CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

18-936/SE5-064

CORRESPONDENCE

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINSTRATION			**OPDRA POSTMARKETING SAFETY REVIEW**
FROM: DDRE I (HFD-430) Kathleen M. Phelan, R.Ph., Safety Evaluator			**DATE:** November 20, 2001 **OPDRA PID #** D010310
TO: DNDP (HFD-120) Russell Katz, M.D., M.P.H., Division Director			
DRUG/APPROVAL:	**TRADE NAME:**	**NDA #:**	**SPONSOR:**
Citalopram 7/17/98	Celexa	20-822, 21-046	Forest Laboratories
Fluoxetine 12/29/87	Prozac, Sarafem	18-936, 20-101, 20-187, 20-974, 21-235	Eli Lilly and Company
Fluvoxamine 9/7/94	Luvox	20-243, 20-350	Solvay Pharmaceuticals
Paroxetine 12/29/92	Paxil, Paxil CR	20-031, 20-710, 20-885, 20-936	GlaxoSmithKline
Sertraline 12/30/91	Zoloft	19-839, 20-990	Pfizer Pharmaceuticals
Venlafaxine 12/28/93	Effexor, Effexor XR	20-151, 20-699	Wyeth-Ayerst Laboratories
THERAPEUTIC CLASSIFICATION: antidepressants, antiobsessional agent (fluvoxamine)			
EVENT: Neonatal withdrawal syndrome			

Executive Summary:

Reports of neonatal withdrawal following *in utero* paroxetine exposure were noted during routine adverse event monitoring. Soon after, an article appeared in the literature describing four cases of withdrawal syndrome in neonates whose mothers had used paroxetine in pregnancy.[1] AERS cases of neonatal withdrawal for the serotonin reuptake inhibitors (SRIs), citalopram, fluoxetine, fluvoxamine, paroxetine, sertraline, and venlafaxine, were reviewed to determine the occurrence and severity of this adverse event. None of the SRIs are currently labeled for neonatal withdrawal syndrome, although all labels except fluoxetine's include mention of withdrawal syndrome in the *Adverse Reactions* sections. For citalopram, fluoxetine, fluvoxamine, paroxetine, sertraline, and venlafaxine, respectively, 5, 4, 2, 35, 8, and 3 possible cases of neonatal withdrawal related to maternal use of the SRI were retrieved from AERS. Literature searches retrieved no possible cases that were not also in AERS. More than half of the cases are from foreign sources. Reported SRI dosages are within labeled recommendations except for one venlafaxine case reporting a dosage of 450 mg per day. Most births occurred at term. Male infants slightly outnumbered female infants. Reported withdrawal effects are similar for all SRIs with excitatory neuromuscular effects, including irritability, jitteriness, agitation, crying, hyperreflexia, hypertonia, and seizures or seizure-like movements, predominating. Breathing difficulties, including tachypnea, apnea, and respiratory distress, and feeding difficulties were also seen. In a few cases, difficulty with temperature regulation was reported. Although reported signs are similar to those of serotonin toxicity, the case definition was designed to exclude cases of serotonin toxicity. Specifically, cases in which signs were present at birth or time to onset was not reported were excluded unless the reporter stated that the case was diagnosed as or suspected to be SRI withdrawal. Treatment involved hospitalization in almost all cases detailing treatment. Resolution or improvement was noted in the vast majority of cases and occurred within 2 months of onset. Data on SRI use in pregnancy is not available, so neither the incidence of withdrawal in SRI exposed pregnancies nor the relative incidence of withdrawal between different SRIs can be estimated. However, paroxetine had both more cases and longer times to resolution than expected based upon relative half-lives of the SRIs.

It can be seen from this review that neonatal withdrawal may occur after pregnancies with chronic exposure up to birth to any of the included SRI medications. This evidence is strongest for paroxetine. For the information of physicians, we recommend inclusion in the pregnancy section of labeling for paroxetine and possibly citalopram, fluoxetine, fluvoxamine, sertraline, and venlafaxine a statement such as, "There have been reports of withdrawal, seen as primarily excitatory nervous and neuromuscular signs, including seizures in some cases, breathing and feeding difficulties, and, rarely, difficulty maintaining body temperature, in neonates born to mothers who received a serotonin reuptake inhibiting medication in late pregnancy up to birth. Reported cases of withdrawal syndrome have resolved completely with symptomatic treatment. Withdrawal syndrome should be considered in differential diagnosis of a neonate with chronic *in utero* exposure to [the specific SRI] up to birth who exhibits such signs."

Reason for Request/Review:
Many descriptions of the difficulty of discontinuing serotonin reuptake inhibitors (SRIs) are in AERS. Reports of neonatal withdrawal from paroxetine have been noted recently during routine adverse event monitoring. In March, 2001, an article by Stiskal, et. al. appeared in the literature describing four cases of withdrawal syndrome in neonates whose mothers had used paroxetine in pregnancy.[1] We decided to review cases of neonatal withdrawal in AERS for the SRIs to determine the occurrence and severity of this adverse event.

Relevant Product Labeling:
citalopram, fluoxetine, fluvoxamine, paroxetine, sertraline, and venlafaxine (exact wording may vary)
Pregnancy Category C
There are no adequate and well-controlled studies in pregnant women; therefore, [drug] should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.
Labor and Delivery--The effect of [drug] on labor and delivery in humans is unknown.

citalopram
Adverse Reactions: Other Events Observed During the Non-US Postmarketing Evaluation of Celexa (citalopram HBr): withdrawal syndrome

fluoxetine
Drug Abuse and Dependence—Physical and Psychological Dependence...the premarketing clinical experience with Prozac did not reveal any tendency for a withdrawal syndrome...

fluvoxamine
Adverse Reactions—Nervous system: Rare: withdrawal syndrome

paroxetine
Adverse Reactions—Nervous system: Rare: withdrawal syndrome
Adverse Reactions—Postmarketing Reports: There have been spontaneous reports that discontinuation (particularly when abrupt) may lead to symptoms such as dizziness, sensory disturbances, agitation or anxiety, nausea and sweating; these events are generally self-limiting.

sertraline
Adverse Reactions—Psychiatric Disorders: Rare: withdrawal syndrome
Physical and Psychological Dependence—Premarketing clinical experience with Zoloft did not reveal any tendency for a withdrawal syndrome.

venlafaxine
Adverse Reactions—Body as a whole: Rare: withdrawal syndrome
Physical and Psychological Dependence—Discontinuation effects have been reported in patients receiving venlafaxine.
Dosage and Administration—Discontinuing Effexor XR: When discontinuing Effexor XR after more than 1 week of therapy, it is generally recommended that the dose be tapered to minimize the risk of discontinuation symptoms. Discontinuation symptoms have been systematically evaluated in patients taking venlafaxine, to include prospective analyses of clinical trials in Generalized Anxiety Disorder and retrospective surveys of trials in depression. Abrupt discontinuation or dose reduction of venlafaxine at various doses has been found to be associated with the appearance of new symptoms, the frequency of which increased with increased dose level and with longer duration of treatment. Reported symptoms include agitation, anorexia, anxiety, confusion, coordination impaired, diarrhea, dizziness, dry mouth, dysphoric mood, fasciculation, fatigue, headaches, hypomania, insomnia, nausea, nervousness, nightmares, sensory disturbances (including shock-like electrical sensations), somnolence, sweating, tremor, vertigo, and vomiting.

Usage Information:
The IMS databases available at FDA do not provide information on use of medications during pregnancy unless the indication for medication use is specifically pregnancy-related.

AERS Searches

Drug Names for all searches: citalopram, fluoxetine, fluvoxamine, paroxetine, sertraline, venlafaxine

Search Date: September 17, 2001
MedDRA Terms: Neonatal neurological system disorders (exc birth trauma) (HLGT: high level group term), drug withdrawal syndrome neonatal (PT: preferred term), necrotizing enterocolitis (PT)
Note: The search terms neonatal neurological system disorders (exc birth trauma) and necrotizing enterocolitis were chosen for the following reasons. A review of preferred terms (PTs) in reports retrieved by an AERS search for drug withdrawal syndrome neonatal (PT) with paroxetine showed that excitatory neurological terms, such as seizures and irritability, predominated, so reports of neonatal neurological disorders were retrieved and reviewed for possible cases of neonatal withdrawal. The Stiskal, et. al. article[1] on paroxetine withdrawal includes two cases of necrotizing enterocolitis, so necrotizing enterocolitis was searched for possible cases of withdrawal.

Search Date: September 17, 2001
MedDRA Terms: Complications of maternal exposure to therapeutic drugs (PT)
Results were scanned for reports that also included drug withdrawal syndrome (PT), and only reports containing this term were retrieved.

Search Date: November 2, 2001
MedDRA Terms: Seizures (HLGT), neurological signs and symptoms nec (HLT: high level term), tremor (exc congenital) (HLT), neuromuscular disorders nec (HLT), disturbance in initiating or maintaining sleep (HLT), neonatal hypoxic conditions (HLT), breathing abnormalities (HLT), autonomic nervous system imbalance (PT), drug withdrawal syndrome neonatal (PT)
Other restrictions: patient age 0 to 3 months.

Literature Searches

Search Date: September 18, 2001	**Search Type:** Embase and PubMed

Search Criteria:
Embase and PubMed searches – 'serotonin uptake inhibitor' AND 'withdrawal syndrome'
PubMed search – 'serotonin uptake inhibitor' AND 'neonatal abstinence syndrome'

Results of AERS and Literature Searches

Search Results - background and studies from literature:
All but 1 of the 12 published case reports of neonatal withdrawal from SRIs retrieved by the literature searches were also found in AERS. The literature case not in AERS is not included in this review because the breast-fed infant did not exhibit signs of withdrawal until the mother discontinued sertraline 3 weeks after the birth.[2] Thus, withdrawal followed transmammary rather than intrauterine drug exposure. Among the 11 literature cases also found in AERS, 3 were excluded from this review[1] for reasons given below in the tabulation of cases. The remaining 8 literature cases also found in AERS are included in this review.[1,3,4,5] In addition to case reports, three studies of maternal fluoxetine use's effects on the neonate[6,7,8] and two general articles that provide background for this review[9,10] were retrieved from the literature.
Schatzberg, et al. propose a definition of SRI withdrawal, which they refer to as a discontinuation syndrome to distinguish it from the withdrawal associated with drugs that cause signs of addiction, such as drug seeking and tolerance.[9] The hallmark features of SRI withdrawal, with adaptations appropriate for the neonatal setting, are (1) the signs are not attributable to other causes, (2) signs emerge after abrupt discontinuation, (3) signs are generally mild and transient but can be troublesome, even leading to missed work days in adults (4) syndrome is self-limiting, (5) syndrome is rapidly reversed by reintroduction of the original medication or substitution of a pharmacologically similar agent, (6) syndrome may be minimized by slow tapering or use of a drug with an extended half-life, such as fluoxetine.[9] Signs and symptoms derived from observations of adults include disequilibrium, nausea and vomiting, flu-like symptoms, sensory disturbances, sleep disturbances, agitation, crying spells, irritability, and movement-related symptoms.[9]

Search Results - background and studies from the literature (continued):

In their 1998 review of neonatal drug withdrawal, the American Academy of Pediatrics Committee on Drugs primarily discuss withdrawal from addictive drugs such as opiates, but a point that is applicable to SRI withdrawal is the importance of eliminating other possible causes for the observed signs, such as infection, hypoglycemia, hypocalcemia, hypomagnesemia, hyperthyroidism, CNS hemorrhage, and anoxia.[10] They also state that preterm infants may be at lower risk for withdrawal and that withdrawal signs exhibited by preterm infants may differ from those of full-term infants.[10]

The three studies of neonates exposed *in utero* to fluoxetine did not specifically focus on drug withdrawal but looked at all postnatal complications. Goldstein, of Lilly Research Laboratories, examined 112 prospectively reported, third trimester fluoxetine exposed pregnancies in Eli Lilly's worldwide fluoxetine pregnancy registry.[7] No evidence of withdrawal effects in the newborns was found.[7] Chambers et. al. compared birth outcomes of 228 pregnant women who were taking fluoxetine and who called the California Teratogen Information Service and Clinical Research Program with birth outcomes of 254 pregnant women who called the program with drug or diagnostic procedure exposure that was not considered teratogenic and who had limited alcohol consumption.[8] A larger proportion of infants exposed to fluoxetine in the third trimester (23.0%) than of infants exposed to fluoxetine only in the first or second trimesters (9.5%) or of infants in the control group (6.3%) were admitted to special-care nurseries. Also, a larger proportion of infants exposed to fluoxetine in the third trimester (31.5%) than of infants exposed to fluoxetine only in the first or second trimesters (8.9%) exhibited poor neonatal adaptation defined as jitteriness, tachypnea, hypoglycemia, hypothermia, poor tone, respiratory distress, weak or absent cry, or desaturation on feeding.[8] The timing of these events and exposure of these pregnancies to other drugs associated with withdrawal syndromes is not reported, so it is not possible to determine whether any of these cases represent fluoxetine withdrawal. Cohen et. al., in a study partly funded by Eli Lilly, compared obstetrical and neonatal records of 11 newborns with first or second trimester fluoxetine exposure with records of 55 newborns with fluoxetine exposure during at least the third trimester and through birth.[6] This study also found higher rates of special care nursery admissions and neonatal complications in infants exposed to fluoxetine late in pregnancy (18.9% and 30.2%, respectively) than in infants exposed to fluoxetine earlier in pregnancy (9.1% and 9.1%, respectively). Because 15 of 17 neonates with complications, including neonates admitted to special care nurseries, were discharged from the hospital with their mothers, it may be concluded that the adverse effects exhibited by the neonates occurred at or very shortly after birth and may not have represented withdrawal from fluoxetine, which has a half-life of days. Thus, these three studies do not provide strong evidence of neonatal withdrawal occurring in infants exposed to fluoxetine *in utero*.

Search Results - cases:

Case definition – Cases were accepted as possible neonatal withdrawal if adverse events not attributable to other causes began hours to days after birth and resolved in a few days to weeks in a neonate born to a mother who had used the medication of interest at the end of the pregnancy. Although it is possible for withdrawal signs to be present at birth, depending on the half-life of the medication and the timing of the last maternal dose, in order to eliminate cases of serotonergic toxicity, cases were excluded if the adverse event was present at birth or if the time to onset was not reported. However, cases that report a diagnosis or suspicion of SRI withdrawal are included even if the events were present at birth or there is insufficient information to assess conformity to case definition because most cases do conform, thus establishing the occurrence of neonatal withdrawal from SRIs.

Most reports do not include complete information about excluded diagnoses. Incomplete data is a general problem with spontaneous reports and it was decided to include cases that do not detail efforts to find other causes for the observed signs if other aspects of the case conformed to the definition and the pattern of signs was consistent with accepted cases.

Search Results – cases (continued):

Citalopram (half-life 35 hours, total number of reports in AERS – 4069)
12 unduplicated cases:

- *5 cases of possible neonatal withdrawal from citalopram*, including 1 case in which the adverse reaction occurred immediately after birth but the infant was diagnosed with withdrawal syndrome[3]

7 excluded cases:

- 4 cases with *in utero* exposure to other drugs associated with withdrawal syndromes (2 benzodiazepine and buprenorphine, 1 buprenorphine, 1 benzodiazepine)
- 2 cases with timing inconsistent with citalopram withdrawal after birth (citalopram discontinued in early pregnancy)
- 1 case in which citalopram was mistakenly administered to a newborn

Fluoxetine (half-life fluoxetine 4-6 days with chronic dosing, half-life norfluoxetine [active metabolite] 4-16 days, total number of reports in AERS – 46,128)
56 unduplicated cases:

- *4 cases of possible neonatal withdrawal from fluoxetine*, including 1 literature case[3]

52 excluded cases:

- 12 cases with *in utero* exposure to other drugs associated with withdrawal syndromes (8 benzodiazepine, 1 buprenorphine, 1 phenobarbital, 1 phenobarbital and benzodiazepine, 1 amitriptyline)
- 12 cases in which timing was not consistent with fluoxetine withdrawal after birth (6 cases in which fluoxetine was discontinued at least 5 months before birth, 3 cases with adverse events persisting 5 ½ months, 7 months, and 2 years after birth, 2 cases with adverse events occurring *in utero*, 1 case of withdrawal after discontinuation of breast feeding)
- 10 cases in which adverse reaction was present at birth
- 8 cases with unclear timing of the adverse reaction in relation to birth, including 1 literature case[6]
- 8 cases of adverse events other than neonatal withdrawal (4 congenital anomalies, 3 adverse events with breastfeeding, 1 dehydration)
- 1 case in which administration of fluoxetine did not relieve signs
- 1 case in which timing of fluoxetine use was unknown

Fluvoxamine (half-life 15 hours, total number of reports in AERS – 3147)
9 unduplicated cases:

- *2 cases of possible neonatal withdrawal from fluvoxamine*

7 excluded cases:

- 3 cases with *in utero* exposure to other drugs associated with withdrawal syndromes (3 benzodiazepine)
- 2 cases in which adverse reaction was present at birth
- 1 case of adverse event other than neonatal withdrawal (1 adverse events with breastfeeding)
- 1 case in which timing of adverse event was unclear

Search Results - cases (continued):

Paroxetine (half-life 21 hours, total number of reports in AERS – 12,439)
78 unduplicated cases:

- *35 cases of possible neonatal withdrawal from paroxetine*, including 19 cases in which the adverse reaction occurred immediately after birth or there is insufficient information to assess conformity to case definition but the physician diagnosed or suspected withdrawal syndrome, and including 6 literature cases[1,3,4,5]

43 excluded cases:

- 14 cases in which adverse reaction was present at birth
- 10 cases with *in utero* exposure to other drugs associated with withdrawal syndromes (8 benzodiazepine, 1 opiate, 1 desipramine[1])
- 10 cases of adverse events other than neonatal withdrawal (3 adverse events occurring in adults, 2 congenital anomalies, 1 hypoglycemia[1], 1 hyponatremia, 1 hypoxia, 1 infection, 1 narcotizing enterocolitis[1])
- 6 cases in which timing was not consistent with paroxetine withdrawal after birth (4 cases in which paroxetine was discontinued at least 2 months before birth, 1 case in which signs are ongoing 3 months after birth, 1 case of withdrawal after discontinuation of breastfeeding)
- 2 cases in which time to onset of adverse reaction was unclear
- 1 case in which the timing of paroxetine use in relation to birth was unclear

Sertraline (half-life 26 hours, total number of reports in AERS – 24,028)
33 unduplicated cases:

- *8 cases of possible neonatal withdrawal from sertraline*

25 excluded cases:

- 11 cases of adverse events other than neonatal withdrawal (3 congenital anomalies, 3 adverse events with breastfeeding, 1 cerebral palsy, 1 meningitis, 1 calming with breast feeding, 1 hypocalcemia, 1 withdrawal in the mother)
- 6 cases in which adverse reaction was present at birth
- 4 cases with insufficient information to allow assessment
- 2 cases in which timing was not consistent with sertraline withdrawal after birth (1 case in which sertraline was discontinued 6 months before birth, 1 case in which signs are ongoing 2 years after birth)
- 2 cases in which time to onset of adverse event was unclear

Venlafaxine (half-life venlafaxine 5±2 hours, half-life O-desmethylvenlafaxine [active metabolite] 11±2 hours, total number of reports in AERS – 9216)
22 unduplicated cases:

- *3 cases of possible neonatal withdrawal from venlafaxine*

19 excluded cases:

- 8 cases with *in utero* exposure to other drugs associated with withdrawal syndromes (4 benzodiazepines, 2 opiates, 2 clomipramine)
- 6 cases of adverse events other than neonatal withdrawal (2 withdrawal in the mother, 1 congenital anomaly, 1 stillbirth, 1 adverse reaction to drug exposure via breast feeding, 1 jaundice and sepsis)
- 5 cases in which adverse reaction was present at birth

Search Results - cases (continued):
Among the 78 unduplicated paroxetine cases were 4 necrotizing enterocolitis cases. These 4 paroxetine cases will be reviewed in a subsequent document. These cases include one in which paroxetine was discontinued in the 5th month of pregnancy, arguing against a relation between necrotizing enterocolitis and withdrawal. No necrotizing enterocolitis cases were retrieved for the other SRIs.

Very brief summaries of some pertinent aspects of the accepted cases follows. See *Attachment 1: Characteristics of Case Series – Possible Cases of Neonatal SRI Withdrawal* for more detailed information about the series of possible cases.

More than half of the cases are from foreign sources, except for sertraline and venlafaxine. Only one case, for sertraline, predates 1997. For paroxetine, the number of cases increases each year from 1 in 1997 to 11 in 2001. Although they have far fewer cases, and year-to-year differences may be random, citalopram and sertraline also have increasing numbers of cases with time. Whether this reflects increased usage, increased awareness of the withdrawal phenomenon, or some other factor is unknown.

Maternal age is not reported in most cases. Depression is the most commonly reported maternal illness. Reported SRI dosages are within labeled recommendations except for one venlafaxine case reporting a dosage of 450 mg per day. Other maternal drugs used included alcohol, cigarettes, and marijuana. Alcohol use in the accepted cases was reported as occasional or "some." Nicotine cessation is known to induce withdrawal and perhaps these cases should have been excluded. However, cigarette use is distributed among the SRIs and appears in very few cases. Marijuana use appears in only one sertraline case.

Most births occurred at term with very few cesarean sections performed. Male infants slightly outnumbered female infants. Reported birth weights ranged from 0.86 kg in one fluoxetine case to 4.23 kg in one citalopram case, with almost all reported weights above 2.7 kg. Times to withdrawal onset ranged from birth to 7 days. The longest median time to onset was 1.5 days for fluoxetine, as expected from it's long half-life. Treatment involved hospitalization in almost all cases reporting treatment modalities. Three neonates received antibiotics on the suspicion of infection, however, infections were not confirmed.

Reported withdrawal effects are similar for all SRIs with excitatory nervous and neuromuscular effects predominating. These include irritability, jitteriness, agitation, crying, hyperreflexia, hypertonia, and seizures or seizure-like movements. Breathing difficulties, including tachypnea, apnea, and respiratory distress, and feeding difficulties were also seen. In a few cases, difficulty with temperature regulation was reported. Although symptoms of SRI withdrawal reported by adults, such as anxiety and headache, cannot be observed in neonates, signs observed in these neonates correspond to signs included in paroxetine and venlafaxine labeling as associated with adult withdrawal. These signs include agitation, tremor, and vomiting. For a complete list of reported effects, see *Attachment 2: Reported Withdrawal Effects.*

Resolution or improvement was noted in the vast majority of cases. However, it must be noted that the case definition specifies withdrawal is a transient event. Therefore, when signs persisted beyond a few months, cases were excluded. Resolution required 2 months in one case each for fluoxetine and paroxetine.

For summaries of selected cases, see *Attachment 3: Selected Case Summaries.*

Discussion:

For fluoxetine ($T_{1/2}$ 1-2 weeks), citalopram ($T_{1/2}$ 35 hrs), sertraline ($T_{1/2}$ 26 hrs), paroxetine ($T_{1/2}$ 21 hrs), fluvoxamine ($T_{1/2}$ 15 hrs), and venlafaxine ($T_{1/2}$ 11 hrs), respectively, 4, 5, 8, 35, 2, and 3 possible cases of neonatal withdrawal related to maternal use of the SRI were retrieved from AERS. These represent the following proportions of possible neonatal withdrawal cases to total reports in AERS for each drug: fluoxetine ($4 / 46{,}128 = 8.7 \times 10^{-5}$), sertraline ($8 / 24{,}028 = 3.3 \times 10^{-4}$), venlafaxine ($3 / 9216 = 3.3 \times 10^{-4}$), fluvoxamine ($2 / 3147 = 6.4 \times 10^{-4}$), citalopram ($5 / 4069 = 1.2 \times 10^{-3}$), paroxetine ($35 / 12{,}439 = 2.8 \times 10^{-3}$). Thus, fluoxetine has the smallest proportion of neonatal withdrawal cases and paroxetine has the largest proportion of neonatal withdrawal cases. This is in keeping with limited studies of withdrawal in adult patients and with the idea that longer half-life drugs are less likely than shorter half-life drugs to produce withdrawal symptoms when discontinued.[12,13,14] However, based on half-life alone, paroxetine has a higher proportion and venlafaxine has a lower proportion of possible neonatal withdrawal cases than expected.

As a comparison, the SRIs may be ranked by increasing proportion of unevaluated AERS reports of drug withdrawal syndrome (a MedDRA preferred term) to total AERS reports as follows: fluoxetine ($450 / 46{,}128 = 9.7 \times 10^{-3}$), citalopram ($49 / 4069 = 1.2 \times 10^{-2}$), fluvoxamine ($49 / 3147 = 1.6 \times 10^{-2}$), sertraline ($623 / 24{,}028 = 2.3 \times 10^{-2}$), paroxetine ($1345 / 12{,}439 = 1.1 \times 10^{-1}$), and venlafaxine ($1182 / 9216 = 1.3 \times 10^{-1}$). In proportion of AERS drug withdrawal syndrome reports, venlafaxine ranks highest, as predicted by it's short half-life. Paroxetine still ranks higher than fluvoxamine, a shorter half-life drug, as does sertraline. However, paroxetine is five-fold higher than fluvoxamine.

Time to resolution is also longer than expected for paroxetine. Time to resolution ranged from 5 hours to 2 months with a median of 10 days for paroxetine. Fluoxetine, with a half-life of days and an active metabolite with a half-life of up to 2 weeks, was the only other drug with a case reporting 2 months to resolution.

Whether neonatal withdrawal is disproportionately higher with paroxetine cannot be determined from these spontaneous data. Also, the small numbers of cases with the other SRIs makes comparisons less reliable. Similarly, studies of withdrawal in adults have included only paroxetine, fluoxetine, and sertraline[12,14]. While the greatest number of cases in the studies occurred with paroxetine, it is the shortest half-life drug among the three drugs and, therefore, expected to have the most withdrawal cases.

The reported withdrawal effects are similar to those of serotonin toxicity.[11] Isbister et al. point out the similarities between signs attributed to neonatal SRI withdrawal and signs of serotonin toxicity and the importance of avoiding misdiagnosis.[15] However, the exclusion of cases with onset immediately after birth unless withdrawal was suspected or diagnosed helps to eliminate serotonin toxicity cases from these withdrawal case series. The median times to onset of withdrawal signs from birth range from 10 hours with venlafaxine to 1.5 days with fluoxetine. Thus, it is not likely that the cases accepted as possible withdrawal syndrome actually represent serotonin toxicity, which would be present at birth in all cases.

Conclusions:

It can be seen from this review that neonatal withdrawal may occur after pregnancies with chronic exposure up to birth to any of the included SRI medications. This evidence is strongest for paroxetine. For the information of physicians, we recommend inclusion in the pregnancy section of labeling for paroxetine and possibly citalopram, fluoxetine, fluvoxamine, sertraline, and venlafaxine a statement such as, "There have been reports of withdrawal, seen as primarily excitatory nervous and neuromuscular signs, including seizures in some cases, breathing and feeding difficulties, and, rarely, difficulty maintaining body temperature, in neonates born to mothers who received a serotonin reuptake inhibiting medication in late pregnancy up to birth. Reported cases of withdrawal syndrome have resolved completely with symptomatic treatment. Withdrawal syndrome should be considered in differential diagnosis of a neonate with chronic *in utero* exposure to [the specific SRI] up to birth who exhibits such signs."

References:

1. Stiskal JA, Kulin N, Koren G, et. al. Neonatal paroxetine withdrawal syndrome. Arch Dis Child Fetal Neonatal Ed 2001;84:F134-5.
2. Kent LSW, Laidlaw JDD. Suspected congenital sertraline dependence [letter]. Br J Psychiatry 1995 Sep;167(3):412-3.
3. Nordeng H, Lindemann R, Perminov KV, et al. Neonatal withdrawal syndrome after in utero exposure to selective serotonin reuptake inhibitors. Acta Paediatr 2001;90:288-91.
4. Nijhuis IJM, Kok-Van Rooij GWM, Bosschaart AN. Withdrawal reactions of a premature neonate after maternal use of paroxetine [letter]. Arch Dis Child Fetal Neonatal Ed 2001 Jan;84(1):f77.
5. Dahl ML, Olhager E, Ahlner J. Paroxetine withdrawal syndrome in a neonate [letter]. Br J Psychiatry 1997;171:391-2.
6. Cohen LS, Heller VL, Bailey JW, et al. Birth outcomes following prenatal exposure to fluoxetine. Biol Psychiatry 2000;48:996-1000.
7. Goldstein DJ. Effects of third trimester fluoxetine exposure on the newborn. J Clin Psychopharmacol 1995 Dec;15(6):417-20.
8. Chambers CD, Johnson KA, Dick LM, et al. Birth outcomes in pregnant women taking fluoxetine. NEJM 1996 Oct;335(14):1010-15.
9. Schatzberg AF, Haddad P, Kaplan EM, et al. Serotonin reuptake inhibitor discontinuation syndrome: a hypothetical definition. J Clin Psychiatry 1997;58 (Suppl 7): 5-10.
10. American Academy of Pediatrics Committee on Drugs. Neonatal drug withdrawal. Pediatrics 1998 Jun; 101(6):1079-88.
11. Mason PJ, Morris VA, Balcezak TJ. Serotonin syndrome: presentation of 2 cases and review of the literature. Medicine 2000; 79(4): 201-9.
12. Rosenbaum JF, Fava M, Hoog SL, et al. Selective serotonin reuptake inhibitor discontinuation syndrome: a randomized clinical trial. Biol Psychiatry 1998 Jul; 44(2):77-87.
13. Stahl MMS, Lindquist M, Pettersson M, et al. Withdrawal reactions with selective serotonin re-uptake inhibitors as reported to the WHO system. Eur J Clin Pharmacol 1997; 53(3-4):163-9.
14. Michelson D, Fava M, Amsterdam J, et al. Interruption of selective serotonin reuptake inhibitor treatment. Double-blind, placebo-controlled trial. Br J Psychiatry 2000 Apr; 176:363-8.
15. Isbister GK, Dawson A, Whyte IM, et al. Neonatal paroxetine withdrawal syndrome or actually serotonin syndrome? [letter] Arch Dis Child Fetal Neonatal Ed 2001 Sep; 85(2):F147-8.

Reviewer's Signature / Date:	**Team Leader's Signature / Date:**

Division Director Signature / Date:

Attachments:

1. Characteristics of Case Series – Possible Cases of Neonatal SRI Withdrawal
2. Reported Withdrawal Effects
3. Selected Case Summaries

Attachment 1
Characteristics of Case Series – Possible Cases of Neonatal SRI Withdrawal

	Citalopram (n=5)	Fluoxetine (n=4)	Fluvoxamine (n=2)	Paroxetine (n=35)	Sertraline (n=8)	Venlafaxine (n=3)
Total AERS reports	4069	46,128	3147	12,439	24,028	9216
Report source	US-2, foreign-3	US-0, foreign-4	US-0, foreign-2	US-7, foreign-28	US-5, foreign-3	US-2, foreign-1
Report type	15day-4, direct-1, literature-1[3]	15day-4, literature-1[3]	15day-2	15day-34, direct-1, literature-6[1,3,4,5]	15day-5, direct-2 periodic-1	15day-3
Year received by FDA	2000-2 2001-3	1998-1 1999-1 2000-1 2001-1	1997-1 1999-1	1997-1 1998-5 1999-8 2000-10 2001-11	1995-1 1997-2 1999-3 2001-2	2000-2 2001-1
Mother's age (yrs)	29, 39 unknown-3	26 unknown-3	unknown-2	31, 34, 36, 39 unknown-31	24, 32 unknown-6	19 unknown-2
Mother's illnesses • nos = not otherwise specified # includes one set of twins with these exposures; each twin counted separately	depression-4 bipolar-1 hypertension-1 c-section-1 unknown-1	depression-2 unknown-2	depression-1 c-section-1	depression-8 UTI-3# anxiety-2 bulimia-1 schizophrenia-1 paranoid disorder-1 infection nos*-1 c-section-3# unknown-22	depression-4 schizophrenia-2 allergies nos-1 asthma-1 hepatitis C+-1 PMDD-1 c-section-1 unknown-2	depression-2 unknown-1
SRI daily dose at end of pregnancy	20 mg (n=1) 30 mg (n=1) 40 mg (n=3)	20 mg (n=3) unknown-1	unknown-2	mean 27 mg median 25 mg range 10-50 mg unknown-11	mean 121 mg range 25-200 mg unknown-2	112.5 mg (n=1) 150 mg (n=1) 450 mg (n=1) unknown-0
Gestation	≥37 wks-5	≥37 wks-1 <37 wks (27) –1 unknown-2	≥37 wks-2	≥37 wks-15 <37 wks (33-35) –4 unknown-16	≥37 wks-6 unknown-2	≥37 wks-1 unknown-2

Attachment 1 (continued)
Characteristics of Case Series – Possible Cases of Neonatal SRI Withdrawal

	Citalopram (n=5)	Fluoxetine (n=4)	Fluvoxamine (n=2)	Paroxetine (n=35)	Sertraline (n=8)	Venlafaxine (n=3)
Neonate's gender	M-3, F-2	M-3, F-1	M-1, F-1	M-13, F-12, unknown-10	M-3, F-1, unknown-4	M-2, unknown-1
Neonate's weight (kg)	2.72, 2.91, 3.4, 3.5, 4.23	0.86, 2.74, 3.2 unknown-1	3.01, 3.14	range 1.9-4.16 mean 3.1 median 3.1 unknown-20	2.75, 3.4 unknown-6	3.24 unknown-2
Apgar scores** 1 min 5 min 10 min single scores	 5, 5, 8, 8 7, 7, 9, 10 8, 9, 10 8	unknown-2 8,9 9,10	 9, 9 10, 10	unknown-22 mean 7 (1-9) mean 8.5 (6-10) mean 8.8 (6-10) 8, 10	unknown-6 7,7 8,9 9	unknown-3
Time from birth to onset of signs of withdrawal	birth to 6 days median 12 hours unknown-0	7 hours to 7 days median 1.5 days unknown-0	"a few hours," 2 days	birth to 5 days median 18 hours unknown-16	birth to 3.5 days median 21.5 hours unknown-2	10 hours unknown-2
Reporter's assessment	diagnosed or suspected w/d-4	diagnosed or suspected w/d-3	diagnosed or suspected w/d-1	diagnosed or suspected w/d-30	diagnosed or suspected w/d-6	diagnosed or suspected w/d-3
Treatment of withdrawal # includes one set of twins with these treatments; each twin counted separately	hospitalization-5 phenobarbital-1 ventilation-1	hospitalization-4 phenobarbital-1 clobazam-1 ventilation-1	hospitalization-2	hospitalization-21# chlorpromazine-5 phenobarbital-4 clonazepam-1 naloxone-1 hydroxyzine-1 antibiotic-1 tube feeding-4 IV fluid-3# oxygen-2 bladder catheter-1 unknown-11	hospitalization-4 phenobarbital-1 antibiotic-1	hospitalization-1 phenobarbital-2 antibiotics-1 oxygen-1

Attachment 1 (continued)
Characteristics of Case Series – Possible Cases of Neonatal SRI Withdrawal

	Citalopram (n=5)	Fluoxetine (n=4)	Fluvoxamine (n=2)	Paroxetine (n=35)	Sertraline (n=8)	Venlafaxine (n=3)
Outcome (time to reported outcome)	resolved-1 (5 days) improved-3 (3 days, 7 days, 18 days) ongoing-1 (8 days)	resolved-4 (2 days, 1 week, 2 months)	resolved-1 improved-1 (5 days)	resolved-20 (median 10 days, range 5 hours to 2 months) improved-5 (18 days, 3.5 weeks, <2 months) ongoing-2 (2 days, 86 hours) unknown-8	resolved-4 (1 day, 2 weeks) improved-3 (8 hours, 1 day, 36 hours) unknown-1	resolved-1 (2 days) unknown-2
Other drug exposure at end of pregnancy # includes one set of twins with these exposures; each twin counted separately	none-1 cigarettes-1 alcohol-2 olanzapine-1 labetalol-1	none-2 cigarettes-1 alcohol-1 marijuana-1		cigarettes-3 cefuroxime-2# metronidazole-2# dexamethasone-2# alcohol-1 aminophylline-1 acetaminophen-1 risperidone-1 salbutamol-1 Rhogam-1 trimethoprim-1	none-1 cigarettes-2 risperidone-2 marijuana-1 diphenhydramine-1 pseudoephedrine-1 albuterol prn-1	none-1 valproic acid-1
Breast-fed after birth	no-2 unknown-3	yes-1, no-1 unknown-2	unknown-2	yes-1, no-2 unknown-32	no-1 unknown-7	unknown-3

* nos = not otherwise specified

** When report did not specify time associated with Apgar scores, two scores were assumed to represent 1 minute and 5 minute scores. Single scores are reported as single scores with no assumptions made about timing.

One set of twins was exposed to these medications or conditions. Each twin counted separately.

Attachment 2 Reported Withdrawal Effects					
Citalopram (n=5)	**Fluoxetine (n=4)**	**Fluvoxamine (n=2)**	**Paroxetine (n=35)**	**Sertraline (n=8)**	**Venlafaxine (n=3)**
posturing-3 seizure-2 hypertonia-2 jittery-2 irritable-2 shivering-1 apneic episodes-1 tachypnea-1 gasping-1 hypothermia-1	hypotonia-2 irritable-2 shivering-1 trembling-1 seizure-1 hypertonia-1 extremity spasms-1 grimacing-1 hyperreflexia-1 agitation-1 hyperactive-1 excitable-1 shallow resp-1 sleep apnea-1 trouble feeding-1 malaise-1 EEG agitation-1	agitation-1 tears-1 myoclonus-1	irritable-13 hypertonia-11 trouble feeding-10 tremor-8 jittery-8 seizures-5 tachypnea-4 vomiting-4 crying-3 trouble breathing-3 posturing-3 agitation-3 screaming-3 jerkiness-2 hypothermia-2 not crying-2 respiratory distress-2 high-pitched cry-2 listlessness-1 hypotonia-1 apathy-1 hypoventilation-1 inconsolable-1 temp unstable-1 deregulated tonus-1 urine retention-1 twitching-1 EEG abnormality-1 tense-1 shivering-1 hyperreflexia-1 grimacing-1 bradycardia-1 neurologically active-1 uneasiness-1 lethargy-1 trouble sleeping-1	jittery-4 tremor-4 agitation-3 hypertonicity-3 tachypnea-2 trouble feeding-2 irritable-2 trouble breathing-2 loose, frequent stools-1 hyperreflexia-1 hyperresponsiveness-1 seizure-like movements-1 increased temp-1 shaking-1 leg rigidity-1 high-pitched scream-1	hyperirritable-1 constant crying-1 jerking of limbs-1 hypotonicity-1 respiratory distress-1 bradycardic episodes-1

Attachment 3
Selected Case Summaries

Paroxetine
AERS ISR# 3366038-0, MFR# 1999025030-2, 1999, Sweden.
Dahl ML, et al. Paroxetine withdrawal syndrome in a neonate. Br J Psychiatry 1997; 171:391-2.
A 36-year-old woman began treatment with paroxetine 30 mg per day during the sixth month of pregnancy for depression. A male infant was born at 39 weeks gestation. Apgar scores were 9-10-10. He was not breast fed. At 12 hours of age, he developed an increased respiratory rate (80 BPM) and jitteriness. In the next few hours, he developed increased muscle tone and tremor. Lab tests, including C-reactive protein, hemoglobin, blood gases, blood glucose, electrolytes, ionized calcium, and brain ultrasound, were all normal. He was diagnosed with neonatal paroxetine withdrawal syndrome. During the third and fourth days of life, signs resolved except for jitteriness. By 1 month of age, all signs had resolved without sequelae. Neonatal paroxetine levels were measured at 68 nmol/L at age 1 day, 75 nmol/L at age 2 days, and 23 nmol/L at age 3 days.

Venlafaxine
AERS ISR# 3447521-6, MFR# HQ0357907JAN2000, 2000, US.
A 19-year-old woman began treatment with venlafaxine 75 mg per day during the third month of pregnancy for depression. Venlafaxine dose was increased to 112.5 mg per day 1 week before term delivery of a 7 pound, 2 ounce male. Ten hours after delivery, the neonate had decreased tone and respiratory distress. Cardiology exam, lung exam, complete blood count, and blood cultures were all normal. Treatment with ampicillin and gentamycin was initiated for possible pneumonia, although chest x-ray was clear. Subsequently, he experienced episodes of apnea, bradycardia, and cyanosis and required supplemental oxygen via nasal canula for 3.5 days. The reporting pharmacist stated that, "although symptoms were not consistent with those associated with Effexor withdrawal, we could not find any other clinical reasons for the infant's symptoms."

Fluoxetine
AERS ISR# 3215119-0, MFR# EWC990202789, 1999, France.
A 26-year-old woman began treatment with fluoxetine 20 mg per day during the second trimester of pregnancy for depression. A female infant was born 10 days before her due date. The neonate weighed 2.74 kg and had Apgar scores of 8 at 1 minute and 10 at 10 minutes. At 7 days old, the neonate had a half-hour episode of malaise with hypotonia and was transferred to neonatal intensive care. EEG showed agitation and sleep records showed apnea. Holter recording, ECG, and transfontenel ultrasound were normal. At 6 months of age, the infant is growing normally and has no malaise. The physician stated the symptoms were possibly due to fluoxetine withdrawal. The mother also used alcohol and cigarettes during the pregnancy.

Sertraline
AERS ISR# 1615096, MFR# 9501959, 1995, US.
A 32-year-old woman took sertraline 200 mg per day throughout her pregnancy for depression and PMDD. She was taking no other medications. She delivered her child at term. At 14 to 18 hours of age, the neonate experienced respiratory problems, possibly apnea, and was transferred to neonatal intensive care. At 4 days of age, the neonate exhibited shaking, tremor, leg rigidity, irritability and high-pitched screaming. Testing, including spinal tap, complete blood count, SMA-23, urinalysis, chest x-ray, and thyroid check, was normal. The neonate recovered at an unspecified time.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Kathleen Phelan
11/27/01 08:13:26 AM
PHARMACIST

Julie Beitz
11/27/01 12:32:29 PM
DIRECTOR

DAVID

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

APR 12 1999

NDA 18-936
NDA 20-101

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

Dear Dr. Brophy:

Reference is made to your Proposed Pediatric Study Request submitted on July 23, 1998 to your New Drug Applications for Prozac (fluoxetine hydrochloride) capsules (NDA 18-936) and solution (NDA 20-101).

We have completed our review of your submission and conclude that your proposed pediatric study request is inadequate. We will provide specific comments detailing deficiencies in your proposal in sections below entitled "Specific Comments on Your Proposed Program for Developing a Drug for Pediatric Depression" and "Specific Comments on Your Proposed Program for Developing a Drug for Pediatric Obsessive Compulsive Disorder," following more general discussions of the kind of information needed to support the safety and effectiveness of Prozac in pediatric populations, in particular, in pediatric patients with either depression or obsessive compulsive disorder.

To obtain needed pediatric information on fluoxetine, 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 following:

PEDIATRIC DEPRESSION

General Advice for Developing a Drug for Pediatric Depression

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

Objective:
The overall goal of the development program would be 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.

Types of Studies:

1. In keeping with the overall objective of a pediatric depression development program, there would need to be a minimum of two adequate and well-controlled trials (to be defined under design below) to determine the effectiveness of the study drug in the treatment of pediatric depression.

2. In addition, there would need to be pharmacokinetic data 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. Data should be collected 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 bioavailability (AUC), half-life, C_{max},

and t_{max} 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, under Clinical/Pharmacological (Draft)].

3. Safety data could come from the controlled efficacy trials, as well as from longer-term open extensions from these trials and/or separate longer-term open safety studies.

Population/Sample Size:
The protocols should include a valid and reliable diagnostic method for recruiting children and adolescents with major depressive disorder (MDD). 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. 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.

Study Design:
For the controlled efficacy studies, ordinarily the design should be for a randomized, double-blind, parallel group, placebo-controlled acute treatment trial, with a recommended duration of 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 should 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.

Efficacy Assessments:
The efficacy assessments should include a validated symptom rating scale specific to pediatric depression and expected to be 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).

Safety Assessments:
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.

Efficacy Endpoints/Statistical Plan:
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. 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.

Specific Comments on Your Proposed Program for Developing a Drug for Pediatric Depression

In your July 23, 1998 proposed pediatric study request for fluoxetine, you proposed to submit the results from two double-blind, randomized, short-term, placebo-controlled trials of fluoxetine in pediatric depression, i.e., studies X065 and HCJE. Study X065 is, in fact, the Emslie, et al, study referred to above, i.e., an 8-week trial evaluating fluoxetine 20 mg/day, and as discussed with you in a March 24, 1998 meeting, you plan to obtain the actual data for this trial and submit a full study report according to usual regulatory standards. Study HCJE is your own trial, and includes a 32-week relapse prevention phase. Study HCJE, a 9-week trial evaluating fluoxetine 10-20 mg/day, was also discussed at our March 24, 1998 meeting, and we reached agreement at that time that these two studies, as designed, would meet our requirement for two adequate and well-controlled efficacy trials in pediatric depression.

You note in your request that there is no evidence to suggest a meaningful difference between adults and pediatric patients in the adverse event or pharmacokinetic profiles for fluoxetine. You further note that both adverse event and serum concentration data will be available for studies X065 & HCJE.

We have the following comments:

- A more detailed statistical plan for both studies X065 & HCJE is needed.
- As discussed at our March 24, 1998 meeting, we do not consider your designated primary outcome measure, i.e., proportion of patients achieving a $\geq$ 30% reduction from baseline to endpoint on the CDRS-R to be the best choice for a primary outcome, and we will consider other measures as well in our overall judgement regarding the outcome of these trials.
- Your request should provide more detail regarding how you will address questions on the safety and pharmacokinetics of fluoxetine in patients with pediatric depression.

PEDIATRIC OBSESSIVE COMPULSIVE DISORDER (OCD)

General Advice for Developing a Drug for Pediatric Obsessive Compulsive Disorder (OCD)

Background Comments on Pediatric OCD

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 OCD 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, and 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. In the case of OCD, we believe a sufficiently strong case has been made for continuity between adult and pediatric OCD to permit a pediatric claim for a drug already approved in adults to be supported by a single independent, adequate and well controlled clinical trial in pediatric OCD. In addition, a pediatric OCD program would need to include pharmacokinetic information and safety information in the relevant pediatric age groups. For pediatric OCD, 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 OCD

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

Types of Studies:

1. In keeping with the overall objective of a pediatric OCD development program, there would need to be a minimum of one adequate and well-controlled trial (to be defined under design below) to determine the effectiveness of the study drug in the treatment of pediatric OCD.

2. In addition, there would need to be pharmacokinetic data 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 from other safety trials. Please refer to the previous paragraph under "Specific Study Requirements for Development Program in Pediatric Depression".

3. Safety data could come from the controlled efficacy trials, as well as from longer-term open extensions from these trials and/or separate longer-term open safety studies.

Population/Sample Size:
The protocols should include a valid and reliable diagnostic method for recruiting children and adolescents with OCD. 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. 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 other positive trials in pediatric OCD have utilized samples of roughly 45-95 patients in each treatment arm.

Study Design:
For the controlled efficacy study, ordinarily the design should be for a randomized, double-blind, parallel group, placebo-controlled acute treatment trial, with a recommended duration of 10 to 12 weeks. Ideally the study would 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 should be stratified by the two age groups studied. Ideally, a relapse prevention trial would follow from the acute treatment trial, 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.

Efficacy Assessments:
The efficacy assessments should include a validated symptom rating scale specific to pediatric OCD and expected to be sensitive to the effects of drug treatment of pediatric OCD, e.g., the Children's Yale-Brown Obsessive Compulsive Scale (CYBOCS), and a global measure, e.g., the Clinical Global Impression (CGI).

Safety Assessments:
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 study demonstrates efficacy in pediatric OCD.

Efficacy Endpoints/Statistical Plan:
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 trial. This trial should have a detailed statistical plan. Ordinarily this trial should be designed with at least 80% statistical power to detect a treatment effect of conventional ($p=0.05$) statistical significance.

Specific Comments on Your Proposed Program for Developing a Drug for Pediatric OCD

Your July 23, 1998 proposed pediatric study request for fluoxetine did not include any mention of your plans for conducting a pediatric OCD study and submitting the results of such a study. We understand that you may have access to data from a study in pediatric OCD that is underway, i.e., study —— The failure to address pediatric OCD in your proposed pediatric study request is a major deficiency that needs to be addressed before we can reach agreement on your pediatric plan for fluoxetine. Consequently, we ask that you amend your request with details regarding the pediatric OCD indication. This amendment should address recommendations included above under the heading "General Advice for Developing a Drug for Pediatric Obsessive Compulsive Disorder (OCD)."

MISCELLANEOUS ISSUES

Labeling That May Result from the Studies

As agreed in the March 24, 1998 meeting, the two depression studies described in your request, if positive, could result in the addition to labeling of information pertinent to these studies. Similarly, a positive study in OCD could result in the addition to labeling of information pertinent to that study.

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 2 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 these studies to your investigational new drug application (IND) for fluoxetine 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 recognize that protocol HCJE has already been submitted to your IND for fluoxetine.)

To avoid uncertainty, we recommend you seek a written agreement with FDA before developing pediatric studies. Please notify us as soon as possible if you wish to negotiate a written agreement by submitting a proposed written agreement. Please 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.

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

Sincerely yours,

/S/ 4/1/99

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

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

NDA 18-936
NDA 20-101

MAY 19 1999

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

Three Years From the Date of The Original WR APR 12 2002

Dear Dr. Brophy:

Reference is made to your Proposed Pediatric Study Request submitted on July 23, 1998 to your New Drug Applications for Prozac (fluoxetine hydrochloride) capsules (NDA 18-936) and solution (NDA 20-101).

We additionally refer to an Agency letter dated April 12, 1999, providing for a pediatric Written Request (WR) to the above Prozac applications.

We are issuing this amended WR to clarify the mandatory terms of the Written Request. Please refer to this amended Written Request to determine the requirements you must fulfill to meet the terms of the Written Request.

To obtain needed pediatric information on fluoxetine, the Food and Drug Administration (FDA) is hereby making a formal amended 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 and Obsessive Compulsive Disorder (OCD) described below.

PEDIATRIC DEPRESSION

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 trials, 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].

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 Studies 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 fluoxetine 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, 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 fluoxetine in adults, nor have specific concerns been identified during the postmarketing experience.

PEDIATRIC OBSESSIVE COMPULSIVE DISORDER (OCD)

Background Comments on Pediatric OCD

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 OCD 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, and 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. In the case of OCD, we believe a sufficiently strong case has been made for continuity between adult and pediatric OCD to permit a pediatric claim for a drug already approved in adults to be supported by a single independent, adequate and well controlled clinical trial in pediatric OCD. In addition, a pediatric OCD program would need to include pharmacokinetic information and safety information in the relevant pediatric age groups. For pediatric OCD, we consider the relevant age groups to include children (ages 7 through 11) and adolescents (ages 12 through 17). In keeping with the overall objective of a pediatric OCD development program, there would need to be a minimum of one adequate and well-controlled trial (to be defined under design below) to determine the effectiveness of the study drug in the treatment of pediatric OCD.

Specific Study Requirements for Development Program in OCD

Types of Studies

Pediatric Efficacy and Safety Studies
Pediatric Pharmacokinetic Study
Pediatric Safety Study

Objective/Rationale

The overall goal of the development program would be to establish the safety and efficacy of the study drug in the treatment of pediatric OCD, 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 study, the design must be a randomized, double-blind, parallel group, placebo-controlled acute treatment trial, with a recommended duration of at least 10 to 12 weeks. Ideally the study would 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 should be stratified by the two age groups studied. Ideally, a relapse prevention trial would follow from the acute treatment trial, 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

- In addition, there would need to be pharmacokinetic data 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 from other safety trials. Please refer to the previous paragraph under "Specific Study Requirements for Development Program in Pediatric Depression".

Pediatric Safety Study

- Safety data could come from 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. Safety data will also be available, of course, from the pediatric depression studies.

Age Group in Which Studies 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 other positive trials in pediatric OCD have utilized samples of roughly 45-95 patients in each treatment arm.

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 fluoxetine 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 OCD.

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 trial.

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
- This trial should have a detailed statistical plan. Ordinarily this trial 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
- The efficacy assessments should include a validated symptom rating scale specific to pediatric OCD and expected to be sensitive to the effects of drug treatment of pediatric OCD, e.g., the Children's Yale-Brown Obsessive Compulsive Scale (CYBOCS), 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, 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 efficacy.

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 fluoxetine in adults, nor have specific concerns been identified during the postmarketing experience.

Labeling That May Result from the Studies
The pediatric depression efficacy, safety, and pharmacokinetic studies described in this request could result in the addition to labeling of information pertinent to these studies. Similarly, the data generated from the OCD efficacy, safety, and pharmacokinetic studies described in this request 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.

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

Sincerely yours,

/S/

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