolofit Pediatric data



mmsinfo.bt

Paul,

We are fine with the wording in this label.

- Alan

-----Original Message-----

**From:** David, Paul A [mailto:DAVID@cder.fda.gov]  
**Sent:** Tuesday, September 09, 2003 7:03 AM  
**To:** 'Dunbar, Alan'  
**Subject:** RE: Zolofit Pediatric data

That's odd. I checked the e-mail that I sent off yesterday, and it contained the attachment. Anyways, I have attached the label to this e-mail. If you do not receive the attachment, let me know.  
-Paul

-----Original Message-----

**From:** Dunbar, Alan [mailto:Alan.Dunbar@pfizer.com]  
**Sent:** Monday, September 08, 2003 3:57 PM  
**To:** 'David, Paul A'  
**Subject:** RE: Zolofit Pediatric data

Paul,

I don't have an e-mail from you with a label. Can you please re-send.

- Alan

"MMS <secure.pfizer.com>" made the following annotations on 09/08/03 15:57:27

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[[INFO] -- Content Manager:  
LEGAL NOTICE:

Unless expressly stated otherwise, this message is confidential and may be privileged. It is intended for the addressee(s) only. Access to this e-mail by anyone else is unauthorized. If you are not an addressee, any disclosure or copying of the contents of this e-mail or any action taken (or not taken) in reliance on it is unauthorized and may be unlawful. If you are not an addressee, please inform the sender immediately.

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\_\_\_\_\_ § 552(b)(5) Deliberative Process

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Paul David  
9/12/03 09:44:21 AM  
CSO

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Within 10 days after the date of this letter, you are required to amend the supplemental application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.120. In the absence of any such action, FDA may proceed to withdraw these supplemental applications. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

Additionally, based upon the safety information reviewed in these supplements, we believe that labeling changes are warranted and, as such, we are requesting that you submit a new labeling supplement. Accompanying this letter (Attachment) is the Agency's requested revisions to the Zoloft labeling. The labeling is based on the last approved labelings for Zoloft (see Agency letters dated May 16, September 18, and September 20, 2002), and includes changes and comments based on your December 14, 2001 labeling proposal. We have used the MS Word "track changes" feature to denote revisions to the labeling, if applicable, and bracketed comments for our reasoning.

We have made some of your proposed changes to labeling with regard to safety, especially in the **Pediatric Use** section. In addition to your proposed changes in this section, we have added specific details of the weight loss observed in the pool of the two MDD studies, since we feel this is important information to include in labeling.

Please submit twenty copies of final printed labeling, ten of which are individually mounted on heavyweight paper or similar material, exactly as specified above as a "**Supplement - Changes Being Effected**" to NDAs 19-839 & 20-990. Incorporate all previous revisions as reflected in the most recently approved package insert. To facilitate review of your submission, provide a highlighted or marked-up copy that shows the changes that are being made.

These supplements should be submitted within 30 days from the date of this letter.

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

Sincerely,

*{See appended electronic signature page}*

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

Attachment

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\_\_\_\_\_ § 552(b)(4) Trade Secret / Confidential

✓ § 552(b)(4) Draft Labeling

\_\_\_\_\_ § 552(b)(5) Deliberative Process

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**MEMORANDUM**

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

**DATE:** September 23, 2002

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

**SUBJECT:** Recommendation for Non-Approval Action for Pediatric Supplement for Zoloft (Sertraline); negative results for Zoloft in the treatment of Major Depressive Disorder (MDD) in pediatric patients

**TO:** File NDA 19-839/S-044 and NDA 20-990/S-010  
[**Note:** This overview should be filed with the 12-14-01 original submission of this supplement.]

**1.0 BACKGROUND**

Sertraline is an SSRI that is approved for the treatment of MDD, OCD, panic disorder, PTSD, and PMDD in adults. It is also approved for the treatment of OCD in pediatric patients. Supplements 044/010 include data from 2 safety and efficacy trials of sertraline in pediatric patients with MDD. This supplement was submitted in support of pediatric labeling for Zoloft in the treatment of MDD. Although the 2 clinical trials failed to individually support the efficacy of sertraline in MDD, the sponsor has proposed pooling the results from the 2 trials. On the basis of this pooling, they feel that the data support a new claim for pediatric MDD.

It should be noted that, at this time, there are no drugs approved for the treatment of pediatric MDD.

It should also be noted that the sponsor had sought pediatric exclusivity for this program under FDAMA, and they were given 6 months of additional exclusivity based on the fact that they conducted the studies required under the Written Request.

Since the proposal was to use the currently approved Zoloft formulations for this expanded population, there was no need for chemistry or pharmacology reviews. The primary review of the clinical efficacy and safety data was done by Andy Mosholder, M.D. from the clinical group. Ohidul Siddiqui, Ph.D., from biometrics, also reviewed the efficacy data. Since pediatric pharmacokinetic data were submitted with the original application for OCD, reviewed at that time, and included in labeling, there

was no requirement to submit PK data in these supplements. Thus, there was no need for a biopharm review.

The original supplements for this expanded indication (S-044/S-010) were submitted 12-14-01. There was no safety update.

We decided not to take this supplement to the Psychopharmacological Drugs Advisory Committee.

## **2.0 CHEMISTRY**

As Zoloft is a marketed product, there were no chemistry issues requiring review for this supplement.

## **3.0 PHARMACOLOGY**

As Zoloft is a marketed product, there were no pharmacology/toxicology issues requiring review for this supplement. We did not include a requirement for juvenile animal data as part of the Written Request. However, we did ask for such studies in a 1-10-01 letter. Pfizer responded to this request in a 1-29-02 letter, essentially arguing that there is no basis for the conduct of such studies, since, in their view, the preclinical and clinical data thus far do not suggest any important effects on growth and development. We have not yet responded to this letter.

## **4.0 BIOPHARMACEUTICS**

As noted, there was no need for a biopharmaceutics review, since pediatric PK data are already included in Zoloft labeling.

## **5.0 CLINICAL DATA**

### **5.1 Efficacy Data**

#### **5.1.1 Summary of Studies 1001 and 1017**

These studies were conducted under an identical protocol. These were 10-week, randomized, double-blind, parallel group, placebo-controlled, flexible dose trials in pediatric outpatients (children, aged 6-11, and adolescents, aged 12-17) with MDD (DSM-IV). Patients were stratified by age group. Sertraline dosing was flexible, in a range of 50 to 200 mg/day, on a qd basis, am or pm. The primary outcome was change from baseline on the total CDRS-R. The primary analysis was ANCOVA, for the ITT population as usually defined. Apparently this plan was not included in the protocol or in any amendments, but rather, for the first time in the study reports.

For study 1001, there were 27 sites (23 US and 4 Indian). The total randomized sample was n=188 (sertraline=97; placebo=91). There were roughly equal proportions of males and females, and children and adolescents, and the patients were predominantly white. The mean sertraline dose at endpoint was 111 mg/day. The ITT samples were n=93 for sertraline and n=88 for placebo. The proportions completing to 10 weeks were as follows: sertraline-67%; placebo-83%. The results on the primary outcome were as follows:

**Efficacy Results on CDRS-R Total Score for Study 1001 (LOCF)**

**Efficacy Results on CDRS-R Total Score for Study 1017 (LOCF)**

**Efficacy Results on CDRS-R Total Score for Pooled Analysis (1001 + 1017:LOCF)**

## 5.2 Safety Data

The pediatric safety data for sertraline in this supplement came from the 2 placebo-controlled studies (1001 and 1017), and also from 3 open studies (R-0246, STL-CDN-94-002, and A0501015). There were a total of 395 patients exposed to sertraline for these studies, in a dose range of 50-200 mg/day, and for durations ranging up to 24 weeks. It should be noted that labeling already partially addresses long-term pediatric safety, on the basis of an earlier supplement. Essentially there were no surprises and no findings suggestive of any unique pattern of risk in this subgroup. However, one finding, i.e., a reduction in weight bears some discussion. The following data, taken from a pool of the 2 placebo-controlled trials, are from Dr. Mosholder's review:

<b>Children</b>	<b>Sertraline (n=84)</b>	<b>Placebo (n=86)</b>
Weight Decrease $\geq$ 7%	7.1%	0
Weight Increase $\geq$ 7%	3.6%	7.0%
Mean change in weight (kg)	-0.17	+0.98 (p=0.001)
<b>Adolescents</b>	<b>Sertraline (n=103)</b>	<b>Placebo (n=94)</b>
Weight Decrease $\geq$ 7%	1.9%	1.1%
Weight Increase $\geq$ 7%	2.9%	4.3%
Mean change in weight (kg)	-0.55	+0.61 (p=0.001)

## 5.3 Clinical Sections of Labeling

The sponsor's proposed labeling for this supplement included additions to several sections, as follows:

-A revised description of the safety findings for sertraline in pediatric patients under Pediatric Use  
-A revised description of safety findings for sertraline in pediatric patients under Other Adverse Events in Pediatric Patients, Adverse Reactions

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However, I agree with Dr. Mosholder that the new findings regarding weight loss with sertraline in pediatric patients should be added to labeling.

## **6.0 WORLD LITERATURE**

The sponsor's literature search discovered 24 publications, none identifying adverse events previously unknown, at least in adults.

## **7.0 FOREIGN REGULATORY ACTIONS**

I am not aware of any foreign regulatory actions regarding the use of sertraline in pediatric patients.

## **8.0 PSYCHOPHARMACOLOGICAL DRUGS ADVISORY COMMITTEE (PDAC) MEETING**

We decided not to take this supplement to the PDAC.

## **9.0 DSI INSPECTIONS**

Two sites for study 1001 were inspected, i.e., Londberg and Quintana. DSI recommended excluding data from the Londberg site, due to protocol violations and findings that were suspect. They also recommended not using data from six patients at the Quintana site, due to missing drug records. As noted, a re-analysis of this study without these patients yielded a convincingly negative p-value.

## **10.0 NON-APPROVAL LETTER**

An non-approval letter acknowledging our decision not to add any information to labeling regarding the use of sertraline in pediatric MDD has been included with the non-approval package.

## **11.0 CONCLUSIONS AND RECOMMENDATIONS**

As I have discussed under section 5.3, it is my view that ~~none~~ of the efficacy results of this negative program for sertraline in pediatric MDD should be noted in labeling. However, I agree with Dr. Mosholder that the weight effects of sertraline in the pediatric population should be added to labeling. Thus, I recommend that we issue the attached nonapproval letter indicating our view that only new safety information should be added to the Zoloft labeling.

cc:

Orig NDA 19-839/S-044 & 20-990/S-010

HFD-120/Division File

HFD-120/TLaughren/RKatz/AMosholder/PDavid

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/s/

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Thomas Laughren  
9/23/02 12:42:34 PM  
MEDICAL OFFICER

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**David, Paul A**

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**From:** David, Paul A  
**Sent:** Friday, May 31, 2002 7:55 AM  
**To:** Graydon Elliott (E-mail)  
**Cc:** David, Paul A  
**Subject:** Zoloft pediatric\_MDD\_efficacy-supplement; 19-839/S-044 & 20-990/S-010

Graydon,  
The reviewing medical officer has the following request in regard to the Zoloft pediatric application:

Pfizer did not provide any analysis of ECG intervals. The submission consisted of a count of the numbers of patients with various ECG abnormalities. In order to complete our review of this application, we are requesting that Pfizer submit the typical kind of analyses conducted for these type of data; i.e., an analysis of mean change from baseline for measured ECG intervals, and a count of the numbers of patients on drug or placebo exceeding potentially clinically significant thresholds. We request that you use the ECG data from the two placebo controlled MDD trials.

If you have any questions, please contact me.

Regards,  
Paul David, R.Ph.  
Senior Regulatory Project Manager  
Division of Neuropharmacological Drug Products, HFD-120  
ODE1; CDER; FDA  
Telephone: 301-594-5530  
Fax: 301-594-2859  
David@cder.fda.gov

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/s/

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Paul David  
5/31/02 07:56:42 AM  
CSO

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Division of Scientific Investigations  
Office of Medical Policy  
Center for Drug Evaluation and Research  
Food and Drug Administration  
Rockville MD 20857

**CLINICAL INSPECTION SUMMARY**

DATE: April 26, 2002

TO: Paul David, R.Ph., Senior Regulatory Project Manager  
Andrew Mosholder, M.D., Medical Officer  
Division of Neuropharmacological Drug Products, HFD-120

THROUGH: Antoine El-Hage, Ph.D., Chief  
Good Clinical Practice Branch II, HFD-47  
Division of Scientific Investigations

FROM: Ni A. Khin, M.D., Medical Officer  
Good Clinical Practice Branch II, HFD-47  
Division of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections

NDA: NDA 19-839/SE5-044  
NDA 20-990/SE5-010

APPLICANT: Pfizer, Inc.

DRUG: Zoloft (sertraline hydrochloride) Tablets and Oral Concentrate

THERAPEUTIC CLASSIFICATION: Type S, Standard Review

INDICATION: Treatment of Pediatric Major Depressive Disorder (MDD)

CONSULTATION REQUEST DATE: February 5, 2002

ACTION GOAL DATE: July 17, 2002

**I. BACKGROUND:**

Sertraline hydrochloride is a selective serotonin reuptake inhibitor, which is currently marketed under the brand name of Zoloft for the treatment of major depressive disorder (MDD), obsessive compulsive disorder, panic disorder and post traumatic stress disorder. In this supplemental NDA, the sponsor has requested the use of Zoloft in MDD in pediatric population.

Inspection assignments were issued on February 21, 2002 for two domestic sites, Drs. Peter Londborg and Humberto Quintana, for Protocol 0501001. The purpose of these assignments was

to validate data in support of pending NDA 19-839 NDA 19-839/SE5-044 and NDA 20-990/SE5-010 using Zoloft oral tablets and liquid concentrate for long term treatment of major depressive disorder in pediatric population.

## II. RESULTS (by site):

NAME	CITY	STATE	ASSIGNED DATE	RECEIVED DATE	CLASSIFICATION
Londborg	Seattle	WA	02-21-2002	03-25-2002	VAI*
Quintana	New Orleans	LA	02-21-2002	04-01-2002	VAI*

\* Final classification pending; the letters to the investigators are currently with Office of General Counsel (GC) for review.

### Londborg

At this clinical site, 16 subjects were screened for protocol A0501001 using flexible dose of sertraline for treatment of MDD in children and adolescents. Fourteen (14) subjects were randomized into the double blind phase of the study to receive either sertraline or placebo. Of the 14 subjects, 11 subjects completed the protocol. The reason for discontinuation was listed as relocate out of state for one subject and lost to follow up for 3 subjects.

An audit of 11 records was conducted. Inspection revealed identical CDRS for baseline and end of study rating scores in 17 out of 25 interviews in 14 subjects conducted. Dr. Londborg did not follow study protocol in that he conducted joint interviews with subjects and their parents for Children's Depression Rating Scale (CDRS-R), which is contrary to protocol recommended separate interviews. This joint interview may have led to identical CDRS-R scores between the subject's and parents' ratings in 17 of 25 visits, which may have skewed the study outcome. In addition, Dr. Londborg did not document his reason(s) for conducting joint interviews nor notified and obtained concurrence from the sponsor.

### Quintana

At this clinical site, 30 subjects were screened for protocol A0501001. Eighteen (18) subjects were randomized into the double blind phase of the study to receive either sertraline or placebo. Fourteen of 18 subjects completed the protocol and 4 subjects were discontinued. The reason for discontinuation was listed as withdrawal of consent for one subject and lost to follow up for 3 subjects.

An audit of 18 records was conducted. Inspection revealed missing drug inventory record for one subject (2058/—); and inadequate drug accountability records for 11 subjects. Of these 11 subjects, 6 subjects records showed minor discrepancies (1-8 tablets); and 5 subjects had discrepancies (10-100 tablets) with inconsistent drug inventory/dosing records in that total amount of drugs returned/dosed could not be determined. (Note: 2060/—: 100 tablets; 2127/—: 40 tablets; 2059/—: 20 tablets; 2146/— and 2147/—: 10 tablets).

HFD-45/Program Management Staff (electronic copy)  
HFD-47/c/r/s  
HFD-47/EI-Hage  
HFD-47/Khin  
HFD-47/Friend  
HFD-45/RF

rd: NK 04/09/02; 04/25/02  
reviewed: AEH 04/26/02

*O:\NK\_CIS\NDA19839SE504 pedsMDD CIS.DOC*

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/s/

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Michele Balser

5/1/02 03:58:02 PM

TECHNICAL

Original Clinical Inspection Summary was signed by Dr. Khin  
on 4/26/02.

Ni Aye Khin

5/1/02 04:21:15 PM

MEDICAL OFFICER

Original clinical inspection summary was through Dr. El-Hage and  
initialed on 4/26/02.

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From: Gerald Fetterly, Ph.D.

To: DOCUMENT ROOM (LOG-IN and LOG-OUT)  
Please log-in this consult and review action for the  
specified IND submission

DATE: <b>4/9/02</b>	IND No.: Serial No.:	NDA No. <b>19-839 (SE5-044)</b> <b>20-990 (SE5-010)</b>	DATE OF DOCUMENT <b>12/14/01</b>	TREATMENT <b>Major Depressive Disorder</b>
NAME OF DRUG <b>Sertraline (Zoloft®) 25, 50, and 100 mg Tablets and 20 mg/ml Oral Concentrate</b>		PRIORITY CONSIDERATION <b>Standard</b>	Date of Formal Consult: <b>1/31/02</b> Filing Date: <b>2/15/02</b>	

NAME OF THE SPONSOR: Pfizer, Inc.

**TYPE OF SUBMISSION**

**CLINICAL PHARMACOLOGY/BIOPHARMACEUTICS RELATED ISSUE**

- |  |  |   |
|--|--|---|
| <input type="checkbox"/> PRE-IND                 | <input type="checkbox"/> DISSOLUTION/IN-VITRO RELEASE                                  | <input type="checkbox"/> FINAL PRINTED LABELING   |
| <input type="checkbox"/> ANIMAL to HUMAN SCALING | <input type="checkbox"/> BIOAVAILABILITY STUDIES                                       | <input type="checkbox"/> LABELING REVISION  |
| <input type="checkbox"/> IN-VITRO METABOLISM     | <input type="checkbox"/> IN-VIVO WAIVER REQUEST  | <input type="checkbox"/> CORRESPONDENCE   |
| <input type="checkbox"/> PROTOCOL                | <input type="checkbox"/> SUPAC RELATED   | <input type="checkbox"/> DRUG ADVERTISING   |
| <input type="checkbox"/> PHASE II PROTOCOL       | <input type="checkbox"/> CMC RELATED   | <input type="checkbox"/> ADVERSE REACTION REPORT  |
| <input type="checkbox"/> PHASE III PROTOCOL      | <input type="checkbox"/> PROGRESS REPORT   | <input type="checkbox"/> ANNUAL REPORTS   |
| <input type="checkbox"/> DOSING REGIMEN CONSULT  | <input type="checkbox"/> SCIENTIFIC INVESTIGATIONS                                     | <input type="checkbox"/> FAX SUBMISSION   |
| <input type="checkbox"/> PK/PD- POPPK ISSUES     | <input type="checkbox"/> MEETING PACKAGE (EOP2/Pre-<br>NDA/CMC/Pharmacometrics/Others) | <input checked="" type="checkbox"/> OTHER (SPECIFY BELOW):<br>Pediatric Written Request |
| <input type="checkbox"/> PHASE IV RELATED        |  |   |

**REVIEW ACTION**

- |   |   |  |
|---|---|--|
| <input checked="" type="checkbox"/> NAI (No action indicated)   | <input type="checkbox"/> Oral communication with<br>Name: [     ]   | <input type="checkbox"/> Formal Review/Memo (attached) |
| <input type="checkbox"/> E-mail comments to:  | <input type="checkbox"/> Comments communicated in<br>meeting/Telecon. see meeting minutes dated:<br>[     ] | <input type="checkbox"/> See comments below            |
| <input type="checkbox"/> Medical <input type="checkbox"/> Chemist <input type="checkbox"/> Pharm-Tox <input type="checkbox"/><br>Micro <input type="checkbox"/> Pharmacometrics <input type="checkbox"/> Others (Check<br>as appropriate and attach e-mail) |   | <input type="checkbox"/> See submission cover letter   |
|   |   | <input type="checkbox"/> OTHER (SPECIFY BELOW):        |

**REVIEW COMMENT(S)**

- NEED TO BE COMMUNICATED TO THE SPONSOR       HAVE BEEN COMMUNICATED TO THE SPONSOR

**COMMENTS/SPECIAL INSTRUCTIONS:**

This submission consists of a pediatric efficacy supplement for the treatment of children and adolescents (age range 6-17 years) with major depressive disorder. As a result of a written request to the sponsor (dated 4/28/99) to conduct pediatric studies with Zoloft in the treatment of major depressive disorder (MDD), the sponsor has submitted a supplemental NDA on 12/14/01. On 8/10/99, the Division acknowledged that the sponsor previously obtained safety and pharmacokinetic data through the development plan in pediatric obsessive-compulsive disorder (OCD). Thus, no further efforts in gathering pediatric pharmacokinetic or safety data are required and the written request letter was appropriately modified to delete the pharmacokinetics study request. Therefore, this supplemental NDA does not need to be reviewed by OCPB at this time.

SIGNATURE OF REVIEWER: \_\_\_\_\_

Date \_\_\_\_\_

SIGNATURE OF TEAM LEADER: \_\_\_\_\_

Date \_\_\_\_\_

C.: NDA 19-839 (SE5-044)/20-990 (SE5-010); HFD-120 (David);  
TL: R. Uppoor; DD: M. Mehta, Central Document Room (Clin.  
Pharm./Biopharm. Files)

Project Manager: \_\_\_\_\_ Date \_\_\_\_\_

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/s/

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Gerald Fetterly  
4/9/02 06:03:21 PM  
BIOPHARMACEUTICS

Ramana S. Uppoor  
4/9/02 06:08:20 PM  
BIOPHARMACEUTICS

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# REQUEST FOR CONSULTATION

TO (Division/Office):

Nancy Szes, HFD-357

FROM:

Don Klein, HFD-120

DATE

1/24/02

IND. NO.

NDA NO.

N18839/N2990

TYPE OF DOCUMENT

SES

DATE OF DOCUMENT

12/24/01

NAME OF DRUG

300mg Tablets  
300mg O/R, Citalopram

PRIORITY CONSIDERATION

CLASSIFICATION OF DRUG

Antidepressant

DESIRED COMPLETION DATE

Strength: 6/15/02

NAME OF FIRM:

Pfizer

## REASON FOR REQUEST

### I. GENERAL

- NEW PROTOCOL
- PROGRESS REPORT
- NEW CORRESPONDENCE
- DRUG ADVERTISING
- ADVERSE REACTION REPORT
- MANUFACTURING CHANGE/ADDITION
- MEETING PLANNED BY

- PRE-NDA MEETING
- END OF PHASE II MEETING
- RESUBMISSION
- SAFETY/EFFICACY
- PAPER NDA
- CONTROL SUPPLEMENT

- RESPONSE TO DEFICIENCY LETTER
- FINAL PRINTED LABELING
- LABELING REVISION
- ORIGINAL NEW CORRESPONDENCE
- FORMULATIVE REVIEW
- OTHER (SPECIFY BELOW):

### II. BIOMETRICS

#### STATISTICAL EVALUATION BRANCH

- TYPE A OR B NDA REVIEW
- END OF PHASE II MEETING
- CONTROLLED STUDIES
- PROTOCOL REVIEW
- OTHER (SPECIFY BELOW):

#### STATISTICAL APPLICATION BRANCH

- CHEMISTRY REVIEW
- PHARMACOLOGY
- BIOPHARMACEUTICS
- OTHER (SPECIFY BELOW):

### III. BIOPHARMACEUTICS

- DISSOLUTION
- BIOAVAILABILITY STUDIES
- PHASE IV STUDIES

- DEFICIENCY LETTER RESPONSE
- PROTOCOL-BIOPHARMACEUTICS
- IN-VIVO WAIVER REQUEST

### IV. DRUG EXPERIENCE

- PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- CASE REPORTS OF SPECIFIC REACTIONS (List below)
- COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP

- REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- SUMMARY OF ADVERSE EXPERIENCE
- POISON RICK ANALYSIS

### V. SCIENTIFIC INVESTIGATIONS

CLINICAL

PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS:

Enclosed Assess.

Citalopram  
acceptable  
Nancy Szes 1/24/02

SIGNATURE OF REQUESTER

Don M. Klein

METHOD OF DELIVERY (Check one)

MAIL

HAND

SIGNATURE OF RECEIVER

SIGNATURE OF DELIVERER

Received 2/1/02  
DK

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/s/

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Nancy Sager  
4/12/02 02:53:49 PM

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**David, Paul A**

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**From:** David, Paul A  
**Sent:** Wednesday, March 20, 2002 9:04 AM  
**To:** Andrew Clair (E-mail)  
**Cc:** David, Paul A  
**Subject:** Zoloft Pediatric Supplement

Andy,

The reviewing medical officer has the following question in regard to the Zoloft pediatric supplement:

Study 1015, the ongoing open label study that is a follow up to the double blind protocols, enrolled 226 subjects as of the cutoff date for the supplement. How many of those subjects received placebo in their double blind trial, and thus were newly exposed to Zoloft in study 1015? Pfizer should know this now that the blind has been broken.

If you have any questions, please give me a call.

Regards,  
Paul David, R.Ph.  
Senior Regulatory Project Manager  
Division of Neuropharmacological Drug Products, HFD-120  
ODE1; CDER; FDA  
Telephone: 301-594-5530  
Fax: 301-594-2859  
David@cder.fda.gov

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/s/

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Paul David  
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Food and Drug Administration  
Rockville MD 20857

NDA 19-839/S-044  
NDA 20-990/S-010

**PRIOR APPROVAL SUPPLEMENT**

Pfizer Pharmaceuticals  
Attention: Graydon Elliott  
Drug Regulatory Affairs  
235 East 42nd Street  
New York, NY 10017-3184

Dear Mr. Elliott:

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

Name of Drug Product: Zoloft (sertraline hydrochloride) tablets (19-839) and oral concentrate (20-990)

Date of Supplements: December 14, 2001

Date of Receipt: December 17, 2001

These supplements propose the use of Zoloft to treat children and adolescents with major depressive disorder.

Unless we notify you within 60 days of our receipt date that the applications are not sufficiently complete to permit a substantive review, these applications will be filed under section 505(b) of the Act on February 15, 2002 in accordance with 21 CFR 314.101(a). If the applications are filed, the primary user fee goal date will be October 17, 2002 and the secondary user fee goal date will be December 17, 2002.

Please cite the application numbers listed above at the top of the first page of any communications concerning these applications. All communications concerning these supplemental applications should be addressed as follows:

U.S. Postal Service:

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

Courier/Overnight Mail:

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

NDA's 19-839/S-044 & 20-990/S-010

Page 2

If you have any questions, call me at (301) 594-5530.

Sincerely,

*{See appended electronic signature page}*

Paul David, R.Ph.  
Senior Regulatory Project Manager  
Division of Neuropharmacological Drug Products  
Office of Drug Evaluation I  
Center for Drug Evaluation and Research

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/s/

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Paul David  
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NDAs 19-839 and 20-990

Pfizer Pharmaceuticals  
Attention: Alan J. Dunbar  
Director, Worldwide Regulatory Strategy  
235 East 42nd Street  
New York, NY 10017-3184

Dear Mr. Dunbar:

Please refer to your new drug applications submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Zoloft (sertraline hydrochloride) 25 mg, 50 mg, and 100 mg tablets (19-839) and 20 mg/ml oral concentrate (20-990).

We additionally refer to an Agency letter dated May 2, 2001, in which we drew your attention to a publication concerning an association between selective serotonin reuptake inhibitor (SSRI) use and upper gastrointestinal bleeding<sup>1</sup>.

Subsequent to our Agency letter dated May 2, 2001, we have requested, in Agency letters dated September 14, 2001, and July 2, 2002, that you explore your safety database for bleeding related adverse events (BRAE). We appreciate your willingness in cooperating with the Agency to further explore this important adverse event.

During the process of reviewing the BRAE issue across the SSRI class, we have noted the recent publication of a retrospective cohort study evaluating the association between inhibition of serotonin reuptake by antidepressants and upper gastrointestinal bleeding<sup>2</sup>. We believe that this study replicates the findings of the de Abajo study and, as such, we are requesting revisions to your labeling in order to incorporate these new findings. Specifically, we are requesting the following revisions to product labeling.

1. ✓

1 de Abajo FJ, Rodriguez LAG, and Montero D. Association between selective serotonin reuptake inhibitors and upper gastrointestinal bleeding: population based case-control study. *BMJ* 1999;319:1106-9

2 Dalton SO, Johansen C, Mellekjaer L, et al. Use of Selective Serotonin Reuptake Inhibitors and risk of upper gastrointestinal bleeding: a population-based cohort study. *Archives of Internal Medicine* 2003; 163: 59-64.

2. Under **PRECAUTIONS-Drug Interactions**, the following new subsection should be added:

**PRECAUTIONS-Drug Interactions-**

3. Under **PRECAUTIONS-Information for Patients**, the following statement should be added:

Please submit twenty copies of final printed labeling, ten of which are individually mounted on heavyweight paper or similar material, exactly as specified above as a "**Supplement - Changes Being Effectuated**". Incorporate all previous revisions as reflected in the most recently approved package insert. To facilitate review of your submission, provide a highlighted or marked-up copy that shows the changes that are being made.

These supplements should be submitted within 30 days from the date of this letter.

Additionally, please note that the Agency is in the process of reviewing all of the bleeding related adverse event data submitted by you as well as the other SSRI sponsors. Based upon our review of these data, further revisions to your labeling may be required.

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

Sincerely,

*{See appended electronic signature page}*

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

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NDA 19-839  
NDA 20-990

Pfizer Pharmaceuticals  
Attention: Andrea Garrity  
Director, Regulatory Affairs  
235 East 42nd Street  
New York, NY 10017-3184

Dear Ms. Garrity:

Please refer to your new drug applications submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Zoloft (sertraline hydrochloride) tablets (19-839) and oral concentrate (20-990).

Reference is also made to an Agency letter dated April 28, 1999, providing for a pediatric Written Request.

We additionally refer to a Federal Register Notice (63 FR 66632) dated December 2, 1998 entitled, "Final Rule: Regulations Requiring Manufacturers to Assess the Safety and Effectiveness of New Drugs and Biological Products in Pediatric Patients".

As stated in our letter dated April 28, 1999, we do not believe that efficacy and safety in the pediatric population can be extrapolated from adult clinical data. Therefore, we had previously requested clinical studies to assess safety, efficacy, and dosing in the pediatric population.

However, we believe that your pediatric assessment, i.e., the data set adequate to characterize the safety and effectiveness of Zoloft for depression and OCD in the pediatric populations, should also include the results of juvenile animal studies.

As part of the Agency's pediatric initiative, we believe that additional studies in young animals will be needed to support a complete pediatric assessment. Since there are no standard protocols in this area, we suggest that you design a study that would address drug effects in animals of an age range which is analogous to that of the proposed patient population. In addition to the usual toxicological parameters, such a study would presumably evaluate effects on growth and neurological, behavioral, and reproductive development.

Once the juvenile animal studies are completed, these data may be submitted to the Agency for review in the form of a "prior approval" supplemental application to be included into product labeling.

Please note, however, that the inclusion of juvenile animal studies to complete your pediatric assessment is not a requirement of our Written Request letter dated April 28, 1999.

NDA 19-839 & 20-990  
Page 2

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

Sincerely,

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

/s/

-----  
Russell Katz

1/10/01 03:26:31 PM

DAVID



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service  
Food and Drug Administration  
Rockville MD 20857

NDA 19-839

FEB 28 2000

Pfizer Pharmaceuticals  
Attention: Andrew G. Clair, Ph.D.  
Director, Drug Regulatory Affairs  
235 East 42nd Street  
New York, New York 10017-3184

Dear Dr. Clair:

Please refer to your New Drug Application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Zoloft (sertraline hydrochloride) tablets.

We additionally refer to an Agency pediatric Written Request letter dated April 28, 1999, and to Agency letters dated May 18, and August 10, 1999, commenting on your pediatric drug development program.

We acknowledge receipt of your submission dated October 7, 1999, providing for proposed changes in the Written Request for pediatric studies.

We have reviewed your proposed changes and are amending the below listed sections of the Written Request. All other terms stated in our Written request issued on April 28, 1999, remain the same.

**• Age Group in Which Study(ies) will be Performed – All Studies**

We are amending this section to provide for the minimum age for the two efficacy studies to be extended from seven to six years old.

**• Types of Studies, Study Design, Number of Patients to be Studied or Power of Study to be Achieved, Study Endpoints, Statistical Information, and Study Evaluations**

All references to conducting or analyzing separate pharmacokinetic or safety studies are removed. We concur with your assertion that this information has been previously submitted when Zoloft was approved for OCD in the pediatric and adolescent population.

All of your other proposed changes to the Written request including 1) employing a flexible dose design in your placebo controlled studies and 2) indicating the CDRS-R as the primary outcome measurement have not been accepted and are not terms of the Written Request.

Reports of the studies that meet the terms of the Written Request dated April 28, 1999, as amended by this letter must be submitted to the Agency on or before April 28, 2002 to possibly qualify for a pediatric exclusivity extension under section 505A of the Federal Food, Drug, and Cosmetic Act.

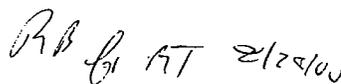
Reports of the studies should be submitted as a supplement to your approved NDA with the proposed labeling changes you believe would be warranted based on the data derived from these studies. When submitting the reports, please clearly mark your submission "**SUBMISSION OF PEDIATRIC STUDY REPORTS – PEDIATRIC EXCLUSIVITY DETERMINATION REQUESTED**" in large font, bolded type at the beginning of the cover letter of the submission and include a copy of this letter. Please also send a copy of the cover letter of your submission, via fax (301-594-0183) or messenger to the Director, Office of Generic Drugs, HFD-600, Metro Park North II, 7500 Standish Place, Rockville, MD 20855-2773.

If you wish to discuss any amendments to this Written Request, please submit proposed changes and the reasons for the proposed changes to your application. Submissions of proposed changes to this request should be clearly marked "**PROPOSED CHANGES IN WRITTEN REQUEST FOR PEDIATRIC STUDIES**" in large font, bolded type at the beginning of the cover letter of the submission. You will be notified in writing if any changes to this Written Request are agreed upon by the Agency.

We hope you will fulfill this pediatric study request. We look forward to working with you on this matter in order to develop additional pediatric information that may produce health benefits to the pediatric population.

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

Sincerely yours,



Robert Temple, M.D.  
Director  
Office of Drug Evaluation I  
Center for Drug Evaluation and Research

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NDA 19-839

Page 3

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Archival NDA 19-839

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HFD-100/R Temple

HFD-120/P David

HFD-120/R Katz/T Laughren/A Mosholder/R Glass

HFD-600/Office of Generic Drugs

HFD-2/MLumpkin

HFD-104/DMurphy

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PEDIATRIC WRITTEN REQUEST LETTER  
INFORMATION REQUEST (IR)

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*Dr. David*

NDA 19-839

AUG 10 1999

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

Dear Dr. Brumfield:

Please refer to your New Drug Application for Zoloft (sertraline hydrochloride) tablets.

Reference is made to an Agency pediatric written request letter dated April 28, 1999.

We acknowledge receipt of your submission dated June 18, 1999, proposing changes in the written request for pediatric studies.

We have reviewed your proposed changes, and we are willing to amend the age group in order to extend the minimum age for children from seven to six years old.

In regard to the other issues outlined in your June 18, 1999 correspondence, we have the following comments:

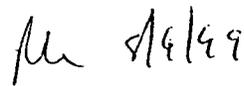
1. You have proposed two 10-week placebo controlled flexible dose studies, rather than employing a fixed dose design as recommended in our April 28, 1999 letter. This study design, although not optimal, is acceptable.
2. We do not believe that you have made a convincing case to remove the requirement to stratify randomization by age group.
3. You have proposed that after one year of attempting to enroll patients in the study, if recruitment is slow, the requirement for the second study should be lifted. While we appreciate the difficulty of recruiting patients, the requirement for two studies is a scientific judgement independent of the ease of obtaining a sample.
4. We note that you intend to use the Children's Depression Rating Scale (CDRS-R) as the primary rating scale. This is acceptable.
5. Since Pfizer has previously accrued safety and pharmacokinetic data from your development plan in pediatric OCD, we concur that no further efforts in gathering pediatric pharmacokinetic or safety data are required beyond what would be ordinarily incorporated in the two double blind depression efficacy trials. Therefore, our request for

pharmacokinetic data, as listed in the April 28, 1999 Written Request letter, would be removed from the Written Request.

If you are satisfied with the changes to the Written Request that the Agency would allow, please submit a formal request, outlining the agreed upon changes, to your NDA. This request should be clearly marked "**PROPOSED CHANGES IN WRITTEN REQUEST FOR PEDIATRIC STUDIES**" in large font, bolded type at the beginning of the cover letter of the submission.

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

Sincerely yours,

Handwritten signature of Russell Katz, dated 4/9/99.

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

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Archival NDA 19-839

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rev:08/02/99am; 08/04/99pd;08/04/99tl

ft:08/09/99pd

INFORMATION REQUEST (IR)

*8-9-99*  
*AM 8/9/99*  
*7/2 8-9-99*

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APR 28 1999

NDA 19-839

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

Three Years from  
The Date of This Letter APR 28 2002

Dear Dr. Brumfield:

Reference is made to your Proposed Pediatric Study Request submitted on August 31, 1998 to your Investigational New Drug (IND) application for Zoloft (sertraline hydrochloride) tablets (IND 18,004).

We have completed our review of your submission and concluded that your proposed pediatric study request is incomplete.

To obtain needed pediatric information on sertraline, the Food and Drug Administration (FDA) is hereby making a formal Written Request, pursuant to Section 505A of the Federal Food, Drug, and Cosmetic Act (the Act), that you submit information from the trials in pediatric patients with depression described below.

**Background Comments on Pediatric Depression**

Under current regulations [21 CFR 201.57(f)(9)(iv)], a new claim in a pediatric population could be established by extrapolating the effectiveness results of adequate and well controlled studies in adults for the same entity if it were believed that depression was essentially the same disease in adults and children. Under FDAMA (1997), a claim might be based on a single study in pediatric patients along with confirmatory evidence from another source, perhaps adult data for that disorder, an approach considered in the draft guidance document entitled "Guidance for Industry - Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products". This approach too requires some degree of belief that the course of the disease and the effects of the drug are sufficiently similar in the pediatric and adult populations to make data from the adult efficacy studies pertinent to pediatric patients. Unfortunately, in our view there is little reason to assume continuity between adult and pediatric depression and our concern about the extrapolability of adult depression data to pediatric depression is more than theoretical. While we, of course, acknowledge the one published positive report of fluoxetine in pediatric depression (Emslie, et al, 1997), we are concerned about the preponderance of negative studies of antidepressants in pediatric populations. We recognize that all of these negative studies utilized tricyclic antidepressants, and that, in addition, there are other possible explanations for the negative outcomes, e.g., sample size, entry criteria, outcome measures, etc. Nevertheless, these negative trials (at least 12 in number) lead to a substantial concern about the ability to extrapolate positive antidepressant findings from adult to pediatric patients. Consequently, we

believe that a pediatric depression claim for any antidepressant already approved in adult depression would need to be supported by two independent, adequate and well controlled clinical trials in pediatric depression. In addition, a pediatric depression program would need to include pharmacokinetic information and safety information in the relevant pediatric age groups. For pediatric depression, we consider the relevant age groups to include children (ages 7 through 11) and adolescents (ages 12 through 17).

### **Specific Study Requirements for Development Program in Pediatric Depression**

#### **Types of Studies**

Pediatric Efficacy and Safety Studies

Pediatric Pharmacokinetic Study

Pediatric Safety Study

#### **Objective/Rationale**

The overall goal of the development program is to establish the safety and efficacy of the study drug in the treatment of pediatric depression, and to develop other information, e.g., pharmacokinetic, pertinent to using the drug in the pediatric population.

#### **Study Design**

Pediatric Efficacy and Safety Studies

- For the controlled efficacy studies, conduct two randomized, double-blind, parallel group, placebo-controlled acute treatment trial, with a recommended duration of at least 6 to 8 weeks. We recommend that at least one of the two studies should be a fixed dose study including two or more fixed doses of the study drug. You may consider dosing patients on the basis of patient weight. Randomization must be stratified by the two age groups studied. Ideally, a relapse prevention trial would follow from the acute treatment trials, involving the randomization of responders from the acute treatment trials to continuation on either study drug or placebo, with follow-up observation for relapse for a period of 6 months or more. Please note that a relapse prevention trial is not required under this written request.

Pediatric Pharmacokinetic Study

- A pharmacokinetic study to provide information pertinent to dosing of the study drug in the relevant pediatric population. These data could come from traditional pharmacokinetic studies, or alternatively, from population kinetic approaches applied to controlled efficacy trials or to other safety trials. You should be aware that a guidance document on population pharmacokinetic studies is available under [[www.fda.gov/cder/guidance/1852fnl.pdf](http://www.fda.gov/cder/guidance/1852fnl.pdf)].

Pediatric Safety Study

- Safety data should be collected in the controlled efficacy trials. Longer-term safety data should be generated in longer-term open extensions from these trials and/or in separate longer-term open safety studies.

**Age Group in Which Study(ies) will be Performed – All Studies**

Both children (ages 7 to 11) and adolescents (ages 12 to 17) should be equally represented in the samples, and there should be a reasonable distribution of both sexes in these strata.

**Number of Patients to be Studied or Power of Study to be Achieved****Pediatric Efficacy and Safety Studies**

- While it is difficult to specify the sample size needed to show a difference between drug and placebo in this population, it should be noted that, in the only published positive antidepressant trial in pediatric depression (Emslie, et al, 1997), there were 48 patients in each of the two treatment arms.

**Pediatric Pharmacokinetic Study**

- A sufficient number of subjects to adequately characterize the pharmacokinetics in the above age groups.

**Pediatric Safety Study**

- A sufficient number of pediatric patients to adequately characterize the safety of sertraline at clinically effective doses for a sufficient duration.

**Entry Criteria**

The protocols should include a valid and reliable diagnostic method for recruiting children and adolescents with major depressive disorder.

**Study Endpoints****Pediatric Efficacy and Safety Studies**

- It is essential to identify a single primary outcome for the controlled efficacy trials, and ordinarily this should be change from baseline to endpoint on whatever symptom rating scale you have chosen for your trials.

**Pediatric Pharmacokinetic Study**

- Pharmacokinetic measurements as appropriate.

**Pediatric Safety Study**

- Appropriately frequent standard measures of safety (clinical - including signs and symptoms and laboratory).

**Statistical Information****Pediatric Efficacy and Safety Studies**

- These trials should have a detailed statistical plan. Ordinarily these trials should be designed with at least 80% statistical power to detect a treatment effect of conventional ( $p=0.05$ ) statistical significance.

**Pediatric Pharmacokinetic Study**

- Descriptive analysis of the pharmacokinetic parameters.

#### Pediatric Safety Study

- Descriptive analysis of the safety data.

#### Study Evaluations

##### Pediatric Efficacy and Safety Studies

- A scale specific to pediatric depression and sensitive to the effects of drug treatment of pediatric depression, e.g., the Children's Depression Rating Scale—Revised, and a global measure, e.g., the Clinical Global Impression (CGI).

##### Pediatric Pharmacokinetic Study

- The pharmacokinetic assessments should be made with respect to the study drug and any metabolites that make substantial contributions to its efficacy and/or toxicity. For the parent and each metabolite followed, the data collected should provide estimates of the pharmacokinetic parameters including AUC, half-life,  $C_{max}$ ,  $t_{max}$ , and apparent oral clearance in pediatric subjects in the relevant age range. You should be aware that a draft guidance document on pediatric pharmacokinetic studies is available under [[www.fda.gov/cder/guidance/index.htm](http://www.fda.gov/cder/guidance/index.htm), under Clinical/Pharmacological (Draft)].

##### Pediatric Safety Study

- Routine safety assessments should include vital signs, weight, clinical laboratory, ECGs, and monitoring for adverse events. Although not a part of this Written Request, we remind you that it may be important to determine the effect of the study drug on the growth and development of pediatric patients, and we encourage you to consider longer-term studies of a year or more to address this question if the acute studies demonstrate antidepressant activity.

#### Drug Information

Use age appropriate formulations in the studies described above. Since the pediatric patient population consists of both children (ages 7 to 11) and adolescents (ages 12 to 17), your marketed solid dosage formulation should be adequate for these studies.

#### Drug Concerns

No specific concerns related to administration to pediatric patients were identified while studying sertraline in adults, nor have specific concerns been identified during the postmarketing experience.

#### Labeling That May Result from the Studies

Results found in the pediatric depression population efficacy, safety, and pharmacokinetic studies could result in the addition to labeling of information pertinent to these studies.

#### Format of Reports to be Submitted

Full study reports or analyses, not previously submitted to the Agency, addressing the issues outlined in this request, with full analysis, assessment, and interpretation.

**Timeframe for Submitting Reports of the Study(ies)**

Reports of the above studies must be submitted to the Agency within 3 years from the date of this letter to be eligible to qualify for pediatric exclusivity extension under Section 505A of the Act. Please remember that pediatric exclusivity extends only existing patent protection or exclusivity that has not expired at the time you submit your reports of studies in response to this Written Request.

Please submit protocols for the above studies to an investigational new drug application (IND) and clearly mark your submission "**PEDIATRIC PROTOCOL SUBMITTED FOR PEDIATRIC EXCLUSIVITY STUDY**" in large font, bolded type at the beginning of the cover letter of the submission. We recommend you seek a written agreement with FDA before developing pediatric studies. Please notify us as soon as possible if you wish to enter into a written agreement by submitting a proposed written agreement. Clearly mark your submission "**PROPOSED WRITTEN AGREEMENT FOR PEDIATRIC STUDIES**" in large font, bolded type at the beginning of the cover letter of the submission.

Reports of the studies should be submitted as a supplement to your approved NDA with the proposed labeling changes you believe would be warranted based on the data derived from these studies. When submitting the reports, please clearly mark your submission "**SUBMISSION OF PEDIATRIC STUDY REPORTS – PEDIATRIC EXCLUSIVITY DETERMINATION REQUESTED**" in large font, bolded type at the beginning of the cover letter of the submission and include a copy of this letter. Please also send a copy of the cover letter of your submission, via fax (301-594-0183) or messenger to the Director, Office of Generic Drugs, HFD-600, Metro Park North II, 7500 Standish Place, Rockville, MD 20855-2773.

If you wish to discuss any amendments to this Written Request, please submit proposed changes and the reasons for the proposed changes to your application. Submissions of proposed changes to this request should be clearly marked "**PROPOSED CHANGES IN WRITTEN REQUEST FOR PEDIATRIC STUDIES**" in large font, bolded type at the beginning of the cover letter of the submission. You will be notified in writing if any changes to this Written Request are agreed upon by the Agency.

We hope you will fulfill this pediatric study request. We look forward to working with you on this matter in order to develop additional pediatric information that may produce health benefits to the pediatric population.

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

Sincerely yours,

A handwritten signature in black ink that reads "Robert Temple" followed by a date "4/28/98". The signature is written in a cursive style.

Robert Temple, M.D.  
Director  
Office of Drug Evaluation I  
Center for Drug Evaluation and Research

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HFD-100/RTemple 4/21/99 4/28/99  
HFD-600/Office of Generic Drugs  
HFD-2/MLumpkin  
HFD-104/DMurphy  
HFD-6/ KRoberts  
Drafted:03/22/99am;rg  
Rev:03/29/99tl; 04/02/99rt;04/12/99tl;4/21/99pdit  
Final:04/22/99pd  
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PEDIATRIC WRITTEN REQUEST LETTER  
INFORMATION REQUEST (IR)

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MEMORANDUM

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

DATE: April 16, 2003

FROM: Carol A. Pamer, R.Ph. Safety Evaluator  
Division of Drug Risk Evaluation, HFD-430

THROUGH: Mark Avigan, M.D., C.M., Acting Director  
Div. of Drug Risk Evaluation, HFD-430

TO: Solomon Iyasu, MD, MPH., Team Leader  
Div. of Pediatric Drugs and Development, HFD-960  
Office of Counter-Terrorism and Pediatric Development

SUBJECT: One Year Post-Pediatric Exclusivity Postmarketing Adverse Event Review  
Sertraline (Zoloft™), NDA 19-839  
Pediatric Exclusivity Approval Date: February 1, 2002

**Executive Summary**

The FDA AERS database was searched for reports of adverse events occurring in association with the use of Zoloft (sertraline) in children aged 16 years and younger. The time period of interest was the one-year period following FDA Pediatric Exclusivity approval, February 1, 2002 through March 1, 2003. Generally, the reports were similar in nature to those received for adults since its time of approval in 1991. A number of the reports, especially psychiatric reactions, may also reflect the disorders for which patients were receiving care.

**AERS Search Results**

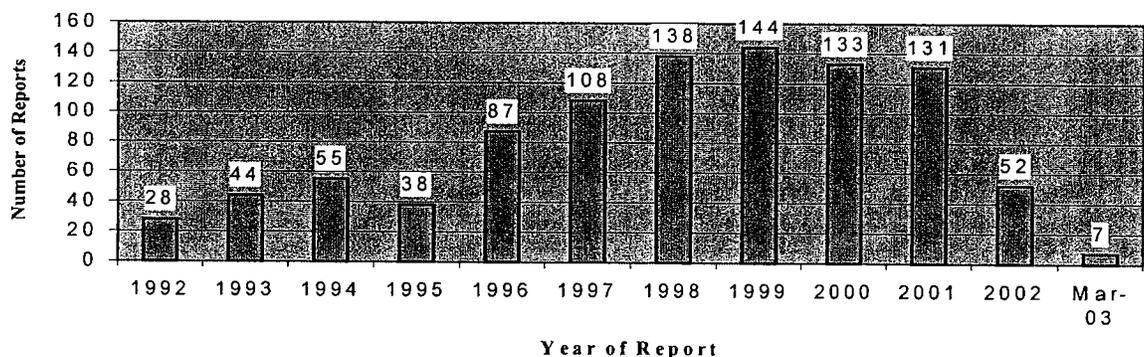
AERS Search Date: April 18, 2003  
Including all sources - U.S. & Foreign Reports

**A. From marketing Approval date (December 30, 1991) to one year post-Pediatric Exclusivity Approval (March 1, 2003):**

**1. Counts of reports:**

	All reports (US)	Serious (US)	Death (US)
All ages	25,748 (20,996)	21,237 (17,312)	1,300 (600)
Adults (≥17)	15,718 (12,072)	13,179 (10,103)	921 (371)
Peds (0-16)	965 (838)	830 (723)	21 (14)

**Reporting Trend for Pediatric Reports  
Time of Approval to One Year post-Pediatric Exclusivity  
Approval (1992 to March 1, 2003)**



**2. Top 20 reported event PTs and labeling status of events (underlined=unlabeled):**

All ages:

Drug ineffective (1538), depression (1411), nausea (1401), dizziness (1395), diarrhea (1335), insomnia (1278), headache (1274), drug interaction (1225), anxiety (1176), tremor (954), sedation (909), asthenia (893), paraesthesia (734), nervousness (720), agitation (732), drug withdrawal syndrome (723), alopecia (662), weight increased (652), dermatitis (631), sweating increased (634)

Adults:

Nausea (1066), dizziness (1047), diarrhea (949), drug ineffective (906), headache (918), insomnia (851), anxiety (790), drug interaction (771), depression (763), asthenia (672), tremor (677), sedation (635), paraesthesia (526), agitation (528), nervousness (503), drug withdrawal syndrome (491), confusion (463), sweating increased (433), vomiting (412), condition aggravated (395)

Children:

Complications of maternal exposure to therapeutic drugs (67), agitation (53), drug ineffective (43), tremor (43), insomnia (41), sedation (39), drug interaction (38), hostility (39), muscle twitching (36), convulsions (34), personality disorder (33), dermatitis (32), dizziness (31), headache (32), suicide attempt (30), pruritis (29), nervousness (28), non-accidental overdose (27), anxiety (27), vomiting (26)

**B. From Pediatric Exclusivity approval date, February 1, 2002 to March 1, 2003:**

**1. Counts of reports:**

	All reports (US)	Serious (US)	Death (US)
All ages	1249 (847)	1039 (692)	182 (123)
Adults (≥17)	889 (591)	774 (508)	134 (90)
Peds (0-16)	54 (41)	40 (28)	5 (5)

**2. Top 20 reported event PTs and labeling status of events (underlined=unlabeled):**

All ages:

Dizziness (116), nausea (82), drug withdrawal syndrome (98), drug interaction (62), depression (66), insomnia (63), headache (66), suicidal ideation (72), anxiety (57), tremor (58), weight increased (49), agitation (64), confusion (57), fatigue (56), vomiting (46), completed suicide (56), depression aggravated (45), aggression (54), feeling abnormal (54), fall (44)

Adults:

Dizziness (97), nausea (70), drug withdrawal syndrome (80), agitation (58), drug interaction (46), confusion (48), headache (51), feeling abnormal (48), suicidal ideation (52), tremor (43), vomiting (37), weight increased (38), insomnia (44), aggression (43), depression (41), anxiety (38), fatigue (38), completed suicide (45), memory impairment (33), abnormal behaviour (32)

Children:

Maternal drug affecting fetus (10), dyspnea (6), aggression (7), insomnia (4), abnormal behaviour (4), caesarean section (4), complications of maternal exposure to therapeutic exposure to therapeutic drugs (5), convulsions (4), crying (4), irritability (3), memory impairment (4), premature baby (3), serotonin syndrome (3), tremor (4), medication error (4), hostility (3), increased activity (3), neonatal disorder (3), psychotic disorder (3), accidental exposure (2)

**Postmarketing Review of All Pediatric Adverse Event Reports, February 1, 2002 to March 1, 2003 (n=54; 2 deleted due to incorrect age coding [adults]. Final=49 unduplicated reports)**

**A. Demographic characteristics of pediatric reports regarding gender, age, indications, doses, and outcomes.**

Gender: Female-21, Male -27, Not stated -1

Age: Standard AERS age breakdown:

0-<1 mo.	9
1 mo.- <2 yrs	5
2-5 yrs	4
6-11 yrs	9
12-16 yrs	22

Primary outcomes: deaths (4), hospitalizations (19), others (life threatening, required interventions, medically important events) (26)

Indications: Depression (16), maternal exposure (prenatal or breastfeeding) (13), ADHD (4), unknown indication (4) obsessive compulsive disorder (3), vocal cord disorder (1), adjustment disorder (1), accidental overdose (3), medication error (1), anxiety (1), abuse (1), intermittent explosive disorder (1).

Doses: Range 25-150 mg (n=25). (Note: overdoses and maternal doses excluded.)

**B. Comments regarding labeling status of the top 20 adverse events from Pediatric Exclusivity period and comparison with the adult adverse event profile.**

Current labeling under "*Precautions, Pediatric Use*" states the following regarding pediatric patients:

"The safety of Zoloft use from studies in children and adolescents, ages 6-18, showed that Zoloft had an adverse event profile generally similar to adults.

**Under "*Adverse Reactions, Other Adverse Events in Pediatric Patients*"** -- "In approximately N=250 pediatric patients treated with ZOLOFT, the overall profile of adverse events was generally similar to that seen in adult studies, as shown in Tables 1 and 2. However, the following adverse events, not appearing in Tables 1 and 2, were reported at an incidence of at least 2% and occurred at a rate of at least twice the placebo rate in a controlled trial (N=187): hyperkinesia, twitching, fever, malaise, purpura, weight decrease, concentration impaired, manic reaction, emotional lability, thinking abnormal, and epistaxis."

All top 20 adverse events are similar to those reported for adults and most are labeled, except for the terms - maternal drug affecting fetus, complications of maternal exposure, and memory impaired. Zoloft has a Pregnancy Category C, that is there are no adequate and well-controlled studies in pregnant women. As stated in the labeling, sertraline should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Accordingly, maternal exposure-related adverse event reporting may not apply to this review. Memory impairment could be considered synonymous to concentration impaired as an expected event.

**C. Comments and analysis of events not recognized for adult population. Recommend actions, if appropriate, after consultation with HFD-950 and review division MO's.**

None.

**D. Comments and analysis of events uniquely identified in children but not reported in adult population, including increased frequency of any expected events. Recommended actions, if appropriate, after consultation with HFD-950 and OND Review Division (HFD-120).**

None.

**E. Summary and comment on fatal reports.**

There were 4 unduplicated cases of death in ages 0-16 during the Pediatric Exclusivity Period. None of the deaths were clearly causally related to sertraline use. Causes of deaths were the following:

1. Family member report of drug toxicity from amitriptyline, clonidine and Zoloft in a 7 y.o. male;
2. Premature infant died at age 14 days. Mother was HIV positive. Hx of Zoloft several other medications during pregnancy;
3. 13 y.o. male committed suicide following one week trial of Zoloft. This report was follow-up to an initial report received in 1997.
4. 15 y.o. male committed suicide (gunshot) following misuse of Zoloft.

## **F. Summary of all pediatric reports**

Based upon the predominant adverse event reported in each case, the 49 pediatric cases could generally be summarized in the following 5 categories. Most reports involved more than one drug, possible confounding medical disorders, and/or described adverse events previously observed with sertraline use. Each category is followed by a brief summary of the cases.

### **1. Psychiatric events: 13 cases**

Aggression/Hostility reported in 7 cases  
Hallucinations, 2 cases  
Aphasia, 1 case  
Self-injurious behavior, 1 case  
Impulsivity/Risk-taking behavior, 1 case  
Withdrawal reactions, 1 case

### **2. Neurologic events: 10 cases**

Extrapyramidal/movement disorders reported in 5 cases  
Tremors, one case  
Seizures, 2 cases  
Possible Serotonin Syndrome, 2 cases

### **3. Congenital anomalies or adverse events in infants exposed via maternal use: 13 cases**

Malformations reported in 4 cases: 2 cardiac defects, 1 limb reduction defect, and 1 facial anomaly  
Possible withdrawal syndrome reported in 4 cases  
Developmental delays or abnormalities, 2 cases  
Premature births, 2 cases (1 fatal described above)  
Birth complications (cord wrapped around neck, meconium staining), 1 case

### **4. Overdose (accidental,intentional)/suicide attempt/completed suicide/medication errors: 9 cases**

Overdose was reported in 5 cases, none of which were fatal. Three (3) were accidental ingestions by children 2 y.o. or younger. Two intentional overdoses were reported for patients 13 and 14 years of age.  
Fatal drug toxicity was noted in one report from a family member. A 7 y.o. male had elevated autopsy liver concentrations of multiple drugs (sertraline, amitriptyline, clonidine)  
Completed suicides were reported in two patients, 13 and 15 y.o.  
A medication error occurred in which an 11 y.o. received Zoloft instead of Zyrtec

### **5. Other events: 4 cases**

The remaining 4 cases consisted of the following: priapism in 14 y.o. male, hematologic disorder (leukopenia, thrombocytopenia), restrictive lung disorder in 13 y.o. patient with hereditary immune disorder, prothrombin time prolonged/rectal bleed in 14 y.o. male.

## Summary

The FDA AERS database was searched for reports of adverse events occurring in association with the use of Zoloft (sertraline) in children aged 16 years and younger. The time period of interest was the one-year period following FDA Pediatric Exclusivity approval, February 1, 2002 through March 1, 2003.

Among the aggregated terms for raw AERS data, the 20 most frequently reported adverse events are similar to those reported for adults. Most of these events are labeled. The following terms are excepted: maternal drug affecting fetus, complications of maternal exposure, and memory impaired. Zoloft has a Pregnancy Category C labeling precaution (e.g. there are no adequate and well-controlled studies in pregnant women). Accordingly, maternal exposure-related adverse event reporting may not apply to this review. The term “memory impairment” could be considered synonymous to “concentration impaired”, which is an expected event. Note that multiple adverse event terms may be encoded for each report.

When a hands-on analysis and elimination of duplicate reports was performed, 49 reports were received for Zoloft (sertraline) during the one-year period following FDA Pediatric Exclusivity approval. The primary adverse events were similar in nature to those received for adults since its time of approval in 1991. A number of the reports, especially psychiatric reactions, may also reflect the disorders for which patients were receiving care.

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Carol A. Pamer, R.Ph.  
Safety Evaluator  
Division of Drug Risk Evaluation (DDRE)

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## Limitations of the Adverse Event Reporting System (AERS)

The voluntary or spontaneous reporting of adverse events from health care professionals and consumers in the U.S reflects underreporting and also duplicate reporting. For any given report, there is no certainty that the reported suspect product(s) caused the reported adverse event(s). The main utility of a spontaneous reporting system, such as AERS, is to provide signals of potential drug safety issues. Therefore, counts from AERS cannot be used to calculate incidence rates or estimates of drug risk for a particular product or used for comparing drug risk between drugs.

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MEMORANDUM

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

DATE: May 1, 2003

FROM: Laura Governale, Pharm.D., Drug Utilization Data Specialist  
Division of Surveillance, Research and Communication Support, HFD-410

THROUGH: Toni Piazza-Hepp, Pharm.D., Acting Director  
Div. of Surveillance, Research and Communication Support, HFD-410

TO: Solomon Iyasu, MD, MPH., Team Leader  
Div. of Pediatric Drugs and Development, HFD-960  
Office of Counter-Terrorism and Pediatric Development

SUBJECT: One Year Post-Pediatric Exclusivity Postmarketing Adverse Event Review: Drug  
Use Data  
Sertraline (Zoloff™), NDA 19-839  
Pediatric Exclusivity Approval Date: February 1, 2002

**Executive Summary**

In keeping with the growing use of sertraline in the adult population, the use of Zoloff™ (sertraline) in the pediatric population appears to be on the rise. The proportion of pediatric patients using sertraline has not changed appreciably in the past three years, and ranges from approximately \_\_\_\_\_ of all use. The most frequent indications for use in children appear to be depressive disorders and anxiety-related disorders.

**I. Introduction**

The following will describe the outpatient drug usage patterns for sertraline in the pediatric patient population in comparison to the adult patient population using the drug utilization databases at the Agency's disposal. Inpatient use was not examined in this analysis.

**II. Outpatient use**

A. National Prescription Audit *Plus?* (NPA Plus? ), IMS Health

NPA Plus measures the retail dispensing of prescriptions, or the frequency with which drugs move out of retail pharmacies into the hands of consumers via formal prescriptions. These retail pharmacies include chain, independent, food store, mail order, discount houses, and mass merchandiser pharmacies, as well as nursing home (long-term care)

pharmacy providers. Information on the specialty of the prescribing physician can also be collected, except for in the long-term care and mail-order settings.

The number of dispensed prescriptions are obtained from a sample of approximately 22,000 randomly selected pharmacies throughout the U.S. and projected nationally. The pharmacies in the database account for 40% of all pharmacy stores and represent approximately 45% of prescription coverage.

The number of prescriptions dispensed annually for Zoloft has increased substantially over the last 5 years (Table 1). This increase has been led by Family Practice and Internal Medicine specialties (Figure 1). The Pediatrics specialty rounded out the top 10 prescriber specialties for Zoloft. For the year 2002, an average of approximately \_\_\_\_\_ prescriptions for Zoloft were dispensed monthly - \_\_\_\_\_ for the entire year by the Pediatric specialty. Use appears to be increasing for most specialties.

### **Limitations of NPA data**

NPA data provide an estimate of the total number of prescriptions dispensed in the U.S. for sertraline. However, it does not include demographic information for the patients receiving these prescriptions, such as age and gender. The inclusion of prescriber specialty data in this report precludes the use of the mail-order and long-term care channels. For the purposes of describing use in the pediatric population, these two channels are not considered to be great contributors of prescription volume.

### **B. National Disease and Therapeutic Index? (NDTI? ), IMS Health**

NDTI is a continuing survey designed and conducted by IMS HEALTH to provide descriptive information on the patterns and treatment of disease encountered in office-based practice in the continental United States. These data may include profiles and trends of diagnoses, patients, and treatment patterns. NDTI collects data on drug products mentioned during visits to office-based physicians in the U.S.

NDTI uses the term “appearances” for drug reports. A drug appearance roughly translates to a mention of a drug during a patient visit, unduplicated by the number of diagnoses for which it may be used. A drug appearance can result from a prescription written, a refill authorized, a sample given, the drug administered in the office, etc., or any combination of these.

The frequency with which sertraline was mentioned during a patient visit in the pediatric population, ages 0-16, increased only slightly from \_\_\_\_\_ in 2000 to \_\_\_\_\_ in 2002 (Table 2). Of this age group, the adolescent age subgroup (12-16 years) represented greater than two thirds of drug use. Similar increases were seen in the adult population as well.

In all pediatric age groups, the preponderance of drug use appeared to be among males for all three years of data, whereas in the adult population (patient age greater than 17 years), the preponderance of use appears to be among females.

The diagnosis, or indication, most frequently appearing in the 12 to 16 year age group appears to be depressive disorders (Table 3). However, for patients between the age of 2 and 11 years, anxiety-related disorders were the most common diagnoses.

In this office-based setting, the top three physician specialties prescribing sertraline in the pediatric population were psychiatry, pediatrics and family practice (Table 4). Similarly, the top three specialties in the adult population are psychiatry, family practice, and internal medicine. This differed somewhat from the results seen from NPA and may be due to over-sampling of psychiatrists in the NDTI physician panel, and the fact that NDTI's smaller sample size makes it difficult to extrapolate these results to the general population.

### **Limitations of NDTI**

Data for NDTI are gathered by a panel of 2000 – 3000 office-based physicians in the continental U.S. For two consecutive days per quarter, the physicians complete and submit a survey of their practice patterns to IMS Health. The data are collected and projected to the national level to obtain an estimate of use. The small sample size can make these data unstable, particularly when use is not prevalent.

### **C. AdvancePCS**

AdvancePCS is one of the largest pharmacy benefit management (PBM) companies in the U.S., currently covering 50 million patient lives and processing 300 million prescription claims annually. Patients whose claims are processed by AdvancePCS include those covered under various types of insurance plans that cover prescription drugs, including some employers' self-insured plans, selected managed care plans, private plans, and selected other traditional insurers. Demographically, these patients appear to represent all 50 states, and include substantial numbers of the elderly, children and women of childbearing age. Their representativeness of all patients receiving dispensed prescriptions in the U.S., however, is not known at this time.

Data from AdvancePCS also suggest that the volume of prescriptions has not changed appreciably in both adult and pediatric populations (Figure 2). The percentage of pediatric use over the 24 months surveyed, March 2001 to February 2003, is approximately \_\_\_\_\_ of the total prescriptions dispensed, averaging approximately \_\_\_\_\_ prescriptions per month (Table 5). Prescriptions dispensed for the adult population over the 24-month period averaged approximately \_\_\_\_\_ prescriptions per month. Prescription volume for both populations appears to be unchanging.

### **Limitations of AdvancePCS**

AdvancePCS data are not projected to approximate prescription usage on a national level due to its closed patient enrollment system. In addition, reliable information for patients less than the age of 1 year is not available.

### **III. Conclusion**

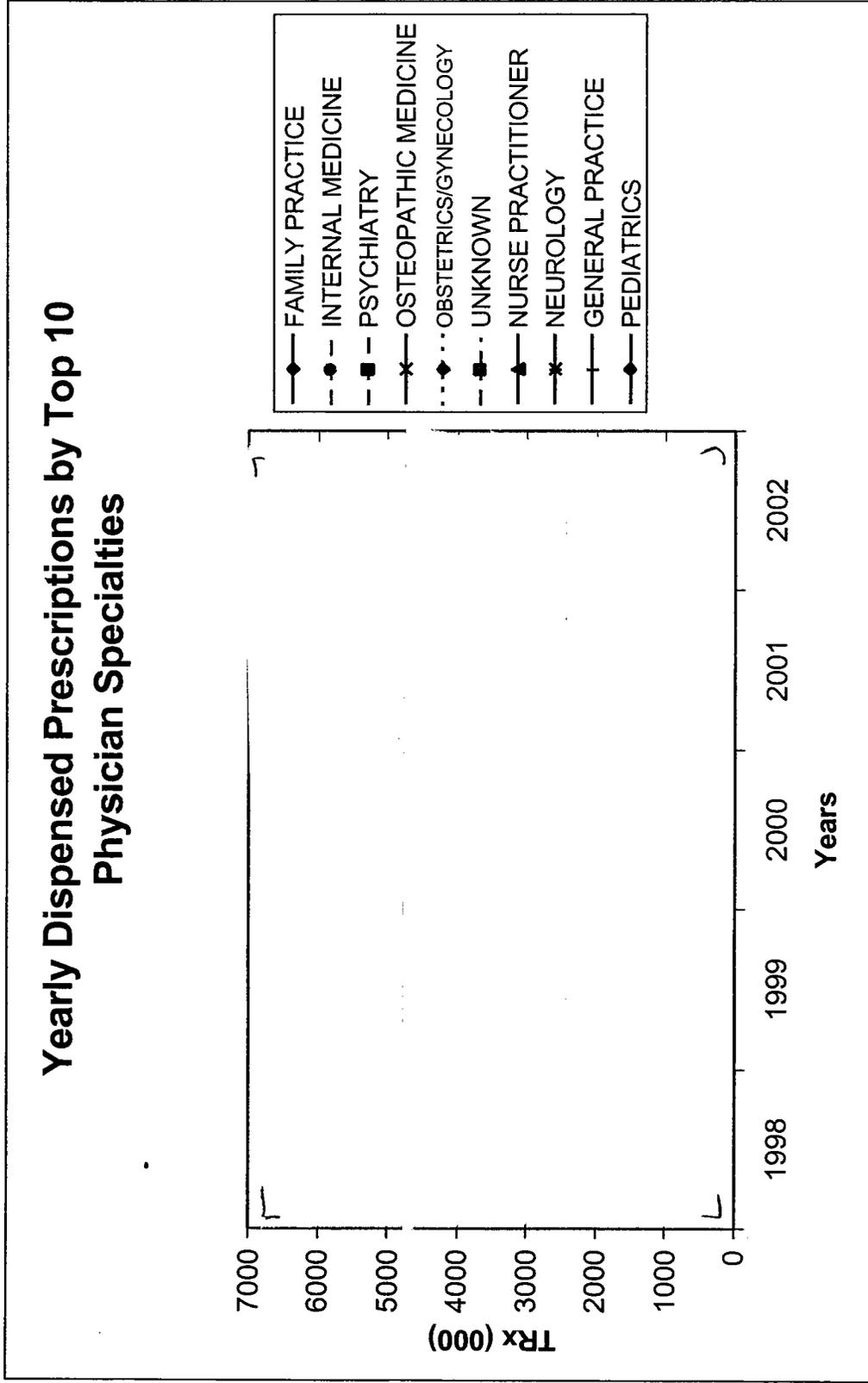
In keeping with the growing use of sertraline in the adult population, the use of sertraline in the pediatric population appears to be on the rise. The proportion of pediatric use has not changed appreciably in the past three years, and ranges from approximately \_\_\_\_\_ of all use. The most frequent indications for use in children appear to be depressive disorders and anxiety-related disorders.

### **IV. Accompanying Tables and Figures**

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Figure 1: NPA Top 10 Prescribing Physician Specialties for Sertraline, 1998 - 2002



Note: Mail Order and Long-Term Care channels not included in this data.

**Table 2: Age/Gender Distribution of Patients Seen in Office Visits Related to Sertraline, 2000 – 2002 (NDTI)**

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Projected Number of Total Drug Appearances <sup>1,2</sup>  
 During Patient Visits <sup>3</sup> in Office-Based Practices  
 in the Continental US  
 for Zoloft

Stratified by Product, Patient Age (Grouped 0-1, 2-11, 12-16, 0-16, 17+), Gender  
 Distributed by Years 2000 - 2002  
 (in thousands; **ADD THREE 0's TO EACH FIGURE**)  
 (percents are absolute numbers)



Variable : P-Default Measure (Thousands)

	P-Drug Appearances YEAR/2000 % V	P-Drug Appearances YEAR/2001 % V	P-Drug Appearances YEAR/2001 % V	P-Drug Appearances YEAR/2002 % V
ZOLOFT				
Patient Age 17+				
FEMALE				
MALE				
Patient Age 0-16				
MALE				
FEMALE				
Patient Age 12-16 (adolescents)				
MALE				
FEMALE				
Patient Age 2-11 (children)				
MALE				
FEMALE				

SOURCE: IMS HEALTH; National Disease and Therapeutic Index™, CD-ROM

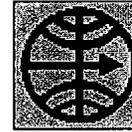
NOTES:

- 1 ---- means no data; a zero means less than 500 total projected
- 2 A drug appearance roughly translates to a mention of a drug during a patient visit (unduplicated by number of diagnoses for which it may be used); A drug appearance can result from a prescription written, a refill authorized, a sample given, the drug administered in the office, a prescription issued by a dispensing physician, hospital order written, recommendation given to purchase OTC product, patient on drug and no action taken, or a combination of these;
- 3 Every patient contact reported is considered a patient visit, regardless of location

\*\*NOTE: DATA NOT TO BE SHARED OUTSIDE OF FDA OR WITH non-FDA STAFF WITHOUT PRIOR CLEARANCE BY IMS HEALTH.  
 Clearance must be requested from IMS HEALTH through the FDA Office of Drug Safety  
 A minimum of 2 WEEKS is required for clearance by IMS HEALTH\*\*

**Table 3: Sertraline Mentions During Office Visits by Patient Age and Diagnosis, 2000 – 2002 (NDTI)**

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Projected Total Number of Drug Uses<sup>1</sup>  
 During Patient Visits<sup>2</sup> in Office-Based Practices in the Continental US  
 For Zoloft  
 Stratified by Product, Patient Age (Grouped 0-1, 2-11, 12-16, 0-16, 17+), Diagnosis 4  
 Distributed by Years 2000 – 2002  
 (in thousands; ADD THREE O's TO EACH FIGURE)  
 (percents are absolute numbers)

Variable: P-Default Measure (Thousands)

	P-Drug Uses YEAR/2000	P-Drug Uses YEAR/2000 %V	P-Drug Uses YEAR/2001	P-Drug Uses YEAR/2001 %V	P-Drug Uses YEAR/2002	P-Drug Uses YEAR/2002 %V
<b>ZOLOFT PFZ 92/02</b>						
<b>Patient Age 17+</b>						
3110 DEPRESSIVE DISORDER NEC						
2962 MAJOR DEPRESS.DIS,SINGLE						
3004 NEUROTIC DEPRESSION						
3000 ANXIETY STATES						
2963 MAJOR DEPRESS.DIS-RECURR						
3083 OTH AC REACTION TO STRES						
3002 PHOBIC STATE						
2967 BIPOLAR AFFECT.DIS-UNSPC						
3003 OBSESSIVE COMPULSIVE DIS						
2957 SCHIZOAFFECTIVE TYPE						
<b>Patient Age 0 -16</b>						
3110 DEPRESSIVE DISORDER NEC						
3000 ANXIETY STATES						
2962 MAJOR DEPRESS.DIS,SINGLE						
3003 OBSESSIVE COMPULSIVE DIS						
3004 NEUROTIC DEPRESSION						
3140 SIM DISTRBNCE ACTVTY&ATT						
2969 UNS AFFECTIVE PSYCHOSES						
2963 MAJOR DEPRESS.DIS-RECURR						
2967 BIPOLAR AFFECT.DIS-UNSPC						
3138 OTH DISTURB EMOT MXD CHL						
<b>Patient Age 12-16 (adolescents)</b>						
3110 DEPRESSIVE DISORDER NEC						
2962 MAJOR DEPRESS.DIS,SINGLE						
3000 ANXIETY STATES						
3004 NEUROTIC DEPRESSION						
3003 OBSESSIVE COMPULSIVE DIS						
2969 UNS AFFECTIVE PSYCHOSES						
2963 MAJOR DEPRESS.DIS-RECURR						
3140 SIM DISTRBNCE ACTVTY&ATT						
2967 BIPOLAR AFFECT.DIS-UNSPC						
3138 OTH DISTURB EMOT MXD CHL						
<b>Patient Age 2-11 (children)</b>						
3000 ANXIETY STATES						
3003 OBSESSIVE COMPULSIVE DIS						
3110 DEPRESSIVE DISORDER NEC						
3140 SIM DISTRBNCE ACTVTY&ATT						
3129 UNSP DISTURB CONDUCT NEC						
2962 MAJOR DEPRESS.DIS,SINGLE						
3083 OTH AC REACTION TO STRES						
3094 ADJ REA DST EMOT CONDUCT						
2965 BIPOLAR AFFECT.DIS-DEPRS						
3159 UNS SP DELAYS DEVELOPMEN						

**SOURCE: IMS HEALTH; National Disease and Therapeutic Index, CD-ROM Source 3 Year 1/00 – 12/02**

**NOTES:**

\* --- means no data; a zero means less than 500 total projected;

<sup>1</sup> A drug use is the mention of a drug in association with a diagnosis during a patient visit. The drug uses are duplicated by the number of diagnoses for which the drug is mentioned.

<sup>2</sup> Every patient contact reported is considered a patient visit, regardless of location

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**Table 4: Sertraline Appearances in Office Visits by Patient Age and Physician Specialty, 2000 – 2002 (NDTI)**

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Projected Number of Total Drug Appearances<sup>1,2</sup>  
 During Patient Visits<sup>3</sup> in Office-Based Practices in the Continental US  
 For Zoloft  
 Stratified by Product, Patient Age (Grouped 0-1, 2-11, 12-16, 0-16, 17+), Physician Specialty  
 Distributed by Years 2000 – 2002  
 (in thousands; **ADD THREE O's TO EACH FIGURE**)  
 (percents are absolute numbers)

Variable: P-Default Measure (Thousands)

	P-Drug Appearances YEAR/2000	P-Drug Appearances YEAR/2000 %V	P-Drug Appearances YEAR/2001	P-Drug Appearances YEAR/2001 %V	P-Drug Appearances YEAR/2002	P-Drug Appearances YEAR/2002 %V
<b>ZOLOFT PFZ 9202</b>						
<b>Patient Age 17+</b>						
PSYCHIATRY						
FAMILY PRACTICE						
INTERNAL MEDICINE						
OSTEOPATHIC MEDICINE						
OBSTETRICS/GYNECOLOGY						
GENERAL PRACTICE						
NEUROLOGY						
CARDIOLOGY						
GASTROENTEROLOGY						
GENERAL SURGERY						
ONCOLOGY/NEOPLASTIC						
PEDIATRICS						
GERIATRICS						
ALL OTHER SURGERY						
PULMONARY DISEASES						
RHEUMATOLOGY						
NEPHROLOGY						
ORTHOPEDIC SURGERY						
ENDOCRINOLOGY						
UROLOGY						
EMERGENCY MEDICINE						
PODIATRY						
OTOLARYNGOLOGY						
ALLERGY						
HEMATOLOGY						
<b>Patient Age 0-16</b>						
PSYCHIATRY						
PEDIATRICS						
FAMILY PRACTICE						
NEUROLOGY						
OSTEOPATHIC MEDICINE						
INTERNAL MEDICINE						
OBSTETRICS/GYNECOLOGY						
GENERAL PRACTICE						
GASTROENTEROLOGY						
ONCOLOGY/NEOPLASTIC						
PULMONARY DISEASES						
RHEUMATOLOGY						
CARDIOLOGY						
ENDOCRINOLOGY						
<b>Patient Age 12-16 (adolescents)</b>						
PSYCHIATRY						
PEDIATRICS						
FAMILY PRACTICE						
OSTEOPATHIC MEDICINE						
NEUROLOGY						
INTERNAL MEDICINE						
OBSTETRICS/GYNECOLOGY						
GASTROENTEROLOGY						
PULMONARY DISEASES						
GENERAL PRACTICE						
ONCOLOGY/NEOPLASTIC						
RHEUMATOLOGY						
CARDIOLOGY						
ENDOCRINOLOGY						
<b>Patient Age 2-11 (children)</b>						
PSYCHIATRY						
PEDIATRICS						
FAMILY PRACTICE						
NEUROLOGY						
OSTEOPATHIC MEDICINE						
GENERAL PRACTICE						
ONCOLOGY/NEOPLASTIC						
GASTROENTEROLOGY						

**SOURCE: IMS HEALTH; National Disease and Therapeutic Index, CD-ROM Source 3 Year 1/00 – 12/02**

**NOTES:**

\* --- means no data; a zero means less than 500 total projected;

<sup>1</sup> A drug appearance roughly translates to a mention of a drug during a patient visit (unduplicated by number of diagnoses for which it may be used);

<sup>2</sup> A drug appearance can result from a prescription written, a refill authorized, a sample given, the drug administered in the office, a prescription issued by a dispensing physician, hospital order written, recommendation given to purchase OTC product, patient on drug and no action taken, or a combination of these;

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**Figure 2: AdvancePCS Total Prescriptions Dispensed for Zoloft**

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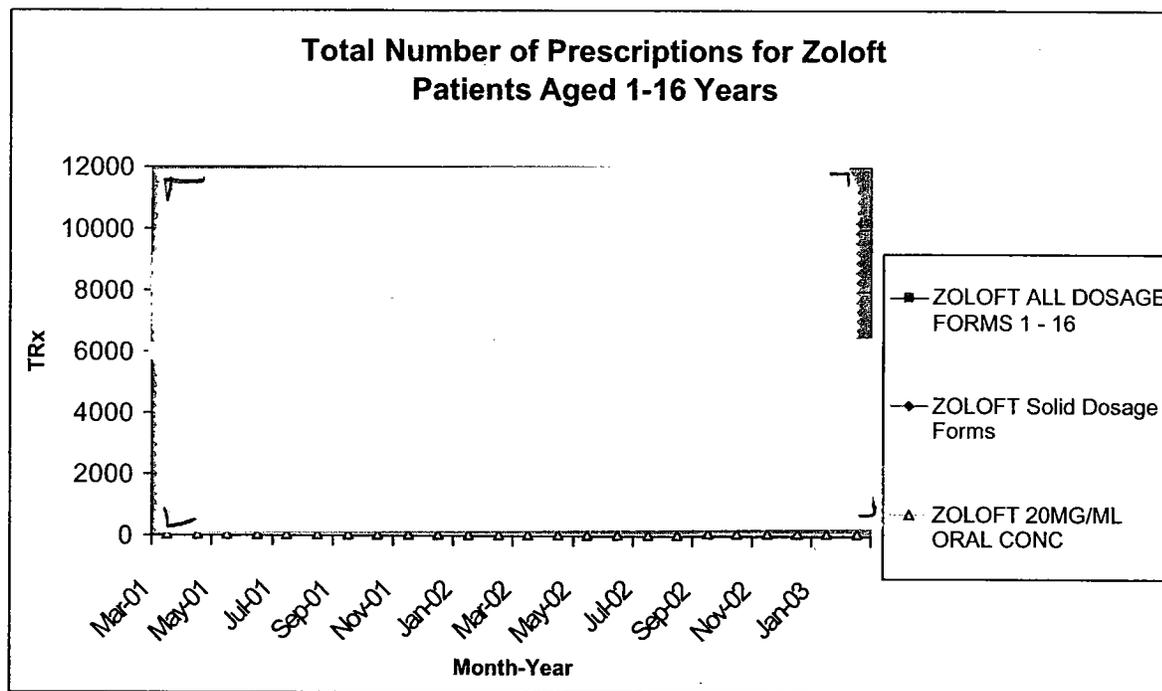
**\*NOTE: NOT TO BE SHARED OUTSIDE OF FDA OR WITH NON-FDA STAFF WITHOUT PRIOR CLEARANCE BY ADVANCEPCS. Clearance must be requested from AdvancePCS through the FDA Office of Drug Safety\***  
 Total <sup>1</sup> Number of Prescription Claims Processed (TRx)

Dispensed by Retail Pharmacies in the Advance PCS™ pharmacy claims processing network<sup>2</sup> for Zoloft

Stratified by Drug Label Name and 1 Year Age Bands (1-16)

Distributed by Month, with most recent appearing first -- February 2003 to February 2001

Counts are ACTUAL. DO NOT ADD ANY ZEROS. Data are NOT projected to represent a national estimate.



SOURCE: AdvancePCS™ Dimension Rx

Notes:

\* A blank cell indicates that "zero" claims were processed for that drug product.

<sup>1</sup> Total includes New and Refill prescriptions

<sup>2</sup> AdvancePCS™ is a pharmacy benefits manager in the U.S. that processes 300 million third-party payer prescription claims annually and covers 50 million patient lives throughout the U.S.

Data are NOT projected to represent a national total, do not include non-AdvancePCS reimbursed Rx's or mail order Rx claims, and do not include prescriptions where the patient paid cash at the pharmacy without subsequent third-party insurance reimbursement.

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**Table 5: Average Prescriptions Dispensed for Zoloft Over 24-Month Period, March 2001 – February 2003 (from AdvancePCS)**

	Age	Total Claims/Rx
Average Peds	1 - 16	
Average Adult	17 +	
Average % Peds of Total		

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