CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 20-793

CORRESPONDENCE

Memorandum

To: NDA 20-793, CAFCIT
From: Hilary V. Sheevers - Pharm./Tox. Team Leader
Re: Team Leader NDA Summary, HFD 570
Date: January 13, 1998 (15) 1-13-98

Cafcit is an injectable form of caffeine intended for neonates diagnosed with apnea of prematurity; the proposed dosage is 10 mg/kg loading dose (IV) followed by a 2.5 mg/kg maintenance dose (IV or oral).

Overall Recommendation (Pharm/Tox): Approval/able

Outstanding Issues: Update labeling; marked-up copy given to the project manager

Summary of Significant Preclinical Studies:

No preclinical studies were performed for this application due to the large amount of preclinical literature available on caffeine, the current off-label use of caffeine in the intended population, and because of the relatively short course of dosing proposed by the sponsor and studied in patients. The label and general knowledge of the toxicological potential of caffeine are taken from the scientific literature.

The general toxicology studies for the most part indicate a toxicity profile associated with an exaggerated pharmacological effect common to methyl xanthines, including diuresis, polydipsia, cardiovascular effects/toxicity, and CNS excitation. Other effects, such as organ weight changes and histological changes in a variety of organs are associated with high doses and /or long-term exposure. Of continuing concern for neonates is the finding of **necrotizing enterocolitis** (NEC). In one bowel ischemia study in weanling rats with aminophylline (a methyl xanthine) in which the GI was clamped and then reperfused, an increased incidence and/or severity of bowel necrosis, bowel perforation, and bacterial overgrowth following reperfusion was noted in the treated animals. The finding of NEC associated with methyl xanthines continues to be an incompletely addressed concern in neonates.

In **reproduction studies,** caffeine caused an increase in cleft palate and exencephaly in mice, and resulted in decreased male reproductive performance in rats when given prior to dosing. Doses were comparable to the clinical doses proposed in this NDA. However, these data are not applicable to neonates due to their young age. The data are included for completeness of the label, and in the pregnancy section the data are introduced in the label with the statement "The

concern for teratogenicity of caffeine is not relevant to infants."

Carcinogenicity of caffeine has been evaluated in a variety of studies. Caffeine was not carcinogenic in a 2-year rat study and an 18-month mouse study at doses at or near the dose proposed in this NDA. These studies appear to be acceptable studies, although we do not know if they would meet today's scientific and regulatory standards due to the relative brevity of reports in the literature. Carcinogenicity studies, however, would normally not have been requested given the proposed short dosing interval of this drug. Again, the studies are included in the label for completeness.

In **Mutagenicity** studies, caffeine appears to potentiate the mutagenicity associated with several genotoxins and enhanced micronuclei formation in folate-deficient mice. In other studies, which include lymphocyte assays and a gene mutation assay, caffeine was negative. In one literature report (MacGregor, 1990) dietary deficiencies, such as folate deficiencies, reportedly may increase the risk of spontaneous chromosomal damage when combined with other factors such as caffeine exposure. This study was preliminary, and has not been followed up with additional studies reported in the literature (personal communication with the author). Without additional information, the pertinence of this study to neonates dosed with caffeine for 10 days appears to be minimal.

Labeling changes are noted in the pharmacology review, and marked up copy has been given to the project manager. The changes from the sponsor's proposed label were made to update the label and reflect recent language conformities.

CC: Division file, Cobbs, Chun

APPEARS THIS WAY
ON ORIGINAL

Printed by Michael Klein

Electronic Mail Message

Sensitivity: COMPANY CONFIDENTIAL

Date: 27-Jan-1998 09:18am
From: Douglas Kramer
KRAMERD
Dept: HFD-170 PKLN 9B45
Tel No: 301-443-4250 FAX 301-443-7068

TO: Cynthia McCormick (MCCORMICKC)

CC: Michael Klein (KLEINM)
CC: Celia Winchell (WINCHELLC)
Subject: Caffeine

Cynthia,
Spoke to Mike Klein this morning. He confirmed that he was not planning to write anything else on the caffeine consult. We believe that the possibility of withdrawal (not abuse) constituted the issue for this product.
Doug

APPEARS THIS WAY
ON ORIGINAL

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION (1S) 12-12-97

TO (*Division/Office*): HFD-170, Michael Klein

FROM: HFD-570 (Division of Pulmonary Drug Products)
Lindsay Cobbs

DATE:	IND NO.:	NDA NO.:	TYPE OF DOCUMENT :	DATE OF DOCUMENT:
December 12, 1997		20-793	NDA	August 22, 1997

NAME OF DRUG:	PRIORITY CONSIDERATION:	CLASSIFICATION OF DRUG:	DESIRED COMPLETION DATE:
Cafcit (caffeine citrate)	Priority	2P	January 12, 1997

NAME OF FIRM: O.P.R. Development, L.P./Roxane (US Agent)

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	STATISTICAL APPLICATION BRANCH
☐ TYPE A OR B NDA REVIEW ☐ END OF PHASE II MEETING ☐ CONTROLLED STUDIES ☐ PROTOCOL REVIEW ☐ OTHER:	☐ CHEMISTRY REVIEW ☐ PHARMACOLOGY ☐ BIOPHARMACEUTICS ☐ OTHER:

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY 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 RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

☐ CLINICAL ☐ PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS: Please review for abuse/withdrawal potential. FYI, I have included a copy of the medical, and biopharm reviews. Pharmacology review to be added Y/F.

cc: Original NDA 20-793
HFD-570/Div. Files
HFD-570/Cobbs,Schumaker,Pina,Himmel,Chen

SIGNATURE OF REQUESTER: /S/

METHOD OF DELIVERY (Check one): ☐ MAIL ☒ HAND

SIGNATURE OF RECEIVER: /S/

SIGNATURE OF DELIVERER: /S/

3 **Page(s) Redacted**

Draft

Labeling

NDA:	**20793**
Drug Product:	**Cafcit**
Sponsor:	**OPR Development, LP**
Referring Division:	**HFD-570 (Division of Pulmonary Drug Products)**
Reviewer:	**Michael Klein, Ph.D.** /S/ 9/9/99
Peer Reviewer:	**Douglas Kramer, M.D.** /S/ 9/10/99
Date of Document:	**June 30, 1999**
Date Received:	**July 23, 1999**
Date Reviewed:	**September 1, 1999**

Background: Caffeine citrate is used for treatment of neonatal apnea. Current NDA will make caffeine citrate available as a 10 mg/mL solution for use in the treatment of apnea of prematurity. Caffeine citrate is currently compounded by hospital pharmacies. Earlier HFD-170 (CSET) review of January 12, 1998 had the primary purpose of assessing evidence of and data in support of a withdrawal syndrome associated with caffeine use in treating neonates. Recommendations were as follows:

1. The label should include the possibility of observing behavioral changes upon withdrawal of caffeine treatment. Such information should be provided to the infants' parents who are likely to have concern about and be watchful for any behavioral changes that may indicate recurrence of apnea. Behavioral changes may result from a withdrawal syndrome or emergence of new symptoms following discontinuation of drug treatment.

2. Sponsor should explore the possibility of withdrawal emergent behavioral changes in infants being treated with caffeine over extended periods of time. The relationship of dose to behavioral findings should be part of such an assessment.

3. Sponsor should conduct a PK/PD analysis of the relationship of caffeine levels to effect.

4. Sponsor should survey hospitals that have extensive involvement of clinical pharmacists in management of caffeine in children with apnea and seek additional information on CNS effects of caffeine in infants.

Material Previously Reviewed: Draft copy of the medical review of the NDA: Copy of the Clinical Pharmacology/Biopharmaceutics Review (11/12/97), copies of the NDA overview (8 pages), copies of the Human Pharmacokinetics and Bioavailability and Integrated Non-clinical Summary portions of the NDA global summary.

New Materials Reviewed: Sponsor conducted a literature search to determine whether similar symptoms occur in preterm infants or neonates exposed to caffeine. The Sponsor submitted the literature search which included MEDLINE (1966 to the present), TOXLINE (1965 to the present), BIOSIS (1970 to the present), Science Citation Index (1992 to the present), International Pharmaceutical Abstracts, and Iowa Drug File.

Caffeine as a Drug of Dependence in Adults: Griffiths *et al.* (1990) examined caffeine dependence and withdrawal in abuse liability studies. Thirty-seven reports (case reports, experimental studies and surveys) were summarized therein describing withdrawal syndromes following chronic caffeine administration. Eighteen were case reports or clinical observations. Nineteen experimental and survey studies were identified that studied a total of approximately 1500 individuals.

Headache was identified as a withdrawal symptom in 19 of 37 reports, with 2 additional case reports describing fullness in the head and pressure in the head or facial flushing as distinct from migraine. Next is fatigue (15 of 37 reports). These terms came from symptoms such as mental depression, weakness, apathy, etc. Symptoms of anxiety (anxious, nervous, jittery, shaky, muscle tension, restless and insomnia) were noted in 8 of 37 reports. *In neonates and infants, these symptoms were reported as irritability, poor sleep, and crying.*

Withdrawal reportedly begins at 12-24 hours after termination of long term administration, and peaks by 2 days, lasting about 1 week. The withdrawal is a specific pharmacological withdrawal syndrome. Ability of caffeine to precipitate and relieve withdrawal appears to be dose-related.

Controlled observations of caffeine withdrawal.

Emergence of caffeine withdrawal symptoms was observed among 7 drug abuse researchers maintained on 100 mg/day caffeine (capsules) for the preceding 116-264 days during prior drug discrimination experiments with caffeine. During the first month of the study, subjects randomly underwent placebo substitution for 12 days. In the second phase , subjects underwent at least 5 random one-day placebo substitutions separated by at least 5 days. During phase 1, subjects completed a 33-item withdrawal questionnaire. In phase 2, subjects completed the Profile of Mood States (POMS) in addition to the withdrawal questionnaire. Placebo substitution for 12 days resulted in a withdrawal syndrome in subjects 1, 4, 5, and 7 that peaked in the first 2 days and returned to baseline in approximately 1 week. The syndrome included headache, lethargy or fatigue, decrease in energy and ability to concentrate. These subjects also experienced muscle aches and chills. Other symptoms such as impaired work/thought, decreased urge to work and decreased satisfaction were statistically significant changes. The magnitude of effects is difficult to discern. The POMS ratings showed increased vigor and confusion and decreased fatigue and friendliness, in addition to showing significant ratings on many of the same caffeine withdrawal measures seen in phase 1. (Griffiths *et al.*, Low dose caffeine physical dependence in humans, J. Pharmacol. Exp. Ther., 1990, 255(3):1123).

The 2nd report described changes in standard measures of mood and performance during a crossover study of adults (18-50 yrs), who consumed caffeine daily (no more than 600 mg/day). Subjects had normal blood pressure and EKG and had no physical condition which contraindicated caffeine, and were not taking medication or using illicit drugs. In one period of the crossover, daily caffeine intake was replaced with caffeine capsules for 2 days (in the subject's average daily dose), in the other, it was replaced with placebo. Observations were made on the second day of each 2-day crossover period. Subjective measures included Beck Depression Inventory, State-Trait Anxiety Inventory, the POMS, a 33-item questionnaire on symptoms of caffeine withdrawal (including headache). Performance tasks included a digit symbol substitution, reaction time, number recall and a numerical Stroop, and tapping tasks. Results: Eligible and accepted participants (N = 62) had a mean caffeine intake of 235 +/- 126 mg/day, with 45% consuming <200 mg caffeine confirmed compliance with dietary caffeine restrictions during this study. Positive mood outcomes based on the proportion of abnormal scores are as follows:

1.High scores on Beck Depression Inventory: Placebo (11%); Caffeine Substitute (3%)
2.High scores on Trait Scale of the State-Trait Anxiety Inventory: Placebo (8%); Caffeine substitute (2%)
3. Low Vigor Score (POMS): Placebo (11%); Caffeine substitution (2%)
4. Hi Fatigue Score (POMS): Placebo (8%); Caffeine Substitution (0%)
5. Headache (moderate or severe): Placebo (52%); Caffeine Substitution (6%).
6. Other results: 13% of patients took an analgesic during placebo period vs. 2% during caffeine period ($p=0.038$). A total of 14 items on the caffeine withdrawal questionnaire did not differ during caffeine and placebo substitution periods. Tapping rate was the only one of the performance tests that differed during placebo and caffeine administration.

Final report described results of a structured psychiatric interview for caffeine dependence and subsequent placebo substitution of caffeine in those volunteers who met criteria for dependence on caffeine. Subjects (18-50 yrs) had normal BP, HR, and EKG, and consumed caffeine on a daily basis and reported problems with their caffeine use based on a diagnostic interview on DSM III R criteria for psychoactive substance dependence. To meet the diagnostic criteria of this study subjects needed to meet 3 of the following 4 criteria: 1. Tolerance, 2. Withdrawal, 3. Persistent desire or unsuccessful efforts to reduce or control use, and 4. Continued use despite knowledge of a persistent or recurrent physical or psychological problem likely to have been caused or exacerbated by substance use. Subjects then went through double-blind administration of caffeine (usual daily dose) or placebo during 2 2-day crossover study periods during which they followed caffeine-free diets. Results: 99 Volunteers were screened by telephone. Of 27 eligible and willing participants, a diagnostic interview provided the following results:

16 were diagnosed as dependent on caffeine and 11 of the 16 underwent a double-blind caffeine withdrawal evaluation; mean daily caffeine consumption was 357 mg (range: [redacted] mg/day). 94% reported withdrawal symptoms. Of the 11 subjects who underwent placebo substitution, at least 1 withdrawal symptom was identified in 9; 7 had maximal ratings of headache during placebo substitution; 7 had alterations in fatigue, depression or vigor; 5 used an analgesic; 6 had decreases in tapping velocity, and 8 patients reported functional impairment of varying degrees.

Lack of Data Related to Dependence from Clinical Evaluation:

The NDA included a single new 9-center placebo controlled trial of caffeine in treating neonatal apnea. Efficacy of caffeine citrate in treating apnea of prematurity by comparing the rate of apnea episodes in patients treated with caffeine to those treated with placebo, to determine the safety of caffeine citrate in apnea of prematurity and to obtain plasma concentrations of caffeine treated for up to 12 days. Loading dose was 10 mg/kg iv over 30 minutes; this was followed by a maintenance dose of 2.5 mg/kg/day (p.o. or i.v.) starting 24 hours after the loading dose. Total duration of participation was 12 days. Patients were to be followed for 4 days after the end of the study, if they did not receive alternative treatment. The primary efficacy analysis (which failed to show efficacy over placebo) was not submitted by the sponsor, who claimed that they did not anticipate the high dropout rate. The pharmacokinetics review in newborns on caffeine noted that among 11 infants on caffeine who were transferred to open label caffeine, all had plasma caffeine levels that were above the traditional therapeutic range of 8 to 20 mg/L, with the highest level being 43 mg/L. Regarding the safety database, no significant differences between treatment groups were noted for mean values of temperature respiratory rate, pulse, blood pressure, and clinical chemistry values. Also, no difference in adverse event rates by treatment were noted. There were no behavioral symptoms that would be expected (e.g., irritability, insomnia, increased wakefulness).

Data from post-treatment follow-up was incomplete. Some patients in both groups were placed on caffeine after the conclusion of the study. Doses, blood levels and duration of treatment were not reported.

Caffeine as a Drug of Dependence in Newborns

Recent review of the scientific literature provided the following information on caffeine dependence in newborns. Dependence developed *in utero* from caffeine large consumption of caffeine by the mother.

Report 1 Case 1: A 1,236 gm, 31 week gestational age, male infant with Apgar scores of 9 and 10 in whom manifestation of apnea may have been related to caffeine withdrawal. The infant developed respiratory distress at birth, had a mild hyperbilirubinemia and transient patent ductus arteriosus murmur. The serum caffeine level determined at 4 days of age was 40.3 mg/L. At 12 days, the infant had 6 episodes of apnea and caffeine was again administered. Maternal history revealed that the mother consumed up to 24 cups of coffee daily for several weeks prior to delivery. It was estimated that serum caffeine concentration at birth was approximately 80 mg/L and judged that the apnea observed in the infant was a manifestation of caffeine withdrawal. Khanna (1984)

Report 2 Cases 2-9: Eight infants born to mothers who were heavy caffeine users exhibited withdrawal symptoms during the newborn period. The authors of this report note that they found no alternative explanations for their observations.

Three cases were described in detail (see immediately below). Mothers ingested 200 to 1800 mg of caffeine daily during pregnancy. Caffeine was detected in the blood of 7 of the 8 infants. Tremulousness/jitteriness (6 infants) and nonbilious vomiting (5 infants) were the most common symptoms observed in these infants. Bradycardia (HR @ 70 bpm N=2) and tachypnea (>60 breaths per minute N=2) were also observed. One infant had marked vasomotor instability. (McGowan *et al.*, 1988)

Case 2: A 2,300 gm female infant with Apgar scores of 7 and 8. Maternal consumption of caffeine was 450 to 535 mg/day during the last 4-5 months of pregnancy. Physical examination at 9 hours of age was unremarkable. The infant became apneic at 19 hours and vomited nonbilious fluid. Infant developed

pallor of the skin of the lower extremities associated with tonic movements of the legs at 24 hours of age. At 40 hours, serum caffeine level was 2 mg/L, and caffeine was the only substance identified in a toxicology screen of the urine. Vomiting and tonic episodes resolved after 6 days, and the infant was discharged at 8 days of age.

Case 3: A 2880g term male infant was born to a 23 year old mother whose pregnancy was complicated by 1st trimester gastroenteritis and poor maternal weight gain throughout pregnancy. Mother's caffeine consumption was estimated at 1,300 to 1,800 mg per day. Spontaneous labor lasted 6 hours with fetal bradycardia just before delivery. Infant was treated for transient tachypnea of the newborn and possible sepsis. At 35 hours he tolerated his first feeding but became bradycardic and cyanotic 3 hours later. He was transferred to an NICU where he was rapidly extubated. Apnea and bradycardia resolved by 5 days of age.

Case 4: A 3,850 gm male infant was born to a mother who consumed 450 to 520 mg of caffeine daily. Because of vomiting and dilated loops of bowel, the infant was transferred to the NICU. Physical examination revealed irritability. The bowel problem and vomiting resolved at 22 hours. Jitteriness and irritability resolved at 45 hours of age. At 72 hours, no caffeine was detected in the serum and the infant was discharged.

Report 3: Case 10-14: 5 Infants exhibited symptoms of caffeine withdrawal. Caffeine was detected in urine of 3 infants; urines of others were not tested. Mothers consumed up to 15 cups of coffee daily or 2 liters of Coca Cola daily. Withdrawal symptoms were observed at approx. 5 days of age, and included excessive crying, irritability, poor sleep patterns and feeding difficulties and "possetting" and vomiting.

Conclusions.

The caffeine withdrawal syndrome in adults has been characterized by headache, lethargy/fatigue, anxiety, depression, minor somatic complaints (muscle aches or feeling flu-like), followed by impaired psychomotor performance, irritability, rhinorrhea, nausea/vomiting, confusion. Prevalence, frequency and severity of withdrawal varies from one group to another, as well as over time within a given individual. There is a dose relationship in severity and frequency of withdrawal symptoms. Infants treated with Cafcit were not observed for sufficiently long time to confirm or rule out these effects in infants. Nevertheless, changes in behavior following withdrawal of caffeine remains possible and is clinically relevant to optimal use of caffeine in the treatment of apnea. Symptoms (such as irritability) have been reported among infants treated with caffeine in published studies of apnea. Also, actual doses may be higher and duration of treatment may be longer than is appreciated from the types of short term trials conducted in neonatal apnea. The possibility of development of tolerance to the CNS stimulating effects of caffeine would be increased in such cases. This is all compatible with behavioral changes emerging at the end of treatment.

There were no reports of withdrawal symptoms following discontinuation of caffeine therapy in preterm infants or neonates. However, several cases of caffeine withdrawal were reported in neonates exposed to high caffeine concentrations (200 to 1800 mg daily) *in utero*. Symptoms included irritability and vomiting. In all cases, normal development of the infants was not impaired by the early dependence on caffeine.

It is recommended that the neonatal withdrawal syndrome be described in the product labeling and that the physician inform the parents of what symptoms they may expect to see in the infant upon termination of caffeine administration.

Suggested Language:

Neonatal Withdrawal Syndrome

Regular intake of caffeine during pregnancy has been reported to affect the fetus with a subsequent withdrawal syndrome. The syndrome has appeared within five days of birth. Symptoms include

irritability, jitteriness, loss of sleep, excessive crying, and feeding difficulties followed by vomiting. Bradycardia, apnea and tachypnea have also been reported. Duration and severity of neonatal withdrawal varies, depending on duration of use, time and dose of last maternal use, and rate of elimination by the newborn. The syndrome has resolved in approximately one week and administration of small amounts of caffeine has been shown to ease the symptoms of withdrawal.

Long term administration of Cafcit to the neonate may lead to physical dependence. The physician should warn the infant's parents to be watchful for possible symptoms of withdrawal following termination of Cafcit administration.

CC: Original NDA 20-743

Division File

HFD-570/Cobbs

APPEARS THIS WAY
ON ORIGINAL

MEMORANDUM

To: Division file
NDA 20-793

From: L. Miriam Pina, M.D.
Division of Pulmonary Drug Products

/S/ 2/10/98

Through: Martin Himmel, M.D.
Deputy Director
Division of Pulmonary Drug Products

/S/ 2/11/98

Date: February 10, 1998

Subject: NDA 20-793, Consult to HFD-170 for abuse/withdrawal potential

This memo is in reference to the December 12, 1997 consult from the Division of Pulmonary Drug Products to the Division of Anesthetic, Critical Care and Addiction Drug Products (HFD-170), and their January 22, 1998 response concerning the evaluation of Cafcit Injection for abuse/withdrawal potential.

I. Summary of HFD - 170 Recommendations

A. The possibility of observing behavioral changes on withdrawal of caffeine treatment should be noted in the label. A self-limited, dose-related caffeine withdrawal syndrome has been described in adults, even though the available data submitted do not confirm or rule out this finding in neonates treated with caffeine citrate.

B. The sponsor should be asked to explore the possibility of withdrawal-emergent behavioral changes in infants treated with caffeine over extended periods of time (e.g., infants treated for ALTE).

C. The sponsor should be asked to conduct a Pharmacokinetic/Pharmacodynamic analysis of the relationship of caffeine levels to effect.

D. The sponsor should be asked to survey major children's hospitals that have extensive involvement of clinical pharmacists in the management of caffeine in children with apnea, for additional information on CNS effects of caffeine in infants and possible effects of caffeine withdrawal with relatively well documented blood levels.

II. Discussion

We agree with HFD-170 that Cafcit will probably be used for longer than 10 to 12 days, and may also be used for indications other than apnea of prematurity. However, there are several issues that should be taken into consideration before extrapolating the potential findings of withdrawal-emergent behavioral changes seen in adults to premature neonates:

a) The reports describing symptoms in adults involve subjects that were already caffeine-dependent (the period of caffeine dependence is not clearly defined in the published papers, but was likely to be of several years for many of them) and some subjects were dependent to other drugs as well, creating a lot of noise in the results obtained;
b) The daily caffeine doses in the adult trials were usually higher that that proposed for premature neonates, and caffeine blood levels were not usually compared to withdrawal symptoms;
c) The caffeine metabolism in neonates is quite different from that in adults. The half life of caffeine in an adult is about 6 hours, whereas in premature infants the mean half life is about 3 days. This difference alone may effect the emergence of symptoms from caffeine withdrawal in neonates, since the blood concentration levels in the premature infant may vary less abruptly than in the adult;
d) The withdrawal symptoms evaluated in adults were mainly subjective and self-reported (e.g., headache, fatigue, sadness, etc.), which may be very difficult if not impossible to evaluate appropriately in neonates.
e) The placebo-controlled trial conducted by the sponsor provided safety information on the patients for 4 days after caffeine was withdrawn. Although the protocol was not focused on capturing these events, the CRFs did not capture evidence of symptoms that could possibly be related to drug withdrawal, or at least, the symptoms were not obvious enough to elicit the investigators to report them.

III. Conclusions

With the above considerations in mind, this reviewer considers that it would be appropriate:

a) to ask the sponsor to look in the published literature, for reports of withdrawal-emergent behavioral changes in neonates treated with caffeine;
b) to ask the sponsor to conduct further pharmacokinetic/pharmacodynamic studies to defined the optimal dose and therapeutic caffeine blood concentration for the treatment of apnea of prematurity;
c) encourage the sponsor to further study other indications i.e., ALTE, and the potential withdrawal-emergent behavioral changes that could be associated to the long term use of caffeine.
d) Because caffeine is currently recommended only for a short term use, it seems difficult to justify asking the sponsor, under the conditions of this NDA, to conduct an observational study as proposed by the consulted Division, after an extended use of caffeine.

cc:

IND
HFD-750 /Division file
/Pina
/Himmel
/Cobbs

MEMORANDUM

DATE: February 12, 1998

TO: NDA 20-793

/S/

FROM: John K. Jenkins, M.D. 2/12/98
Director, Division of Pulmonary Drug Products HFD-570

SUBJECT: Overview of NDA Review Issues

Administrative

NDA 20-793, for Cafcit (caffeine citrate) Injection was originally submitted by O.P.R. Development, L.P. on August 25, 1997. This application was determined by the division to meet the Center's guidelines for a priority review. An information request letter listing CMC deficiencies was issued by the division on December 2, 1997. The application was discussed at a meeting of the Pulmonary and Allergy Drugs Advisory Committee on December 15, 1997. The current user fee goal date for NDA 20-793 is February 25, 1998.

Clinical

The sponsor proposes that Cafcit Injection be indicated for the treatment of apnea of prematurity. In support of this indication, the sponsor submitted the results of a single, randomized, double-blind, placebo-controlled trial in neonates with apnea of prematurity along with a large number of supporting studies obtained from the published medical literature. This data package was in accord with an agreement reached between the division and the sponsor that a single, convincing placebo-controlled trial with supportive data from the published literature would be adequate to support approval of caffeine citrate for this indication. Caffeine citrate is widely used in the neonatal community based on a belief that it is safe and effective; however, there is currently no formulation approved for this indication. Caffeine citrate for injection is currently compounded extemporaneously by individual hospital pharmacies for use in their neonatal ICUs. Please refer to the review prepared by Dr. Pina and the Medical Team Leader Memorandum prepared by Dr. Himmel for more complete details of the clinical data which support the proposed indication.

As noted by Drs. Pina and Himmel, the results of the clinical trial conducted by the sponsor failed to show statistically significant differences (i.e., $p<0.05$) for the primary endpoints as defined in the protocol; however the p value for the analysis of the number of patients with a $\geq$ 50% decrease in apnea episodes during hours 24-48 after the double-blind loading dose was 0.07. Statistically significant differences for this endpoint were observed on days 4, 5, 7, 8, 9, and 10. A post-hoc analysis of the number of patients with a 100% reduction in apnea events during hours 24-48 was statistically significant in the favor of Cafcit on days 2, 4, 7, 8, and 9. It is also noteworthy that for each efficacy endpoint analyzed in the trial where Cafcit was not

statistically significantly more effective than placebo, there was a consistent numerical trend which favored Cafcit. The positive results of the sponsor's study are supported by a large number of reports in the clinical literature. Unfortunately, the majority of these reports are from uncontrolled trials or from trials which compared the efficacy of caffeine to that of theophylline; theophylline is not approved for this indication and none of the trials demonstrated a statistically significantly greater effect for caffeine over theophylline. As noted by Drs. Pina and Himmel, the study conducted by Murat et. al., provides the most convincing data in support of the efficacy of caffeine. While the study was not double-blinded, it did employ a concurrent control group and collected outcome data in a very objective manner.

I concur with Drs. Pina and Himmel that the overall weight of evidence from the sponsor's trial and the medical literature support a conclusion that caffeine citrate is effective for the treatment of apnea of prematurity. It is worth noting, however, that caffeine citrate is not effective for this indication in all patients. In fact the treatment effect size for caffeine citrate for this indication is surprisingly small given its widespread acceptance in clinical practice as standard treatment for this disorder. The PADAC agreed that the available data were adequate to conclude that caffeine citrate was effective for the proposed indication.

The primary safety concern raised in the review of this application is the possible association between use of caffeine citrate, or other methylxanthines, and the development of necrotizing enterocolitis (NEC) in neonates. The safety data from the sponsor's clinical trial demonstrated an increased incidence of reports of NEC and sepsis in caffeine-treated neonates versus placebo; however, the overall numbers of reports were small and did not support a definitive conclusion. Similarly, the reports from the medical literature were suggestive of an association but do not support a definitive conclusion. This issue was discussed at length by the PADAC and they indicated their continued concern that this may be a real association and expressed their belief that the sponsor should conduct further studies to evaluate this possibility. There was also discussion at the PADAC meeting regarding the possibility that existing neonatal clinical databases such as the Vermont-Oxford and NICHD Neonatal Network might contain data which could further address this issue. Following the PADAC meeting the division held an internal meeting with Dr. Bilstad to discuss this concern further. It was concluded that the possible association of caffeine citrate and NEC was of significant concern to warrant requesting that the sponsor assess the ability of existing neonatal clinical databases to address this question further prior to approval of this application. If the databases contain data usable to address this issue further, the sponsor will be asked to design, in consultation with the division, and conduct a study using these databases to further evaluate the possible association between use of caffeine, and other methylxanthines, and the occurrence of NEC.

Other outstanding clinical issues include a request that the sponsor commit to conduct further Phase 4 studies to evaluate the optimal dose and therapeutic plasma concentrations of caffeine citrate in the treatment of apnea of prematurity. The sponsor will also be asked to evaluate the possibility that neonates will experience withdrawal signs/symptoms following discontinuation of caffeine treatment. The division will provide the sponsor with comments regarding the proposed draft labeling in the action letter, including a request that a patient package insert be

developed for this product.

Pre-clinical

The sponsor did not conduct any pre-clinical studies in support of this application. This is acceptable given the large amount of preclinical data on caffeine available in the medical literature and the short course of treatment under the proposed indication. For further details of a review of the available preclinical data on caffeine, please refer to the review prepared by Dr. Chun and the Pharmacology/Toxicology Team Leader Memorandum prepared by Dr. Sheevers. The proposed draft labeling has been reviewed and comments regarding the pre-clinical sections will be included in the action letter.

There are no outstanding issues and the application is approvable from a preclinical perspective with acceptable labeling.

CMC

Cafcit is a sterile solution for injection that is packaged in single-use vials containing [redacted] ml of a [redacted] mg/ml caffeine. For a more detailed analysis of the CMC sections of the NDA, please refer to the CMC reviews prepared by Dr. Shah. As noted above, an information request letter was issued by the division on December 2, 1998, with numerous CMC deficiencies. To date, the sponsor has not responded to those deficiencies and the same list will be included in the action letter. The CMC reviewer has also reviewed the draft package insert and draft carton and container labeling and comments will be included in the action letter.

There are numerous outstanding deficiencies that have not yet been addressed by the sponsor that prevent approval from a CMC standpoint at this time.

Clinical Pharmacology and Biopharmaceutics

The sponsor did not conduct any human pharmacokinetic studies in support of this application. They did submit a summary of articles from the published literature and a NONMEM analysis of plasma caffeine levels obtained from a sample of the patients who participated in the Phase 3 clinical trial. For a more detailed review of these data, please refer to the review prepared by Dr. Chen. In summary, the sponsor has provided adequate rationale to support the dosing of caffeine in neonates on a mg/kg basis and they have also provided an adequate justification for dosing instructions that allow the drug to be dosed either IV or PO (the drug was administered in the Phase 3 clinical trial both IV and PO). The NONMEM analysis of the pharmacokinetic data from the Phase 3 clinical trial did not provide convincing data of a PK/PD relationship of caffeine and decrease in apnea; i.e., no therapeutic range of plasma concentrations was identified. The sponsor also did not conduct any dose-ranging trials with caffeine. See above under Clinical for a discussion of the Phase 4 commitment the sponsor will be asked to make to address these issues. Dr. Chen has reviewed the draft package insert and comments will be provided to the sponsor in the action letter.

There are no outstanding clinical pharmacology and biopharmaceutics issues that must be addressed prior to approval other than acceptable labeling. A Phase 4 commitment will be

sought to better establish the dose of caffeine for this age group and the therapeutic plasma concentration.

Data Verification

The Division of Scientific Investigations performed audits of four clinical sites involved in the Phase 3 clinical trial for this NDA. One site was rated as NAI and the other three sites were rated as VAI. The reports of these audits were reviewed by Dr. Pina. While there were some discrepancies noted, these findings were adequately addressed by the sponsor and were minor in nature. Based on the results of the DSI audits, and based on the limited auditing of the NDA performed by the medial reviewer, there are no reasons to suspect any serious data integrity problems with the NDA database.

Labeling

The trademark "Cafcit" was reviewed by the Labeling and Nomenclature Committee and found to be acceptable. The division raised the concern to the LNC that the proposed trademark included components of the generic name of the product. The LNC did not voice objection to this and the name is, therefore, acceptable to the division. The draft package insert submitted by the sponsor have been reviewed by each discipline as appropriate and numerous comments will be provided to the sponsor in the action letter.

Conclusion

There are outstanding clinical, CMC, and labeling issues for this application that preclude approval. The application is clinically approvable provided the analysis of the neonatal clinical databases do not confirm an association between caffeine and NEC that would warrant a reconsideration of the risk/benefit ratio for the product. Therefore, the sponsor should receive an APPROVABLE letter listing the various deficiencies noted above. The sponsor will be encouraged to interact with the division is formulating a plan to address the outstanding issues, particularly the clinical deficiencies.

cc:
NDA 20-793
HFD-570 Division Files
HFD-570/Jenkins
HFD-570/Cobbs
HFD-570/Himmel

APPEARS THIS WAY
ON ORIGINAL

INTEROFFICE MEMORANDUM

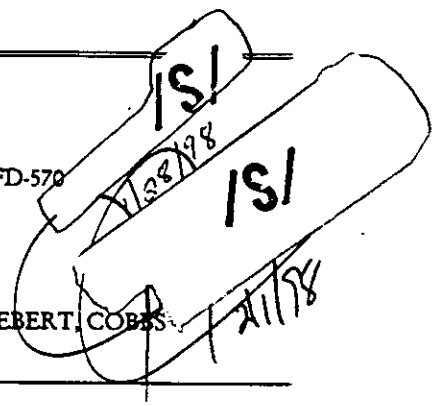
TO: NDA 20-793

FROM: MARTIN H. HIMMEL, M.D. - DEPUTY DIVISION DIRECTOR, HFD-570

SUBJECT: SECONDARY MEDICAL REVIEW MEMO

DATE: JANUARY 26, 1998

CC: HFD-570: DIVISION FILE, JENKINS, HIMMEL, PINA, WILSON, GEBERT, COBBS



This NDA was submitted by O.P.R. Development for caffeine citrate injection for the indication of apnea of prematurity. The proposed proprietary name for the drug is Cafcit. This name has been found to be acceptable by the Labeling and Nomenclature Committee. Based on previous discussions with the Division, the clinical section of the NDA consists of one double blind, randomized, placebo controlled trial of Cafcit and literature data regarding the safety and efficacy of caffeine citrate for this indication. The reason only one study was conducted was because the sponsor had indicated to the Agency that, because the use of methylxanthines is standard of care for this indication, it would be very difficult to enroll investigators willing to participate in a placebo controlled trial. In addition, there is an extensive body of literature data regarding the use of caffeine citrate for this indication which could be reviewed. Therefore, it was determined that the NDA, which contains published literature and the one placebo controlled trial (this is the only randomized placebo controlled trial conducted with caffeine citrate for neonatal apnea that I am aware of) is reviewable and was filed as a Priority NDA .

With regard to the sponsor conducted clinical trial, as stated above, this was a randomized, placebo controlled, double-blind study of 10-12 days duration. The patient population consisted of infants post conceptual age of 28 to <33 weeks with at least 6 apnea episodes (>20 seconds) in a 24-hour baseline period or less. These infants were treated with either placebo or a dosing regimen consisting of a loading dose of 10 mg/kg (1 ml/kg) intravenously over 30 minutes followed by a maintenance dose of 2.5 mg/kg daily (given orally or IV) beginning 24 hours after the loading dose. A patient could be rescued with open label caffeine citrate if by 24 hours after the loading dose the number of apnea events was not $<50\%$ of baseline and it was felt by the investigator that continued double-blind treatment placed the patient at an unacceptable risk. Patients could be treated for up to 12 days with open label caffeine citrate as part of the study. The primary endpoint originally identified in the protocol, and used for the power analysis, was the success rate in each treatment arm, with success defined as a $\geq$ 50% reduction from baseline in apnea rate at 24 - 48 hours post loading dose. In a subsequent IND amendment, the primary endpoint was redefined to be the rate of apnea episodes during hours 24 - 48 after the double-blind loading dose.

When the results of this trial were analyzed, a statistically significant ($P<.05$) difference from placebo was not seen for either primary endpoint, although the P value for the endpoint as initially defined by the sponsor was .07, thus making this a statistically relevant outcome. In addition, there was also a statistically significant difference in the percent of patients with at

least a 50% reduction in apnea events between Cafcit and placebo on days 4, 5, 7, 8, 9, and 10. Perhaps an even more clinically significant outcome is the percent of patients achieving a 100% reduction in apnea rate. With regard to this endpoint a statistically significant difference between Cafcit and placebo, favoring Cafcit, was seen on days 2, 4, 7, 8, and 9. Of note, day 2 was the day pre-specified by the sponsor for evaluation of there primary endpoint. Also seen in this trial were statistically significant differences, favoring Cafcit, in the number of days patients experienced a 50% and 100% reduction in apnea rate. The only safety issues that were identified that are of concern were the increased incidences of sepsis and necrotizing enterocolitis (NEC) in Cafcit treated patients compared to the controls. While these findings were in general not found to be statistically significant (other than sepsis when only placebo treated subjects who did not receive any caffeine was used as the control arm) the rates were consistently higher in treated subjects compared to controls, regardless of the analysis used. In addition, this finding is also of worrisome because there has already been concern raised in the medical literature regarding the possibility of an association between methylxanthine use and NEC.

With regard to the medical literature and the extent to which it supports the efficacy of caffeine citrate for this indication, there is a large body of published papers which demonstrate that infants with apnea of prematurity who are treated with caffeine citrate experience alleviation of the extent to which they have apnea. Most of the literature data, however, comes from uncontrolled studies or comparisons between caffeine citrate and theophylline (none of the published studies demonstrated a statistically significant difference in outcome between caffeine citrate and theophylline). As noted in the medical officer review, the study by Murat can be considered an additional well controlled and designed study which supports the efficacy of caffeine citrate. While the study was not double-blinded, it, in fact, collected efficacy data in a more objective manner than the sponsor did in their clinical trial. Therefore, based on this study, the weight of evidence of the medical literature and the sponsor's clinical trial of Cafcit, adequate data do exist to support the efficacy of caffeine citrate for the treatment of apnea of prematurity. The clinical development program to date is deficient with regard to having adequately identified the most appropriate dose of caffeine citrate to use and with regard to providing physicians with information regarding the therapeutic serum levels of caffeine that should be targeted. Because no dose related toxicity were identified in this NDA, the sponsor may address the Pk/Pd issues during phase 4 of this drug development program.

Because there is concern, both in the published literature as well as from the sponsor's own trial, about a possible association between methylxanthines and NEC, all data that is currently available should be evaluated prior to approval of this NDA. As such, as part of an approvable action, the sponsor should be requested to evaluate currently existing neonatal network databases, such as the Vermont-Oxford and the NICHD Neonatal Networks, to determine whether an epidemiologic study could be conducted to help shed additional light on this question. The medical reviewer has made preliminary inquiries of both these networks and determined that they do contain large numbers of infants in the birth weight range that we are concerned about and that they collect both drug exposure and outcome data. If, based on the sponsor's inquiries they also find that these databases can be studied, the sponsor should be requested to submit a protocol for such a study and, after FDA review, carryout and submit the data from the study. If they believe the databases cannot address this issue, the sponsor

should, as part of their response to an approvable letter, provide a justification for why such a study cannot be done.

As noted in the medical officer review, the sponsor should also be requested to develop a patient package insert for this drug product. Additional labeling comments can be forwarded to the sponsor after they respond to the approvable letter. Also noted in the medical officer review is the fact that there are no data quality issues that have been identified by DSI which need to be addressed.

Division Director's Memorandum (addendum)

Date:	Tuesday, September 21, 1999
NDA:	20-793
Sponsor:	OPR Development, L.P.
Proprietary Name:	Cafcit (caffeine citrate) injection - 20mg/ml caffeine citrate (10 mg/ml caffeine base)

Introduction: This is a resubmission of the Cafcit NDA to answer an "approvable" letter in February 1998. The response was received . There were deficiencies identified in CMC, clinical and labeling at the time of submission. All of these have been successfully answered at this point and the product will be approved. A few points are made below by discipline.

Biopharmaceutics: There are no additional data submitted by the sponsor nor new analyses to address the issue of PK/PD relationships nor of optimal dosing (issues raised particularly by the PADAC discussion of the application). A phase 4 commitment to supply such PK/PD data – either from reanalyzing serum sampling data from the pivotal trial or through a new study is needed. Similarly, the sponsor will be given a phase 4 commitment to address renal failure and its effects on pharmacokinetics in premature neonates.

Clinical / Stastical: In the approvable letter, the sponsor was asked to better assess the potential of a causal relationship between Cafcit use and necrotizing enterocolitis (NEC) – potentially through epidemiology studies in neonatal networks. The sponsor made a compelling argument as the substantial obstacles out of doing a meaningful epidemiology study. However, they did supply literature data that spoke to background rates of occurrence and variability. These data suggest that the NEC rate seen in the treated group was not out of range with expected and that in other reports, the NEC rate for caffeine-treated infants was not consistently higher than that seen in other comparable aged neonates.

Two consults were obtained during the response review – one to DDMAC related to the patient package insert - proposed at our request by the sponsor. The second was regarding potential abuse/addiction issues. After consideration of DDMAC's well taken points regarding the PPI, it was decided to approve the intravenous dosage form without the PPI, presuming that out of hospital [redacted] use of this product is really "off-label." A suitable PPI will need to be negotiated for the [redacted] however. The drug abuse/addiction consult largely addressed caffeine withdrawal in infants of heavy consuming mothers. As there were no indications of withdrawal in the clinical study of Cafcit and since there is no specific therapy for withdrawal, DPADP elected not to place any language related to this syndrome in the labeling.

Labeling: The major notable action related to labeling in this cycle (beyond not approving a PPI for this product as discussed above) is the change to referring to the caffeine citrate dose and concentration primarily and the caffeine base secondarily. Given the near perfect double-multiple of the two (i.e., caffeine citrate's MW = 2 x caffeine base), there appeared to be a significant chance of confusion regarding dosing.

Therefore, all references to dosing will clearly state the recommendations both in as the salt, and as the base.

Conclusions: This application should be approved for the treatment of apnea of prematurity with phase 4 commitments to address PK/PD relationships and to address PK consequences of renal failure.

/S/

Robert J. Meyer, MD 9/21/99
Director,
Division of Pulmonary and Allergy Drug Products.

APPEARS THIS WAY
ON ORIGINAL

DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

MEMORANDUM

DATE: September 17, 1999

FROM: Mr. J. Lindsay Cobbs, R.Ph. /S/
Regulatory Project Manager, DPADP

SUBJECT: DDMAC consult dated September 2, 1999
Medical Abuse Liability consult dated September 9, 1999

TO: NDA 20-793 Division File

1. The DDMAC consult provides useful recommendations that are entirely related to the proposed Patient Package Insert (PPI). However, since there will be a later submission specifically for an [redacted] product, the Division has elected not to require a PPI for this application (which is primarily an IV formulation), and therefore will differ any action based on the consult until consideration of the [redacted] application.

2. The Medical Abuse Liability consult provides recommendations for the PI or PPI that address the potential for withdrawal in babies born of mothers who used caffeine prior to giving birth. The NDA itself showed no evidence of withdrawal in the treated infants, and the relevance of the caffeine withdrawal syndrome above to these infants is questionable. Further, it is not clear what action a caregiver would take if some signs and/or symptoms of withdrawal were to be experienced (i.e., no change in care or medical intervention would be recommended). Therefore, the team agreed that the recommended language contained in the medical abuse liability consult was not germane for this PI or the subsequent PPI.

CC:ORIGINAL NDA 20-793
DIVISION FILE
HFD-570/COBBS
HFD-570/HIMMEL
HFD-570/MEYER
HFD-570/SCHUMAKER

APPEARS THIS WAY
ON ORIGINAL

CDER LABELING AND NOMENCLATURE COMMITTEE

RECONSULT #	722	HFD#	570	PROPOSED PROPRIETARY NAME:	PROPOSED ESTABLISHED NAME:
ATTENTION:	Lindsey Cobbs			Cafcit Injection	caffeine citrate injection
RE:	NDA/IND #	20-793			

A. Look-alike/Sound-alike

Potential for confusion:

	Low		Medium		High
	Low		Medium		High
	Low		Medium		High
	Low		Medium		High
	Low		Medium		High

B. Misleading Aspects:

C. Other Concerns:

D. Established Name

_____ Satisfactory

_____ Unsatisfactory/Reason:

Recommended Established Name

E. Proprietary Name Recommendations:

XXX ACCEPTABLE _____ UNACCEPTABLE

F. Signature of Chair/Date /S/ 8/9/99

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

C (51) 5-21-99

TO (Division/Office): Labeling and Nomenclature Comm. Attn: Dan Boring			FROM: HFD-570 (Division of Pulmonary Drug Products) Lindsay Cobbs	
May 20, 1999	IND NO.:	NDA NO.: 20-793	TYPE OF DOCUMENT: Trademark Review	DATE OF DOCUMENT: April 28, 1999
NAME OF DRUG: Cafcit Injection	PRIORITY CONSIDERATION: Priority		CLASSIFICATION OF DRUG: 2P	DESIRED COMPLETION DATE: July 20, 1999

NAME OF FIRM: O.P.R. Development, L.P.

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)*: Review of drug name

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
☐ TYPE A OR B NDA REVIEW ☐ END OF PHASE II MEETING ☐ CONTROLLED STUDIES ☐ PROTOCOL REVIEW ☐ OTHER:	☐ CHEMISTRY REVIEW ☐ PHARMACOLOGY ☐ BIOPHARMACEUTICS ☐ OTHER:

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY 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 RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS: Please evaluate the proposed name and/or make recommendations.

cc: Original NDA 20-793
HFD-570/Div. Files
HFD-570/Cobbs, Jafari, Schumaker

SIGNATURE OF REQUESTER: /S/	METHOD OF DELIVERY (Check one): ☐ MAIL ■ HAND
SIGNATURE OF RECEIVER:	SIGNATURE OF DELIVERER:

REQUEST FOR TRADEMARK REVIEW

To: Labeling and Nomenclature Committee
Attention: Dan Boring, Chair (HFD-530), 9201 Corporate Blvd, Room N461

From: Division of Pulmonary Drug Products	**HFD-570**
Attention: Lindsay Cobbs	**Phone:** (301) 827-1051
Date: May 21, 1999	
Subject: Request for Assessment of a Trademark for a Proposed New Drug Product	
Proposed Trademark: Cafcit Injection	**NDA/ANDA#** 20-793
Established name, including dosage form: caffeine citrate Injection	
Other trademarks by the same firm for companion products: NA	
Indications for Use (may be a summary if proposed statement is lengthy): Indicated for short-term treatment of apnea of prematurity in infants between 28 and <33 weeks gestational age.	
Initial Comments from the submitter (concerns, observations, etc.): NA	

Note: Meetings of the Committee are scheduled for the 4th Tuesday of the month. Please submit this form at least one week ahead of the meeting. Responses will be as timely as possible.

cc: Original 20-793; HFD-570/division file; HFD-570/Cobbs,Jafari,Schumaker

APPEARS THIS WAY
ON ORIGINAL

PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

TO (*Division/Office*): Labeling & Nomenclature Comm. Attn: Dan Boring (HFD-530)			FROM: HFD-570 (Division of Pulmonary Drug Products) J. Lindsay Cobbs	
DATE: September 18, 1997	IND NO.:	NDA NO.: 20-793	TYPE OF DOCUMENT: Trademark Review	DATE OF DOCUMENT: August 22, 1997
NAME OF DRUG: Cafcit(caffeine citrate) Injection	PRIORITY CONSIDERATION: Priority		CLASSIFICATION OF DRUG: 2P	DESIRED COMPLETION DATE: November 1, 1997

NAME OF FIRM: O.P.R. Development, L.P. (Agent: Roxane Laboratories, Inc.)

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*):
  Review of drug name.

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
☐ TYPE A OR B NDA REVIEW ☐ END OF PHASE II MEETING ☐ CONTROLLED STUDIES ☐ PROTOCOL REVIEW ☐ OTHER:	☐ CHEMISTRY REVIEW ☐ PHARMACOLOGY ☐ BIOPHARMACEUTICS ☐ OTHER:

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY 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 RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

☐ CLINICAL ☐ PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS: Please evaluate the proosed name and/or make recommendations. The Committee evaluated the name at the December meeting. The Committee noted the following look-alike/sound-alike conflicts have a low potential for confusion (1) [redacted] (2) [redacted] and (3)Ceftin. There were no misleading aspects found in the proposed proprietary name, and the Committee found no reason to find the proposed name unacceptable. We are requesting reevaluation of the proposed proprietary name as several months has passed since your decision. In addition, please provide the committee's rationale to use part of the established name as the proprietary name.

cc: Original NDA 20-793
HFD-570/Div. Files
HFD-570/COBBS,SHAH,SCHUMAKER

SIGNATURE OF REQUESTER: /S/	METHOD OF DELIVERY (Check one): ☐ MAIL ☒ HAND
SIGNATURE OF RECEIVER:	SIGNATURE OF DELIVERER:

REQUEST FOR TRADEMARK REVIEW

TO: Labeling & Nomenclature Committee
Attention: Dan Boring, Chair (HFD-530)
Corporate Building, Room N461

FROM: Division of Pulmonary Drug Products HFD-570
Attention: Vibhakar Shah, Ph.D. Phone: 7-5579

DATE: **September 19, 1997**

SUBJECT: Request for assessment of the proposed name.

Proposed Trademark: - Cafcit Injection

NDA Number: 20-793

Established name (including dosage form): caffeine citrate Injection

Other trademarks by the same firm for comparison products:

Indications for use (may be a summary if proposed statement is lengthy):

Treat apnea of prematurity.

Initial comments from submitter: (concerns, observations, etc.)

Caffeine citrate Injection is formulated as a sterile solution of caffeine citrate witha a concentration of 10 mg of caffeine base/mL. It is intended for either intravenous [redacted] administration.

Note: Meetings of the Committee are scheduled for the 4th Tuesday of the Month. Please submit this form at least one week ahead of the meeting. Responses will be as timely as possible.

APPEARS THIS WAY
ON ORIGINAL

Printed by Lindsay Cobbs

Electronic Mail Message

Date: 14-Jan-1998 02:07pm
From: Dan Boring
BORINGD
Dept: HFD-530 CRP2 N461
Tel No: 301-827-2391 FAX 301-827-2510

Subject: Cafcit

'Lindsey,

The LNC found no additional conflicts with the name CAFCIT and has no reason to find it unacceptable.

dan

APPEARS THIS WAY
ON ORIGINAL

---------- NEW PAGE ----------

Attention:Dan Boring, Chair (HFD-530), 9201 Corporate Blvd, Room N461

722

rom:
Division of Pulmonary Drug Products
HFD- 570

Attention: Mr. Dan Boring
Phone: 827-2333

Date: December 4, 1996

Subject: Request for Assessment of a Trademark for a Proposed New Drug Product

Proposed Trademark:CAFCIT
NDA# 20-793

Established name, including dosage form:
caffeine citrate

Other trademarks by the same firm for companion products: NA

Indications for Use (may be a summary if proposed statement is lengthy):
Apnea associated with prematurity

Initial Comments from the submitter (concerns, observations, etc.):
This will be a priority review (6 months only) when it arrives as an NDA in late Dec 1996 (NDA # was preassigned). Please provide feedback as soon as possible. Thanks!

APPEARS THIS WAY
ON ORIGINAL

cc: NDA#
HFD-570/DIV FILE

Consult #722 (HFD-570)

CAFCIT caffeine citrate injection

The Committee noted the following look-alike/sound-alike conflicts: [redacted] and CEFTIN. The Committee feels these conflicts have a low potential for confusion. There were no misleading aspects found in the proposed proprietary name.

The Committee has no reason to find the proposed name unacceptable.

/S/ 2/5/97, Chair
CDER Labeling and Nomenclature Committee

APPEARS THIS WAY
ON ORIGINAL

[redacted]

FACSIMILE TRANSMISSION

TO: Ms. Betty Kuzmik

Food and Drug Administration

FAX No: 301-827-1271

DATE: December 8, 1996

FROM: [redacted]

cc:

TOTAL NUMBER OF PAGES INCLUDING THIS NOTICE: 1

Subject: Brand Name

The brand name for the caffeine citrate product will be CAFCIT. Please note that all letters in the name are capitalized.

Please contact me if you have any questions or need any additional information.

Best regards,

[redacted]

Kuzmik
6545
12-5-96

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

TO (*Division/Office*) Labeling and Nomenclature Committee Attention: Dan Boring (HFD-530)			FROM: Division of Pulmonary Drug Products (HFD-570)	
mber 4, 1996	IND NO.	NDA NO. 20-793	TYPE OF DOCUMENT Trademark Review	DATE OF DOCUMENT December 3, 1996
...E OF DRUG: Proposal for CAFCIT (caffeine citrate)		PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG Priority	DESIRED COMPLETION DATE January 28, 1996
NAME OF FIRM: O.P.R. Dev				

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURINGCHANGE/ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE-NDA MEETING
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- ☐ 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	STATISTICAL APPLICATION BRANCH
☐ TYPE A OR B NDA REVIEW	☐ CHEMISTRY REVIEW
☐ END OF PHASE II MEETING	☐ PHARMACOLOGY
☐ CONTROLLED STUDIES	☐ BIOPHARMACEUTICS
☐ PROTOCOL REVIEW	☐ OTHER
☐ OTHER	

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY 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)*
- `MPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

☐ CLINICAL ☐ PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS:

The NDA for caffeine citrate will be submitted on 12/31/96 according to the sponsor. It will be a priority review with only 6 months review time. The Division is trying to complete as many consults as possible beforehand. Please comment before the end of January 1997. Thanks!

cc:IND and NDA 20-793/Div File HFD-570/Bertha/Schumaker/Kuzmik

SIGNATURE OF REQUESTER	METHOD OF DELIVERY *(Check one)*
12/4/96	☐ HAND ☒ MAIL
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

/S/

REQUEST FOR TRADEMARK REVIEW

To: Labeling and Nomenclature Committee

ttention: Dan Boring, Chair (HFD-530), 9201 Corporate Blvd, Room N461

From: Division of Pulmonary Drug Products	**HFD- 570**
Attention: Mr. Dan Boring	**Phone:** 827-2333
s: December 4, 1996	
Subject: Request for Assessment of a Trademark for a Proposed New Drug Product	
Proposed Trademark: CAFCIT	**NDA#** 20-793

Established name, including dosage form:
caffeine citrate

Other trademarks by the same firm for companion products: NA

Indications for Use (may be a summary if proposed statement is lengthy):
Apnea associated with prematurity

Initial Comments from the submitter (concerns, observations, etc.):
This will be a priority review (6 months only) when it arrives as an NDA in late Dec 1996 (NDA # was preassigned). Please provide feedback as soon as possible. Thanks!

APPEARS THIS WAY
ON ORIGINAL

Cable

FEB 23 1998

NDA 20-793

O.P.R. Development, L.P.
C/O Roxane Laboratories, Inc.
P.O. Box 16532
Columbus, Ohio 43216

Attention: Sean Alan F.X. Reade
Director of Regulatory Affairs

Dear Mr. Reade:

Please refer to your new drug application dated August 22, 1997, received August 25, 1997, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Cafcit (caffeine citrate) Injection.

We acknowledge receipt of your pre-submission dated December 28, 1996.

We also acknowledge receipt of your submissions dated September 12, 25, and 26, October 3, 20, and 23, November 7, 12, and 18, December 12, 1997, and February 4, 1998. The user fee goal date for this application is February 25, 1998.

We have completed the review of this application as submitted with draft labeling, and it is approvable. Before this application may be approved, however, it will be necessary for you to submit the following information.

1. The numerical increase in the incidence of necrotizing enterocolitis (NEC) found in the caffeine-treated group is of concern, particularly since the association of methylxanthines with an increased risk of NEC has previously been questioned in the literature. To ensure that all available data that may shed light on this question are adequately evaluated, we request that you assess whether existing neonatal databases, such as the Vermont-Oxford and the NICHD Neonatal Networks, contain data that could address this issue. If such data are available, you should design and conduct a study(ies) using these data to further evaluate the association, if any, of caffeine citrate and NEC. The results of these evaluations and the protocols that were followed in carrying out the analyses should be submitted to this Agency for review. We strongly recommend that you consult this Division regarding the design of the

required study(ies) prior to initiation of the study(ies).

2. The following comments pertain to the proposed specifications (test attributes, limits and test methods) for the drug substance, caffeine, anhydrous:

   a. The proposed specifications for the total microbial limit (e.g., [redacted] each for total bacterial count and yeast/mold count) are not justified by the observed values (e.g., "none isolated") as reported in the certificate of analysis (Volume 1.08, p. 04 0344). Please tighten the proposed specifications for the total microbial limit (e.g., [redacted] each for total bacterial count and yeast/mold count) to reflect the actual observed data or justify the proposed specifications with additional supportive data.

   b. As indicated in our letter, dated July 3, 1997 (comment 2.a.), each test method should be tracked by a unique method number which changes sequentially with each revision of that test method and the date of revision, if applicable.

   c. With regard to the tracking of the specification document by a unique number and a successive addition of an alphabetic letter for each revision, it is also recommended that the following be clearly indicated in the specification document:

      (1) Revision version # (e.g., 6056000D).

      (2) Superseding version # (e.g., 6056000C).

      (3) Identification of the change (e.g., change in test attribute, limit, test method etc.).

   d. Please revise the drug substance specifications to include the recommendations above in comments 2.a., 2.b., and 2.c. and resubmit the updated drug substance specifications.

3. With reference to the specifications proposed for the in-process bio-burden limits (p. 0128, Volume 6.01) for the drug product, please explain the meaning of response level #1 [redacted] and response level #2 [redacted] In addition, establish an upper limit (e.g., [redacted] for the in-process bio-burden test

as an acceptance criterion and justify it with appropriate data. Furthermore, as a part of the master batch record documentation, clearly indicate the type of action to be initiated and its ramifications, in the event the bio-load test results exceed the proposed in-process specifications (e.g., [redacted]).

4. The following comments pertain to the proposed regulatory specifications for the drug product, caffeine citrate injection, 10mg/mL (caffeine base equivalent).

   a. The specification limits proposed for particulate matter [redacted] for particles [redacted] and [redacted] for particles [redacted] are not justified in comparison with the actual observed data and need to be significantly tightened to reflect actual data, for example:

      (1) Particles [redacted] (i.e., not more than [redacted] particles greater than [redacted]

      (2) Particles [redacted] (i.e., not more than [redacted] particles greater than [redacted].

   b. We recommend that the impurities/degradation products be listed as an independent entry, separate from the "Assay" and expressed in "% w/w unit" rather than "% area/area unit" wherever it is appropriate, both for the drug substance as well as the drug product (e.g., release specifications, certificate of analysis, and stability data).

   c. The proposal to follow the numbering convention used in stability results for the related compounds (p. 011, Volume 6.01, Amendment dated October 3, 1997) is acceptable; however, this numbering convention should be consistent throughout the application. For example, the test methods for the determination of related compounds, finished product specifications, and certificates of analysis should be revised to reflect this change and resubmitted.

   d. It is recommended that each test attribute of the drug product (attachment M, p. 134, Volume 6.01) be associated with the appropriate traceable analytical method number and the corresponding specification limits. Furthermore, in order to facilitate review, this information may be summarized concisely in a tabular format similar to the Ben Venue

Laboratories' finished product specification format (attachment L, p. 129, Volume 6.01) and provided on one page, preferably preceding the method description section of the specification document. This comment is equally applicable to the drug substance specifications.

e. Please revise the drug product specifications to include the recommendations above in comments 2.b., 2.c., and 4.a. through 4.d., and resubmit the updated drug product specifications.

5. The following comments pertain to the stability protocol and the stability data provided for the drug product, caffeine citrate injection, 10 mg/mL (caffeine base equivalent).

a. As requested earlier in the letter dated July 3, 1997 (comment 10.b.), the stability protocol for the post-approval marketed product should be updated to include the following:

(1)

(2)

* *Necessary only if significant changes are observed at*

b. We recommend that the sampling plan, defined on p. 030196, Volume 1.02 for the three primary stability lots be duplicated in the post-approval stability protocol. Please revise the stability protocol to include the above recommendations and resubmit the updated stability protocol.

c. The available data at this time (1 batch, Lot 959068B: 36 month and 2 other batches, Lots 959046 and 959047: 18 month at 30°C/70% RH) may not justify the proposed expiration dating period of ( ) months. Please update the available stability data.

d. With reference to the stability testing, please clearly identify the facility that performs the sterility and bacterial endotoxin testing of caffeine citrate injection with appropriate documentation (p. 030174, Volume 1.02).

6. The following comments pertain to the vial label. An example of the revised vial label is enclosed (5% shaded area). Please note that the panel names are not meant to be printed as such on the vial label but are for ease of following the recommended changes.

a. Revise the orientation of the "product composition statement panel" and the "storage conditions statement panel" to match the orientation of the central panel (Product name) for ease of reading.

b. The product name should read: "CAFCIT™ (caffeine citrate) Injection."

c. Revise "Single Dose Vial" to read "Single Dose Vial (50 mg)."

d. Revise "For intravenous [redacted] use only" to "For intravenous use only."

e. From the left panel, move "Sterile, Nonpyrogenic, Preservative Free" to center panel below "For intravenous use only."

f. Revise [redacted] to "Mfd. For: O.P.R. Development, L.P., Lawrence, Kansas, 66047" and move to the right panel below "For Single use only, discard unused portion."

g. Revise [redacted] to read "For single use only, discard unused portion" and move from left panel to right panel below CAUTION statement.

h. Revise [redacted] on right panel to read "Control Room Temperature 15° [redacted] (59° - [redacted]".

i. Revise the product composition statement as follows:

Each mL of CAFCIT™ Injection contains: 10 mg caffeine base equivalent prepared in solution by the addition of 10 mg caffeine anhydrous to [redacted] mg citric acid, monohydrate, [redacted] mg sodium citrate, dihydrate, and water for injection.

j. From the right panel, move "Mfd. by: Ben Venue Laboratories, Inc., Bedford, OH 44146" to left panel below composition statement.

k. Expiration dates should be provided on all labels and cartons.

7. The changes suggested above for the vial label (especially comments 6.b., 6.c., 6.d., 6.f., 6.g., 6.h., 6.i., and 6.k.) are equally applicable to the vial carton label and multi-vial shelf carton label (v2.03, p 0003-0004). It is recommended that these changes be followed appropriately.

8. The enclosed mocked-up draft physician labeling is being provided to you as preliminary comments on the labeling submitted in the NDA. Additional comments may be forthcoming based on new data submitted in your response to this letter. In addition, please clarify the terms [redacted] in the Adverse Events table, and submit data to support the Drug/Laboratory Test Interaction statements.

9. Design a patient's package insert to be provided to caretakers of patients receiving Cafcit. This package insert should include the following:

a. Instructions about the administration of Cafcit.

b. A warning that vials are for single use only and that any unused medication should be discarded.

c. A warning against dosage increases without prior medical consultation and specific direction from the physician.

d. Relevant, expected adverse events.

10. Because signs and symptoms of withdrawal have been reported in adults exposed to caffeine, please evaluate the medical literature to determine if signs or symptoms of withdrawal have been reported in neonates exposed to caffeine.

11. In order to better identify the optimal dose and the therapeutic plasma concentration range of caffeine citrate in premature infants, we request that you commit to conduct additional Phase 4 pharmacokinetic/ pharmacodynamic studies in the target population. We strongly encourage that the protocols for these studies be submitted to the Agency for review prior to initiation of the studies.

12. We recommend that you collect and analyze plasma caffeine levels in preterm neonates with renal impairment in Phase 4 studies to address the need for dose adjustment of caffeine citrate in this patient population.

You are advised to contact the Division regarding the extent and format of your safety update prior to responding to this letter.

Within 10 days after the date of this letter, you are required to amend the application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. In the absence of such action FDA may take action to withdraw the application.

Under 21 CFR 314.102(d) of the new drug regulations, you may request an informal or telephone conference with the Division to discuss what further steps need to be taken before the application may be approved.

The drug may not be legally marketed until you have been notified in writing that the application is approved. In addition, please submit three copies of the introductory promotional material that you propose to use for this product. All proposed materials should be submitted in draft or mock-up form, not final print. Please submit one copy to this Division and two copies of both the promotional material and the package insert(s) directly to:

Food and Drug Administration
Division of Drug Marketing, Advertising and
Communications, HFD-40
5600 Fishers Lane
Rockville, Maryland 20857

If you have any questions, please contact Mr. J. Lindsay Cobbs, Project Manager, at (301) 827-5580.

Sincerely yours,

John K. Jenkins, M.D. F.C.C.P.
Director
Division of Pulmonary Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure

18 **Page(s) Redacted**

Draft

Labeling

Cobbs

NDA 20-793

APR 3 0 1999

O.P.R. Development, L.P.
[redacted]Roxane Laboratories
P.O. Box 16532
Columbus, OH 43216-6532

Attention: Sean Alan F.X. Reade, M.A.
Director, Drug Regulatory Affairs

Dear Mr. Reade:

We acknowledge receipt on March 24, 1999, of your March 22, 1999, submission to your new drug application (NDA) for Cafcit (caffeine citrate 10 mg/mL) Injection.

This submission completes your response to our February 23, 1998, action letter.

We consider this a complete class 2 response to our action letter. Therefore, the user fee goal date is September 22, 1999.

If you have any questions, contact Mr. J. Lindsay Cobbs, Project Manager, at (301) 827-1051.

Sincerely,

Cathie Schumaker, R.Ph.
Chief, Project Management Staff
Division of Pulmonary Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

APPEARS THIS WAY
ON ORIGINAL

DEC 2 1997

NDA 20-793

O.P.R. Development, L.P.
c/o Roxane Laboratories, Inc.
P.O. Box 16532
Columbus, Ohio 43216

Attention: Sean Alan F.X. Reade
Director of Regulatory Affairs

Dear Mr. Reade:

Please refer to your submission dated August 22, 1997, that contains the Chemistry, Manufacturing & Controls (CMC) section for your proposed new drug application (NDA) for Cafcit (caffeine citrate) Injection.

We also refer to your amendment dated October 3, 1997.

We have completed our review of the (CMC) information and have identified the following deficiencies.

Redacted 2

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secret and/or

confidential

commercial

information

We would appreciate your prompt written complete response within 30 days so we can continue our evaluation of your NDA. Please note, however, that while we are providing these comments to you at this time in order to allow you as much time as possible to address them, providing a response to these comments will not necessarily preclude the issuance of an action letter.

If you have any questions, please contact Mr. Lindsay Cobbs, Project Manager, at (301) 827-5580.

Sincerely,

John K. Jenkins, M.D., F.C.C.P.
Director
Division of Pulmonary Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

APPEARS THIS WAY
ON ORIGINAL

Cobbs

JUL 3 1997

NDA 20-793

O.P.R. Development, L.P.
c/o Roxane Laboratories, Inc.
P.O. Box 16532
Columbus, Ohio 43216

Attention: Sean Alan F.X. Reade
Director of Regulatory Affairs

Dear Mr. Reade:

Please refer to your submission dated December 28, 1996 that contains the chemistry, manufacturing and controls (CMC) section for your proposed new drug application (NDA) for Cafcit (caffeine citrate) Injection.

We have completed our review and have identified the following deficiencies.

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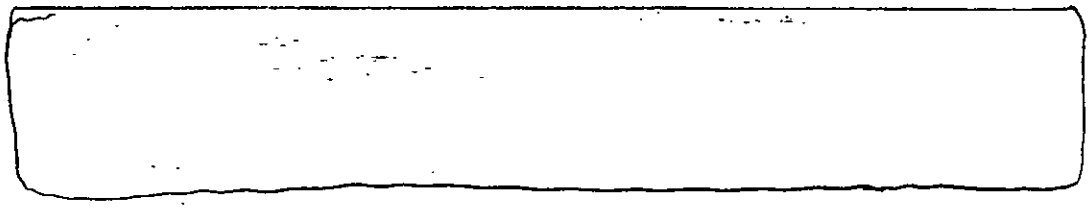
commercial

information



The above data should be included in your NDA submission.

If you have any questions, please contact Mr. Lindsay Cobbs, Project Manager, at (301) 827-5580.

Sincerely,

John K. Jenkins, M.D.
Director
Division of Pulmonary Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

APPEARS THIS WAY
ON ORIGINAL

Cobbs

TELECON RECORD

Date: April 19, 1999

NDA: 20-793

Product: Cafcit

FDA Participants: J. Lindsay Cobbs, Project Manager
Ladan, Jafari, Project Manager
Guirag Poochikian, Chemistry Team Leader
Vibhakar Shah, Chemistry Reviewer

Sponsor:

Roxane Laboratories: Mehendra Dedhiya, Director, Product Development
Julie Economou, Manager, Product Development
Virginia Fojas, Manager, Drug Regulatory Affairs
Ed Gunn, Manager, Product Management
Sean Alan Reade, Director, Drug Regulatory Affairs
Beverly Wynne, Director Medical Affairs

Ben Venue Laboratories: Pratrima Patel, Supervisor, Regulatory Affairs

Background: Roxane requested a meeting with the Chemists to present their rationale regarding the chemistry issues of the approvable letter dated February 24, 1998. Please see the meeting request dated February 17, 1999, and the amendments dated April 2 and 15, 1999, for details.

1. The Division noted that the previously submitted data does not support the proposed particulate matter [redacted] specifications. If Roxane would like to revisit this issue following approval of the application, data supporting the proposal should be provided as a prior approval supplement.

   a. Roxane noted USP specifications for particulate matter as their rationale for the proposed specifications and inquired about the Division's rationale for tighter specifications. The Division informed Roxane that the request for tighter specifications is data driven, proposed specifications should reflect the data provided and that Roxane's data indicated capability of the manufacturing process to produce batches with significantly lower particulates with respect to USP specifications. Hence, a batch that produces a large number of particulates (i.e., number of particulates exceed the pre-set specifications) should cause concern

regarding that batch production. This in-process control would prevent batch failure and would be advantageous to Roxane.

b. Roxane noted that they understood the Division's rationale but inquired about the purpose of USP specifications. In addition, Roxane referenced the telephone facsimile dated April 15, 1999, noting applications previously approved by the Agency.

- The Division informed Roxane that USP specifications are worst case scenario and is the minimum expectation for drug development and restated that specifications are data qualified. The Division indicated that the applications referenced in the April 15, 1999, telephone facsimile were not reviewed by this Division and that we could not address the approval action on applications regarding data we did not review.

c. Roxane asked if the specifications proposed by the Division for particulate matter is a requirement for approval of this application.

(i) The Division noted that Roxane should provide adequate data to support approval of their proposal.

(ii) Roxane noted that the request to amend their pre-set specification proposal must be discussed with Ben Venue and that a response would be provided as quickly as possible via telephone facsimile and then hard copy.

2. The Division reminded Roxane of their commitment to withdraw the request to market the [redacted] vial in the original application.

3. Roxane referred to the executive summary of the general correspondence dated December 23, 1998. Please see the meeting request dated April 2, 1999, for details.

- Roxane noted that the formulation of the [redacted] and the 3 mL injection are identical in the manufacturing, filling, sealing, [redacted] sterilization, inspection, labeling and packaging procedures. The only difference is the fill volume.

4. The Division inquired if there are additional DMFs for any of the packaging components other than those previously provided?

- Roxane indicated that there were no additional DMFs. Roxane added that the container closure is identical including the rubber closures and that the only

difference is the vial size for the 3 mL vial. The only difference between the aluminum seal of the 3 mL and [redacted] vial is the imprinted information. The material of the seal is identical to the [redacted] vial. The specifications and analytical methods of the 3 mL are identical to the [redacted] except for the unique specification and method numbers.

5. Roxane and Ben Venue agreed to amend the specifications for particulate matter provided for the [redacted] vial that the Division recommended for the 3 mL vial.

6. The Division inquired if there were any changes to the stability protocol?

   - Roxane indicated that the protocol was amended in response to the approvable letter to include the Division's recommendations and that the only outstanding issue is the particulate matter element.

7. Roxane noted that the data provided for the 3 mL vial includes 3 months stability data on 3 lots and that the 6 month interval data is due the end of April and inquired if this is sufficient?

   - The Division noted that the 6 month data should be provided as soon as possible and that the 9 month data thereafter. In addition, the Division noted that the review process will proceed and that an action may be taken without the 9 month data if not provided in a timely manner.

6. Roxane agreed to provide a letter of authorization (LOA) from the DMF source for the 3 mL vial to include the new product code.

Conclusion

1. Roxane and Ben Venue agreed to the particulate matter specifications for the 3 mL vial.

2. Roxane agreed to provide the 6 month data by May 15, 1999.

cc: NDA
HFD-570/Division File
HFD-570/Cobbs
HFD-570/ POOCHIKIAN
HFD-570/SHAH/5-18-99
HFD-570/JAFARI
DRAFTED BY:LCOBBS/May 17, 1999

APPEARS THIS WAY
ON ORIGINAL

TELECON RECORD

Date: February 2, 1998

NDA: 20-793

Product: Cafcit

FDA Participant: J. Lindsay Cobbs, Project Manager
Albert Chen, Biopharm Reviewer

Sponsor: Dr. Ludden, consultant to Roxane for O.P.R.

Purpose: Discuss sponsor's response dated November 12, 1997, to our fax dated October 16, 1997.

Summary: Dr. Ludden could not provide an analysis for patients 419 and 421 because this data was not provided to him. Clin Trials would provide this data to him as soon as possible and he would re-analyze the data. Dr. Ludden did not feel that 2 patients would change the outcome of his analysis but could not say definitively without reviewing the data. The re-analysis will take approximately 2 weeks.

cc: NDA 20-793
HFD-570/Division File
HFD-570/Cobbs
HFD-570/Chen/2-3-98

Drafted by LCobbs/2-3-98

APPEARS THIS WAY
ON ORIGINAL

Chemistry, Manufacturing & Controls (CMC) Telecon
Cafcit (caffeine citrate) Injection
January 8, 1998

TELECONFERENCE

Representing **Roxane Laboratories, Inc.**:

Sean Alan Reade, Director, Regulatory Affairs
Dr. Mahendra Dedhiya, Director, Product Development
Ann Waldbilig, Regulatory Liaison, Scientific Affairs
Jonathan Dohnalek, Sr. Submissions Specialist, Regulatory Affairs
Beverly Wyn, Director Clinical Affairs

Representing the **Division of Pulmonary Drug Products**:

Lindsay Cobbs, Project Manager
Guirag Poochikian, Chemistry Team Leader
Vibhakar Shah, Chemistry Reviewer

Background: The Division issued an Information Request (IR) dated December 2, 1997, to Roxane Laboratories. Roxane requested a teleconference to discuss several CMC issues regarding the correspondence. Please see a copy of the facsimile dated January 6, 1998, for details.

Issue 1

1. Filing of amendment or supplement for 3 mL Cafcit Injection
   - Since the NDA should be complete upon submission, the Division recommended that Roxane submit a supplement to the NDA post-approval to change the vial size from [redacted] to 3mL. The supplement may be submitted with an expedited review request. However, such a request will be dependent upon the Division's current commitments at that time.

Issue 2

2. Question 1.b. and c. of the IR letter dated December 2, 1997.

   - Roxane indicated that their existing tracking method is unique and traceable for each test method. In addition, Roxane's internal history card will be utilized to trace all changes made to methods which are a part of the specification document. Roxane also indicated that implementing the Agency's recommendations will be extremely difficult and require additional resources (e.g., new computer system).

The Division disagreed with Roxane's rationale and reemphasized the recommendation from the IR letter dated December 2, 1997. Dr. Poochikian recommended that Roxane submit a proposal that would satisfy the Agency's concern of traceability and accountability of changes to each method.

Issue 3

3. Question 3.a. of the IR letter dated December 2, 1997.
   a. Roxane stated that their drug product manufacturer Ben Venue Laboratories proposed specifications comply with the USP specifications for small volume parenteral (SVP) and their current process capabilities will not allow them specifications tighter than the standard USP specifications.
   b. The Division indicated that the data submitted suggest that the process is capable of producing the drug product with less than [redacted] (greater than [redacted]) The particulate matter specifications for USP are the maximum allowed for particulate matter for any SVP. The specifications are set based on the available production as well as stability data for the drug product and the data provided for Cafcit do not support the proposed specifications. Therefore, the current specifications should be tightened.
   c. Roxane asked if an "alert level" specification in addition to the existing proposed specification be acceptable. The Division indicated that the USP specifications for SVP are not acceptable for this product. However, a reasonable "Alert level" specification concept that would trigger an investigation may be acceptable.

Issue 4

4. Question 4.a. and b. of the IR letter dated December 2, 1997.

   - Roxane agreed to the Division's recommendation. In addition, the following commitments were agreed to.
     a. [redacted] testing for first 3 production batches on "side" as well as reference [redacted] in the stability protocol.
     b. Long-term conditions are the same as described in question 3.
     c. Include the sampling plan as recommended.

Summary

1. Roxane agreed to submit the vial size change as a post-approval supplement.
2. Roxane agreed to discuss with Ben Venue their tracking method for each test method and get back to the Agency.
3. Roxane indicated that their response will be complete and submitted by January 30, 1998.

cc: Original NDA 20-793

HFD-570/Cobbs
HFD-570/Poochikian/2-2-98
HFD-570/Shah/1-23-98

Drafted by LCobbs/1-16-98

Roxane Laboratories, Inc.

P.O. Box 16532 • Columbus, Ohio 43216-6532 • Phone 614 276-4000 • Fax 614 274-0974

Date: January 6, 1998

To: Mr. J. Lindsay Cobbs
Project Manager, CDER, FDA
Phone (301) 827-5580
Fax (301) 827-1271

From: Jonathan Dohnalek
Roxane Laboratories
Phone (614) 276-4000, ext. 2075
Fax (614) 276-0321

Subject: Teleconference Issues
NDA 20-793 - Caffeine Citrate Injection, 10 mg/mL

Schedule: Thursday, January 8, 1998, 2:00 - 3:00
Roxane will call FDA conference room, (301) 827-1050

Roxane Attendees:

Sean Alan Reade, Director, Regulatory Affairs
Dr. Mahendra Dedhiya, Director, Product Development
Ann Waldbillig, Regulatory Liaison, Scientific Affairs
Jonathan Dohnalek, Sr. Submissions Specialist, Regulatory Affairs

Dr. Edward Brewton, Vice President, Scientific Affairs (possible attendee)
Dr. Martin Williamson, Assistant Manager, Regulatory Affairs (possible attendee)

Issues to be discussed are as follows:

1. **Filing of amendment or supplement for 3 mL Caffeine Citrate Injection**

2. **The following questions in the FDA Deficiency Letter of December 2, 1997.**

Redacted 2

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secret and/or

confidential

commercial

information

Cobbs

TELECON RECORD

Date:	September 25, 1997
NDA:	20-793
Product:	Cafcit (caffeine citrate)
FDA Participant:	J. Lindsay Cobbs, R.Ph
Sponsor:	Roxane for O.P.R.
Purpose:	Discuss categorical exclusion (CE) of their Environmental Assessment (EA).
Background:	Roxane submitted EA for the above NDA in the pre-submission dated December 28, 1997. As of August 28, 1997 some sponsors may be eligible for a CE.
Summary:	I informed Sean Reade of the July 29, 1997, Federal Register Notice and referred any questions to Nancy Sager at (301) 594-5629.

cc: Original NDA 20-793
HFD-570/Division File
HFD-570/Cobbs
HFD-570/SCHUMAKER

Memorandum of Telephone Facsimile Correspondence

Date: October 16, 1997

To: Sean Alan Reade
Director Regulatory Affairs

From: J. Lindsay Cobbs, RPh
Project Manager

Through: Cathie Schumaker
Chief, Project Management Staff

Subject: Request for information.

We are providing the attached information via telephone facsimile for your convenience, to expedite the progress of your drug development program. This material should be viewed as unofficial correspondence. Please feel free to contact me if you have any questions regarding the contents of this transmission.

Thank you.

/S/

J. Lindsay Cobbs, RPh
Project Manager
Division of Pulmonary Drug Products

APPEARS THIS WAY
ON ORIGINAL

It was reported that during the clinical trial OPR-001, 546 blood samples were collected and measured for caffeine plasma levels by an [redacted] method at [redacted] (page 08/2168). Among those measured, 284 caffeine plasma levels obtained from 58 infants were analyzed using NONMEM program for population pharmacokinetics (page 06/0765). Please provide detailed information regarding the following requests:

1. Among those 284 plasma samples that were analyzed using NONMEM, only 19 were marked as "concentration time data reliable" What is the definition and/or criteria for determining whether a concentration-time data point is reliable or not reliable?

2. Several infants (e.g., Nos. 419 and 421; page 08/2189) had caffeine plasma levels reported by [redacted] in the analytical report as usable samples (USE), but their plasma data were not used in the NONMEM analysis. Furthermore, several infants (e.g., Nos. 206 and 420; pages 08/2185 and 08/2189) had more caffeine plasma levels analyzed/reported than were used in the NONMEM analysis. Please review the raw data and provide a rationale as to why these discrepancies occurred or why those caffeine plasma levels were not used in the NONMEM analysis?

In your summary of literature review for drug-drug interactions, erythromycin (page 06/0145) was reported to decrease the clearance of caffeine due to its capability of suppressing cytochrome P450 isozymes. However, no literature article was cited. Please provide appropriate literature support for the above interaction, if it is available.

It was concluded in the summary of literature review for drug-drug interactions that coadministration of some drugs with caffeine resulted in decreased or increased caffeine elimination. In addition, it is stated in the package insert that caffeine should be administered with caution in infants with impaired renal or hepatic function. Please provide information on to what extent the dose for pre-term infants should be adjusted under the above various conditions, if it is available.

CC: ORIGINAL NDA 20-793
DIVISION FILE
HFD-570/COBBS
HFD-570/CHEN/10-16-97
HFD-570/CONNER/10-16-97
HFD-570/PINA/10-16-97

DRAFTED BY:LCOBBS/10-16-97

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

APPLICATION TO MARKET A NEW DRUG, BIOLOGIC, OR AN ANTIBIOTIC DRUG FOR HUMAN USE
(Title 21, Code of Federal Regulations, 314 & 601)

Form Approved : OMB No. 0910-0338
Expiration Date: April 30, 2000
See OMB Statement on last page.

FOR FDA USE ONLY

APPLICATION NUMBER

APPLICANT INFORMATION

NAME OF APPLICANT
O.P.R. Development, L.P.

DATE OF SUBMISSION
April 15, 1999 (30.01)

TELEPHONE NO. *(Include Area Code)*
614-276-4000

FACSIMILE (FAX) Number *(Include Area Code)*
614-276-0321

APPLICANT ADDRESS *(Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued)*:
425 Volker Boulevard
Kansas City, Missouri 64110

AUTHORIZED U.S. AGENT NAME & ADDRESS *(Number, Street, City, State, ZIP Code, telephone & FAX number)* IF APPLICABLE
Sean Alan F. X. Reade, M.A.
Director of Regulatory Affairs
Roxane Laboratories, Inc.

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER (If previously issued) NDA 20-793

ESTABLISHED NAME *(e.g., Proper name, USP/USAN name)*
Caffeine Citrate Injection

PROPRIETARY NAME *(trade name)* IF ANY
CAFCIT

CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME *(If any)*

CODE NAME *(If any)*

DOSAGE FORM:
Sterile Aqueous Solution

STRENGTHS:
10 mg/mL

ROUTE OF ADMINISTRATION:
Parenteral and oral

(PROPOSED) INDICATION(S) FOR USE: Apnea of Prematurity

APPLICATION INFORMATION

APPLICATION TYPE
(check one) ☒ NEW DRUG APPLICATION (21 CFR 314.50) ☐ ABBREVIATED APPLICATION (ANDA, AADA, 21 CFR 314.94)
☐ BIOLOGICS LICENSE APPLICATION (21 CFR part 601)

IF AN NDA, IDENTIFY THE APPROPRIATE TYPE ☐ 505 (b) (1) ☐ 505 (b) (2) ☐ 507

IF AN ANDA, OR AADA, IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION
Name of Drug — Holder of Approved Application

TYPE OF SUBMISSION (check one)
☐ ORIGINAL APPLICATION ☒ AMENDMENT TO A PENDING APPLICATION ☐ RESUBMISSION
☐ PRESUBMISSION ☐ ANNUAL REPORT ☐ ESTABLISHMENT DESCRIPTION SUPPLEMENT ☐ SUPAC SUPPLEMENT
☐ EFFICACY SUPPLEMENT ☐ LABELING SUPPLEMENT ☐ CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT ☐ OTHER

REASON FOR SUBMISSION
Response to FDA request for information

PROPOSED MARKETING STATUS (check one) ☒ PRESCRIPTION PRODUCT (Rx) ☐ OVER-THE-COUNTER PRODUCT (OTC)

NUMBER OF VOLUMES SUBMITTED[1]

THIS APPLICATION IS ☒ PAPER ☐ PAPER AND ELECTRONIC ☐ ELECTRONIC

ESTABLISHMENT INFORMATION

Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g. Final dosage form, Stability testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.

Cross References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs and DMFs referenced in the current application)

DMFs:

Os:

FORM FDA 356h (4/97)

This application contains the following items: *(Check all that apply)*	
	1. Index
	2. Labeling (check one) ☐ Draft Labeling ☐ Final Printed Labeling
	3. Summary (21 CFR 314.50 (c))
	4. Chemistry section
	A. Chemistry, manufacturing, and controls information (e.g. 21 CFR 314.50 (d) (1), 21 CFR 601.2)
	B. Samples (21 CFR 314.50 (e) (1), 21 CFR 601.2 (a)) (Submit only upon FDA's request)
	C. Methods validation package (e.g. 21 CFR 314.50 (e) (2) (i), 21 CFR 601.2)
	5. Nonclinical pharmacology and toxicology section (e.g. 21 CFR 314.50 (d) (2), 21 CFR 601.2)
	6. Human pharmacokinetics and bioavailability section (e.g. 21 CFR 314.50 (d) (3), 21 CFR 601.2)
	7. Clinical Microbiology (e.g. 21 CFR 314.50 (d) (4))
	8. Clinical data section (e.g. 21 CFR 314.50 (d) (5), 21 CFR 601.2)
	9. Safety update report (e.g. 21 CFR 314.50 (d) (5) (vi) (b), 21 CFR 601.2)
	10. Statistical section (e.g. 21 CFR 314.50 (d) (6), 21 CFR 601.2)
	11. Case report tabulations (e.g. 21 CFR 314.50 (f) (1), 21 CFR 601.2)
	12. Case reports forms (e.g. 21 CFR 314.50 (f) (2), 21 CFR 601.2)
	13. Patent information on any patent which claims the drug (21 U.S.C. 355 (b) or (c))
	14. A patent certification with respect to any patent which claims the drug (21 U.S.C. 355 (b) (2) or (j) (2) (A))
	15. Establishment description (21 CFR Part 600, if applicable)
	16. Debarment certification (FD&C Act 306 (k)(1))
	17. Field copy certification (21 CFR 314.5 (k) (3))
	18. User Fee Cover Sheet (Form FDA 3397)
	19. OTHER (Specify)

CERTIFICATION

I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including, but not limited to the following:

1. Good manufacturing practice regulations in 21 CFR 210 and 211, 606, and/or 820.
2. Biological establishment standards in 21 CFR Part 600.
3. Labeling regulations 21 CFR 201, 606, 610, 660 and/or 809.
4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR 202.
5. Regulations on making changes in application in 21 CFR 314.70, 314.71, 314.72, 314.97, 314.99, and 601.12.
6. Regulations on reports in 21 CFR 314.80, 314.81, 600.80 and 600.81.
7. Local, state and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act, I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.

The data and information in this submission have been reviewed and, to the best of my knowlege are certified to be true and accurate.

Warning: a willfully false statement is a criminal offense, U.S. Code, title 18, section 1001.

SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT	TYPED NAME AND TITLE	DATE
/S/	Sean Alan F. X. Reade, M.A. Director of Regulatory Affairs,	15 April 1999

ADDRESS *(Street, City, State, and ZIP Code)*	Telephone Number
P.O. Box 16532 Columbus, Ohio 43216-6532	(614) 276-4000

Redacted 22

pages of trade

secret and/or

confidential

commercial

information

NDA 20-793
Cafcit Injection
Roxane Laboratories
June 5, 1998

TELECONFERENCE

Representing **Roxane**:
Jonathan Donalek, Manger Regulatory Affairs
Ed Gunn, Manger Product Management
Julia Economou, Section Product Development

Representing the **Division of Pulmonary Drug Products**:
Lindsay Cobbs, Project Manager
Albert Chen, Biopharmaceutics Reviewer
Marty Himmel, Deputy Director, DPDP
John Jenkins, Director, DPDP
Miriam Pina, Medical Reviewer
Steve Wilson, Biostatics Team Leader

Background: The original application and amendments filed to date propose a [redacted] Injection. During the development phase, Roxane simultaneously researched a [redacted] Roxane inquired about amending the pending application to a 3 mL IV vial from the [redacted] IV vial and to include the [redacted] product. Please see the meeting request dated April 13, 1998, for details.

1. The Division emphasized that it is not standard practice to allow a dosage form change amendment to a pending application. However, the Division would allow Roxane to amend the application to propose a 3 mL vial for safety reasons, i.e., reduce the risk of serious adverse events from accidental overdosage significantly, especially in the home maintenance setting, providing that the request to market the [redacted] vial is withdrawn concurrently. The Division also informed Roxane that a pending application could not be amended to include a new dosage form (i.e., the proposed oral product).

   - Roxane noted that they understood the Division's position and agreed to amend the application to include the 3 mL fill vial data only. The [redacted] form may be submitted as a supplement following approval of the application or as an NDA (userfee is required). However, in light of the deficiencies of the original application the Division recommended that Roxane adequately address the deficiencies of the IV dosage form prior to turning their focus to the [redacted] form.

2. Roxane noted that the data available for the [redacted] vial are for the [redacted] and not the 3 mL vial for injection. Roxane also stated that the drug product for the [redacted] is identical to the drug product for the injection.

   - The Agency requested that the data supporting the [redacted] be submitted for review to determine if the data is adequate to support approval of the 3 mL IV product.

3. Dr. Jenkins emphasized that we are attempting to accommodate Roxane to get a product on the market. The review of this application has become extremely confusing and allowing an applicant to amend a pending application is an unusual circumstance. We are allowing this amendment only because we feel it improves to some degree the safety of the product to prevent an overdose situation. We are spending an inordinate amount of time trying to sort out what data you have or don't have and is in fact quite frustrating for us to sort out. The best course is for you to submit the data you have for review. It may be that the [redacted] data will be useful to support approval of the 3 mL IV, but we need to see the data to make that determination. We are not going to approve the [redacted] at this time. The [redacted] form is a separate issue, and will have to be a supplement to the current NDA. Also be aware that the application will not go back on the review clock until we have a complete response to the approvable letter. The CMC data may be submitted early but review of the data would be dependent on the Division's workload at that time.

   - Roxane noted that they appreciate the Division's efforts and will provide a package containing the available 3 mL data.

Conclusion

1. Roxane agreed to amend the pending application with 3 mL vial data as support to the proposed 3 mL IV vial and concurrently withdraw the request to market the [redacted] vial.

2. Dr. Jenkins reemphasized that this is not standard procedure to allow a sponsor to amend a NDA after it is submitted to change or add a dosage form. We are only making this exception (i.e., amend the application to 3 mL IV vial) in interest of getting a product on the market, and also because we think it meets a clause in our policy which states that such an exception is appropriate if the Agency requested the change. Since there have been conversations between Roxane and the Agency concerning the safety by having a smaller dosage size, we are allowing this amendment based upon this clause in our policy.

cc: Original NDA 20-793
HFD-570/COBBS
HFD-570/JENKINS
HFD-570/HIMMEL
HFD-570/WILSON
HFD-570/PINA
HFD-570/SCHUMAKER
HFD-570/CHEN

Drafted: LCOBBS/JUNE 5, 1998
INITIALED: Pina/6-23-98
Himmel/6-23-98
Jenkins/6-25-98

MINUTES OF PRE-NDA MEETING

IND 33,665 Date: December 8, 1995
Drug Product: Caffeine citrate
Sponsor: O.P.R. Development, L.P.
Attendees:

FDA John Jenkins, Martin Himmel, Miriam Pina, Steve Wilson, Joe Sun, Y. Soo Choi, Craig Bertha, Guirag Poochikian, Dale Conner, Ramana Uppoor, Betty Kuzmik

Industry William Duncan, Edward Brewton, Kirk Shepherd, Kristen Mosdell, Donald Chmielewski, Julia Economou, Allen Erenberg, Richard Leff, James Schwenke, Eric Hoffman Ann Depaoli, Douglas Brott, Kathy Oliva-Whalen

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BACKGROUND

Reference is made to the background package dated October 13, 1995 in which the sponsors acknowledged that the pivotal clinical study for caffeine citrate, Protocol No. OPR-001, entitled "Clinical Evaluation of Sterile Caffeine Citrate Solution in the treatment of Apnea of Prematurity" is nearing completion. A Pre-NDA meeting was requested to accomplish the following objectives. 1. To reach a consensus on the planned statistical analysis for the pivotal clinical data; 2. To establish agreement between the sponsor and the Agency on the presentation of data from the pivotal clinical study and on the integration of the pivotal data with clinical data from the published literature in the NDA; 3. To obtain comments and suggestions from the Agency on the proposed content and format of the NDA; and 4. To identify if there is any additional information or data which the Agency wishes the sponsor to include in the NDA.

INTRODUCTION

Drs. Duncan, Hoffman, Schwenke, and Brewton presented a 30 minute overview on the background of caffeine citrate, the study protocol, its current status, and the statistical analysis plan.

CHEMISTRY

Dr. Bertha, FDA chemist, presented his review of the Pre-NDA package. He stated that any issues not addressed in the package could be discussed at a later date. A copy of the CMC comments were given to the sponsor. See Attachment B.

MICROBIOLOGY

Dr. Hughes, FDA microbiologist, recommended that a separate microbiology section be included in the CMC section. She also gave them a copy of "Guidelines for Submitting Documentation for Sterilization Process Validation in Applications for Human and Veterinary Drug Products (December 1993)." They were encouraged to follow those guidelines pertinent to the sterilization process they will be using.

PHARMACOLOGY/TOXICOLOGY

The following four points were emphasized.

1. A summary of preclinical studies generated through a literature search should include primary pharmacology, safety pharmacology, and the toxicology profile of caffeine; including potential for local irritation & in vitro hemolysis data, if available.
2. Toxicology data should be provided for labeling in the mutagenesis and carcinogenesis/ impairment of fertility section. and pregnancy category section.
3. The sponsors should provided a comprehensive ADME section.
4. The sponsors should attempt to presubmit as much data as possible for a review prior to an NDA submission.

BIOPHARM

Dr. Uppoor presented her review of the Pre-NDA package. Comments and requests were given to the sponsor. See Attachment C.

CLINICAL

The following points were discussed and clarified. See Attachment A.

The sponsor clarified that the apnea monitors did not have recording memory. The nurses recorded the duration of apnea episodes with a scoring system. FDA pointed out that for some numeric values the scoring could overlap given the fact that a rating of 1 was assigned to apnea episodes lasting in excess of 1 to 10 seconds, and a rating of 2 was assigned to episodes lasting from 10 -20 seconds. Thus, apnea episodes lasting 10 seconds could be assigned a 1 or a 2. The sponsor stated that since evaluation of duration of apnea was not precise, this is not a problem. FDA recognized that without the data on actual duration of apnea episodes, the scores registered by the nurses would be subjective. Consequently, the result of the analysis of this variable would be difficult to interpret vis a vis clinical significance.

Severity of an apnea episode was determined by the nurse who documented if the apnea episode was assosciated with O_2 desaturations (and to what percent) or with changes (decelerations) in heart rate. They also documented the degree of intervention reauired to resolve the apnea episode.

FDA emphasized that they need follow-up on the patients in order to accrue as much information as possible for labeling. They were advised not to limit their analysis to 24-48 hours post treatment. Rather, they should analyze the data for each day of the treatment period, including the first 24 hours.

The sponsors were asked to submit as much information as possible before the NDA submission to expedite the process of reviewing it. This should include all case report forms and references. Since there are about 1,000 references in the literature, the sponsors and FDA agreed that they could limit their submission to those on controlled and relevant uncontrolled clinical trials and dose ranging trials (about 150). They were asked to submit their list of references by category, i.e., uncontrolled, controlled studies, individual reports, etc., with a list of the databases used and the strategy used in their literature search. The rationale for choosing the references should also be included in the NDA.

The sponsors did not know whether or not caffeine citrate is commercially available as an approved drug anywhere else in the world, but they will investigate this.

Dr. Jenkins told the sponsors that an NDA submission would likely receive a Priority review. In 1996, that would still mean a 12 month review under the User Fee Program but he stated that the Division would attempt to review it in only 6 months. If there is evidence of the drug's effectiveness, then the Division would also wish to discuss it in a PADAC meeting about 3-4 months after its submission.

Dr. Jenkins suggested that the sponsors and the Division work together to design audit forms with data from each patient. The FDA is in the process of preassigning audit sites to the Division of Scientific Investigation (DSI) before the NDA arrives. Supplying that information in an audit form (one page for patient), as soon as possible, would allow for a more timely review.

BIOMETRICS

Dr. Wilson stated that the way they are analyzing their primary endpoint is acceptable. If they meet their categorical endpoint, then they are in good shape. He made several comments and recommendations which were given to the sponsor. See Attachment D.

[redacted]

Betty Kuzmik, Project Manager

cc:
Original IND
HFD-570/Division File
HFD-570/Himmel/12-27-95
HFD-570/Pina/12-14-95
HFD-570/WilsonS
HFD-570/Conner/12-14-95
HFD-570/Uppoor/12-14-95
HFD-570/Pocchikian/12-14-95
HFD-570/Bertha/12-14-95
HFD-570/Sun/12-22-95
HFD-570/Choi/12-18-95
HFD-570/Schumaker/12-15-95
HFD-570/Kuzmik/12-14-95
HFD-160/Hughes/12-14-95
HF-35/McCormick

APPEARS THIS WAY
ON ORIGINAL

R/D by BKuzmik/12-14-95
Edited by Mpina/12-14-95 and 12-28-95; JSun/12-22-95; Mhimmel/12-27-95 and 1-19-96; Jjenkins/12-28-95 and 1-19-96

Attachment A

CAFFEINE CITRATE

QUESTIONS AND COMMENTS TO THE SPONSOR

A. PIVOTAL CLINICAL STUDY

1. Demographics should include
   a. a comparison of the maternal history and,
   b. patients' characteristics: GA at birth and age at entry into the study, birth weight, race, gender, past complications, etc.

2. Efficacy analysis
   a. Baseline parameters
      Should include besides apnea rate, SaO2: average, mean lowest and duration at <85% during apneic spells; HR: average, mean lowest and duration at < 80 bpm during apneic spells; and mean duration of baseline

   b. Endpoints
      - Results should be presented by ITT and evaluable populations.
      - The analysis should be done not only for the 24-48 hr post dosing period, but also for every day of the treatment period.
      - Censored observations. Please explain.
      - The duration of the baseline will be variable, and the pattern of presentation of apneas in premature babies is also variable. These observations add some

complexity to the analysis of the primary endpoint. Please explain in more detail your proposed method of analysis of the primary endpoint. We suggest the following calculations:

- analysis of categoricals (success-failure) using # of baseline events or rate of baseline apnea events;
- Change from baseline (# of events vs. rate of events);
- Mean of apnea rate using baseline # of events vs. rate of events;
- Matching the 24 - 48 hour period with the baseline # of hours.
- Weighting the comparison by the duration of the baseline period.

- The duration of apnea events should be analyzed in terms of the mean of their actual durations, instead of the proposed scoring system.
- A daily analysis of the # of patients that had a > 50% decrease in their apnea rate should be included in the analysis of efficacy.

3. Safety analysis

   a. AE's should be correlated to caffeine levels.
   b. All AE's and withdrawals should be reported.
   c. CRF's of all patients should be submitted.
   d. Data listings should include all raw values entered in the CRF's, presented by treatment group and center. We can discuss the proper format at a later time.

4. Other suggestions

   a. Submit all references and CRF's ASAP.
   b. Submit data in an electronic form. Microsoft ACCESS and a copy of the Report and the protocol in Word Perfect 6.0.

B. NDA FORMAT

1. A Microbiology section should be included.
2. Clinical data
   a. A summary of the clinical Pharmacology should be included and this should incorporate dose-ranging and dose-response trials.
   b. All studies available in the literature should be reported and analyzed by type of studies, i.e., controlled, uncontrolled, individual reports, foreign and domestic, etc.
   c. Is there any spontaneous report system functioning?
   d. The NDA should state the strategy used in the literature search. It also should list the databases.
   e. A copy of the articles referenced should be included in the submission.
   f. We are looking forward to working together in the months to come to expedite the review process of this important drug product.

Attachment D

CMC Notes on the Pre-NDA Meetings for Caffeine Citrate (IND 33,665)

External Meeting Dec. 8, 1995, 1:00PM, CR-C 3rd floor

The following CMC comments and issues resulted from a preliminary review of the pre-NDA package only. Other issues are not addressed. If other issues arise which were not covered in your pre-NDA package, you may consult us. Please also refer to previous correspondence from the agency regarding CMC issues for IND [redacted]

CMC comments:

- The identification test for the active ingredient in the drug product proposed indicates a retention time comparison.

  We would like to see a test that would provide sufficient assurance to verify the identity of the active drug substance in the drug product. Alternately, two less specific tests could be used, however, they have to be complementary.

- The type of method for the related substances assay is not proposed yet. The method used should be stability indicating, i.e., the method should be able to resolve the drug substance, excipients, and degradation products from the drug substance and excipients, and be able to quantify these.

- Section on sterilization should be in the method of manufacture section and we would also like it to be in the microbiology section for ease of consult.

- We need authorization to review the DMFs for caffeine citrate from [redacted] and [redacted]

- The containers and closures should be qualified by USP tests. In this regard please refer to chapters <87>, <88>, <381>, and <661>. In addition letters of authorization should be submitted for the appropriate DMFs in support of the containers and closures.

- For the stability protocol we recommend that for one set of the conditions you store the containers in the upright position as a control for comparison to side storage.

APPEARS THIS WAY
ON ORIGINAL

IND [redacted] Attachment C

Caffeine citrate

BIOPHARMACEUTICS' COMMENTS:

1. The sponsor should provide the pharmacokinetic data and PK analysis from the pivotal clinical study in the Human PK and Biopharmaceutics' section.

2. In the pivotal clinical trial, since few samples will be drawn and sparse data will be available, the sponsor should analyze the plasma caffeine and its metabolite levels by population methods of analyses (assuming sufficient data is obtained). The sponsor should document the demographic characteristics of the patients such as age, weight, height of the patient, severity of disease, dose administered, accurate time of dosing and accurate time of sampling.

The population modeling approach can be used to obtain several pieces of information from a population, such as defining a typical pharmacokinetic profile for a patient in that population, quantifying the influence of individual covariates such as age, optimizing the risk/benefit ratio and developing guidelines for treatment. The advantages of using the non-traditional population modeling approach is that actual patient data can be used, and the intra and inter-subject variability can be determined. The individual patient does not need to be fully characterized as in the traditional method. This means that fewer samples are required from any individual, since the aim is to obtain the central tendency in response for the population rather than an individual, and also to obtain information on the variability in response. Such analyses can be done using available software packages such as NONMEM (Non linear mixed effects modeling), P-Pharm etc.

3. The sponsor should also provide this data on disk in a spreadsheet format (preferably Excel). The spreadsheet should include patient demographics (such as age, weight, height, severity of disease state etc.) along with individual plasma concentration data and pharmacokinetic parameters. Data files from statistical analysis should also be provided (preferably in SAS format).

4. The sponsor should include assay validation information in the NDA. Please refer to the journal article in *Pharmaceutical Research 9: 588 - 592, 1992* for more information.

5. We also request that the sponsor provide a soft copy of all of the literature PK data on disk along with the hard copy of the NDA. Tables of individual plasma concentrations and also PK parameters should be provided in a spreadsheet (EXCEL or LOTUS) format.

6. The literature information should also be categorized if possible under categories such as single dose pharmacokinetics, multiple dose pharmacokinetics, metabolism, studies in special populations etc.

APPEARS THIS WAY
ON ORIGINAL

Attachment D

December 8, 1995

IND # [redacted]

Applicant: O.P.R. Development, L.P.
[redacted] (FDA communications and clinical aspects)

Name of Drug: Caffeine Citrate

Indication: Apnea of prematurity

Documents Reviewed: Meeting Package (10/13/95)

Meeting Type: Pre-NDA Meeting

Meeting Date: 8 December, 1995

RECOMMENDATIONS:

1. **Designation of review support team:** Names and phone numbers (including beeper numbers, if available) of regulatory/statistical/data management/ personnel and a description of SOPs for scientific review communication between sponsor and agency scientists.

2. **Pre-Submission of electronic database and program files with appropriate documentation** (list of files, index of variables in each file, detailed description of derived variables, annotated CRFs/collection instruments, etc. -- both paper and electronic documentation). In addition, please submit electronic (wordprocessing) desk copies of the study reports, tables and graphics (if not included in reports) and protocols (with dated ammendments).

3. **Times/Dates and raw data.** Please include all recorded times, dates, raw data, comment fields, etc. in the submitted database. Analysis files would also be useful in the review.

4. **Additional analyses.** To save time in the review, noting that the original study design was based on a categorical variable, the sponsor is encouraged to submit <u>all</u> appropriate analyses (parametric, non-parametric, exploratory as well as primary--with rationale and documentation) applied to these data. It is also recommended that both evaluable and intent-to-treat analyses be submitted with the NDA.

Looking forward to your continued cooperation regulatory collaboration. If there are any additional questions, please feel free to call me at **(301) 443-4710 or 443-4594 (Fax no. 301 443-9279**

Dr. Steve Wilson
Division of Biometrics II
Center for Drug Evaluation and Research, FDA
5600 Fishers Lane Rm 18B-45
Rockville MD, 20857

IND [redacted]: For 11/4/96 meeting

5/7/91 Meeting : Division requested the submission of as complete a summary as possible of available animal toxicity data along with information on local irritation, including the results of extravasation and hemolysis testing.

3/3/93 : My request was overruled by Dr. Taylor - See Record of Telephone Conversation by Cathie Schumaker.

8/17/93 Meeting : The sponsor was notified that NDA submission needs to include adequate pharmacology and toxicology information.

10/13/95 Submission : The sponsor requested a Pre-NDA Meeting. READ THE REVIEW and NOTE 3 previous submissions and recommendation that they submit the preclinical data ASAP.

12/8/95 Pre-NDA Meeting : See PRECLINICAL ISSUES CONVEYED TO THE SPONSOR in the Minutes of Meeting; and the following items on preclinical issues should be amended as follows :

Item 1 : Add "including information on the potential for local irritation and in vitro hemolysis data, if available.

Item 2 : Add " and Pregnancy Category Section".

APPEARS THIS WAY
ON ORIGINAL

E L E C T R O N I C M A I L M E S S A G E

Date: 14-Dec-1997 07:47pm EST
From: Leander Madoo
MADOOL
Dept: HFD-021 CHAP 200
Tel No: 301-443-5455 FAX 301-443-0699

TO: Janet Woodcock (WOODCOCKJ)
TO: Murray Lumpkin (LUMPKIN)
TO: John Treacy (TREACY)
TO: Adele Seifried (SEIFRIED)
TO: bston1 (bston1@oc.fda.gov@internert)
TO: msegal (msegal@oc.fda.gov@internet)

Subject: Short Post Meeting Update PADAC 12/15/97

To All:

A Pulmonary-Allergy Drugs Advisory Committee (PADAC) Meeting was held in Open Session from 8:00 a.m. to 3:45 p.m. on December 15, 1997, in Bethesda, Md. At the meeting the committee discussed the safety and efficacy of new drug application (NDA) 20-793, Cafcit (caffine citrate injection, 10 milligram/milliliter) for intravennous or oral use in the treatment of apnea of prematurity. The sponsor was Roxane Laboratories.

Results on the vote for approvability of caffine citrate injection-

Question: Taking into consideration the overall benefits and risks of using caffeine citrate for the treatment of apnea of prematurity do you recommend that this drug be approved for marketing?

Answer: 13 panel members voted in favor of approval and 1 panel member voted against approving. The one member who voted against approval said that efficacy evidence was insufficient and expressed concern about possible association of caffine citrate exposure and necrotizing enterocolitis. Eight panel members agreed that the labeling of Cafcit should have precautionary language regarding the concern of necrotic enterocolitis (NEC) and caffeine. All panel members agreed that compared to theophylline, caffine had a similar safety profile, but milder and less frequent adverse events. Interms of postmarketing studies which the PADAC would recommend - the panel suggested more evaluation of any association of Cafcit and NEC. Also Phase 4 dose ranging studies were endorsed.

Thanks for your interest,

Leander Madoo

FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

MEETING OF

THE PULMONARY-ALLERGY DRUGS ADVISORY COMMITTEE

8:02 a.m.

Monday, December 15, 1997

Embassy Ballroom

Ramada Inn

8400 Wisconsin Avenue

Bethesda, Maryland

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C O N T E N T S

NDA 20-702, Cafcit (caffeine citrate injection) for Intravenous or Oral Use in the Treatment of Apnea of Prematurity

C O N T E N T S (Continued)

P R O C E E D I N G S

DR. LI: Good morning, ladies and gentlemen. My name is James Li. I'm the Chair of today's Pulmonary Allergy Drug Advisory Committee, and welcome to everybody here. Thank you for coming.

I would like to start by having the panelists and the committee members introduce themselves. I'm an allergist at the Mayo Clinic. I've been on the committee for about three or four years.

Perhaps we could go around the table and have each individual just introduce themselves and where they are from, perhaps what their specialty is.

DR. GOLDSMITH: I'm Jay Goldsmith from the Ochsner Clinic in New Orleans. I'm a neonatologist.

MS. CONNER: Good morning. I'm Brenda Conner. I'm a nurse with 20 years pediatric asthma and allergy experience. I'm from Atlanta, Georgia. I'm the consumer representative to the committee.

DR. SESSLER: Good morning, I'm Curt Sessler. I'm an adult pulmonary and critical care specialist at the Medical College of Virginia, at Virginia Commonwealth University in Richmond.

DR. CROSS: I'm Carroll Cross, University of California, Davis, adult pulmonologist-intensivist.

DR. SZEFLER: I'm Stan Szefler from Denver,

Colorado, Director of Clinical Pharmacology at the National Jewish Medical and Research Center.

DR. CHINCHILLI: Vern Chinchilli, biostatistics, Penn State, Hershey Medical Center.

DR. ROTHSTEIN: Peter Rothstein, Columbia Presbyterian Medical Center, Babies and Children's Hospital. I'm a pediatric anesthesiologist and was a neonatologist in my previous life.

MR. MADOO: Leander Madoo, FDA, by way of Yale University.

DR. OSBORNE: Molly Osborne, pulmonary and critical care, Oregon Health Sciences University, in Portland.

DR. JENNE: John Jenne, adult pulmonary medicine, formerly Hines VA in Loyola, Chicago.

DR. JOBE: Alan Jobe. I'm a neonatologist and I'm from Cincinnati Children's Hospital.

DR. KELLY: Bill Kelly from the University of New Mexico Health Sciences Center. I'm pediatric pulmonary and critical care.

DR. HENDELES: Leslie Hendeles, University of Florida. I'm a clinical pharmacist in the pediatric pulmonary division.

DR. HIMMEL: Marty Himmel. I'm Deputy Division Director of the Division of Pulmonary Drugs.

DR. PINA: Miriam Pina, medical reviewer, Division of Pulmonary Drug Products.

DR. JENKINS: I'm John Jenkins. I'm the Director of the Division of Pulmonary Drug Products, FDA.

DR. BILSTAD: Jim Bilstad, Office of Drug Evaluation II.

DR. LI: Thank you. Dr. Jenkins, would you or any of the members of the FDA like to make some introductory comments?

DR. JENKINS: Thank you, Dr. Li. I'd first like to just start by thanking the members of the advisory committee, the sponsor, my FDA colleagues, and the members of the audience for attending today's meeting, which should be very interesting.

First I'd like to make several acknowledgments for members of the panel, to make it known what their new positions may be or to acknowledge their presence.

First I'd like to thank you, Dr. Li, for agreeing to serve as chair of the advisory committee for the remainder of your term. We look forward to working with you on the issues that come to the committee over the next six to seven months.

We also have a couple of members joining us today as consultants who will be official committee members as soon as the paperwork is finalized. First is Brenda

Conner. She's is currently the acting consumer representative, but will be in that position permanently soon, we hope. Also Dr. Bill Kelly from University of New Mexico will be joining us on the committee as well. We look forward to working with you over the next several years as you continue your service on the committee.

Finally, given the nature of today's topic, we have asked several consultants to join the committee to bring their unique expertise to this issue. First, Dr. Jobe, who is a former member of our advisory committee who is joining us, as well as Dr. Goldsmith and Dr. Rothstein. We appreciate your willingness to review the materials and join us today in our discussion. And also Dr. Les Hendeles, who is also a former member of our advisory committee. Thanks, Les, for agreeing to attend today also.

I think today's meeting will be very interesting. It is an indication for which this committee, to my knowledge, has never had an advisory committee discussion, that being apnea of prematurity. It is also a unique situation for our committee because I don't recall in the last several years a situation where the drug product being brought before the committee was one for which we have essentially one adequate and well-controlled study prepared by the sponsor, as well as numerous reports from the literature, and the widespread common use of ad

hoc compounded versions of caffeine citrate for this indication.

So, we look forward to the committee's discussion of this new indication and also this new type of data set. Thanks.

DR. LI: Thanks, John. Next Mr. Madoo will read the conflict of interest statement.

MR. MADOO: Yes, and I also have some general announcements. The committee will see in front of them desk copies of today's slide presentations. The black folder pertains to the sponsor, Roxane's presentation. Feel free to take any notation you require on these. Then we have FDA's slide presentation, Dr. Pina's presentation, and that's clipped here.

Also I would like to reiterate that Brenda Conner and Dr. Kelly will shortly be on board. In fact, I think their formal appointment is in fact signed off and it is just a formality and they will be with us very shortly as full-fledged members.

I'd also like to note that all of our invited consultants have been granted, from Dr. Woodcock, voting status at this meeting, so everyone around the table will be in a voting mode.

Let me proceed on to the conflict of interest statement.

The following announcement addresses the conflict of interest with regard to this meeting and is made part of the record to preclude even the appearance of such at this meeting.

Based on the submitted agenda and the information provided by the participants, the agency has determined that all reported interests in firms regulated by the Center for Drug Evaluation and Research present no potential for a conflict of interest at this meeting.

In the event the discussions involve any other products or firms not already on the agenda for which an FDA participant has a financial interest, the participants are aware of the need to exclude themselves from such involvement, and their exclusion will be noted for the record.

With respect to all other participants, we ask in the interest of fairness that they address any current or previous financial involvements with any firms whose products they may wish to comment upon.

Thank you.

Dr. Li?

DR. LI: Thank you, Mr. Madoo. We will move on to the open public hearing phase of today's meeting. My understanding, Mr. Madoo, is that we have not heard from anyone who requested time to speak to us this morning.

MR. MADOO: That is correct, Dr. Li. No one has contacted us prior to the meeting. Of course, anyone in the audience who has comments germane to the issue at hand can feel free to approach the mike in the audience area.

DR. LI: Is there anyone in the audience who would like to address the committee?

Hearing none, we will proceed to the sponsor's presentation from Roxane Laboratories, and we look forward to hearing the sponsor's presentation. I would ask the speakers to help us keep on schedule.

MR. READE: Good morning. Welcome to O.P.R. Development's presentation of Cafcit for the treatment of apnea of prematurity to the Pulmonary Allergy Drug Products advisory committee meeting. My name is Sean Alan Reade. I'm Director of Regulatory Affairs and I will introduce this session and tell you a little bit about the chronology of how we got here.

I will be followed by five speakers on this morning's program. Dr. Kirk Shepard will present the history of caffeine development. Dr. Allen Erenberg will talk about apnea of prematurity. Dr. Kristen Mosdell will present an overview of literature base for caffeine's efficacy and safety. Dr. Beverly Wynne, assisted by Dr. Dennis Haack, will present the clinical data for Cafcit.

On September 20th, 1988, Pediatric Pharmaceuticals, Inc. was granted orphan drug designation for caffeine citrate for the treatment of apnea of prematurity.

On 3 December 1991, the ownership of the product and the IND was transferred to Oread Laboratories.

On the 23rd of February, 1993, the ownership and the IND was transferred once again to O.P.R. Development, L.P. This partnership includes Pediatric Pharmaceuticals, NAIAD for Oread Holding, and Roxitrate for Roxane Laboratories. From this you can see how the acronym O.P.R. was derived.

On 28 December, 1996, Roxane Laboratories was appointed as the U.S. agent for Cafcit by O.P.R. Development.

We pre-submitted the CMC section of the NDA 6 January of this year. We submitted the NDA 22 August. It was logged in on 25 August, and after accelerated review we are here today, 15 December, for the PADAC meeting.

The next speaker will be Kirk Shepard. He'll will present the history of caffeine development. Dr. Shepard is Senior Vice President of Medical Affairs, Marketing and Product Development for Roxane Laboratories. He is an integral piece of our active R&D program at Roxane. He is also an assistant clinical professor of

medicine at the Ohio State University Comprehensive Cancer Center, where he is a board certified hematologist and oncologist. Dr. Shepard?

DR. SHEPARD: Thank you, Sean. Good morning.

Regarding the history, in 1985 the FDA contracted the University of Iowa to perform a literature search and review and provide a summary of published data concerning the use of selected drugs used to treat newborns. Caffeine was one of the seven drugs selected for review.

The completed FDA contract report was submitted to the agency in April of 1986 and indicated that caffeine was being used to treat apnea of prematurity and concluded that the literature provided persuasive evidence of caffeine's effectiveness.

The report also cited that theophylline was used and was useful for treating apnea of prematurity, but indicated that caffeine was the drug of choice to treat apnea of prematurity, based on the following features of the drug: caffeine's larger therapeutic index, once-daily administration, smaller fluctuations in plasma concentrates due to a longer half-life, penetration into the cerebral-spinal fluid, more potent central respiratory effect, and fewer adverse effects.

The FDA contract report concluded that it would

be in the interest of public health to encourage an NDA for caffeine for the treatment of apnea of prematurity in that there was no approved indication for the use of caffeine or other drugs for apnea of prematurity. There was no commercially available caffeine for this indication, but caffeine preparations were, and still are, prepared individually by hospital pharmacies for use in the neonatal intensive care units. And, three, although a volume of literature exists in the use of caffeine treatment through the 1970's and 1980's, there had never been a placebo-controlled, double-blind clinical study completed and published on the use of caffeine in apnea of prematurity.

Subsequent to the completion of the FDA contract report, caffeine was designated as an orphan drug for the treatment of apnea of prematurity. Development of caffeine citrate injection was initiated and formulated by Roxane Laboratories as a standardized product. A solution of 10 milligrams of caffeine base per milliliter with all the associated quality attributes that come only with a commercially manufactured product, including sterility assurance, pyrogen free and particle free control for materials, with tightly controlled impurity profiles.

Following discussions with the FDA, a doubleblind, placebo-controlled study was planned, supported by an extensive literature report.

Now I'd like to introduce Dr. Alan Erenberg who will discuss the clinical aspects of apnea of prematurity. Dr. Erenberg has been Director of Neonatology at the University of Iowa and Chair of Pediatrics at the University of Kansas, and currently Medical Director at Kern Medical Center in California.

DR. ERENBERG: Thank you, Kirk.

Apnea of prematurity is one of the most common problems that is identified in the neonatal intensive care unit. Apnea is defined as respiratory pauses varying between 10 and 20 seconds in duration and associated with bradycardia, which is defined as a heart rate of less than 80 beats per minute.

Short respiratory pauses are often associated with startles, movement, defecation, or swallowing during feeding in these preterm infants, but are self-limiting and not associated with bradycardia.

Apnea of prematurity must be distinguished from periodic breathing. There are three types of apnea described: central, obstructive, and mixed, which has a component of both central and obstructive causes. The literature has noted that the more preterm the infant, the greater its frequency and its occurrence.

The major concern as a physiologic consequence of apnea is hypoxemia. Often reflux effects of these

apneic episodes may include hypotension, bradycardia, and change in cerebral perfusion. The literature has stated that apnea of prematurity will most frequently occur during REM sleep. Preterm infants will spend 80 percent of their day in a sleep state, of which 50 percent of that is in an active state.

The proposed actions of methylxanthines include a decreased frequency or elimination of the episodes of apnea, normalization of respiratory patterns, or an altered sensitivity of the medullary respiratory center to carbon dioxide.

Apnea of prematurity is a rule-out diagnosis, which requires a detailed history, a complete physical examination, and laboratory tests if indicated. Once these are done, the diagnosis can be made.

If one consults standard textbooks, one will find there are various modalities advocated for treatment of apnea of prematurity, including continuous positive airway pressure, tactile stimulation, and although there are no approved indications, pharmacologic simulations with either caffeine or theophylline or aminophylline.

Now I would like to introduce Dr. Kristen Mosdell, who was formerly the Clinical Research Manager at Roxane Laboratories and now is a consultant to the company.

DR. MOSDELL: Good morning. The following is a

review of efficacy and safety data from the published literature describing the use of caffeine citrate for the treatment of apnea of prematurity. Studies included in this review were identified through a comprehensive literature search which included databases such as Medline, Toxline, Excerptamedica, Biosis, and International Pharmaceutical Abstracts.

You will see that there is a large body of literature to support the efficacy and safety of caffeine for the treatment of apnea of prematurity. This is noteworthy, considering the fact that neither caffeine nor theophylline are currently indicated for this use.

The literature search which we conducted identified over 1,000 articles on the use of caffeine. From this database we identified 22 studies which described the efficacy of caffeine for the treatment of apnea of prematurity. An additional five studies were submitted to the FDA. However, these are not included in this table because they were considered to be review articles in nature.

All of these studies used extemporaneously compounded formulations of caffeine. Controlled clinical trials either compared caffeine to theophylline, of which there were seven studies, or used historical or untreated controls, of which there were two studies each. In

addition, 11 uncontrolled clinical trials were published.

A wide range of infants were studied. Mean gestational age ranged from 24 to 33 weeks and mean birth weight ranged from 0.7 to 1.89 kilograms. The duration of these studies was from 24 hours to over 3 months.

This slide summarizes the results of these efficacy studies. It's important to note that numerous endpoints were used in these studies, and not all endpoints were used for all studies. Therefore, it was extremely difficult to identify the primary efficacy variable to use for the double-blind study. Overall, the following can be said about the conclusions from these articles.

First, both caffeine and theophylline were equally efficacious in reducing the number or frequency of apnea episodes compared to baseline.

In addition, significant decreases in the following parameters were identified. First, a decrease in the total number of apnea attacks. Also, a decrease in apnea density, which is defined as the time spent in apnea per 100 minutes of sleep.

Studies also demonstrated a decrease in apnea index, which is defined as the average number of apnea episodes per 100 minutes. Studies also showed a decrease in the number of episodes of bradycardia, a decrease in oxygen desaturation, decrease in pCO_2, and a decrease in

periodic breathing and percent periodic breathing.

Studies also demonstrated a significant increase in respiratory rate and a normalization of pneumocardiograms.

In summary, the following conclusions can be gleaned from efficacy studies.

First, both caffeine and theophylline were equally efficacious in reducing the efficacy or frequency of apnea episodes compared to baseline.

Second, significant improvement was noted in caffeine-treated infants when compared to untreated or historical controls.

And last, reports from uncontrolled trials indicated that caffeine was efficacious according to various parameters.

Moving on to the safety data, this chart reviews the safety studies which have been published. These studies were only studies that discussed caffeine. Studies that only discussed theophylline were not included in this review.

Overall, there was a total of 41 studies identified, including 887 caffeine-treated infants. Sources of these data included six studies that compared caffeine to theophylline, four studies that used untreated or historical controls, five uncontrolled studies, one

clinical pharmacology study, two pharmacokinetic studies, and 23 studies which discussed specific safety parameters concerning the use of caffeine.

This next table is a further breakdown of the safety data and it describes the number of subjects that were exposed to caffeine and the number of studies which were published by type of adverse event. It's important to note that the most frequent adverse events involved the central nervous system, the cardiovascular system, and the gastrointestinal system.

Beginning with the central nervous system, the most frequently reported adverse event was central nervous system stimulation. This included irritability, restlessness, and jitteriness. Seizures were only reported following overdose, of which there was one case, or following the use of caffeine for the treatment of near sudden infant death syndrome, of which there were two cases.

It's interesting to note that although this is a common adverse event, some studies did not report central nervous system adverse events. Data also seem to suggest that tolerance to these adverse events develops over time.

Cardiovascular adverse events published in the literature were variable but generally less than those observed with theophylline, particularly tachycardia.

Increased left ventricular output and stroke volume was observed with caffeine in some studies. It has been hypothesized that methylxanthines could decrease cerebral blood flow by causing hyperventilation, resulting in decreased carbon dioxide tension and resulting cerebrovascular vasoconstriction.

Cerebral blood flow could also decrease through antagonism of adenosine, a compound known to be involved in the regulation of cerebral vascular resistance. Studies, however, have not shown caffeine to adversely affect cerebral blood flow. Theophylline, on the other hand, has been shown to decrease cerebral blood flow.

This slide reviews gastrointestinal adverse events which were reported in the literature. Both caffeine and theophylline were shown to increase gastroesophageal reflux in infants at risk for developments of sudden infant death syndrome. Gastrointestinal adverse events, however, were generally less in caffeine-treated compared to theophylline-treated infants. One study demonstrated that mean gastric aspirate was significantly higher with theophylline compared to caffeine in one study.

It's important to take a few minutes to discuss the fourth bullet point on this slide, which is necrotizing enterocolitis. Necrotizing enterocolitis is a very common disorder in the preterm infant. Incidence has been

estimated to be up to 15 percent. The etiology of necrotizing enterocolitis is currently unknown, and the association of methylxanthines with enterocolitis is unclear.

Reviewing the 41 safety studies, we found no direct reports associating necrotizing enterocolitis to caffeine treatment. In some of the studies which compared caffeine to theophylline, necrotizing enterocolitis was identified in theophylline-treated infants. An additional study stated that there was no significant difference between caffeine and theophylline-treated patients in the incidence of necrotizing enterocolitis. However, this study failed to provide the frequency of enterocolitis in each of these groups.

Several long-term studies were published which described effects after use of caffeine for the treatment of apnea of prematurity. In these studies caffeine was not shown to adversely affect neurological development or growth parameters.

Some additional conclusions can be stated regarding safety data in the literature. First, most of the adverse events that were published were mild to moderate in severity. Of the 41 studies which we reviewed, only one death was reported. This death was due to cytomegalic inclusion disease and occurred 30 days after

the last caffeine dose.

As previously stated, there were no long-term sequelae, and caffeine appears to have a very large margin of safety. In cases of overdose, caffeine levels up to 346 milligrams per liter have been observed without reports of neurological sequelae or death.

Several studies have identified advantages of caffeine versus theophylline for the treatment of apnea of prematurity. One study demonstrated that there was a faster increase in respiratory rates in caffeine-treated versus theophylline-treated infants. Less cardiovascular, central nervous system, and gastrointestinal adverse events have been described with caffeine compared to theophylline. And last, less variability in plasma caffeine concentrations compared to plasma theophylline concentrations have been observed.

In conclusion, there is a large body of evidence to support the efficacy and safety of caffeine citrate for the treatment of apnea of prematurity.

I would now like to introduce Dr. Beverly Wynne, Medical Director, Medical Affairs Department at Roxane Laboratories, who will discuss the double-blind study OPR-001. Thank you.

DR. WYNNE: Thank you, Kristen.

Also, Dr. Dennis Haack, our consultant

biostatistician, is in the audience and can answer any biostatistical questions.

OPR-001 is the one double-blind, randomized placebo-controlled study that was conducted for this application. Patients were randomly assigned to receive caffeine citrate, or placebo, and the investigators had the option of transferring these patients at any time to an open-label caffeine phase.

According to the protocol, the efficacy was to be in a 24- to 48-hour period, at least a 50 percent decrease in apnea episodes. I bring that to your attention because it will become very important later on. So, at that point they were able to transfer the patients to open-label caffeine.

This was a difficult study to conduct, as you may well know, because caffeine and the other methylxanthines have been used for the treatment of apnea of prematurity for many years. So, some physicians became quite nervous when they did not know whether their patient was receiving caffeine or placebo.

The population were preterm infants, age 28 to 32 weeks post-conception at the time of study, and had apnea of prematurity.

The primary objective was to determine the efficacy of caffeine as compared to placebo, comparing the

rates of apnea episodes. Secondary objectives were to determine the safety of caffeine as compared to placebo, and thirdly, to obtain plasma concentrations of caffeine in premature infants treated up to 12 days.

I'm just going to quickly review the inclusion and exclusion criteria for you. The inclusion, at least 6 episodes of apnea in 24 hours or less, defined as cessation of breathing for greater than 20 seconds, had to be clinically observed and documented in the neonatal intensive care unit. Post-conceptual age was between 28 weeks, 0 days, and 32 weeks, 6 days, and the infant had to be greater than 24-hours old. There had to be of course a signed, written informed consent by the parent or the guardian.

The exclusion criteria included infants with CNS disorders, primary lung disease, generalized disturbances, metabolic disturbances, cardiovascular abnormalities, abnormal temperature, and obstructive apnea defined as visual observation of chest wall movement, with presence of bradycardia, cyanosis with respiratory effort, and/or airway obstruction.

Infants were also excluded if the blood urea nitrogen was greater than 20 grams per deciliter, the serum creatinine was greater than 1.5 milligrams per deciliter, and after the first 48 hours of life, the urine output was

less than 1 milliliter per kilogram per hour.

Infants were excluded if their AST or ALT was greater than three times the upper limit of normal, or they required mechanically assisted ventilation.

Previous treatment with methylxanthines within 7 days prior to study enrollment or previous treatment with H2 antagonists were also exclusionary factors.

Babies were excluded if they were receiving or experiencing the effects of CNS active medication at the time of enrollment.

So, I'm sure you understand with this very strict criteria that we had to actually screen almost 1,000 babies before we were able to enroll the study population that I'm going to describe.

Also, I would like to note at this time that because this was a placebo-controlled trial, and the methylxanthines have been used for many years, as you well know, some institutions felt it was unethical to conduct this trial. So, we doubt if it could ever be conducted again, but just to give you a feeling for the difficulty.

This shows you the loading dose and the maintenance dose, and this was based on what is in the literature. Of course, this is not the only recommendation but we felt it was the most frequently recommended dose. The loading dose was 10 milligrams per kilogram of caffeine

base, or 1 milliliter per kilogram of caffeine citrate solution, or placebo. This was administered intravenously over a 30-minute period.

The maintenance dose was then followed with 2.5 milligrams per kilogram of caffeine base, which is .25 milliliters per kilogram of caffeine solution, or babies received placebo. This could be administered intravenously over 10 minutes or administered orally. The maintenance dose was to be administered every 24 hours for the length of the study.

For infants that were transferred to open-label caffeine, they received another loading dose, again 10 milligrams per kilogram of caffeine base administered intravenously, followed by a maintenance dose not of 2.5, but it was increased to 3 milligrams per kilogram, based on the fact, or the assumption I should say, that these babies had failed in the double-blind phase and some of them were in the caffeine arm. Again, it was administered intravenously or orally every 24 hours.

Success for this study really reflected what is primarily seen in the literature, and that is at least a 50 percent reduction in the number of apnea episodes from baseline on days 2 through 10. Now, you'll see that actually drug could be administered up to 12 days. This was the fifth amendment, but only 4 patients were enrolled

after the fifth amendment that received drug longer than 10 days.

So, therefore, we could not actually assess these after 10 days because of the small numbers. So, all the data henceforth will be included from 2 to 10 days.

We also decided to do another very strict analysis, and that is looking at the elimination of apnea on days 2 through 10.

The study population were 87 patients, 46 of whom were randomly assigned to caffeine citrate and 41 to placebo. However, 2 of these 87 patients, both placebo, never received drug. Therefore, our safety database is 85 patients, 46 of whom received caffeine citrate and 39 who received placebo.

For the efficacy, 3 of these 85 patients were excluded. They were excluded because they had less than 6 apnea episodes at baseline. They never should have been enrolled in the study because they didn't qualify and were discontinued when they were identified by this major protocol violation. There was very little data that could not be evaluated.

The baseline characteristics, you'll see sex, race, mean gestational age, mean post-conceptual age, mean baseline apnea episodes, and mean baseline weight. You can see the values here. I would just like to draw your

attention to the right-hand side of the slide and you will note that there are no significant differences in any of these baseline parameters. So, the two groups were similar. There were no significant differences between caffeine and placebo in the double-blind trial at baseline.

We wanted to look at what was the disposition of these patients. It becomes very important because as you'll see, a lot of patients were discontinued from the study or transferred to open-label. I think this really bears special attention.

Of the 45 patients that were randomly assigned to caffeine, 20 patients actually completed the double-blind phase. Of the 37 that were assigned to placebo, 11 completed the double-blind phase. 14 patients in the caffeine group and 16 in the placebo group were transferred to open-label, and I am going to tell you a little bit more about these patients in a moment.

Also, 10 patients and 9 patients, respectively, in the caffeine and the placebo groups were permanently discontinued. 1 patient in caffeine and 1 one patient in the placebo also received 8 and 7 days of therapy. They weren't really, according to the protocol, discontinued prematurely, so we bring those as a little separate category. The caffeine patient actually was transferred to another hospital after 8 days of therapy as a success.

elimination of apnea. On the other hand, the placebo patient remained in the study for 7 days and was then transferred, but the patient was a failure at the time of transfer.

Now, looking at the reasons for permanently discontinuing therapy on these patients, and this is presented as it was on the case report form. There were 2 adverse events in the caffeine, and 1 was dyspnea, the second was sepsis, and 1 in the placebo, and that was necrotizing enterocolitis.

Apnea recurrence was given as the reason for permanently discontinuing 5 patients in the caffeine group and 6 in the placebo group, as was investigator discretion for discontinuing 2 in the caffeine group and 2 in the placebo. 1 infant was transferred to a referring hospital. So, there were a total of 10 patients in the caffeine group and 9 in placebo that were permanently discontinued from the study.

I'd like to draw your attention to those 14 and 16 patients that were transferred to open-label caffeine. We can see that on day 1 there were 2 in the caffeine group. However, at the time of transfer, 1 of these patients had at least a 50 percent decrease in apnea episodes, so at the time of transferring was actually a success as defined by the protocol.

5 of the placebo patients that were transferred on day 1, among those none actually had at least a 50 percent decrease.

Looking at day 2, 11 patients were transferred from the caffeine double-blind group to open-label caffeine. You will note that 5 of these actually had at least a 50 percent decrease at the time of transfer, so again, according to our protocol definition, were successes. 6 were not successes at the time of transfer.

Among the 9 patients in the placebo group, 2 had a 50 percent decrease at least in apnea episodes and 7 did not.

I'd like to draw your attention to the bottom of the slide and you will see that among the 14 patients that were transferred from caffeine double-blind to caffeine open-label, approximately 43 percent of these patients, according to the definition of success, at least a 50 percent decrease in apnea events, actually were responding to therapy at that time, or at least I should say had a decrease in apnea events. Whereas, if you look at the placebo, among those 16, only 18.8, or approximately 19. So, there was a difference in the decrease in apnea episodes between the caffeine and the placebo patients.

Looking at exposure, the mean exposure was 6.13 days in the double-blind for caffeine as compared to 5.05

for placebo. There was no significant difference between these groups.

Now I'd like to talk about success or efficacy as we previously defined it, at least a 50 percent reduction in apnea events. First of all, I'd like to draw your attention to a scale to 24 hours. What we did, because we had different time periods, if there were 6 apnea events reported in 12 hours, that would be scaled to 12 in 24 hours or any fraction of the 24-hour day they were all scaled so that there would be uniformity across.

Also, we conducted a last value carried forward. So, if the patients were a success at the time of discontinuation or transferred to open-label, they remained a success for the succeeding days. The numbers, as you saw, got very small because of the high number of transferred and discontinuations. If they were a failure at the time of discontinuation, they remained a failure for this analysis.

I'd like to draw your attention to day 2. You will note that there is an approximate 20 percent difference in response rates in favor of the caffeine group, and you will notice that that trend of a 20 percent difference, a 20 percent improvement for caffeine, is noted through to day 10. This resulted in a significant difference in favor of caffeine for days 4, 5, 7, 8, 9, and

10.

This slide shows that what we were trying to do is how many days did a baby have at least a 50 percent reduction. I'd like to draw your attention to day 10 and you will see the yellow bars are the caffeine. 22 babies had 10 days of a 50 percent reduction as compared to 10 for the placebo. You will see for the other days that caffeine was better on days 9, and actually on day 2 when there is no white bar, it's a zero.

There were significant differences in favor of caffeine. You will see that for both the T-test analysis and the Cochran's chi square test for trend. It shows that caffeine was significantly better than placebo.

We also did a second analysis, which I previously described, and this shows elimination. At this point I want to tell you that when infants were transferred from double-blind caffeine to open-label, although I showed you that some had at least a 50 percent decrease, none of them had elimination. So, actually for this analysis, those babies with the last value carried forward are failures. So, this becomes a very, very stringent analysis.

Again, if you would direct your attention to day 2, you will see an approximate 20 percent difference in favor of caffeine and again, the trend is carried forward

to day 10. This resulted in a significant difference in favor of caffeine for day 2, day 4, day 7, 8, and 9.

We then compiled the data, and you can see that for days 10, 9, and 7 and day 2, that there were more infants that had elimination of apnea. Again, this difference was significant in favor of caffeine, highly significant both by the T-test analysis and the Cochran's chi-square test for trend.

If we compile this data, we look at the caffeine and the placebo in the double-blind, and we look at just 7 to 10 days. We chose that. We thought it was a strict criterion among the 10 days. How many babies actually had success based on this? We find that 69 percent had at least a 50 percent reduction apnea in the caffeine as compared to 43. There you see the approximate 20 percent difference again. This was highly significant in favor of caffeine.

Elimination of apnea, 24 percent had 7 to 10 days as compared to 0, again highly significant difference in favor of caffeine.

That concludes the efficacy portion and I would now like to turn our attention to the safety evaluation, and this again is in the double-blind. We looked at vital signs, which were taken daily. Temperature, respiratory rate, pulse, blood pressure evaluations were done daily.

We looked at daily weight.

Laboratory parameters in the double-blind were taken at baseline and when the infant was discontinued from the double-blind, and you can see the parameters which are listed.

There was no clinically significant differences between caffeine and placebo, vital signs and weight, and no clinically significant differences between caffeine and placebo for any of the laboratory parameters that are listed there.

Adverse events. We looked at overall adverse events. Again, we're looking at the double-blind, and then we looked at the COSTART body systems. If we look at patients with at least one AE, you see the p values on the right-hand side of the screen show there's no significant difference. There were also no significant differences in any of the COSTART body systems, which included body as a whole, cardiovascular system, digestive system, hemic and lymphatic system, metabolic and nutrient disorders, nervous system, respiratory system, skin and appendages, special senses, and urogenital systems. No significant differences looking at the Fisher's Exact Test.

We want to draw your attention to the fact that there were some adverse events. Actually there were 10 AE's reported in 8 patients that the investigator

attributed some association with caffeine.

The first one is a little unusual. It says, definitely related to drug, drug level increased. There were some underlying conditions in this baby, constipation, PDA, and this baby, just to give you a little history, was randomly assigned to caffeine, had persistent apnea, was transferred to open-label caffeine, still had persistent apnea. So, the investigator asked for the drug level.

These drugs levels of course were not given to investigators in the double-blinds because it would break the double-blind.

It was 31.4. Based on this, we can only assume that the investigator thought the drug level was too high based on the literature because the therapeutic range, usually the higher limit is 20 or 25 based on the literature and this is slightly above this.

There was no adverse event that was attributed to caffeine, and I'm sure as you well know, there are really no serious toxicities reported in the literature at levels below 50 micrograms per ml, but we report that for full disclosure.

Also, possibly drug-related, there was one case of enterocolitis, which was considered severe. The little cross on the one patient means they were in open-label at the time. GI disorder moderate, 1 patient. Feeding

disorder mild, 1 patient in open-label caffeine. Tachycardia was reported in 1 patient and possibly associated with caffeine citrate. It was mild, 1 patient in open-label caffeine.

Also there were several adverse events that were considered remotely associated with the administration of caffeine. Injection site inflammation, moderate in 1 patient. Actually there were about five or six cases, both in the placebo and in the caffeine infiltration of the IV and inflammation. However, this was remotely associated with caffeine.

Hyponatremia, severe, one case was reported in open-label caffeine.

Lung edema and anemia, mild, was also reported.

So, these were 10 AE's in 8 patients.

Necrotizing enterocolitis, as previously described by Dr. Mosdell, was also reviewed for this study. As you well know, it's a worldwide problem in preterm infants. According to one investigator, Dr. Aranda, the second most common cause of neonatal death. Although not all authors agree it's the second most common cause, it certainly is a significant cause of mortality in this preterm infant population.

The pathogenesis of this disease remains enigmatic. It is characterized by GI and systemic signs

and symptoms, feeding intolerance, abdominal distention, poor perfusion. Advanced cases also have acidosis shock and bacteremia.

The incidence is inversely proportional to birth weight and age of immaturity. The incidence, according to the paper which I have quoted, Uauy, is 10.1 percent. This is a fairly recent paper, 1991, although as you previously heard from Dr. Mosdell, the incidence has been reported as high in previous papers as 14 to 15 percent.

In this study, in the OPR-001 study, there were four cases of NEC for 8.9 percent. 2 of these babies died, and there were 2 placebo patients, 5.1 percent, and 1 death.

Three serious adverse events were submitted to the FDA. One infant, 30 weeks gestation, received 5 days of double-blind caffeine, and was transferred to the referring hospital. He was re-admitted 3 days later for a bowel resection for NEC and PDA ligation and died of related causes, complications and prematurity.

Another infant, also 30 weeks gestational age, received 3 days of double-blind caffeine, followed by house caffeine, not open-label, but house caffeine compounded by the pharmacy for an additional 6 days. The infant developed NEC and died the next day.

A third infant, who was 29 weeks gestational age, received 2 days of double-blind placebo and was transferred to open-label caffeine. It's noteworthy that on the day of transfer an ileal resection was performed. Caffeine was subsequently administered for 10 days, 18 days later the patient died, and NEC was diagnosed at autopsy.

We feel that the information, the results that I've just described, indicate that caffeine citrate is safe and effective for the treatment of apnea of prematurity.

I thank you and this concludes the sponsor's presentation.

DR. LI: I would like to thank the sponsors for their very clear and concise presentation. I'd like to invite our committee members to ask questions to the sponsors.

MR. MADOO: If I might note, Dr. Crim, who's a committee member, arrived a little late and we're pleased to have him at the table.

Another bit of housekeeping is for people who are unaware of our procedures, we have the full final agenda in your blue folders in front of you, and appended to the agenda will be the finalized questions for committee discussion.

You'll also note behind that, by way of familiarization with your colleagues around the table, that

there is a comprehensive roster of both consultants and members.

Thank you.

DR. LI: Questions for the sponsor? Yes, Dr. Jobe?

DR. JOBE: I'd like to ask the submitters what information they have about the use of caffeine in the nurseries they were evaluating this drug in, before the initiation of the drug. I think the committee might be interested to know in this population of 28- to 32-weekers, what was the use of caffeine off label. If I can guess I'd say it was 70 percent.

DR. ERENBERG: The majority of the nurseries that enrolled in the study were those that were using caffeine as the primary pharmacologic intervention prior to the use of the study though some of them would on occasion use the theophylline or aminophylline, or if they sent the infant home obviously would send them home on theophylline.

DR. JOBE: And the use in the nursery, what percent of the babies were --

DR. ERENBERG: The actual percentage?

DR. JOBE: Because you actually surveyed 1,000 infants to get these 80. Do we know how many of those infants were actually receiving --

DR. ERENBERG: The 1,000 infants were the

consecutive admissions during the study period. The majority of these infants were eliminated because of gestational age or one of the other exclusion factors.

I would estimate that the use of caffeine was somewhere between 50 and 70 percent in the 28- to 32-week gestation infant.

DR. JOBE: Another point that people probably ought to be aware of is that probably most of the babies that you surveyed were less than 28 weeks gestation and that group between 24 and 28 weeks gestation are frequently treated with caffeine. In fact, probably most of them are on caffeine around the country.

Many of those infants in fact are on caffeine on ventilators because the babies are being weaned from the ventilator and are initiated on caffeine therapy. So, those are exclusions from your study but actually it is the major population of infants being treated with caffeine.

DR. LI: Do you actually have any numbers of the percentage of infants that were screened and excluded from the study? What percentage of those received caffeine?

DR. ERENBERG: I don't believe we have that information. We do not require that of our study centers.

DR. LI: Dr. Goldsmith.

DR. GOLDSMITH: I have a whole series of

methodological questions and I don't wish to nitpick but this is one study that we have.

First of all, there is no maternal history of mothers taking caffeine or coffee. I'd like to know that incidence for both placebo and treated patients.

Secondly --

DR. LI: Maybe we can take these one at a time. If we could have one of the sponsor's representatives address these, if possible, especially if you have a whole series. Otherwise, questions may get lost. Maternal history.

DR. WYNNE: We don't have that. We did not collect that information.

Dr. Erenberg has something to add.

DR. ERENBERG: If an infant had a serum level of caffeine, I think it was greater than 2 microgram per deciliter, they were eliminated from the study as a priori evidence that either they had received the drug or possibly from mom.

DR. LI: Why did you want to know that, Dr. Goldsmith?

DR. GOLDSMITH: In other words, there was a serum level done before the first dose was given and that would exclude if it was greater than 2. Is that correct, Dr. Erenberg?

DR. ERENBERG: Yes, that is correct.

DR. GOLDSMITH: All right.

Secondly, most apneic episodes have been shown in most nurseries to be missed by nurses. Were hard copies done of printouts for apnea, bradycardia and oxygen saturation so that these could be looked at in a scientific way rather than just on clinical observation?

DR. ERENBERG: This was not done. This was not required in our protocol.

DR. GOLDSMITH: Number three, were the incidents of patent ductus arteriosis in the placebo and treatment groups looked at? PDA is noted to cause apneic episodes and may be a cause for nonresponse in babies that were either treated or in the placebo group that went to open-label.

DR. ERENBERG: If a PDA was diagnosed and was untreated -- in other words if the infant was in the investigator's opinion in congestive heart failure -- that was an exclusion criteria, so they were not started on the study.

I do not believe we looked at specifically infants who developed PDA during the process, though I do believe that could have been indicated by the investigator as the cause for removal of the infant from the study.

DR. GOLDSMITH: There was one child that was

discussed in the previous presentation that had a nonresponse and had a patent ductus arteriosis. Are you saying that that child developed the PDA during the treatment, or was there echocardiographic evidence prior to beginning treatment of no ductus?

DR. ERENBERG: That child was one who was transferred from the study site to the original referring hospital and then was transferred back, and at that time the patent ductus had been noted. So, there was a 3-day time period between the infant being in our study site and the infant returning.

DR. GOLDSMITH: How about the incidence or the use of gavage feeding tubes and the correlation between bradycardia and hypoxemia leading to apnea versus apnea being the initial event, then going to bradycardia and hypoxemia? In other words, were the nurse clinicians differentiating between apnea as the primary event, or could bradycardia and hypoxemia be the initial event which led to apnea?

DR. ERENBERG: I can't guarantee that all of them were like that but the study centers were to identify the infants that had apnea first with subsequent bradycardia and not the reverse, bradycardia with subsequent apnea.

DR. GOLDSMITH: And finally, we've noted after

prolonged treatment -- the treatment here only went 10 to 12 days, but after prolonged treatment with theophylline and caffeine, significantly in babies less than 1,000 grams a very significant hyponatremia. That was reported here in one infant. Both theophylline and caffeine are diuretics and naturetics.

I want to know a little bit more about that infant, and if this drug is going to be approved for prolonged treatment, how we are going to monitor sodium levels, especially in these very small infants.

DR. WYNNE: We aren't able to describe that one baby with hyponatremia at this time, but we can review it and have it for you a little later for you in the program.

DR. GOLDSMITH: Thank you.

DR. LI: Les.

DR. HENDELES: I was wondering if you could provide some additional information on the relationship between caffeine drug level and treatment failure, and also what kind of range of levels resulted from the loading dose and how that contrasted with the levels from the maintenance dose, and how many patients were greater than 20 micrograms per milliliter.

DR. WYNNE: Sorry for the delay.

You'll see at the point when the serum concentrations were to be taken, basically at baseline

after the loading dose on days 2 and 12, and then subsequently as they are listed there.

Actually we did not see any consistent pattern between the mean serum concentrations for any of the days in the double-blind and response, whether we looked at a greater than 50 percent reduction or elimination for any of the 10 days.

These are the mean serum concentrations looking at a grenter than or equal to 50 percent reduction and less than a 50 percent reduction. Looking at the mean concentrations, you can see there is no pattern that we could relate to response.

Also, if we looked at the mean concentration and those infants that had no apnea events or had greater than 1 or equal to 1 apnea event, again no consistent pattern could be derived.

Dr. Ludden, would you like to make any further comments on this?

DR. LUDDEN: The only thing that I would comment about is that in the correlations that we looked at with the pharmacokinetic analysis of this sparse sampling data was that there appeared to be a relationship between the clearance value and body weight that was obvious. There also appears to be, as I understand it from the response data, a correlation between responsiveness to the

drug and body weight, the larger children getting maybe a better response the larger they are. Yet they are going to have a higher clearance and therefore lower blood levels.

Because there was a very limited range of dosing, in fact it was almost a fixed dose type of study, you don't get the kinds of ranges of concentrations within an individual subject that allow for a good pharmacodynamic type of analysis of the data.

But I have personally not looked at the data in that way. But just given that type of correlation, one could imagine a bit of a difficulty in pulling that out.

MR. MADOO: Sir, for the benefit of the record, could you articulate your affiliation, your name, and whether you are a consultant of Roxane, your manner of conveyance to this meeting?

DR. LUDDEN: Yes, I'm a consultant to Roxane. I am Professor and Chair of Pharmaceutical Sciences at the University of Nebraska Medical Center in Omaha.

DR. LI: Any other questions for sponsor? Dr. Osborne?

DR. OSBORNE: Dr. Wynne, I hate to say this just as you are sitting down, but just one other question.

It certainly struck me reading this -- and I may not have it quite straight and you also mentioned this -- that there were these 20 percent success rates, if you

will, both for placebo and for caffeine. Would you care to comment on why? Did you look at those individuals to see if there was anything that could predict success with the caffeine? I can think of a host of variables, but perhaps that's something you have considered already.

DR. WYNNE: Yes, we did. Let me just show you the backup slide for that.

What we wanted to do when we looked at success, to see if there was anything -- we looked at individual babies, but we wanted to look at baseline characteristics to determine if there were any predicting factors that we could correlate to response.

If you see on this slide, we looked at gestational age and we looked at both zero apnea events or elimination and the days 1 to 6, 0. This is of course the strict evaluation, and at least 7 days. If you look across for gestational age, you'll see that they are very comparable. Post-conceptual age, very comparable. Number of baseline apnea attacks. Actually in the last column on your right you'll see that those with at least 7 days of 0 apnea events had slightly fewer apnea events at baseline, and actually, as far as weight, you'll see those again that had at least 7 days of elimination of apnea, that they were a little heavier. The other variables are similar. So, those are the variables.

We looked at individual babies and we just could not see any correlation. There was nothing that we could say would be a predicting factor for those who might have a spontaneous evolution of apnea as compared to those who would need treatment with methylxanthine.

DR. OSBORNE: And did you do any logistic regression adjusting for sepsis or some other causes of apnea that might have confounded the data?

DR. WYNNE: No, we did not.

Did you want to add anything to that, Dr. Haack? No. No, we did not.

DR. ROTHSTEIN: Using the least value carried forward analysis, looking at the data a different way, one could conclude that if there is no effect on the first day, there is no effect with this drug.

DR. WYNNE: The results seemed to be predictive of that, yes. Actually I think you see that in the literature too. I know you see that in the literature, that within this 24- to 48-hour period that not all babies but some babies respond.

You did start to see that trend but it became stronger, so not all babies would respond in that 24 to 48 hours. I couldn't say absolutely if you don't see a response in 24 hours, but there is some prediction that that's when the response occurs.

Dr. Haack would like to --

DR. HAACK: My name is Dennis Haack and I'm the biostatistical consultant to Roxane Labs. One thing that should be noted, this study was not designed to look at what would happen if you removed caffeine once you saw a response.

Again, an aside to your question, if the infant did respond at day 2, we don't know that that response would go away if we removed caffeine. That was not part of the design.

DR. ROTHSTEIN: No, I'm looking at the other issue, how long does one treat an infant with caffeine if in fact there's no response by day 1 or 2? This will eventually carry over perhaps into the labeling.

DR. WYNNE: Yes. Actually according to our protocol, we did ask investigators to look at the response within 24 to 48 hours. If there was not at least a 50 percent decrease, that's when they had the option of transferring to open-label caffeine. So, I think that indirectly answers your question, although as you saw, some of them had responded that were transferred.

DR. HAACK: And there were a few that actually responded, had 7 days of apnea-free existence, and we don't know if those were the last 7 days. We haven't checked that. We could do that for you, but there were a number

that had 7 days or 8 days.

DR. WYNNE: The other thing that I think Dr. Ludden mentioned, this was like a fixed-dose study. They didn't have the option of increasing the maintenance dose. As you well know from the literature, this is often the case in the neonatal unit. They didn't have the option of changing the dose. They had to transfer the baby, discontinue the baby, put them on alternative therapy, or they had to transfer them to open-label caffeine. So, I think that restriction also has to be kept in mind.

Did I answer your question?

DR. ROTHSTEIN: Somewhat.

DR. JENNE: According to the literature in one fairly recent paper on a large population, mean half-life was 144 hours. There is such a tremendous spread in half-life. I was wondering if you had the data. Were you satisfied when you looked at the 2-hour versus the 12-hour levels, that there were not some levels that were really climbing up? I don't have a feeling of the spread of those 12-hour levels.

DR. WYNNE: Would you like to address that, Dr. Ludden?

DR. LUDDEN: Yes. I don't have the definitive data on that. We looked at this more as a whole because the sampling was spread across time and not at fixed times

in every infant, so you don't get a nice uniform picture of was going on at some of these specific times.

I would say that there was a reasonable spread in the data, though in a given subject, in a given individual the loading dose and the maintenance dose seemed to match up fairly well. There wasn't a lot of variability after the first day or two, looking like there was dramatic accumulation or drop across the plasma levels when there were 10 days' worth of blood levels.

The half-life that we get from our data is about 100 hours, which is somewhat less than that previous report in a population style analysis and we're probably closer to, I think, the Thompson paper that was published a little before that in that regard.

DR. LI: Thank you.

Dr. Szefler?

DR. SZEFLER: I have two questions in two broad areas. In looking at the documentation, there is a mention of sepsis and you mentioned that. It seems to stand out in the caffeine group but it really doesn't stand out in the statistics. Can you comment on what was going on there?

DR. WYNNE: Yes, I'd like to do that.

Actually while I'm looking for the backup slide. I'll tell you that we looked at the double-blind and I think because of the variation when they are treating and

when the infants are getting older, we wanted to look at that first.

We see that there are two in the caffeine group and none in the placebo group. However, when I reviewed these cases, one of these cases of sepsis actually was either present at the time the baby was enrolled or this baby had a history of sepsis. So, there was only one of these cases --

DR. SZEFLER: Does this document the sepsis because it's kind of like rule out sepsis.

DR. WYNNE: For the case I'm mentioning, it never said culture-proven sepsis. It doesn't say rule out sepsis. It said history of sepsis. That was a preexisting condition according to what was on the case report form.

The second case that we see actually was not present at baseline and was culture-proven.

So, what we have in the double-blind portion, which I feel is the way to really evaluate these, although we have to talk about long term I realize, is that there was one case that actually occurred during the double-blind.

If we look at the open-label, and we'll go on to that, again, here you see now the open-label, so you see 4 patients in open-label that had sepsis. That's for a total of 6. And actually the 2 in the placebo -- placebo

means that they were randomized to placebo but this is open-label caffeine, so they are actually receiving caffeine. So, there were 8 cases total when they were receiving caffeine.

DR. SZEFLER: And once again these were, having dealt with this in the past, there's like rule out sepsis and then there's a small percentage that are actually documented.

DR. WYNNE: Several of these were rule out sepsis. They are not all documented culture-proven sepsis.

DR. SZEFLER: The second broad area I was going to ask you about is I know there's another preparation that's out there called caffeine benzoate. My recall is it was used as a respiratory stimulant in adults. Have you done any studies in adults, and do you anticipate that this particular preparation will be used in adults?

The reason I ask that, in the population you studied you can't identify subjective adverse effects, but certainly in adults you get a better feel for subjective adverse effects. Do you have any feeling for that?

DR. WYNNE: You're talking about the benzoate preparation?

DR. SZEFLER: Right. I don't know the extent of its use now, but I remember --

DR. WYNNE: As you well know, it's not used in

infants because of the toxicity of the benzoate and the benzyl alcohol. At this time we don't have any studies planned at all for benzoate in the adult population.

DR. HENDELES: I don't think it's available.

DR. LI: Dr. Kelly, you had a question?

DR. KELLY: The question was answered primarily but it had to do with the blood levels. You didn't have a response in the first two hours after the loading dose but you got a response later on and that was my question. Do the concentrations of the drug drift up or drift down, or are we just seeing that patients enrolled in this study in general are going to get better and this drug will have a minimal effect?

You would think if it has pharmacologic action, direct action, that right after the loading dose, you would see your basic therapeutic response.

DR. LUDDEN: This is Tom Ludden again. If I can respond to that.

The loading dose gives on average -- if you take the kinetic parameters of volume and clearance, the loading dose given produces an average level of about 12 to 14. If you look at the clearance values generated, it's somewhat above that, around 14 to 18. So, there is a possibility we're getting that.

You don't see that very clearly in the data,

though, because of the variability among individuals and because of the fact that as time goes on in this study the dropout rate from at least the randomized part of this study is quite significant.

DR. KELLY: At least one of the trials that compared theophylline to caffeine used two different caffeine doses in the historical trials. They used double the dose that was used in this trial, showed a more immediate effect and a better effect. So, there was an apparent concentration or dose-related phenomenon, but you weren't able to find anything at all?

DR. LUDDEN: No. I have not looked specifically at response versus concentration in individual subjects.

DR. LI: Dr. Chinchilli?

DR. CHINCHILLI: Yes, I have a couple of questions. The first one has to do with the NEC.

You were reporting from the literature, you and Dr. Mosdell, about the incidence that is reported in the literature. My basic question is, does the incidence of NEC increase with earlier gestational age, so the more premature, the higher at risk you are for that. If that's the case --

DR. WYNNE: That's what's documented in the literature, yes.

DR. CHINCHILLI: You reported incidences of 10 percent and possibly even up to 15 percent for the gestational age that you had enrolled in this study, which is 28 to 32 weeks. Is there anything in the literature that says what the incidence of NEC would be for that range of gestational age?

DR. WYNNE: Can you answer that, Dr. Erenberg?

DR. ERENBERG: The reference that Dr. Wynne referred to was in infants under 1,500 grams, which would be the approximate population that we reported. The incidence of necrotizing enterocolitis is very difficult to determine because it is so episodic within a given institution, where one can go several years without having a single case, and then one can have an outbreak of having several cases, never determine the etiology, and then it disappears.

The reference is a review of a very specific population which is infants under 1,500 grams, which would be very similar to the infants that were in our study group.

DR. CHINCHILLI: The next questions I have probably Dr. Haack needs to address. The first has to do with the sample size calculation, and I don't know if you were involved with that. I saw somewhere that when the sample size was calculated for this study, it was assumed

there would be a 70 percent success rate for the caffeine and 20 percent success for the placebo. This seems extremely ambitious results to expect. Were you involved with this?

DR. HAACK: No, I was not. I was not involved in that sample size calculation.

DR. CHINCHILLI: I was just wondering what the basis was for this type of expected success rate.

DR. WYNNE: Can you answer that question, Dr. Erenberg?

DR. ERENBERG: It was a guesstimation. There's nothing in the literature on placebo treatment of infants with methylxanthines, so it was just an estimated guess and that's how we came up with the 20 percent.

DR. CHINCHILLI: Didn't you consider that to be rather ambitious, though, to expect such a strong result like that?

DR. ERENBERG: We have faith in caffeine.

(Laughter.)

DR. CHINCHILLI: My last question has to do -- I'm sure Dr. Haack can answer this one. This was a multi-center trial with nine different centers but I didn't see anywhere -- if it was, it wasn't very specific or direct -- any mention of adjusting for center in any of the statistical analyses.

I realize you have small numbers of subjects per center, but did you do any analyses that had looked at center effects and center-by-treatment interactions?

DR. HAACK: No, we did not. We did look at changes and percent changes which would eliminate the center effects, but we did not look for center effects in that model to see if there was an interaction. So, that was not done.

DR. CHINCHILLI: I'd like to ask a question about the study design and the definition of success. As I saw the presentation, the definition of success in many of your slides was a 50 percent reduction in apnea episodes. I would ask, at what point in the study design was that determined to be the primary efficacy variable, so to speak, and were there other primary endpoints that you considered?

DR. WYNNE: Would you like to address that, Dennis?

DR. HAACK: I wasn't involved in that earlier, but as was just brought out, the sample size calculation was based on what they thought the 50 percent reduction would be. To my understanding, that was an early success variable. The elimination was an ad hoc analysis that we came up with after the study.

DR. LI: But the variable then of the 50

percent reduction was decided upon at the time of the study design?

DR. HAACK: Yes, it was early on because that's where they calculated. The sample size was based on their best guess as to what the percentage of patients would have a 50 percent reduction in placebo and caffeine.

DR. WYNNE: This was based on the literature and discussing with experts. If you look into the literature, most of the literature assesses success with a 50 percent reduction in apnea, so that's where we based ours. It's my understanding. I wasn't there at the earlier part of this trial either.

DR. LI: In some of the documents there was a reference to the actual rate of apnea episodes during a 24- to 48-hour period, and I take it that was rejected as a success measure early on. Is that correct?

DR. WYNNE: Would you like to address that, Dennis?

DR. HAACK: Yes, the actual rate. I think early on they were looking at the percentage of success, at least a 50 percent reduction, but the actual rate was mentioned in some of the earlier documents. We did do some analyses on the actual rates but we used the primary as the success, as a 50 percent reduction.

DR. ERENBERG: At the initial meetings, the

rate was discussed but it was felt going to a specific rate as defined as success without referring to what the initial baseline was would make it difficult to really get an answer to our question.

DR. LI: Dr. Rothstein.

DR. ROTHSTEIN: This is more of an observation than a question. During your presentation, you mentioned that you thought it would probably be unethical to try and repeat a study like this. During the power analysis, it was felt that there would be a 20 percent effect in the control population, and I presume that you talked to a number of neonatologists when you set up this study.

This is probably the most powerful placebo that I've ever seen, where the placebo has in effect somewhere between 40 and 50 percent. It speaks to the necessity of in fact continuing in many areas with blinded placebo-controlled studies, and that some of our clinical assumptions -- we've been working with newborns for years and no one was able to predict that the placebo would come up with an efficacy rate this high.

DR. WYNNE: Yes, I couldn't agree with you more. We were very surprised. In fact, when we went back to the literature, there's nothing in the literature of course to determine. There was one study that was described as a placebo but treatment was given very early

in that. So, we had no idea what the placebo effect would be.

I'm only echoing what neonatologists have said when I said it was difficult to do the study because of the fact that methylxanthines are used so extensively.

DR. LI: Dr. Cross.

DR. CROSS: I was a little bit unclear on the study population. I'd be interested in the 1,000 patients that were screened. What percent of that 28 to 32 age group that had apnea were excluded because of other reasons? I suspect that the drug will be used in those sicker babies that have other things going on and I was interested, did you recover into your study group most of those that had apnea episodes and were 28 to 32 gestational age? Was in half, was it less than half, was it more than half? For example, in that age group you picked and who actually had apnea, what percent were thrown out as not being appropriate to study?

DR. WYNNE: Dr. Erenberg is going to answer. I was not there early enough.

DR. ERENBERG: We were looking for a specific population, which is those that have apnea of prematurity, which as I mentioned is a real diagnosis. If there are other etiologic factors, yes, caffeine may be used concomitantly. But for this particular group we wanted one

indication and wanted to remove all the other variables such that if you have an infant with patent ductus arteriosis, controlling congestive heart failure could eliminate the apnea. If you give caffeine concomitantly, which one is the one that had the major effect?

DR. CROSS: It certainly cleans up your study to do all those exclusions, but can you give any sense of what percent of the babies that had apnea by definition of prematurity, they were in your age group but for other criteria were thrown out?

DR. ERENBERG: We have the logs of the infants but we do not have how many of them had apnea and exclusion criteria.

DR. LI: Dr. Crim?

DR. CRIM: I just have some questions in my mind about this particular condition, and then as it pertains to its treatment.

In the literature review that was presented, as I understand the duration of the studies ranged from 24 hours to over 3 months, and I guess my question in that regard is, what was the duration of treatment of the infants in these various studies?

In other words, I don't have a sense and perhaps the pediatricians can give me a sense for this. How long were these babies treated with caffeine anyway for

this problem. I'm trying to get a sense, for instance, does a baby -- as they get older, they grow out of it, so to speak.

And then along the same lines, one of the questions that had come up was the babies that have the sepsis as far as this history of sepsis. How old were these babies at the time from birth that they were treated? I can't understand how a person can have a history of sepsis if they are enrolled in a study soon after birth.

I'm trying to get a sense in terms of these time lines, in terms of treatment, as well as the time lines, in terms of how old these babies were at the time they were enrolled in the study, as opposed to gestational age, but from birth.

DR. WYNNE: You'd like to know in our study how old they were?

DR. CRIM: I'll just kind of restate them one at a time.

One, as far as the review of the literature, although the duration of the studies range from 24 hours to 3 months, do you have a sense of how long the infants were treated in this study? I know your study was approximately 10 to 12 days. How long were these babies treated in the studies that were reviewed in the literature?

DR. MOSDELL: It is very difficult from the

literature to say that there is an average duration. The 24-hour study was just trying to -- it was one particular trial that was trying to evaluate the effects within the first 24 hours.

There's quite a wide range. I don't really have an average that I can provide to you. Some studies were specifically designed to be 7 to 10 day trials, as ours was. Others treated babies until they responded, so you had very long durations of treatment.

Perhaps Dr. Erenberg could talk about the clinical use of the drug, but the literature really has a wide range of durations used and it is difficult for me to say that primarily they were 7 to 10 days or they were longer than that.

DR. JOBE: Perhaps I could give you a picture of the practice. Apnea of prematurity is extremely common. The more immature the infant is, the more likely the infant is to have it, and the more dense the apnea is likely to be. In general, normal infants will grow out of their apnea of prematurity by 32 to 34 weeks gestation.

So, the standard of practice is that if an infant has apnea, he's put on either theophylline or caffeine. Then at 32 to 34 weeks, if there are no apneic episodes, the baby is tested off the methylxanthines.

Then if the apnea recurs, the baby is put back

on the methylxanthine and then tried off again before discharge. Some of the babies are sent home on methylxanthines.

So, the period of use is from severe prematurity at 24 weeks up to 32 to 34 weeks for most of these infants and then they are taken off and tested.

DR. CRIM: Is it initiated at birth?

DR. JOBE: It is initiated at a point in time when you want them to breathe spontaneously. So, if they are on a ventilator being ventilated, then it's not given in general, but as you wean the baby, there are several studies reporting the efficacy of using caffeine to get babies off ventilators. So, it is initiated before they are extubated very often in small babies.

Now, none of this is done by randomized controlled trials. That's just what practice is.

DR. GOLDSMITH: Unfortunately, there is also the confusion between apnea of prematurity and ALTEs, acute life threatening events, or near-miss SIDS, whatever you what to call it. Many physicians continue methylxanthines past the time of 36 weeks, some without testing, some with testing by pneumocardiogram, which has a very controversial background and Allen says is worthless. But in one study on successive days, pneumocardiograms were rated as normal, then abnormal, then normal again in a high percentage of

times, so it really is very variable.

But we'll see babies on methylxanthines up to a year of age home on apnea monitors.

This panel is talking about the use of caffeine in the neonatal unit and properly up to 36 weeks, but in practicality this drug, if it's licensed, I'm sure will be used because of its ease to be given once a day rather than three or four times a day as theophylline is, that will be used as a prescription drug, probably up to a year of a age in children for acute life-threatening events.

DR. CRIM: I was trying to get a sense for that in that these babies -- not on mechanical ventilation as part of the enrollment, and that's what I'm trying to get a sense for. How old were these babies in terms of after birth before they were enrolled into this study as far as initiated in the sense of how soon would this apnea have been recognized before they would have been enrolled in this study. That's what I'm trying to get a sense for.

DR. ROTHSTEIN: That's one of the questions. Maybe the sponsor can clarify it. Looking at their data, it looked to be that the average time of enrollment was about day 4 or 5 of life. Is that correct?

DR. ERENBERG: It was about between 7 and 10 days, approximately.

DR. CRIM: Would these babies have been

recognized as having apnea since they would not have been on mechanical ventilation as part of the inclusion or exclusion criteria? Would they have been recognized as having apnea before they would have been enrolled in the study?

Obviously, they would have to have it before being enrolled in the study. I'm just trying to get a sense for how many days they would have had these apnea events before they would have been enrolled.

DR. ERENBERG: As soon as they had 6 apneic events within a 24-hour period and did not fulfill any of the exclusion criteria, they were enrolled.

Now, these infants may have been ventilated prior to enrollment, but because of the problem that Dr. Jobe mentioned, it is often tradition that infants receive caffeine prior to extubation. We eliminated those infants from our study. In fact, several study sites refused to participate because they felt it was important that they do use caffeine in the extubation process.

DR. LI: Dr. Sessler.

DR. SESSLER: I have two unrelated questions.

The first is in regards to the study itself. What was the duration of enrollment for the nine centers to get these 80 patients enrolled?

DR. WYNNE: We started in March of 1994 -- I

omitted that from my presentation -- until October of 1995. So, it was approximately 18 months.

DR. SESSLER: And the second question is in regards to NEC. Looking at it kind of in reverse, are there any studies where large groups of patients with NEC have been evaluated for risk factors and, preferably in a multi-variate fashion, have identified methylxanthines as a significant risk?

DR. WYNNE: I think Dr. Mosdell can answer that question. She did research on that.

DR. MOSDELL: There is one study. I think the FDA reviewed this in their write-up. The study is by Davis, et al., published in 1986. It was a retrospective review of 275 infants and they compared those who developed NEC to see if they were receiving methylxanthines.

In that particular study, they did not find an association between the treatment with methylxanthines and the development of NEC.

It has to be countered by the fact that this really wasn't a case match controlled study. It was a retrospective review, and there are some limitations to that type of study design. But that is the one study that evaluated, more in a systematic rather than just reports, the association of NEC with methylxanthines.

Certainly there is a large body of evidence

that has looked at various parameters that are associated with the development of NEC. By and large, the largest or the primary factor which is always associated with NEC in these trials is prematurity. Other than that, you see quite a range of varying variables that have been identified having association with this disorder.

DR. GOLDSMITH: As a clinician, the problem with evaluating NEC and methylxanthines is that apnea causes decreased blood flow, and decreased blood flow is a common denominator in the pathogenesis of NEC. So, if you start with a child who is having apneic episodes and he is having decreased blood flow to his gut and then you add on top of that as treatment methylxanthines, what's the cause? Is the cause the decreased blood flow problem or is the cause the drug?

DR. LI: Dr. Jenne?

DR. JENNE: Well, we'll probably get into this later, but I wondered what your view was of the therapeutic range. You took a level which is common in the literature and most of these papers that you referred to used calculations based on caffeine citrate, which when corrected to caffeine, is the same dose that you are using basically.

But in a large study in Journal of Pharmacologic Therapeutics, 1997 by Lee, the conclusion in

their discussion is that many infants require levels in the range of 35 micrograms per milliliter.

There's another paper that Dr. Kelly mentioned, a paper by Scanlon, I think, in which 30 was better than 15 in severe apnea.

Now, you allowed your study patients to break protocol, and apparently some of them went up into the 40 range or so after another loading dose, which is what happened.

Can you say that in those cases you seemed to get beneficial effects by increasing the dose once you went off label and gave a second loading dose?

DR. ERENBERG: I believe, first of all, Dr. Scanlon's study showed that the infants responded quicker to the higher dose, but the success rate may not necessarily have been greater.

DR. JENNE: I see.

DR. ERENBERG: Dr. Ludden, do we have values with the second loading dose?

DR. LUDDEN: Yes, there are blood levels in the data set for that, so I think that could be looked at. I haven't looked at it yet.

DR. ERENBERG: We went with the fixed-dose study. One of our original previous versions we were going to look at a multi-dose escalating study for nonresponders,

but it was decided ultimately that for this study we would be with a fixed dose with a strong safety net for nonresponders, which is what we put together.

DR. JENNE: Well, this will probably be kicked around later in the day.

DR. LI: Les?

DR. HENDELES: I have some questions about the package insert, the labeling. Is now the appropriate time, or would that be postponed until later?

DR. LI: Go ahead and ask your question. We will probably be discussing that in more detail later, but I think it's reasonable to bring it up, Les.

DR. HENDELES: One of the questions I have -- I have several, but one of them relates to the fact that there is no information in the labeling on adjusting the dose for decreased renal function. You excluded that in the study design but the drug is actually going to be given to patients who have varying amounts. There's a brief warning sign but it seems to me that there needs to be some very specific dosing guidelines since the drug is as much as 86 percent eliminated from the body by urinary excretion.

DR. LI: Does anyone want to comment on that? Otherwise I think we probably will be able to bring that up after we hear from the FDA. Yes, Stan.

DR. SZEFLER: I had some questions on the pharmacology of the drug, and it ties in with this NEC question and the observation that Dr. Rothstein made on blood flow.

I can't recall where it is, but somewhere in this literature there's a mention that caffeine does not affect cerebral blood flow, whereas theophylline does. That seems to be posed as an advantage of caffeine in treatment. This may tie it together because also there seems to be the observation that the NEC has occurred with theophylline use and not with caffeine.

Is there a common link here that should be addressed in terms of the pharmacology of the drug?

DR. MOSDELL: I can review those studies that discuss cerebral blood flow.

I think in terms of NEC we have to keep in mind that there was one study that stated that there was no statistical significant difference between caffeine and theophylline. There was no frequency in that study so we can't say how many patients in each group developed that adverse event. That seems to suggest it may have occurred in the caffeine group.

Nonetheless, the literature has been predominantly associated with theophylline in terms of NEC.

I can if you wish go through the data with

cerebral blood flow if you are interested in those studies.

DR. SZEFLER: I don't think you need to take time. Just to summarize would be fine.

DR. MOSDELL: Basically the literature that's out on cerebral blood flow, one study compared caffeine to theophylline on its effects on cerebral blood flow. In that study caffeine was not shown to adversely affect cerebral blood flow, whereas theophylline was shown to decrease cerebral blood flow.

There were two additional studies that examined cerebral blood flow. These were caffeine only looking at baseline compared to after treatment. In those two studies caffeine was not shown to affect cerebral blood flow.

So, those are the three studies that comprise the data by suggesting there is no decreased cerebral blood flow with caffeine, but perhaps with theophylline.

DR. SZEFLER: And these are all neonatal subjects?

DR. MOSDELL: The cerebral blood flow studies were all in infants.

DR. LI: Yes, Molly?

DR. OSBORNE: Again, staying with mucosal injury and the necrotizing enterocolitis and caffeine, it's certainly not a field I'm familiar with. So, I looked through this epidemiology of necrotizing enterocolitis that

was included in your documents, Clinics in Perinatology, 1994. So, I'm going to say, is this a reasonable hypothesis, and then help you give me feedback to see if this is a way to think about it.

My concept of what's going on here is that if someone who is premature, for whatever reason, develops mucosal injury in the GI tract and then has a caffeine kind of drug administered, there's the potential, perhaps in a slight population, for that mucosal injury to occur, perhaps because of a presser effects of the caffeine that would then further decrease blood flow in an area that's already injured. Then with inflammation developing, one could then end up with necrotizing enterocolitis.

Is that a reasonable hypothesis? Is that how to best put this information together that in some patients with underlying mucosal injury, caffeine could then have an exacerbating effect?

DR. ERENBERG: I think that is a potential. There is no data to substantiate it. One of the proposed etiologies for necrotizing enterocolitis is hyperosmolar ether formula or medications. Caffeine is hypo-osmolar, compared to theophylline, which is hyperosmolar. If the mucosal injury has already occurred then I think that is a potential. Does the oral administration of caffeine cause the mucosal injury, which would then go on, I don't think

is.

Unfortunately, infants with necrotizing enterocolitis, before they are clinically recognized, may present with apnea, without the abdominal distention and other signs and symptoms of necrotizing enterocolitis. So, therefore, the potential does exist that the clinician may initiate methylxanthine therapy prior to the full-blown picture or the ability to make the diagnosis of necrotizing enterocolitis.

DR. OSBORNE: Thank you. I'm just trying to address how we're going to put together a warning.

DR. LI: Yes. Maybe the last question for right now. Stan?

DR. SZEFLER: Just one question because I'm not sure if we're going to be able to come back to Roxane later.

DR. LI: We can.

DR. SZEFLER: Okay, good.

The quick question is, in the documentation that we have, I didn't get a feel for what the study sites were like. Were these clinical research sites that participated in this study, or were they clinical sites that had the opportunity to participate in research? What was the distribution of the nine sites?

DR. ERENBERG: There were nine study sites.

All of them were affiliated with universities. None of them had CRC's per se, but all had experience in clinical research, and Dr. Wynne could list her study sites.

DR. WYNNE: I would like to refer you to your briefing document. I don't know if you all have it or not. It's actually page 8-19. I'll just go through these for you very briefly.

The University of Kansas enrolled 3 patients. Cooper Hospital enrolled 5. Medical College of Virginia, 14. Denver, Colorado Children's Hospital, 19. Women and Infants Hospital of Rhode Island, 5. Oakwood Hospital, 3. University of Texas Health Science Center, 12. University of California, Irvine Medical Center, 17. And 4 at the Carolinas Medical Center.

So, you can see there are three that enrolled quite a few patients. The others enrolled a few.

DR. LI: I'd like to thank the sponsor for their very forthright answers to the questions from the committee.

Let's take a 15 minute break and we'll have the FDA presentation at 10:15.

(Recess.)

DR. LI: Ladies and gentlemen, the sponsor and Dr. Wynne have asked for just one or two minutes to have the opportunity to answer some of the questions that came

up earlier this morning. They have been able to find some additional information that might be helpful to us.

Dr. Wynne, before Dr. Pina's presentation, if you would go ahead.

DR. WYNNE: Yes, thank you very much. One of the questions that you raised earlier was, why were these approximate 1,000 patients excluded from entry into the trial? I do have that information for you.

The exact number of patients screened was 1,029, 87 of whom were enrolled. The patients excluded then were 942. Reasons for exclusion were, 482 patients did not meet the age requirement or apnea event requirement. 248 were already receiving theophylline or they were on ventilation. Parents refused or were unable to give consent, 63 of the patients. Underlying disease, CNS, cardiovascular, sepsis, 55. Death, 52; patient transferred, 17; other, 13; and then there were 12 patients with no reason stated. I think that will give you an overview of the approximate 1,000 patients that were screened.

A second question that came up earlier was the incidence of PDA during the study. Actually there were two reports -- I'm talking now about the double-blind -- in the caffeine group and two in the placebo group. An additional 2 patients that were transferred from the placebo into the

caffeine open-label also were reported to have PDA.

I hope that answers the questions that you asked earlier. Thank you very much.

DR. LI: Thank you, Dr. Wynne.

I'd now like to invite Dr. Pina, who is the FDA medical reviewer, to give the FDA's presentation. Dr. Pina.

DR. PINA: Good morning. I am Miriam Pina, the medical reviewer from the Division of Pulmonary Drug Products. I thank the members of the pulmonary committee and consultants for being here today to discuss this important drug, caffeine citrate injection, for the treatment of apnea of prematurity.

I also would like to publicly acknowledge the hard work of the other members of my review team: Dr. Jim Gebert, statistical reviewer; Vibhakar Shah, our chemistry reviewer; Misoon Chun from pharmacology-toxicology; Albert Chen from biopharmacology; and our tireless project manager, Lindsay Cobbs. Thank you very much for your help.

We heard a detailed presentation of what apnea of prematurity is all about, and the data that the studies with caffeine citrate have generated from the sponsor. Thus, I would like to focus only on some issues that are either complementary for the understanding of the data or of concern from the regulatory point of view regarding the

study design and the results of trial OPR-001, and from the data available from the literature. I will end my presentation with a summary of the issues for discussion.

I will start with trial OPR-001.

As the sponsor explained, trial OPR-001 was a multi-center randomized double-blind placebo-controlled parallel study with an open-label rescue phase.

The target population was premature babies between 28 and less than 33 weeks of gestational age, with at least 6 apnea episodes in 24 hours or less. Apnea for this trial was defined as a respiratory pause of 20 seconds or more, with or without bradycardia. These events were to be observed and recorded by the attending personnel.

As presented by Dr. Wynne, patients with underlying causes of apnea were excluded from the trial. I would like to explain here that the 2 patients in the placebo group who were excluded because they were not treated, they did not receive any treatment because they were advanced from CPAP to mechanical ventilation before they even started the treatment.

During the double-blind phase, the patients received either caffeine citrate or an equivalent volume of placebo. A patient could be rescued with open-label caffeine citrate if the number of apnea events did not remain less than 50 percent of the baseline rate and the

investigator felt that continuing double-blind treatment placed the patient at unacceptable risk.

The original maximum duration of treatment was 10 days, but the treatment period was extended to 12 days in the last amendment, and only 16 patients were enrolled under this provision. As Dr. Wynne explained, only 4 patients completed the treatment to 12 days.

I should point out here that the primary endpoint defined in the original protocol was the success rate defined as having a 50 percent reduction of the baseline number of episodes of apnea during hours 24 to 48 after the double-blind loading dose. But this primary endpoint was revised, was amended to apnea rate on day 2 during amendment number 5. So, the final version of the protocol has the primary efficacy endpoint, apnea rate on day 2.

As we will see shortly after, both definitions failed to show a statistically significant difference between the treatment groups.

Secondary analyses of the apnea rate, the primary endpoint, were number one, the reduction in apnea episodes by at least 50 percent and, number two, the elimination of apnea events, that is, no apnea events reported for that day by treatment day or by total number of days reported without apnea.

The secondary efficacy endpoints were, for those patients who continued to have apnea events, they analyzed the lowest heart rate, lowest oxygen saturation, and the duration of apnea events. A sample size of 78 patients was chosen based on the original primary endpoint. The sponsor assumed that a 50 percent reduction of apnea events during hours 24 to 48 after the double-blind loading dose would be seen in 70 percent of the caffeine-treated patients and only 20 percent or less in the placebo-treated patients.

The difference in success rates was lower than the sponsor had predicted. It was about 20 percent, as we have seen. According to our statistical reviewer's calculations, the study was estimated to have only 44 percent power to pick up the observed difference in success rates.

Before discussing the study results, let's look at the number of patients receiving double-blind therapy by treatment day as a result of the design of the study. Let's remember that the study allowed for patients to be transferred to open-label caffeine treatment if the investigator considered it necessary.

From this light we note the marked reduction in sample size in both groups after treatment day number 2. Here we have study days baseline to day 10, and the number

of patients who completed that study day on baseline we have 100 percent of patients in the caffeine and in the placebo group. As you see, there is almost half of the patients by the end of day number 2.

The number of patients who were transferred to open-label caffeine or were permanently discontinued from the trial was similar in the caffeine and in the placebo groups, 53 percent in the caffeine group versus 65 percent in the placebo group.

As explained before, the protocol-specified primary efficacy endpoint was apnea rate on day 2. The sponsor did not submit this analysis. Therefore, the statistical reviewer performed the primary analysis of the primary protocol-specified efficacy endpoint. For this analysis he used scaling of the duration of baseline and of the study days to 24 hours and the last value carried over method.

Here we have the number of apneas in 24 hours and the results on day 2. As we can see, the caffeine group has an apnea rate of about 4.95 apneas in 24 hours. In the placebo group, the apnea rate was 7.2. The difference was not statistically significant.

The sponsor analyzed the apnea rate on day 2 by identifying those patients who had a reduction in apnea events equal to or greater than 50 percent of the baseline

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apnea rate. In this chart we have the percent of patients and the results on day 2.

From the total of patients, about 76 percent of the patients had a reduction of 50 percent or more of the apnea rates on day 2, and in the placebo group, 57 percent of the patients met this endpoint on day 2. The difference was not statistically significant.

Analyzing the 50 percent reduction of apnea events by treatment days, we have here the percent of patients and the number of treatment days. Each treatment day up to day number 10. We see that on day 2 there was no statistically significant difference, but the difference was significant for days 4, 5, 7, 8, 9 and 10.

We should note, however, that this is a post hoc analysis. In addition, it carries forward the apnea rate value of 10 on the last day of double-blind treatment for those patients who were transferred to open-label caffeine or were discontinued from the trial.

I would like to explain that 10 patients in the caffeine group, that is, 28 percent, and 6 patients in the placebo group, 25 percent, had a reduction of 50 percent in their apnea rate the day that they were transferred to open-label caffeine or that they were discontinued from the trial.

There were several reasons why they were

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transferred from the trial. These were frequent bradycardic events without apnea, persistent apnea events, although the rate was still less than 50 percent of the baseline period, or the patient was referred to another hospital.

Keeping in mind that these are post hoc analyses, we wanted to know how many patients in the double-blind phase maintain the beneficial effect of the drug until the end of the study period, how many patients that had a 50 percent reduction of their apnea events, once they reached the endpoint, how many maintained that effect. Here is the graphic.

Here we have percent of patients. This y axis uses as a denominator only the patients who achieved at least once this endpoint. Here we have those patients who maintained the drug effect, and those who did not maintain the effect. That is, some days they had a reduction of 50 percent and some others did not reach this endpoint.

These two columns do not add to 100 percent because we excluded those patients who reached this endpoint but were transferred to open-label or were discontinued from the trial.

The difference between the patients who maintained the effect and those who did not plus those who were discontinued is statistically significant.

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Another way of analyzing the apnea rate was the percent of patients with zero apnea events reported for 24-hour periods. This table shows the percentage of patients with no apnea events at each treatment day. Here we have on the y axis the percent of patients who reached this endpoint on treatment day number 1 up to day number 10. As we can see, those with the asterisks, the difference was statistically significant in favor of caffeine.

I would like to point out at this point that on day 2 the difference was statistically significant. Day 2 was the day chosen by the sponsor to measure the primary endpoint.

This graphic shows the analysis of the number of patients by the total number of days spent without apneas. That is, on the y axis we have how many patients remained apnea-free for how many days. Here we don't have treatment days, but total number of days with no apneas.

I would like to focus your attention on these days, where about 10 patients in the caffeine group remain apnea-free for 8 or more days. No patients in the placebo group remained apnea-free for this long.

To answer one of Dr. Rothstein's questions, regarding once the patients remained with no apneas for 24 hours, how many patients remained without apnea for the rest of the period, I should say that from these 10

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patients, 6 of them remained apnea-free continuously from the first time they reached that endpoint.

We've also wanted to see how many patients remained apnea-free once they reached that endpoint, and that's what I said before. On the y axis we have those patients who at least once -- is the percent of patients who at least once presented no apneas for 24 hours, and how many of those were able to maintain that effect until the end of the study period.

Again, we see at 29 percent of the patients in the caffeine group maintained that effect versus 1 patient, which is 7.6 percent, in the placebo group. This patient, 1 patient in the placebo group, achieved this endpoint on the last 2 days of the study period. Really, no patient was in the placebo group apnea-free for more than 5 days, and neither one in a row. There were some days yes and some days no.

This table shows some of the characteristics that you were asking before of those patients in the caffeine group who met different efficacy endpoints, and those who never met any of the efficacy endpoints. Here we have some of the characteristics, gestational age, what was the baseline apnea rate, the weight at entry, and the caffeine plasma levels.

For those patients, 12, who had a reduction of

50 percent for more than 7 days, who had 0 apneas for more than 7 days, and this is the failure group who never had a greater than 50 percent reduction of their apnea rates. We have 9 patients here.

As you can see, there is not a particular subset of characteristics other than maybe weight at entry, where those patients who had no apneas for greater than 7 days after the treatment was started were slightly heavier than the other two groups.

Other secondary efficacy endpoints were lowest heart rate associated with apneas. The mean values between the caffeine and placebo groups were similar and not statistically significantly different. They were between 67 to 78 beats per minute.

The lowest oxygen saturation associated with apneas. The values were similar in both groups, 78 to 84 in the caffeine group and 77 to 87 in the placebo group.

The duration of apnea events was another secondary efficacy endpoint. The durations were recorded by the attending nurse once the apnea alarm went off. Because the nurse was not always at bedside at the time the apnea alarm went off, the manner of recording of the duration of the apnea events can be considered unreliable.

The sponsor presented the duration of the apnea events by day for the double-blind and the open-label

treatment periods for each treatment group, but did not provide the analysis of the data for this endpoint.

According to the statistical reviewer's calculations, the overall analysis of the summarization of duration of the apnea events submitted by the sponsor did not show a significant effect of caffeine on the duration of apnea events.

From the safety point of view, the sponsor has already presented a detailed description of the results in OPR-001 trial. I would like to focus my discussion on two issues only: some main adverse events and deaths.

The assessment of adverse events between the treatment groups in this trial was difficult. Firstly, the complex design of the trial allowed some patients in the placebo group to be exposed to open-label caffeine at different times, and secondly, the high frequency of complications encountered in this population did not help in many cases.

We tried to assess the main adverse events in several ways to overcome some of these difficulties. I will present to you the data by analyzing the incidence of adverse events by exposure to caffeine and by randomization.

The first analysis assessed the incidence of adverse events by exposure to caffeine. The exposed group

includes all the patients randomized to the caffeine group plus those patients in the placebo group who were transferred to open-label caffeine. The not exposed group includes the patients in the placebo group who were not transferred to the open-label caffeine.

As you can see, no significant differences were noted in the incidence of adverse events analyzed between the treatment groups. It is clear, however, that the small sample size could have made it difficult to pick up significant differences in safety parameters, had there been any. However, it is of note the numerical increase of necrotizing enterocolitis, 5 versus 1; sepsis, 8 patients versus 0; and death, 3 patients versus 0.

Another analysis studied the adverse events that occurred to patients by their randomization, regardless of their exposure to caffeine. We did this analysis to overcome the time factor, where some patients in the placebo group were transferred to open-label caffeine quite early, with the possibility that they did not have enough time to develop some complications that may have occurred had they been allowed to continue in the same treatment group for a longer time period. Again, no significant differences were noted between the treatment groups.

About mortality, there were 3 deaths reported

and all of them had been exposed to caffeine. Again, very small numbers are difficult to interpret the meaning of this.

I would like to discuss the data in the literature for efficacy. The database consisted of 27 articles to provide data on efficacy, and we have 59 articles to provide data on safety. We have more safety articles than the sponsor reported because we did our own search.

From the efficacy point of view, 10 controlled and 17 uncontrolled trials were submitted and reviewed. In our review, we noted that no study was placebo-controlled, all were open-label, and several different clinical endpoints were studied. Except for one study, there were no follow-up data after caffeine was discontinued.

However, all the investigators concluded that caffeine improved the patients' apnea endpoints, when compared to the patients' own baseline. However, we should note here that apnea of prematurity tends to improve simultaneously over time.

At this point I would like to bring your attention to a particular study conducted by Murat, et al., in 1991. This is perhaps the best designed trial that supports efficacy of caffeine in the literature. 18 premature infants were studied in this prospective

randomized parallel controlled trial. The dosage regimen was similar to that used in trial OPR-001. Its primary endpoint was apnea index on days 1, 5 and 15. Apnea index was defined as the average number of apneic events per 100 minutes, obtained from the total number of events recorded within a 24-hour period.

24-hour cardiorespiratory recordings were performed to monitor apnea events on days 1, 5, 15 and on day 8 after the therapy was discontinued.

The study by Murat, et al. showed a statistically significant improvement of the apnea index in the treated group on day 1 and day 5. I will show you later the numbers obtained.

A substantial dropout of patients in the control group made the analysis not significant at day 15. This study also showed that apnea did not recur on day 8 after the discontinuation of caffeine.

Here we have the results on day 1, 5, and 15. The apnea index was .24 versus .74 in the untreated controls, and on day 5 we have .11 versus .57. This apnea index of .24 would be an equivalent of about 3 apneas in 24 hours versus 10.6 apneas in 24 hours in the control group, and the difference was statistically significant.

On day 5 we have an apnea rate of about 1.6 in the caffeine group versus about 8 apneas in 24 hours in the

control group. Again, the difference was statistically significant.

On day 15 the control group from 9 patients had dropped to 3 patients only. The others had to be treated with caffeine or were intubated. This apnea index is about .5 apnea rate in 24 hours, and this is about 1.7, and the difference was not statistically significant.

Regarding safety, the database from published clinical trials and from our own search included over 800 premature infants exposed to caffeine. Instead of going over the data on safety that the sponsor has already presented, I would like to emphasize two particular issues. The association of methylxanthines with the incidence of necrotizing enterocolitis and the information currently available on drug-drug interactions.

In general, the adverse events reported in the literature for caffeine are similar to those reported for trial OPR-001, and when caffeine was compared to theophylline, the adverse events were usually less frequent.

Because of its morbidity and high mortality, and the question raised in the literature regarding its association with the use of methylxanthines, I would like now to focus your attention on necrotizing enterocolitis.

As the sponsor has explained, NEC is a major

cause of morbidity and mortality in premature infants. Its reported incidence ranges from 2 to about 15 percent, with the highest incidence seen in the lowest birth weight groups.

The reported mortality varies from 20 to 50 percent according to other medical factors involved. Factors like the use of umbilical artery catheters, some pharmacological agents like aminophylline, theophylline, caffeine and vitamin E, in high density formulas have all been implicated with the incidence of NEC and infant survival.

Some of the issues obtained from the literature are as follows. Robinson, et al., in 1980 was one of the first ones to suggest the association of xanthine treatment with the development of NEC. The others published three cases of NEC in premature infants after treatment with aminophylline, and postulated that in these cases NEC was related to bacteria overgrowth due to decreased GI motility which followed the use of xanthines.

Grosfeld, et al., in 1983 studied the effect of aminophylline in an experimental bowel ischemia model and suggested that aminophylline had an adverse effect in animals with ischemic bowel insults.

After these reports, several other studies tried to address this question. In most cases theophylline

was the xanthine studied, probably because theophylline was the most widely used methylxanthine.

A retrospective analysis by Davis, et al., in 1986 demonstrated that 124 infants treated with theophylline had a similar incidence of NEC as did 151 infants who were not treated with theophylline.

In other papers, theophylline was compared to caffeine. Bairam, et al., in 1986 studied the effect of caffeine in 10 babies compared to those of 10 babies on theophylline. In this trial, 4 infants in the theophylline group were stopped for GI intolerance. 2 of them were reported to have developed signs of NEC.

The caffeine group did not develop significant GI symptoms. These results were not compared to a placebo or untreated arm for a background incidence of NEC.

Larsen, et al., in 1995 reported no differences in the incidents of necrotizing enterocolitis between the caffeine group -- 82 patients were treated with caffeine -- and theophylline, 98 patients. However, the actual incidence of NEC in each group was not published.

I will close this section by stating that overall the findings in the literature are not conclusive. Whether the exposure to methylxanthines in general and to caffeine in particular is associated with an increased incidence of NEC, nor if there is a subset of patients at

higher risk of developing this disease if exposed to caffeine. One of my personal goals for today is to hear your opinion regarding this issue.

The second issue on safety derived from the literature is the drug interactions with caffeine. The biopharmacology data base consisted of 71 studies, mainly from adult healthy volunteers or patients. Only 1 pediatric patient was submitted for a discussion of drug-drug interactions. This paper reported three cases of increased clearance of caffeine within co-administration of phenobarbital.

The data provided very limited information on caffeine dose adjustments that may be needed following the coadministration of drugs prescribed to preterm neonates. Lower or higher doses may be needed following coadministration of drugs like cimetidine, ketoconazole, and phenobarbital. But the manager of the adjustment is not yet known.

In summary, study OPR-001 is the only randomized double-blind placebo-controlled trial in which caffeine was studied for the treatment of apnea of prematurity. It failed to show a statistically significant difference in the primary endpoint apnea rate on day 2 after the loading dose in favor of caffeine. But it showed a statistically significant effect in reducing or

eliminating apnea events in the target population. These calculations, however, were not protocol-specified.

Most trials in the literature were small and not adequate and well-controlled. However, caffeine was consistently shown to improve the patients' endpoint studied when compared to the patients on baseline.

Based on the results from study OPR-001 and the data available in the literature, do you consider that there is enough evidence to support efficacy of caffeine citrate for the treatment of apnea of prematurity? That's our question.

Regarding safety, study OPR-001 had a complex design with a high rate of dropouts early in the study that made difficult the interpretation of the data. It showed no clinically significant differences in adverse events by body system between caffeine and placebo-treated patients.

The numerical increase in the incidence of necrotizing enterocolitis found in the caffeine-treated group is of concern, admitting that the association of methylxanthines with an increased risk of NEC has previously been questioned in the literature.

The data in the literature were consistent with the findings in the clinical trial.

Regarding the association of NEC with the use of xanthines, the findings are not conclusive in either

direction.

And regarding the drug-drug interactions, no data are available to adjust caffeine dose with the coadministration of other drugs.

We would like to hear the opinion of the panel whether the effects shown to you today constitute sufficient evidence of the safety of caffeine citrate for the treatment of apnea of prematurity.

Thank you very much.

DR. LI: Thank you, Dr. Pina.

I'd like to ask the committee if they have any questions for Dr. Pina.

DR. CRIM: I have a question relating to both the efficacy and the safety from the literature review. I think it would help in terms of my question on the efficacy if you can pull back up your slide 36 that gave the results of that Murat study.

The question I had was in terms of the number or frequency in which patients would get better over time anyway. My question as far as this efficacy is, it looks like there's a decrease in this apnea index for both groups over time. Although you don't have either standard error or standard deviation data for day 5, just looking at the control group, is it possible to glean from that study as to whether the difference between day 1 and day 5 for the

control group, or between day 5 and day 15 is improving statistically within groups?

DR. PINA: Yes, they did check that in the study and it was statistically significant from here to here.

DR. CRIM: And what about for the control, between the .74 and the .57, and .57 to .12 for the control? That statistically improved?

DR. PINA: It was, yes.

DR. CRIM: And then the other thing regarding the safety, which I guess you have on slide 41, was the study by Davis that saw similar incidents of NEC between the theophylline-treated and the non-theophylline infants.

I guess my question for that, was there any statement in that study as to the duration of exposure to theophylline in 124 infants? In other words, was this any exposure, or 10-day exposure, or 2-week exposure and an effect not being found, or was this, for instance, 1 day of exposure in the theophylline?

DR. PINA: I don't know if the sponsor has that article with you, but this is a retrospective study. This was a study for something else. So, inside of the study they looked for the patients who were treated with theophylline and those who were not treated with theophylline with apnea events.

I'm not sure if they evaluated duration of treatment of theophylline.

DR. SZEFLER: I'd like to congratulate you and also Roxane for some excellent presentations and interaction on the evaluation of the data.

The one question I had was, these primary efficacy variables are very hard to choose and they are so important. In the development of this protocol and the FDA involvement, how much discussion was there around the primary efficacy variable?

Is the Murat study the study that was kind of counted on for these estimates of 70 percent efficacy and 20 percent placebo? Did you have general agreement or disagreement on the primary efficacy variable?

DR. PINA: I know from the sponsor's point of view, nobody there was at the preliminary discussion of the original protocol. From our side, I was not here when this was started.

DR. SZEFLER: Because I believe these start from the IND phase.

DR. PINA: Yes. We had discussed with them from the beginning the design of this protocol and we went through a lot of arrangements trying to find the ideal design for this trial.

I think the sponsor has something to add.

DR. LI: Does the sponsor want to make a brief comment?

DR. ERENBERG: I guess I have the historical memory because I was at all of those. You are absolutely correct. We did go through what we could glean from the literature, looked at the various endpoints, apnea density, number of apneic events. We tried to come to a conclusion as to what would be reasonable estimates, and we came to the protocol as it is designed here.

DR. PINA: The original protocol-specified primary endpoint was the 50 percent reduction, and then it was changed to apnea rate on day 2.

What I can say is that even no apneas on day 2 are all different analyses of the same event, which is the number of apnea events on day 2 and just a 50 percent reduction or no apneas, or apnea rate per se on day 2. They are just different analyses of the same clinical endpoint.

DR. LI: Dr. Goldsmith?

DR. GOLDSMITH: If we look at safety as well as drug-drug interaction, I want to come back to a comment by Dr. Osborne before looking at potential causes of necrotizing enterocolitis. If we say that there is mucosal injury and ischemia, and then the potential for something that might cause a change in blood flow, some drug that

might cause a change in blood flow, and then in addition a bacterial aspect to this or an invasion of an organism, then I'm concerned about the interaction between methylxanthines and any H2 blockers, any H2 antagonists, where we change the flora in the gastrointestinal system. So, the combination of caffeine and cimetidine, or any of the other H2 blockers would the very important.

Is there any information with regards to NEC on that combination drug-drug interaction or safety that you know about or that the sponsor knows about?

DR. PINA: Not from our point of view.

DR. WYNNE: I think I'm going to address this question to Dr. Mosdell, who just returned. Could you repeat the question please?

DR. GOLDSMITH: The question was, is there any information regarding incidence of NEC in combination with H2 blockers, methylxanthines with H2 blockers, since the H2 blockers may change the bacterial flora by changing the pH of the gastrointestinal tract?

DR. MOSDELL: The primary focus that we did in our literature search involved caffeine and its association with NEC, and also an additional analysis that looked at theophylline and its association with NEC. In none of those trials was it mentioned that histamine blockers could be associated with an increased incidence of NEC, or the

combination of the two increased the incidence of NEC. Although our literature search did not focus on histamine blockers, so we may not have collected all the articles.

In specifically looking at caffeine or theophylline literature, what I could read didn't have any type of association that was described.

DR. HENDELES: To Dr. Pina. You commented on a study on drug interactions involving premature infants, but I don't recall, what were the drugs and what were the findings of that study?

DR. PINA: There was only one paper submitted addressing drug interactions. One paper in premature infants. This paper was just a report of three cases of phenobarbital interaction with caffeine, where they didn't find caffeine levels. They had to increase the caffeine dose.

DR. HENDELES: The reason why I bring that up is there were all these other papers on interactions in adults. I don't see the relationship. If the premature infant lacks cytochrome P450 1A2, which is the primary site of interaction in adults, I don't know that any of those have any relationship to this population at all.

DR. LI: Curt?

DR. SESSLER: The high rate of sepsis and NEC in the caffeine-exposed patients may be concerning, but it

also might be related to other factors, including severity of illness. Was there any severity adjustment considered in that analysis or other comments you might make in that regard?

DR. PINA: I'm sorry. Can you repeat your question?

DR. HENDELES: I'm struck by the fact that the sepsis rate was 13 percent in the caffeine-exposed patients and 0 percent in the not exposed patients. But it may be that the not exposed patients were less premature and had less in the way of other medical illness.

Did you attempt to adjust for severity in any way in your analysis?

DR. PINA: No, we didn't. What I see is that sepsis could be one of these cases where you start having apneas before the child is diagnosed with sepsis. We thought that these patients could have the apnea and then be enrolled in the trial and then start having the culture positive or the other signs of sepsis.

It's one of these cases where it is also common to find sepsis in this population and not in the study.

DR. SESSLER: If I may follow, I'd be interested in any thoughts really from the sponsor or other members of the committee or others in this room along those lines as far as experience with severity of illness and its

relationship to this condition.

DR. ERENBERG: I think the neonatologists on the panel would also agree that many infants are labeled as suspect sepsis as soon as they develop any form of symptomatology. We know of only one infant who was culture proven. The question is, of these increased number, how many of them were culture proven and how many of them were suspect sepsis because of just development of apnea, were treated for a very limited time period, and then discontinued.

I think you're correct in that if a child does become symptomatic, you automatically list certain potential disease processes, and sepsis is always very high.

The key is what happens 48 to 72 hours later after you get your blood cultures back, what was the response of the child to your therapeutic interventions.

DR. PINA: What is difficult to know here is that in many cases even when the culture was not positive, the patient did receive complete treatment with antibiotics. I don't know what to say in those cases.

DR. SESSLER: May I follow up with further on that?

DR. LI: Yes.

DR. SESSLER: Let me ask, perhaps to the

sponsor again, was any severity of illness scoring system used to further define the population? Typically in adult ICU populations you routinely will use an Apache score or something akin to that.

DR. ERENBERG: No, we did not use that. The only thing we used were the number of apneic spells at the baseline for enrollment.

DR. LI: Dr. Goldsmith?

DR. GOLDSMITH: Throughout this discussion I have not heard any distinguishing features of the apnea, whether it was obstructive or central. In many of the extremely premature infants, obstructive apnea can merely be from body position in an incubator.

Were any differentiations made by the sponsor? Did you see anything, Dr. Pina, in any of the literature that would distinguish between the types of apnea as the studies were done?

DR. PINA: Mainly they were addressed as central apneas and that was the entry criteria.

DR. GOLDSMITH: Defined as what, and proven by what?

DR. PINA: It was clinically assessed.

I think that you do have some pneumograms at the beginning but we found so many technical problems that at the end it was decided not to continue doing

pneumocardiogram recordings.

DR. LI: I think based on some of the differences that were found between the treatment and the placebo group, you came to the conclusion that the study was under-powered. Do you have an estimate of how large a study would have been necessary to increase the power of the study from the 44 percent to about 80 percent or so?

DR. PINA: Do you want to answer that question?

DR. GEBERT: Jim Gebert, Division of Biometrics. I did not do any calculations to see what size study would have been needed to have, let's say, 80 percent power.

DR. LI: Dr. Osborne.

DR. OSBORNE: Along those lines, just to make a comment and then ask Dr. Pina if I'm off base or this is a correct kind of comment. It strikes me that looking at table 7, which is a very nice way of looking at the patients and the caffeine group and the placebo group, this is page 13 in the document that we got. I actually don't know if you have something comparable for the sponsors.

It nicely goes through both the patients who got caffeine and placebo, and as a reminder, the sample size estimates had hoped for a 70 percent reduction, 70 percent of the patients having greater than 50 percent reduction in the caffeine group, 20 percent having greater

than 50 percent in the placebo group.

Although we certainly don't see those numbers, what I see are very consistent numbers for both the caffeine group and the placebo group and they are different. We've talked about two sources of problems that might give us a type 2 error that we might not see a difference that's really there: number one, the small sample size, which has been alluded to, which I think is a crucial factor, and number two, the possibility that in fact the group that got caffeine was sicker.

One might think with the open-label modeling of the design that we might actually be incorporating in the caffeine group those that have a higher severity of illness score. Certainly they were, at least by numbers, more patients with sepsis.

Those kinds of problems in a small sample size and perhaps a difference in severity in the two groups would actually argue that we would not expect to see an effect. So, I'm actually impressed that we've seen consistent numbers in the two columns, even though it's not quite 70 percent for caffeine, and it's certainly not 20 in placebo. That's my comment.

The question is, is that on base? And if it is on base, were any trend analyses done for the very nice data that you did show, the post hoc analyses that did show

significant differences in the two groups and zero apneas and so forth because the trend analyses might help with putting together these day-by-day comparisons.

DR. PINA: Yes, your analysis of this is correct except that the part of the sicker patients -- this is analysis of only the double-blind phase, where both groups were exactly the same by randomization. When they were transferred to open-label, the value of that day was carried forward. So, it doesn't take into account what happened to those transferred to open-label from the placebo group.

DR. OSBORNE: Do you do trend analyses on the data that you showed this morning or just pair-wise comparison?

DR. PINA: No, we did not do that analysis.

DR. LI: Dr. Kelly?

DR. KELLY: It seems to me with the way the study was designed that you can go to an open-label caffeine that sort of a survival analysis would have been a nice thing to look at in terms of separation of the groups. Did you do Kaplan-Meier survival type analysis?

DR. PINA: I think we did try to do that but it was not possible due to this design also. It's not one event. The first time you have the event is the event on each day so it was not possible to do that design. I think

Dr. Chinchilli will talk about that.

DR. CHINCHILLI: Yes, I did an analysis like that which I'll present this afternoon.

DR. KELLY: Okay.

DR. LI: Dr. Osborne.

DR. OSBORNE: One more quick question. In all fairness again, asking if I'm on base here. It sounds like the FDA and the sponsor did agree on these endpoints, at least at some point during the development of this study. Although we might all look back and do it differently, this was something that was agreed upon over several iterations -- is that correct -- over the last few years.

DR. PINA: Yes, we did agree on the design.

DR. LI: And to follow up on Molly's point, the conclusion of the presentation is that the agreed-upon primary efficacy variables endpoints in fact were negative in result in that there was no statistically significant difference between the treatment group and the placebo on those agreed-upon primary efficacy variables, although the post hoc analysis of various sorts with multiple comparisons did show certainly trends, perhaps even strong trends toward support of the idea that the treatment was more effective than the placebo.

Is that a fair characterization?

DR. PINA: Yes.

DR. SZEFLER: Jim, just to follow up on that line of thought, are there enough variables that you see because if you take enough tests, you're going to find something that works. But in here there seemed to be, at least to me, a pretty large proportion of those kind of numbers. Maybe you looked at larger numbers and this represents a small population of those numbers. Are you pretty convinced that clinically meaningful parameters, that a large proportion of those numbers seem to go in the right direction?

DR. PINA: Well, I hope Dr. Chinchilli will talk about that analysis this afternoon, but that's one of the puzzles we have that we are asking you to help us with. If there's really enough evidence, can we extrapolate this small number to a larger number of patients?

DR. LI: I think to follow up, I think that's probably the crucial question. For example, with the multiple comparisons that were performed, I see that statistical analyses were done and generally p less than 0.05 was used as a cutoff for significance, arbitrarily of course. Is there any reason to think, I guess based on what Stan just said, whether we ought to be using a more stringent criteria for statistical significance based on the multiple comparisons that were done?

DR. PINA: Exactly. That's one of our questions.

Actually sample size is one of the things that we asked the sponsor if they were sure the sample size was calculated correctly because that was one of our concerns. Is the sample size enough to show the efficacy of caffeine? Now it's one of the things that see is a problem that maybe is the problem.

DR. SZEFLER: I think your approach was excellent. Where the lack was was in past data. That's what Vern was asking the question about previously is what literature do you have to make those kind of estimates because I think what we need to hone down on is what was that past literature and what are clinically meaningful results that bear some risk. I'll kind of address those comments later on.

DR. LI: Again, along those lines, how much confidence do you have in the data from the Murat study given the analysis is based on published information and I take it you haven't had a chance to analyze the data and certainly didn't proctor the study.

DR. PINA: I think that the Murat trial -- one of them, it was an open-label, so it is a negative point. But the recording of the apnea events not only observed by the nurse, which is not always at the bedside -- that's I think one of the deficiencies of the trial OPR-001. But in the Murat trial, they did a 24-hour recording of apnea

events. So, that makes an objective evaluation of the primary endpoint. So, even though it was an open-label, we have a reasonable objective primary endpoint that we can talk about.

DR. LI: As a follow-up, would it be feasible currently to conduct a study using an apnea monitor rather than counting apnea episodes on nurses' observations? Is that practical and feasible or not?

DR. PINA: I would let the neonatologists, but I think that it would have been the ideal if we had a monitor with a recording capability.

DR. GOLDSMITH: Absolutely possible now because most of the monitors have memory and you can go back for several days. Probably to prove it, you'd have to hook some sort of printout mechanism to it, but most of the monitors in use now in NICU's all over this country have memory that goes --

DR. LI: But was that technology not available a year or two ago?

DR. GOLDSMITH: I think that has been changing over the last five years or so. The other neonatologists can comment, but as people have been upgrading their monitoring systems, all the new ones now have memory.

DR. PINA: And many babies go home with these type of monitors.

DR. GOLDSMITH: Which also has memory.

DR. PINA: Right.

DR. LI: Dr. Crim.

DR. CRIM: My question may have been addressed when the sponsor presented their data. Maybe you can comment upon it.

Just take an observation of the high dropout rate over the course of the study such that, for instance, by day 10 there were only 11 in the placebo group, and recognizing that apparently there was a great deal of reluctance of the various study centers to enroll patients just because of the fact it appeared that they felt that the caffeine was standard treatment.

Do you have a sense of -- and maybe it was again presented. The subjects who were taken out of the double-blind and put into an open-label -- I'm just wondering whether or not there was some degree of bias on the part of the investigators, since they were not enthusiastic about giving their patients placebo in the first place, to what degree they were inclined to take their patients out of the blinded and put them in the open-label in terms of the number of apnea events prior to them being taken out of the blinded and placed into the open-label. Were there any major differences between the placebo --

DR. PINA: I think there was some kind of bias, that investigators felt not sure that this patient is on caffeine because in many cases I could see a drop of the apnea rate below 50 percent of the baseline and this patient was still transferred to open-label caffeine. So, it at least tells me the investigator was blind but was not sure that it was in the right drug, and so many patients were transferred to open-label caffeine even though they were responding, not meeting the endpoint criteria but some of them were meeting a 50 percent reduction.

DR. CRIM: In even some of the placebos?

DR. PINA: In some of the placebos.

DR. LI: It shows the power of the placebo design of the study, as Dr. Rothstein said I think. Clearly the response in the placebo group was greater than one might have anticipated.

Stan?

DR. SZEFLER: Just to follow up, I think you have an important question. As I was going through the literature, I was asking myself questions on the pharmacodynamics because I hadn't had a chance to look through all the articles, but what doesn't kind of come out is the pharmacodynamics. My understanding, in talking to several people, is the onset of effect is immediate, like within minutes and certainly within hours. So, that time

of 24 hours would certainly be an area where you could characterize whether somebody was a responder or nonresponder.

I think that gets to be critical because in my understanding of this population -- we'll probably talk about it more later -- there are dramatic responders and there are nonresponders and then there are responders who then become nonresponders later on. This probably is the most detailed observation period in terms of the effect of the drug versus placebo that would be published I think.

DR. CRIM: I guess I'll say, along the same lines, were there individuals who responded one day, didn't respond the next, and then responded again a subsequent day?

DR. SZEFLER: I think without that kind of monitoring that was mentioned previously, the dynamics wouldn't be as clearly elucidated as you would like.

DR. PINA: I think those who responded with no apneas, those who responded well to the treatment, maintained that effect, and 50 percent reduction, we see a little more variability from day to day. I don't think we have data as to onset of effect after the double-blind loading dose.

There is one article in the literature where two different doses of caffeine -- if you please look at

table 21 from the medical review of the NDA, table 21 and the author is Scanlon, et al., 1992. Two different doses of caffeine were studied versus theophylline, and the higher dose of caffeine seemed to have had a better response earlier than the lower dose, but at the end, the effect was about the same in both groups. The higher dose was similar to the theophylline group. The lower dose, it seemed that it took a little longer to hit in, and then the response was about the same in both groups. That's about what we have regarding onset of effect.

DR. LI: Are there any other questions for Dr. Pina?

(No response.)

DR. LI: Well, we remain ahead of schedule. Let's break for lunch and return at 12:20. That will give us an extra 10 minutes that we can recapture for this afternoon. So, we'll plan to reconvene and begin promptly at 12:20.

(Whereupon, at 11:30 a.m., the committee was recessed, to reconvene at 12:20 p.m., this same day.)

AFTERNOON SESSION

(12:30 p.m.)

DR. LI: Welcome back. I'd like to reconvene our meeting this afternoon.

We've taken the liberty of asking three of our committee members to prepare some comments and thoughts for us. So, we will begin our open discussion with presentations, first from Dr. Rothstein. Then we've already had a tantalizing preview from Dr. Chinchilli, and he'll be able to fill us in on the meat of his presentation secondly. Last but certainly not least, Dr. Szefler will give us some comments, perhaps give us the big picture on the issues before us today.

I think we will also have time for questions or discussions after each presentation.

So, Dr. Rothstein, do you have some comments and some slides for us?

DR. ROTHSTEIN: Dr. LI asked me to make some comments about the topic, and given some of the questions today, as the expression goes at meetings, I just happen to have a few slides with me.

(Laughter.)

DR. ROTHSTEIN: For those of you who spend most of your life with the 3,000-week old infants --

(Laughter.)

DR. ROTHSTEIN: -- newborn encompasses a tremendous range in terms of development and function, and those infants who are born without the benefit of the last trimester, when there are tremendous changes in organ function and development, are working at a disadvantage. But it is very difficult to lump a 28-weeker together with a 37-weeker and come up with any sort of coherent conclusions.

The questions were raised about incidence of various diseases. The younger you are, the more likely you're to have any of these afflictions: RDS, patent ductus, enterocolitis, retrolental fibroplasia, bronchopulmonary dysplasia, intraventricular hemorrhage. As you can see, the numbers go up the younger the infant.

I've got a couple slides just on sort of developmental pharmacokinetics and dynamics in terms of looking at various parameters. This happens to be response to the drug isoflurane, which most of you do not use but is common in the operating room. I use it only to show that -- these are term newborns here. These are 32-37-weekers. These are less than 32-weekers. And there's not great data on 27-, 26-, 28-weekers in terms of various drugs. But the y axis can represent any drug effect you want, ED50, ED95. There is going to be a markedly different response the younger the infant.

This happens to show the development in term infants of the neuromuscular junction. A term infant, when born, does not have the same level of development that you or I do.

In terms of variation of response, this happens to be a response to curare, one of my favorite drugs, but looking at the difference in response to a given dose to produce a uniform endpoint, the variation response between newborns is about three times what it is in older kids and adults.

What causes some of these differences in response? Drugs that are distributed through the extracellular fluid space -- again, these are neonates. These are term neonates, not even including some of the micro-beings that we're discussing this morning and this afternoon. But the extracellular fluid space is significantly larger than it is in adults.

This is steady state distribution volume again for curare which mirrors the extracellular fluid space.

People have raised the issue of renal function. Again, GFR is about a third to a quarter of what it is in adults in term newborns. I notice one of the exclusion criteria for this study was a creatinine I believe greater than 1.7. By the time your creatinine is 1 as a newborn, you're essentially approaching renal failure in terms of

clearance.

Again, 24-hour excretion. Given the low GFR, any drug that depends on renal excretion, there will be accumulation in the young infants.

Variability of response. This happens to be elimination half-lives of morphine in a population of newborns, essentially almost a six-fold difference in half-life. So, the differences that are being seen with caffeine or theophylline are no different than seen with any other drug. What it's going to depend on is a given 28-weeker or 32-weeker, what was the development of the kidney?

And it can vary tremendously. All 32-weekers are not the same. All volumes of distribution are not equal in any given population of 31-weekers. Then you start mixing and matching all these various factors, and one comes up with some parameters with tremendously wide standard deviations.

Let's skip these last two and we'll go to the overheads.

One of the difficulties in the literature in apnea of prematurity starts with the definition. Even this morning, we heard two definitions of apnea of prematurity. As one goes through the older literature, people introduce concepts of short apnea, apnea defined as 10 seconds, 15

seconds, 20 seconds. So, there may be either different processes going on that are being looked at or there's a tremendously broad range of the problem that people have examined.

The incidence of the problem, depending on what series and how the study was conducted, in infants under 1,000 grams, the incidence of apnea, anywhere between 84 or 85 percent and 100 percent. In infants below 2,500 grams, it's quoted as about 25 percent.

The peak frequency of apnea occurs by day 7. It's influenced, as was mentioned this morning, by the sleep state or the awake state that the child is in. That's increased in REM states.

Another area that impacts on apnea is the tremendously different responses to carbon dioxide and hypoxia in the newborn compared to you and I.

This data is from the classic studies of Henry Gaye Rigatto looking at responses to carbon dioxide depending on gestational age. The 32-weeker, as the inhaled CO2 is increased, has less of a response than does a 37-weeker. One would normally think that one doesn't give CO2 in the newborn unit, but any process that may increase CO2 in the newborn, whether it's fever, whether it's hypoventilation from any cause, the response to that is diminished the younger the infant.

Looking at it another way, at day of life 2 versus day of life 27, there is an increasing response to a given stimulus with chronologic age. One of the problems we're dealing with in looking at apnea is we saw in the data that in the control population there is a decrease in apnea from whenever time 0 is chosen for that infant, but there will also be changes in response to hypoxia or hypercarbia depending on the chronologic age of the child and it will change as one goes farther into the study.

This is a composite looking at changes in minute ventilation at 32 weeks versus 37 weeks versus CO2 and then again looking at it with advancing chronologic age.

A significant difference in newborns compared to us is the response to hypoxia. Hypoxemia in you or I is a respiratory stimulant. Otherwise no one would have ever climbed Mount Everest. They all would have dropped off when they hit the first base camp. In a premature neonate, there is initially an increase in ventilation in response to decreased oxygen, and then hypoxia becomes a respiratory depressant. This response, as you can see -- with advancing chronologic age, there is an increase in ventilation initially, but there is still then a decrease in ventilation very shortly after the institution of a hypoxic event.

The interaction of levels of oxygenation, hypoxia with increase in carbon dioxide, again as one sees with a 15 percent oxygen stimulus, there is a depression of the CO2 response curve.

As we do the entire newborn physiology state in 10 minutes, this is looking at ventilatory responses in various sleep states given a hypoxic challenge, and one can see in the awake and REM state that hypoxia is a respiratory depressant. It's only in non-REM state that hypoxia is a respiratory stimulant.

Finally just to sum up the various treatments that are available and that have been used to treat apnea, one is just having someone standing there flicking the infant's foot every time they slow down. One of the things I did not hear today is with the apnea events, what was the treatment of these events. Was stimulation instituted when the saturation hit 70, when it hit 60, or when the heart rate hit 90 or 80? That I'm not clear about.

We've heard a lot about the drug treatment.

The use of continuous positive airway pressure as a respiratory stimulant is used in many units.

In some cases increasing the inspired oxygen has been used from room air up to 25 percent.

Finally, as one increases the hematocrit, one can decrease the incidence of apnea in these kids.

In summary, what we're dealing with is a problem where these kids have multiple medical problems, multiple interventions, and whose organ development and responses is changing, and possibly rapidly changing, over a period of time that the infants are exposed to the drug.

Thank you.

DR. LI: Thank you very much, Dr. Rothstein.

What I'd like to do is maybe spend 5 or 10 minutes now to open the floor for questions from the committee for Dr. Rothstein. There may be a lot of questions. I'll probably just cut it off and move on to Dr. Chinchilli since we will have time for general discussion. But right now I'd like to open the floor for questions.

Dr. Jobe.

DR. JOBE: Just as a comment, one of the issues this morning was this issue of the placebo effect, the large effect of the placebo. I think you hit on the probable explanation for most of that, and that was other interventions. Perhaps the sponsors could comment about the use of higher oxygen or CPAP or other kinds of things in these babies because clearly the physicians didn't just give methylxanthines and then sit back and watch, but they intervened. And those interventions are known to be effective ways of decreasing the amount of apnea. So,

that's probably the placebo effect we're seeing.

DR. LI: If you could put up your last overhead, Peter, maybe if I could ask the question in a slightly different way. How effective are these other nonpharmacologic modalities in treating neonatal apnea?

And another question is, just in general what is the standard of care nowadays for this disorder?

DR. ROTHSTEIN: In answer to the first question, someone can correct me, but I'm not sure that there are any random controlled trials of any of the other therapies. There are series with small numbers of patients, three in one group, four in another, but there are not numbers to make any coherent --

DR. LI: So, that would be true of the stimulation, the CPAP, oxygen, and increasing the hematocrit. Okay.

So, the second question, just in your view, what is the standard of care? What is the range of the standard of care for neonatal apnea?

DR. ROTHSTEIN: A lot. Since medicine is like religion, it depends which church you believe and pray at, there are some units that will use stimulation. We've heard a lot about the use of methylxanthines in units. People will use multiple modalities in the treatment. I don't know of units that use a single modality in a pure

approach, that they will only use methylxanthines or they will only use CPAP. Everyone is constantly kicking the Isolettes to get the kids to breathe.

DR. LI: Do you have questions, Dr. Goldsmith?

DR. GOLDSMITH: I don't want to be a wet dish rag here. We started with the premise, or at least it's mentioned in the materials sent to the committee, that apnea of prematurity causes brain injury. I don't think that has ever been proven in modern neonatal intensive care units.

When that statement was made, probably back in the late 1960's and early 1970's, we didn't have continuous monitoring of babies available, and babies often went for a prolonged period of time with apnea and bradycardia before it was recognized based on the nurse-to-patient care ratios.

In modern intensive care units, babies would not be allowed to go past 15 or 20 seconds, wherever you set your alarm, and assuming appropriate care ratios, which most states require in their neonatal intensive care units, babies would respond just by stimulation.

So, the question is, what are we treating? And if we are treating it, is it going to make a difference?

I assume, although that I didn't hear it this morning, also that there was exclusion criteria of brain

injury such as an intraventricular hemorrhage prior to putting these patients into the study.

However, without long-term follow-up for injuries such as periventricular leukomalacia, which there is a correlation between apnea of prematurity and PVL later that takes two to three weeks to show up, how do we know the babies who didn't respond didn't have a brain injury associated with an injury that does not show up as an intraventricular hemorrhage or something visible on day 1 or 2 or up to day 10 of life?

Peter, do you want to comment on those?

DR. ROTHSTEIN: There is so much going on in the unit with these kids, and the endpoint may not be even at 3 weeks, as you state. It may be much farther out. Given the I spend most of my time working with kids, we sometimes deal with endpoints that are 1 year or 10 years out from the treatment, and until you start looking, one doesn't know.

Case in point. And I know it's going farther afield than this. Back in the 1970's and 1980's, the treatment for transposition of the great vessels was something called a mustard procedure. It was only on 10-year follow-up that people found out that none of these kids were in sinus rhythm 10 years out and all required pacemakers.

So, we're looking at endpoints that need to be defined and may not even be known at the present time. I think that, if anything, what's coming out today is there is a tremendous opportunity for long-term, well-constructed trials to try to look at some of these issues, but I can't tell you where one starts and stops.

I certainly agree with you. I do not accept, you know, if you don't treat this, the kid is going be brain damaged, which comes up a lot. I don't accept that premise.

DR. LI: Molly.

DR. OSBORNE: Another obvious question. We're going to be asked to recommend the dosing period and whether it be restricted. That's one of our questions.

But just to ask you in terms of a clinical comment, once people are put on methylxanthines, can you comment on duration of treatment just for our edification?

DR. ROTHSTEIN: To go way out on the limb, I suspect the treatment and treatment times will bear no relationship to the kinetics or the dynamics of the drug. There is really no data looking at higher dosing, looking at kinetics, looking at the questions that were asked this morning. Is there a correlation between blood concentration and effect? Is there an ED50 or an ED95 at a given blood concentration? I suspect that will not be

looked at. I suspect that very few units have ever looked at renal excretion or maturation of renal function versus the dose of drug they're giving.

DR. OSBORNE: So, there's nothing like the dose-response curve that we often see in adults.

DR. ROTHSTEIN: No.

DR. LI: Okay, last question for right now. Dr. Jobe.

DR. JOBE: Just as a comment, I don't want people to leave this thinking that apnea isn't a problem because apnea is actually a severe problem in preterm infants and the selection of the therapies is at least clinically driven by least intervention. It turns out that if a small preterm infant gets significant amounts of apnea, the consequences of that are continual stimulation, continual bagging, interference with feeding, and ultimately going on a ventilator. What that gets the baby is basically chronic lung disease. So, there are a lot of down sides to having apnea independent of if it caused brain damage or not.

— And I would agree that these babies don't end up with brain damage because people intervene. On the other hand, the interventions are not benign.

I would think that most people would accept as a standard of practice, that once one thinks that one has

apnea of prematurity, the first thing you give is methylxanthines because it's less invasive than continually stimulating the baby and it's less invasive than using CPAP which then can cause stomach inflation and then you can't feed the baby and so on and so forth.

So, in general, I think what most people do is assess the baby. If they think it's apnea, they start with methylxanthines. If it doesn't work, then they up the ante with more stimulation or with CPAP or with increasing oxygen or those sorts of things. Again, I think that's why so many of these babies that were in the placebo group got better, is presumably because these other things were being done.

DR. ROTHSTEIN: I'm not claiming that any of the other interventions are more or less invasive, and certainly I can tell you about major complications with any of them. If in fact decreasing the incidence of apnea decreases the amount of -- instead of having a nurse assigned to an infant around the clock because he stops breathing every 10 minutes, you can free up personnel, then that may be a major endpoint in terms of treatment also.

DR. LI: Okay. Thank you.

Next we'll have Dr. Chinchilli give us some comments about his views on the subject.

DR. CHINCHILLI: As we know, this was a

randomized, double-bind study comparing caffeine citrate injection and placebo with respect to treatment of apnea of prematurity.

Because of safety concerns, the patient could be transferred to open-label caffeine citrate rescue between day 1 and day 8 of the randomized treatment phase under two different scenarios: one, if the number of apnea episodes in a 24-hour period exceeded 50 percent of the number of baseline apnea episodes, or the investigator suspected that the randomized treatment placed the patient at risk. And we saw with the data that were presented this morning by the sponsor and the FDA, that there was quite a bit of investigator discretion.

Also, the patients in the double-blind, randomized phase could be permanently discontinued from participation due to adverse event, apnea recurrence, or investigator discretion. I've just reproduced here one of the tables that the sponsor provided in terms of how the two randomized groups compared in that regard, again looking at just the numbers they used for the efficacy analysis with 37 randomized to placebo and 45 to caffeine. You can see that there was a higher percentage of caffeine babies that completed the study and a slightly less rescue rate when compared to the placebo.

Now, this major feature of the design I feel

yields a natural primary outcome variable which should be considered and that's mainly the number of days until rescue or discontinuation. It was I thought a very ethical design. You're worried about placebo in this instance putting the neonates at risk, and so this is an ethical procedure in terms of designing the study. You monitor them very carefully and as soon as there's a problem, you immediately come to their rescue.

This is not unprecedented. In some of the asthma studies with which I'm involved, we do that with adult asthmatics, take them off their inhaled steroids, monitor them closely, as soon as they run into a problem, we immediately come rescue them with prednisone or something else. So, it's not unusual to have this type of a design in this type of a situation, but if you do, it seems to me that a natural variable to analyze and what we do with our asthma studies is look at time until rescue or discontinuation.

So, that's the analysis I'm going to present right now very quickly. I just got the data on Wednesday from the agency, so I completed this on Friday. So, I don't have a lot of detailed analyses but just some straightforward things.

First, if we just look at some descriptive statistics, the median number of days until rescue or

discontinuation, you can see there was an advantage to the caffeine group. The median number of days until rescue or discontinuation was 6 for the caffeine group and 3 days for the placebo group.

I have the Kaplan-Meier survival plots, as Bill Kelly asked this morning. Again, there's not a big difference here between the two groups, but you notice then later on, as you get out to, say, 3, 4, 5, and 6 -- say days 4 through 8 of the study, you can distinguish a difference here in the survival curve. Remember, survival is surviving the study. You survive being rescued or discontinued. That doesn't happen to you. So, you can see that the caffeine group is doing slightly better in terms of the Kaplan-Meier survival curves.

So, the question naturally arises, well, is it statistically significantly better? Obviously, the descriptive statistics indicate there's an advantage to caffeine, but is it statistically significant?

That did not turn out to be the case. You probably saw this when I had this up there earlier. I did the usual, the logrank test and the generalized Wilcoxon test, and the p values, you can see, are on the order of .2 and .23 in both cases.

One more overhead. So, I thought, well, maybe I could get a little bit more precision because -- this is

a small sample size, by the way, for doing this type of analysis. I thought maybe I could get a little bit more precision by accounting for investigator site and baseline number of apnea attacks. So, I tried to do a more sophisticated analysis to account for them.

So, I did a proportional hazards regression where I had 8 degrees of freedom for the covariates for site and 1 degree of freedom for the baseline number of apnea attacks. I did use the scale baseline number of apnea attacks, the way the sponsor did.

The estimated hazard ratio or relative risk of caffeine to placebo in this case is .73. A risk of 1 means there's no difference in terms of the hazard risk for the group when you compare caffeine to placebo. In this case, there's a reduced risk. We saw that with the Kaplan-Meier curves. Numerically that comes out to a relative risk of .73. I did not get increased precision here, getting a p value along the same lines, .28. The 95 percent confidence interval for the relative risk was .41 to 1.30, and you can see that it coincides with the p value because a relative risk of 1 can be embedded within the confidence interval.

So, although there seems to be a numerical advantage to the caffeine in terms of this type of analysis, again it wasn't statistically significant, as the other analyses with the primary variables that the FDA

considered this morning.

So, I did do a calculation if you designed the study in this way and planned to do this type of primary analysis, what sample size would be necessary to have 80 percent statistical power. My calculations were that we would need a sample size of 210 patients, which is sort of like two and a half times the size that the current study was done.

Just one other comment about the analyses that were done. There was some question this morning about whether or not multiple comparison adjustments should be made since the sponsor and the FDA both looked at analyses, say, at day 2, day 3, et cetera, all the way up through day 10.

My feeling is that that's not really critical in this instance simply because the analyses that were done used this last value carried forward approach. That approach works relatively well when you don't have a lot of dropouts as we did here. When you have 5 percent, 10 percent dropouts, that type of data imputation of missing values works reasonably well.

In this case, since we had such a high percentage of dropouts, I wouldn't recommend that type of analysis anyway. So, I think it's interesting to look at the results in terms of descriptive statistics, but I

wouldn't rely on that type of analysis looking at what happens, say, at day 8, 9, 10, when so many values are being carried forward. I think this is a natural approach to take in terms of the way to analyze this particular study simply because of the design, but again it was a little bit -- well, quite a bit under-powered to detect a difference, although it did show a numerical advantage to the caffeine group. So, I think it's supportive and gives similar results as the analyses we've seen this morning, but again there wasn't a statistical significance.

DR. LI: Thank you very much, Vernon.

Any questions from our committee? Yes, Dr. Hendeles.

DR. HENDELES: Could you help me understand why there was such a large placebo response? Was that an artifact of how the data was analyzed?

DR. CHINCHILLI: No. I think one of the reasons this happened -- I don't know obviously all the physiology here, but I think there's a regression to the mean effect, and I've mentioned that to a couple of people on the board already this morning. A lot of these infants are detected to have high levels of apnea episodes early on at their peak. You get to the point where they're having a lot of episodes, and so naturally they're going to fall and come back down. So, I think that's what's happening. Part

of the placebo response could be that there's a regression to the mean effect. You're catching these infants when they have a high number of episodes, and then they're going to naturally going to start coming back down.

DR. HENDELES: What do you think of just analyzing the number of apneic episodes right at the early period right after the loading dose and not carrying that data forward?

DR. CHINCHILLI: Well, I think that's why the FDA was focusing on that primary analysis of, say, the number of episodes at day 2 or a 50 percent reduction, how many infants had a 50 percent reduction in number of episodes at day 2. I think that's why the sponsor indicated that was the primary response as well.

DR. LI: Vernon, it would seem to me that there would be at least two ways to interpret the data that you presented, which is the same data, of course, that we heard from the sponsor and the FDA. That's actually almost easier to think about it in the way that you presented it to us.

So, one interpretation would be that, indeed, the caffeine is effective and more effective than placebo in reducing apneic episodes but that the study was in some way under-powered to show that, 80 patients instead of perhaps a necessary 210 or so.

The other hypothesis would be that the drug in fact is no different from placebo, and the small differences that we do see that fail to reach a statistical significance is simply because there is no effect or the effect itself is minuscule.

Do you have any sense of which one of those hypotheses may be correct?

(Laughter.)

DR. LI: Or is there a way to think that through from a study design or statistical point of view?

DR. CHINCHILLI: Well, we laugh when statisticians always get asked that particular question. There's incomplete observations. A study, it turns out, either had a design flaw or was under-powered, and so you're asked to make a determination based on incomplete information. It's easy for me to stand up here and criticize this issue and that issue because I'm not the ones doing the study. But still, it comes down to the point, as we have to today. We have to come to some kind of recommendation and decision.

I think given the amount of consistent results in the literature, even though most of the studies, if not all of them, were uncontrolled studies or not double-blind or placebo-controlled type of studies, I think there are indications in the literature that this is effective.

DR. LI: That it is or isn't?

DR. CHINCHILLI: That it is effective. I think there's indications of that. I'm not saying it's convincing, but I'm saying there are indications that it's effective.

So, I think given that this study too -- given that this is double-blind and randomized and placebo-controlled, showing similar types of results, maybe not as strong an effect as we had anticipated seeing, but given that there is this effect that's consistent with the literature, I'd say, yes, there is very good evidence that this is effective.

However, I could be wrong too. Again, I'm using my subjective judgment based on incomplete information, just as the rest of you will be asked to do.

DR. LI: If I can put the question in a slightly different way. We look at the post hoc analyses, which are very much more convincing.

DR. CHINCHILLI: Right.

DR. LI: To what extent is that analysis flawed by the very basis of the post hoc nature of it?

DR. CHINCHILLI: Well, just the way you've indicated. Given that it's post hoc, that there's a chance to look at the data and decide are there other things we could identify -- now, some were identified as secondary

variables by the sponsor and they weren't, I wouldn't say, entirely post hoc. They were identified as secondary variables, and they did come out to be significant.

This is really a judgment call. I don't think here is a situation where a statistician is much help.

(Laughter.)

DR. LI: Well, you have helped us so far. Thank you.

Peter.

DR. ROTHSTEIN: In response to some of your comments, if you have a treatment that's being widely used for a condition that is widely present, but where there are other interventions going on or the natural history of the course of the disease is to get better on its own, then many of these previous studies will come up with a positive effect.

DR. CHINCHILLI: That's true.

DR. ROTHSTEIN: But we are over-estimating the effectiveness of a particular treatment, in this case the caffeine or the theophylline or whatever.

DR. CHINCHILLI: Yes. I think the one study I'm really relying on too is that Murat study that was discussed this morning by the FDA.

DR. ROTHSTEIN: Who, I should point out, went on also to be a pediatric anesthesiologist.

(Laughter.)

DR. CHINCHILLI: So, I think although that was open-label and it's a small study size, much smaller even than this study we're discussing, it did show a significant effect. You have to wonder how much bias there is given that it was open-label, but there was something there.

DR. LI: If you look at the Murat study, that study might have been judged as under-powered too. There were only, what, 18 patients or so, and yet they were able to find a fairly sizable effect with good statistical significance.

DR. CHINCHILLI: You have to wonder how much is due to bias. Given it's open-label, it's hard to really quantify how much of this was really due to some bias.

DR. LI: Courtney.

DR. CRIM: Just from a statistical standpoint you mentioned about the median days before they went to the open-label. I think it was 3 and 6 for the two groups.

DR. CHINCHILLI: Right, either rescue or discontinuation.

DR. CRIM: With the number of subjects from the nine institutions ranging from, I think, 3 to 17 max, to what degree could that difference or any of the other differences be related to, let's say, a bias at one institution, thinking that they should be in an open-label

basically moving the bulk of their patients to an open-label, and therefore that would affect -- see, I don't know to what degree these outliers in terms of a hospital moving their three or four patients to an open-label would make those differences.

DR. CHINCHILLI: Right. I didn't do those kinds of sensitivity analyses to see, well, let's eliminate this site or that site and see if the results change in any way.

They're going to be very sensitive doing that simply because the overall sample size is small. So, typically the types of multi-center trials you see here where you have a couple of hundred subjects or even close to a thousand subjects in a trial, you do those types of sensitivity analyses to see if one or two or a cluster of centers has that type of impact.

Here I'd expect that, yes, one or two centers do have a big impact. I think there were three centers that had, say, more than 15 subjects or close to that. You're going to see that. You remove those three and obviously things will change. Or if you remove a couple of the smaller ones. Given that the overall sample size is so small, I think that's probably why I didn't pursue that endeavor because I would be able to find things along that line.

DR. LI: Yes, Dr. Osborne.

DR. OSBORNE: Certainly sometimes when there are small sample sizes, in many studies meta-analyses are done. Are there obvious reasons why a meta-analysis would not be helpful in this case?

DR. CHINCHILLI: Well, you have the precursor to a meta-analysis. You have both the sponsor and the FDA doing sort of a very thorough literature review. But I think the studies were so different. You have to decide which studies you're going to use in the meta-analysis. Are you just going to use randomized studies? Well, that's going to eliminate most of them. Are you going to use placebo-controlled studies? Well, then we've got a problem. We've got one. So, I think that's probably why they didn't pursue that, and that was prudent on both the sponsor's and the FDA's part not to try to do a meta-analysis.

DR. LI: Yes, Curtis.

DR. SESSLER: Vern, did you look at any of the safety data in terms of reworking the statistics?

DR. CHINCHILLI: I didn't do that. Obviously I noticed the -- I forget it now. What is the --

DR. OSBORNE: Necrotizing enterocolitis.

DR. CHINCHILLI: Yes, that thing.

(Laughter.)

DR. CHINCHILLI: Yes. I had some concerns about that as well, and I realize the analysis that was presented this morning -- I'm trying to remember now. I guess there were five or six in the caffeine group. If you looked at safety in terms of whether or not they received caffeine at all, even if they had been switched, I think the percentages gave you something that wasn't statistically significant. But again, given the small sample size, that probably is the reason why.

I don't know enough about this to know if this is a cause-effect relationship or if this is something concurrent that happens with these neonates. I think there's reason for concern, and my recommendation would be, obviously, this needs to be closely monitored. If this is approved and gets on the market, I think in the phase IV type of studies I think this really would have to be monitored very closely as to sepsis and this side effect as well. So, I didn't analyze them just because the numbers were small, but there is concern about the proportions.

DR. LI: Dr. Kelly?

DR. KELLY: In the Murat study, their entry criteria was three apnea episodes in a 24-hour period versus the six in this. I know that we heard previously that there was not a relationship or predictive phenomenon of baseline apnea levels or severity. I guess my question

is, is there a more sensitive way of looking at that in terms of controlling for the level of the baseline apnea episodes or number than was looked at by the groups here?

DR. CHINCHILLI: Well, the FDA did an analysis where they used that as a covariate, and that's mentioned in the biostatistical report. I did something similar here with the proportional hazards regression to try to adjust for the baseline level, and it wasn't significant. When I looked at the p value for the covariate, it was well above .5. So, it's not to say that it's not an important factor, but I think there was a good balance between the placebo and caffeine groups in terms of the baseline levels.

DR. KELLY: But if you just looked at the patients who got caffeine and looked at who responded and who didn't respond, would that be a better way of doing it than just comparing the two groups the way they did? It just seems like the dramatic effect of the Murat study was -- they took in potentially significantly less severe patients than they did in this study.

DR. CHINCHILLI: I mean, that could be the case. I don't know. I'm still concerned about the bias too with an open-label study of the Murat as well.

DR. LI: Dr. Pina?

DR. PINA: I just would like to clarify that the entrance criteria for the Murat study was three

episodes of apnea associated with bradycardia less than 100. So, the definition is not exactly the same as in this trial which was just apneic events with or without bradycardia. So, that was the difference.

DR. LI: Okay. Thank you very much, Vernon, for that helpful discussion.

Next on our agenda is Dr. Szefler who I've asked to give some comments on his view of the evidence presented before us. Dr. Szefler is Director of Clinical Pharmacology at a major medical center.

DR. SZEFLER: Thank you, Dr. Li.

I received a package in the mail about 10 days ago. It was about this thick with all the information, and I said, well, I'll get through this before the meeting. Then I think the following Monday, Dr. Li called me and said, I've got a challenge for you here and I want you to be the primary reviewer. It was a little shocking for me, and I asked him, well, why? He said, well, you're a pediatrician. You're a clinical pharmacologist. You've published on theophylline and you're in a respiratory center. I said, well, let me clarify a few things here.

(Laughter.)

DR. SZEFLER: Theophylline is not caffeine and the respiratory center I deal with works with asthma and not neonates.

But, nevertheless, I really enjoyed the experience because one of the other things that I do in my spare time is I'm on the Committee on Drugs for the Academy of Pediatrics. I've been on this committee for a year and a half and I've seen several areas discussed. I'm beginning to associate Dr. Jenkins with landmark discussions in pulmonary medicine.

I think this one here is a landmark because this is an area that has been largely -- I would not say neglected, but poorly defined, the neonates and the young children in product information. So, I really congratulate them on taking the challenge to discuss this issue because it has great impact for the future.

As you all know, the legislation has been moving to get better information on medicine in children, and on that ground, I'd like to congratulate Roxane for taking on this challenge because, as you heard this morning, it's really a challenging area with a lot of new information to be identified.

Having not touched a neonate for about 20 years, the approach that I took was to look at the literature and to call two people that I respect very much in terms of their opinions in this area. To this point their names haven't been mentioned.

One is Jacob Aranda, who's in Montreal, who has

published more extensively in the area of caffeine than anybody else that's listed there. I would recommend that his opinion be solicited, if this is approved and if guidelines are developed for its use, if it hasn't already.

The second person is Robert Ward who's the chair of the Committee on Drugs in the Academy of Pediatrics and also is a neonatologist at the University of Utah.

Both of them gave me the impression that if this preparation was available, one, they would feel it's important and, two, they would use it if it was FDA approved.

So, what I'd like to do is take you through some steps in approaching this issue.

I got the impression from reading this literature that the incidence is, indeed, high in terms of this problem. It occurs in 25 percent of preterm infants with a birth weight under 2,500 grams, and there does seem to be a relationship to the extent of prematurity in that it occurs in approximately 84 percent of those with a birth weight less than 1,000 grams. So, I think this is a significant medical problem that deserves attention because of its high prevalence in this population.

Risk. I got the impression from reading the literature that there was significant risk in terms of

morbidity, that this can lead to irreversible neurological damage secondary to hypoxia and acidosis.

Mortality also is mentioned in the literature and that it may lead to death if it's untreated, for example, in 23 percent of cases where no treatment is administered or postponed due to mild apnea, and about 34 percent required mechanical ventilation. Again, these are points that can be discussed because this is a population of patients at risk for a number of disorders that kind of tie together.

What are the available methods of management? Some of these were discussed, but I don't think they were really compared. There's monitoring, physical stimulation, bagging which would also include use of CPAP. I think this study is an excellent format for doing a pharmaco-economic analysis if the data is there in terms of looking at comparative care because, as physicians, we're all being faced with cost effective management.

The treatments available are theophylline for those who want to use an approved drug in an unapproved application. It has the disadvantage of a narrow therapeutic range, significant forms of toxicity with overdose, including mortality.

Caffeine sodium benzoate was another choice, but Les said it's not on the market, plus it's not an

applicable preparation here because it interferes with bilirubin binding which in and of itself can result in neurological damage if it's not recognized and controlled.

What is being used in this patient population -- and it's used quite extensively, and perhaps a fact analysis should be conducted. Caffeine citrate by extemporaneous formulation seems to be the medication of choice. This is fraught with problems in terms of it's prepared in the pharmacy. It has poor stability. I'm told that it only is stable for about 24 hours, and the quality control can be poor. There are reports of toxicity in the literature with overdose due to errors in extemporaneous formulation. So, that in itself highlights a problem.

What are the potential benefits of this type of preparation? If this is approved, it will come under FDA guidance in terms of application of safety principles for the commercial preparation, and it will also come under the guidance that would facilitate better information and better stability of the product, a better quality controlled type product.

Continued monitoring of the use of this medication would improve its application. I think today -- I've been away from it, but I've heard the best discussion of this type of problem and the medical management of this problem focused on a specific drug that I've heard in a

very long time and probably in this area of management. So, I think it opens the door for continued improvement and continued evaluation of this medical disorder.

What are the benefits over available preparations? I touched on that, but the long half-life of this drug facilitates once-daily administration and reduces day-to-day and within-day variability of serum caffeine concentrations. That in itself is an advantage over theophylline.

The stability and quality control would be an advantage.

Caffeine is a medication of choice based on the communication of several opinion leaders. I asked Jack Aranda and Bob what their feeling would be if this medication was approved, and both of them indicated to me that if this preparation was available, this would be the one that they would use in their nursery. So, I think it would have application.

There was another point that I mentioned earlier that caffeine has no effect on cerebral blood flow, whereas theophylline appears to have that effect.

What's the information that's there to support the application? Extensive past literature and I think very nice analyses were done both by the company and by the FDA showing some pretty strong evidence that it does have

some effect. However, there was no placebo-controlled trial with caffeine in the past literature.

It appears, from reading the literature, that both the sponsor and the FDA worked pretty closely to develop a plan to look at this drug very carefully. It followed some of the initiatives that have been proposed in looking at medications in a small population in an area of need and also seems to support the movement in terms of getting better medications in children. So, I think the steps were taken and it seemed like it was a friendly exchange of knowledge to get us where we are today. It followed the orphan drug step, carefully reviewed the supportive literature, and a single study was conducted was recommended in the design that was also recommended.

As a result of that, the overall efficacy, even though the key variables didn't work out, seemed to support the past literature.

The adverse effect profile for this medication seemed to be pretty reasonable. The central nervous system effects -- again, these are objective findings. We have no way of assessing subjective findings unless adult studies were done in terms of this preparation. But the objective findings were irritability, jitteriness, restlessness which appears in the literature, and it's also indicated that tolerance to these adverse effects can develop. Again,

that comes from the literature.

The literature doesn't point to any long-term effects on growth and neurological development. Seizures can occur with overdose, but prior to this study, there were no deaths reported. The literature with theophylline indicates seizures can develop and there have also been reports of death with theophylline.

The clinical experience shows that it also seems to have a very good profile. Rapid onset of effect. It seems to be the drug of choice with the ones available. It has a better safety profile than theophylline with equivalent efficacy, the advantage of once-daily administration, potential therapeutic advantages. Again, I haven't looked at the pharmacology literature, but better CNS preparation.

The extemporaneous preparations are widely used indicating, at least to me, that a number of people feel this drug is effective and they're using it whatever way they can get their hands on it.

The area of concern, as we discussed, is that the primary efficacy variable was not met. Maybe this was just bad luck or poor study design, but I think Vern kind of alluded to numbers of patients that would be required and I think you alluded to the difficulties in obtaining these kind of patients. So, I think the efforts were made,

but just the primary efficacy variable didn't come out.

The risk of necrotizing enterocolitis. Reading the literature provided, this seems to be the second most common cause of neonatal death. So, it's not a side effect that we can ignore. However, it is a concomitant disorder in this patient population. It has about a 10 percent incidence. The patient population is at risk with or without the methylxanthines. Unfortunately, there are no good studies that show the relative prevalence.

I think based on your discussions and the IRB discussions, it would be hard-pressed to think in terms of doing a study that would give us the kind of numbers that would be needed and it would take a long time to design the study, get the approval, and if that was held back, we'd be holding back about two or three years before the drug could be approved. I don't know if there's anybody else that's ready to stand up to the plate with a product with the kind of studies that would be used to allay our anxieties about this.

It seems to be that caffeine has less risk than theophylline, the approved medication.

If indeed this drug was approved and could be available, what kind of information should be out there to the physicians to prevent any catastrophic episodes? That's where we get to the product information.

In terms of the dosage guidelines, the doses that were recommended and studied seem to be consistent with the past literature and seem to be adequate for the target population. However, I think the product information could benefit by some information on pharmacodynamics in relationship to the onset of effect, the time of maximum effect, the expected time of maximum effect, and the offset of effect when discontinued.

It should indicate that there are responders. In talking to Drs. Aranda and Ward, they seem to paint the picture that there are responders, dramatic responders, there are nonresponders, and then there are patients who respond initially but then kind of break through later on. I think that kind of discussion needs to come out so that there's some information on how to use the drug because you have to remember it will be used in academic centers, but then it will also be carried on in other types of centers. So, the more information available on how to use the drug safely, the better.

Also discussing the duration of treatment I think came up earlier. Dr. Jobe addressed the extent of use, that a 12-day limitation won't be realistic in terms of its application. So, some guidance in terms of discussing the duration of treatment, when to consider stopping and how to do it, whether a tapering schedule

should be used or just discontinuation when the time seems appropriate.

There are some precautions in terms of approving this drug that should be considered. It is a limited study population. There is an absence of data in adults. As I mentioned before, I think there are situations -- and maybe Dr. Jenne can address this that in some of the patients on respirators, apnea in adults, that preparations like this may be used, and if there is anticipated use, studies should be programmed.

There is an absence of data in premature newborns. Dr. Aranda pointed out to me that the literature has been very scarce in the population less than 1,000 grams, and I think this study has that population in it and maybe some analysis to see what kind of efficacy it has in that young group would be helpful. There's a Scandinavian study that he alluded to that I think is in our information in 1995 that also includes some information on these younger patients.

There was mention that there are some subset differences, and this needs to be explored a little bit more in terms of some of the populations. The Hispanic population has higher volume of distribution, and patients with higher frequency of apnea have higher clearance. It would be interesting in the future to explore this in terms

of its pharmacodynamic implications.

Also I think there needs to be some better information on guidelines for monitoring levels. I forget the term that's in the product information now but it's kind of loose in terms of being recommended to obtain it, but some kind of general knowledgeable guidelines like obtaining a serum concentration once a week would be useful.

In terms of this issue about tolerance, Dr. Aranda mentioned that in some of the patients who initially respond and then break through that an increase in dose is helpful. That doesn't come through in the product information and potentially needs to be addressed.

If it was approved and the product information was developed, what would be the considerations in terms of post-marketing surveillance? Information to date does not indicate long-term adverse effects, but this needs to be followed, particularly for the drug and for the preparation. I think a new drug out there in a new population would recommend cautions in terms of some surveillance systems being set up. I don't know how to do them but that would be useful.

Limited use of product to date. The extent has been only in these 46 patients in terms of the clinical experience. So, that in itself would merit some long-term

follow-up.

The product would be used if available and would likely become preparation of choice for the management of apnea of prematurity. I think monitoring its use would be very helpful in setting up some kind of system to see if it is being used in populations. I would hate to have this kind of legislation kind of be the way of getting drugs approved for the future, to take the simple way out, get a drug approved for the simplest indication, and then have more extensive use. So, I think the FDA should watch out for that kind of application. I'm not sure, based on the discussion here, that it has application in older patient populations.

It would be useful, as I said before, to assess the pharmacodynamic implication of the patient subsets with varying pharmacokinetics.

I think this particular drug, if it's approved and the nature that it's approved, is a landmark initiative. It seems to fulfill the intention of the new and emerging initiatives in better medication guidelines for children. As such, this application and potential approval needs to be monitored in terms of its application and use to develop principles for other medications that will be coming along in the same direction. So, I think there are a lot of lessons to be learned in terms of this

particular process.

DR. LI: Thank you very much, Dr. Szefler, for those thoughtful comments.

Are there any questions for Dr. Szefler? Yes, Brenda?

MS. CONNER: This one really isn't for Dr. Szefler as much as maybe the neonatologists in the group. If you would clarify for me -- we've talked about management methods, and we've seen that methylxanthines are used regularly. What percentage of the time would someone choose an extemporaneous formulation of caffeine over a standardized theophylline product, and does that change on discharge when you're sending a patient home?

DR. JOBE: I can try to address that only because I recently moved from UCLA to Cincinnati where there are two different practice styles.

In many institutions, a theophylline preparation is used not because people like it but because it's easier to get plasma levels, and that's what happened at UCLA. Basically we used theophylline because we didn't have a caffeine assay.

In Cincinnati all the babies for a 50-mile radius are on caffeine. It's made up extemporaneously and they have an in-house assay. So, it's used there because it's felt to be less toxic, more effective, and because

there's an assay for measuring drug level.

MS. CONNER: Are those formulations available for discharge?

DR. JOBE: Actually the pharmacy makes them and they're prescribed as outpatient medication.

DR. GOLDSMITH: It really depends on the institution. There are a lot of institutions that will not make up caffeine because it has to be made on site, and stability and the problems.

Dr. Szefler, Alan touched on a problem and that is most institutions have the ability to do levels in house because they are monitoring theophylline levels for older people and asthma, et cetera. I would dare say less than 20 percent -- maybe less than 10 percent -- of hospitals in this country have the ability to do caffeine. Is that our concern or will that naturally follow if this drug gets approved and everybody will put those procedures in place?

DR. SZEFLER: Les will address this but I think they have the availability. It's just a matter of getting the right kit.

DR. HENDELES: Yes. The Abbott TDX method of measuring drug levels and drugs of abuse in the urine is the most common. It's a fluorescence polarization immunoassay, and there is a caffeine kit for it that can be obtained. It's expensive to do that if you only have one

level a month and labs may not be willing to do it unless you can increase the number of levels. But it is commercially available.

DR. LI: Stan, did you come across any evidence that the homemade preparations of caffeine have actually caused clinical problems?

DR. SZEFLER: As I read through the literature, there was reference to a couple of publications on that. I didn't get a chance to read them to see exactly what was going on there and tease them apart, but it's mentioned several times in the document.

Perhaps the company would want to comment on that.

DR. MOSDELL: These are two cases of overdoses which resulted from errors in extemporaneous compounding. You can see that some of the errors were fairly significant.

The first error was actually a tenfold calculation error made by the pharmacy which was discovered 66 hours after the end of the overdose. The level was 160 milligrams per liter.

The second level -- it didn't say the amount of an overdose it was. However, at the time that the error was recognized, the caffeine levels were 346 milligrams per liter.

In both of these cases, the infants had significant adverse events during the course of the overdose.

DR. LI: Thank you.

Any other questions for Dr. Szefler? John?

DR. JENNE: Well, I just wanted to mention in regard to caffeine in adults and respiratory failure that Dr. Szefler mentioned in his comments.

I know that about 10 years ago Supinski -- I forget his first name -- in Cleveland published some studies in dogs in which caffeine was considerably superior to theophylline as far as increasing force of contraction. When I was at Hines, theophylline was not the most popular drug in patients being ventilated, despite my efforts, although we did have some patients on it.

But it seems to me that this would be an ideal population to study not only in ventilated patients, but patients with severe COPD such as Obay has done with theophylline to see what effects it has on pCO2 and so forth. There may be others that have some better understanding of the literature to date than I do.

DR. LI: Thank you, Dr. Szefler, for those thoughtful comments. I know you took a lot of time preparing this for us.

I'd like to continue our open discussion of the

use of caffeine citrate. Rather than just right at this moment focusing exclusively on the questions that we would like to address for the FDA, let's see if we can just focus just somewhat on the broader areas of efficacy and safety, and keep the discussion open, not necessarily exclude comments. Then maybe in another 20 minutes or so we can address in a very much more focused way the questions that we have on our handout.

Yes, Dr. Cross.

DR. CROSS: I'd just like to mention something that hasn't been discussed probably. Many intensive care units -- and our hospital is among them -- do review and keep a record of their problems with drugs or drug reactions and complications. In our neonatology unit, on many occasions the number one drug problem has been calculation errors in dosing the drug being administered, and number two has been methylxanthines often.

I think that this is one thing that has to be taken into consideration as quality control measures are more rigorously reviewed in intensive care units. We meet once a month and discuss such things as the aggregate total of reported drug complications in the patients, units, deaths, et cetera.

This is a possible retrieval of information, and I'm sure our hospital wouldn't be the only one where

methylxanthines continue to be high on the list of drug complications in hospitalized patients.

DR. LI: So, how do you see that as impacting --

DR. CROSS: I would see both of those issues impacting the neonatology unit. The methylxanthines are tremendously hard to dose. I'm sure that the young neonate is sort of like the very aged patient. It's hard to know what dose to give a 90-year-old and it's hard to say what dose to run the other way. We're all used to this 10 to 20 or 5 to 20 dose range, but 15 may be toxic to a 90-year-old, and we see kids that have had no complications and their theophylline level is 30.

Now we move down this slope, and we've seen it. I have a problem with Dr. Szefler's wanting a lot of monitoring in dosage in a range where there's tremendous individual variability at one age, and now we're on that steep neonate curve which is going down from 36 months downward where not only are we dealing with individual variability but tremendous variability, I suspect, on gestational period in terms of the kinetics of a drug that most of our hospitals, including UCLA, aren't even monitoring the drug level.

So, I think it would be very, very difficult, and I think it probably points to the complications of

theophylline administration in this same age group. I suspect if one looked at neonatology intensive care units, they'd find that methylxanthines were pretty high up on the list of drug complications.

DR. LI: So, is the basic idea that if caffeine is available, it would reduce the use and therefore the errors associated with theophylline or aminophylline?

DR. CROSS: Yes, I think that would be a very important point and that you would have the data because I think it's probably collected.

DR. LI: Dr. Rothstein.

DR. ROTHSTEIN: A question for our pharmacology friends. If you had a hospital that's got, say, 40 newborns and 10 or 15 of them are on caffeine, and so the lab is being sent 5 or 10 assays every couple days, how easy would it be to set up those assays?

DR. HENDELES: It would be real easy. Again, if they use the TDX machine, it's just buying the kit, and if they don't, it's a very simple, cheap HPLC assay.

DR. GOLDSMITH: With regard to the complications of theophylline, I also sit on a drug review committee. Most of the ones we see are minor overdoses without tremendous clinical significance, but because in assay it was greater than what our limit is, if it's 15 or 20 for theophylline and the child has a symptom, which

could be tachycardia alone which will resolve over a few hours, it gets brought to the committee.

The ones that are devastating -- at least the ones that we've reviewed -- had to do with packaging in that the packaging of the product in different concentrations is very similar. I don't know if that has been changed or not recently, but it can vary by 25-fold in the amount of drug per unit volume. If that's done incorrectly, then you have a disaster.

So, we're not here to discuss theophylline, but obviously if you're going to do different packaging with different concentrations per unit volume, that's an extremely difficult problem for the neonates who have, obviously, limited ways of excreting the drug.

DR. HENDELES: I think what Dr. Goldsmith is referring to is the fact that aminophylline is a 25 milligram per cc solution. So, if you want to use it in a neonate, you really have to dilute it down to 1 milligram per cc. You increase the risk of errors when you extemporaneously prepare a preparation as opposed to getting it commercially from a company.

I think that's just one of the many reasons why bringing a product like caffeine on the market will really reduce the risks to this patient population for serious and potentially fatal toxicity because it's very clear that

caffeine at levels of 50 micrograms per milliliter seem to not cause any serious neurologic problems, whereas theophylline at that same level can cause very devastating effects.

DR. GOLDSMITH: What I'm suggesting is that if we're approving this or moving towards approval for a neonatal indication, then it should be packaged in a neonatal volume that's appropriate, not to be put into an adult volume that has to then be diluted on site by the pharmacist.

DR. HENDELES: Well, it's 10 milligrams per cc, and the dose for an adult would be in the 300 milligram range. So, you'd have to use many vials.

DR. LI: I have a question on a slightly different topic and that has to do with looking at the information that's available to us now and maybe just looking at one of the future questions having to do with future studies.

My question really to the panel would be, what is the feasibility and how realistic is it to expect or request a study involving 200 patients using computerized monitoring in order to at least get a chance of getting additional data that would perhaps make this decision easier? The question would be, what is the feasibility given the difficulties with the study that was already

conducted? I just want to maybe have a guess or an opinion from some of our panelists. We'll start with Stan.

DR. SZEFLER: It sounded like it would be difficult. It sounded like the study design was reasonable. It just feel short in terms of the efficacy variable and the number of patients. It sounded like you lost sites, one because of their IRB's.

I guess the other question would be how long did it take to recruit because if the nine centers fulfilled their quota in one month, then I would say there's a lot of population available, but if the deadlines were extended, then it sounds like recruitment was very difficult in some very good centers.

DR. LI: Dr. Sessler.

DR. SESSLER: I had similar questions. I guess I'd like to ask in a fashion that gets to some of the data that might help us come to conclusions. If we had somewhere between 16 and 18 months at nine centers, that's what? 15 center-years or something. How many centers are there that are out in the United States that are capable of doing this sort of work, looking specifically at the neonatologists here who might be in the know as to how many more than nine? Are there 100? Are there 50? Are there 12?

DR. GOLDSMITH: Well, it depends on who you

ask. Because the protocol was written so narrowly and with great constraints, it was very difficult to sign up patients. Roxane did the best they could and I congratulate them on it, but it's a very difficult protocol.

If we're looking at babies per year, 1.1 percent of babies in this country are born less than 1,500 grams and fall into what we call the very low birth weight group. I would imagine 50 to 70 percent of those babies -- let's say 50 conservatively -- are going to get on some sort of methylxanthine at some point in time. That's 20,000 babies a year. So, if we're looking only at safety issues, how many of these babies versus another population are going to get NEC or any other kind of safety issues, that information should be easy to come by.

To get the kinds of effects that Roxane tried to get, in terms of a very narrow protocol with so much methylxanthine already being used and with all the other problems and all the exclusion criteria, that's very difficult.

There are probably 1,200, 1,300, 1,400 neonatal intensive care units in this country. I would imagine probably 1 in 5 to 1 in 10 is capable of doing this kind of study or wants to do this kind of study, to be involved.

They are now beginning to have some consortiums

like groups of institutions looking at problems together like the Vermont Oxford group and the NIH group, but it's difficult to get a study like this to get the power that you need, the numbers of patients that you need.

DR. SESSLER: May I ask the sponsors how many centers they approached to get their nine centers that agreed to participate?

DR. ERENBERG: I don't remember exactly, but I think it was somewhere in the 2 to 1 range. I think we had approached 15 to 18 different centers looking for people who would be willing to follow the narrow protocol with all the various constraints that have been cited.

DR. GOLDSMITH: Has the company made an estimate of the amount of use that this would have if it were approved in terms of manufacturing and how many babies a year would get this? I mean, is 20,000 unreasonable?

DR. ERENBERG: Mr. Gunn?

MR. GUNN: My name is Ed Gunn. I'm Marketing Manager for Roxane Laboratories.

The potential patient base for methylxanthine therapy right now currently, looking at babies that would be actually available to treat, would be around the 70,000 patient range a year. Of that, obviously there would be a portion that would go to caffeine. Looking at how many neonatal intensive care units out there that are currently

using caffeine to treat, we predict of those 70,000 in NICU units, approximately 10,000 of those patients are receiving caffeine now.

DR. ERENBERG: As Mr. Gunn did focus groups, one of the major problems has been availability of caffeine levels, and if this were resolved, I think people would look at the data and look at dosing, the cost of getting multiple theophylline levels versus one caffeine level a week and look at the medical economics, as has been stated before.

DR. HENDELES: Dr. Erenberg, it's not clear that you'd need to do that if the patient was responding and had normal renal function. Would there be any rationale for doing a caffeine level under that circumstance?

DR. ERENBERG: I think those of us who have used caffeine for a long time feel very comfortable with it. I think people who are going to be switching from theophylline, where it is required to do levels to know on an individual baby, especially when you first start, where they are -- I think people will probably want to do a level until they get comfortable with the use of the drug and know what the clinical response is.

DR. LI: Yes, Molly?

DR. OSBORNE: I have a question actually about

the labeling since this seems to be just a open period of discussion here just because I don't know very much about the cytochrome P450 1A2 system in neonates, let alone in adults, I'm ashamed to say. I'm confused about how the drug interactions will actually work. I certainly know them for adults, but it seems that for the neonate it might be different. I know that there were exclusion criteria in the studies that Roxane performed, the sponsor performed, and so I'm wondering how to best approach what should be in the package insert since it might be different depending on a neonate or somebody -- I don't know -- early-life infant, et cetera.

DR. KELLY: The major problem is that caffeine is excreted primarily unchanged in the kidney, and so most of the drug interactions that are related to both theophylline and methylxanthines in adults aren't going to happen because all of those are metabolic in nature. You can see from the literature search that they did that you don't achieve adult levels till about 6 months of age, at which time, if it's apnea of prematurity, you're not going to have any more apnea of prematurity.

So, it's unclear to me as well how they're going to address these interactions because in the patient population that they're using the drug in, it's very unlikely that these drug interactions may occur except for

in patients whose mothers got phenobarbital and they have then some enzymes in their liver and are metabolizing. But other than that, it's very unclear.

Just to list them all I think would actually create some false information that these actually even have a potential for occurring.

DR. LI: Yes, Les?

DR. HENDELES: On the other hand, the package insert doesn't contain any advice on how to adjust the dosage if a patient has renal dysfunction. Since in your study you eliminated all of those patients, there's a huge population of these patients that have varying degrees of renal dysfunction and are going to get the drug once it becomes commercially available.

So, I think it's really essential that both a dosage guideline be provided for reduced renal function since that's a major way of getting rid of the drug, and then secondly, some advice on when to measure levels and how to use that information to adjust dosage, similar to what we have in the theophylline package insert.

DR. JENNE: We're talking about the package insert now, and one of my impressions is that it comes down a little too strongly that the therapeutic range is 8 to 20. I think this may have real legal ramifications -- I mean, to state it as positively as it is stated. There

should be some buffer there or some reference to higher levels being relatively safe in certain series and so forth.

The other thing in regard to the necrotic enterocolitis, there was one study mentioned here in the review where there was a comparison between theophylline and caffeine on enterocolitis I believe. It seems to me that a better way to state the caffeine situation is to say that there is no evidence at this time that it's associated with enterocolitis, whereas there is a question whether theophylline is associated with enterocolitis. In other words, I think we're tending to condemn the drug a little prematurely here on the basis of what we know right now.

DR. LI: I think it's a reasonable time now to proceed to the very specific questions that the committee has before them, and we'll start with the first question on efficacy and again open with just a discussion but discussion now focused on this particular question, which I will read.

Do the effects shown in study OPR-001 and the published literature constitute sufficient evidence of the efficacy of caffeine citrate for the treatment of apnea of prematurity? I suppose the key word here is "sufficient."

I'll again open it up for discussion. Then maybe we'll have a comment or an opinion from each of our

committee members, and then finally we'll actually take a vote. Dr. Chinchilli.

DR. CHINCHILLI: Yes. I have a question for Dr. Jenkins which I warned him about at lunchtime.

(Laughter.)

DR. CHINCHILLI: And that is, what are the ramifications of something like this? If the committee recommends approval in terms of efficacy and safety based on one multi-center trial where there wasn't statistical significance for efficacy with the primary response variable, is this going to set a precedent for the FDA, and is it going to cause ramifications for other drug products and biological products that's going to cause problems for the agency?

DR. JENKINS: I think that is a very important question and it's one that we have debated internally quite a bit. Since you provided me warning at lunch that you were going to ask me this, I provided my boss warning that I was going to defer the question to him --

(Laughter.)

DR. JENKINS: -- because he has so many more years of experience in the area than I do.

But before I let Dr. Bilstad address some of those issues, we should go back and look historically. The sponsor presented this morning that there was a literature

review conducted in the mid-1980's for the agency. The agency concluded that the data at that time based on the literature were not adequate to support the efficacy of caffeine in this indication, and that's why we requested that adequate and well-controlled trials be conducted.

We actually did take some heat for that recommendation because some people thought it was unethical to have a placebo-controlled trial in this disease because they were so convinced that caffeine was effective and was standard of care.

To Roxane's credit, they did take on the task and complete the study we've heard about today.

The agency did agree at that time that given the literature-based evidence of efficacy, that one adequate and well-controlled trial could potentially serve as the basis for an approval action if the data were favorable for the effectiveness of caffeine.

It's correct that generally we focus on the primary endpoint that's specified by the sponsor and hopefully agreed to by the agency in advance in the protocol before the data are unblinded in making our determinations of efficacy in clinical trials. We usually expect that there will be prespecified analyses plans also in place before the data are unblinded.

However, that does not mean that the agency

doesn't have some flexibility in how we can interpret the overall results of clinical trials. We're not bound to limiting ourselves just to the prespecified primary endpoint/primary analysis.

Finally, in anticipation that this question would come up, you'll notice that in our package to the committee from the agency, we included a draft guidance document that the agency issued recently which tries to spell out some information for the industry about what the effectiveness standard is for the approval of drugs. Hopefully you had a chance to look that over and see some of the legal and scientific bases for the standard that has generally been two adequate and well-controlled trials, but also there was a lot of detailed descriptions in there of situations where the agency could or has made determinations based on a data set of less than two adequate and well-controlled trials which met the primary effectiveness endpoint.

Dr. Bilstad has had a lot more experience in this area than I have, and I think he has been thinking about this most of the day and I'll let him give you some of his thoughts on what level of flexibility there is in the effectiveness standard and also what, if any, precedent an action favorable to caffeine might have on the agency and the industry.

DR. BILSTAD: Well, there currently are some weaknesses in the efficacy database provided for this drug, and we see that as a regulatory challenge. Is there enough evidence to be able to say that the drug is effective for approval for marketing?

At the same time, I think it's fair to say that we don't view the data on its face as being completely inadequate. If we viewed it that way, we would not have presented it to the committee for review. We believe this falls into a gray area where judgment really is needed.

The Food, Drug and Cosmetic Act, which provides the framework under which we operate, refers to substantial evidence consisting of adequate and well-controlled trials. As Dr. Jenkins mentioned, we have interpreted that in most circumstances to mean that there needs to be some sort of independent substantiation of the results, data from more than one source.

At the same time, we believe that we have some flexibility in how we can interpret that legislative standard, and we believe that we can take into consideration expert judgment that the studies and the database, taken as a whole, do provide substantial evidence of effectiveness.

There are some factors that can be taken into consideration in this situation, factors of multiple

sources of data, looking at the data as a whole. To some extent, feasibility can be addressed, although that's a difficult one. Feasibility is a factor in all drug development programs to some extent, somewhat more in programs that deal with orphan drugs, and sometimes there is the ethical question on the feasibility of conducting studies which can be taken into consideration.

So, I guess I would say in summary we believe that we, from a regulatory standpoint, have some flexibility in this situation, but we certainly would like your expert judgment, taking all the data as a whole, whether there really is in your view substantial evidence of effectiveness.

DR. LI: Thank you for those comments, Dr. Bilstad.

Yes, Dr. Osborne.

DR. OSBORNE: Specifically I'd just like to say that the attachment that we received, the draft guidance on level of evidence, I thought was absolutely outstanding. It helped me. It clarified certainly in my own mind exactly how the FDA does look towards drugs in terms of safety and efficacy and would also, of course, point out that for me it was very helpful to read that our expert judgment could conclude that studies together represent substantial evidence of effectiveness. This leaves us a

tremendous amount of flexibility, in the case where there's substantial evidence in the literature, to help make a recommendation here. Somehow it doesn't mention statistics at all.

(Laughter.)

DR. LI: What I think we'll do next is go around the table, and I'll ask for an opinion and thoughts about the issue that's before us on evidence. Is there substantial evidence or sufficient evidence of efficacy in order to move forward toward a possible vote toward approval or approvability?

If you feel strongly, feel free to actually voice what your vote will be. I'm not asking for a vote right now. I'm just asking for thoughts and impressions and what you think the major issues are. Perhaps we'll go around the table and hear from everyone, starting with Dr. Goldsmith.

DR. GOLDSMITH: You would make me start.

(Laughter.)

DR. GOLDSMITH: I just want to point out that there's a substantial difference between question number 1 and question number 2. I know we're not at question number 2. But it says in question number 2, short-term use. It doesn't say short-term use in question number 1, and I think that needs to be added because that's basically what

we're looking at. I am concerned that once the drug is there, it will be used for months rather than days.

But I think given the literature review, my tendency at this point is to say that the published literature in conjunction with the one study, despite the flaws of the study and the lack of power, is adequate information at this point.

DR. LI: Brenda?

MS. CONNER: I think the literature review that we have with us, as well as the post hoc evaluation after the study, and the anecdotal information that Dr. Szefler provided us from his other experts that he talked with, as well as who I consider the experts on the panel, the general consensus that it would be used and that it is needed, I think that helps substantiate the efficacy.

DR. SESSLER: I have some difficulties with it. I think the "sufficient evidence" is the key phrase there, and we're bending two rules. I think we're moving away from using two randomized controlled trials to one, and I think in order for that to work frankly, that the one randomized controlled trial should be of sufficient strength to stand pretty firmly on its own.

I think there are serious questions about the powering of this current study. Some of the other literature is consistent, but again it's almost entirely

open-label.

If we went with these criteria, I think we would have several monoclonal antibodies or similar such agents available for adult critical care in treatment of sepsis. I know we'd have interleukin-1 receptor antagonist, for example, and probably many others. So, I think we need to look clearly at whether bending both rules is the right thing to do.

DR. CROSS: I, like Molly, read parts of the document that the FDA prepared as their draft on the way out here from the coast, and I thought it was outstanding and was amazed at the flexibility. I thought that was great.

I also appreciate Dr. Goldsmith's proviso that we should maybe consider short-term on this first question. I still have problems of mechanism, general CNS stimulant, tolerance, et cetera, et cetera on the longer-term studies.

It's interesting that their electrolytes didn't show any changes in CO2 which I might have expected if it was a long-term stimulant driving respiration.

I feel much more comfortable with the short-term use approval rather than long-term use.

And that's all my comments.

DR. SZEFLER: I reviewed my comments there, and what I was alluding to is the literature seems to support

its efficacy and seems to support the need for a product out there that could be used safer than what's being used right now.

DR. CHINCHILLI: Well, I definitely think there's evidence and whether or not it's sufficient is what I'm debating internally right now. I guess if I had to put a probability on it, I'd probably say there's a 65 percent chance I'll vote yes.

(Laughter.)

DR. LI: Spoken like a true statistician.

(Laughter.)

DR. ROTHSTEIN: I like waffles for breakfast.

(Laughter.)

DR. ROTHSTEIN: I think there's evidence for some efficacy of this drug.

I'd also throw out a problem with drugs and with kids. Let's say you have two drugs, both of which have absolutely no effect at all but are used widely because of the belief that the drug has some effect, but one of those two drugs is safer than the other. If approving a second drug will drive the first less safe drug off the market, then there may be a rationale for approving the drug.

But going back to the efficacy, I think there's some efficacy. I think it's overrated but there is an

indication of efficacy.

DR. LI: I'll just voice my own opinion. I think it's again a tremendous asset that we have this placebo-controlled trial before us so at least we have some evidence on which to base a decision.

I do share some of the concerns that were voiced earlier, and as I looked through the FDA guidelines on what constitutes sufficient evidence, again I'm struck that the usual standard is two well-controlled, placebo-controlled trials and in certain cases a single trial can be considered sufficient generally when that single trial is especially strong or the results are especially strong.

I'll add that more likely than not I would support the idea of having the indication include some duration of treatment, be it, say, 10 to 12 days or 10 days or so. My opinion there is based on the evidence that's available to us that was presented which goes up to about 10 days or so. So, it would be to me difficult for us later on to advocate an indication for longer than 10 days. So, I support the idea of including the short-term caveat.

I think our decision today is going to be based on the particulars with this drug in this setting. So, there are extenuating circumstances in this case that are in some ways unique in terms of the orphan drug, the difficulty in conducting this trial and future trials. As

Dr. Rothstein said, we need to consider the risk of approval, as well as risk perhaps of not recommending approval.

I think the theoretical down side perhaps would be that, if we recommend approval and actually eventually the drug becomes available on the market, the drug in fact is not effective because that's certainly a possibility that we have to entertain whether that's true or not.

But even theoretically, even just as Dr. Rothstein said -- I think my rationale is the same. Even in a worst case scenario, so to speak, if the drug turns out to be no better than placebo, in some ways we're still better off. So, I guess my own view is --

DR. ROTHSTEIN: Excuse me. I didn't say no better than placebo. No better than theophylline, and if this replaces theophylline and the attendant problems with theophylline, then --

DR. LI: Right, fair enough.

Actually my own view would be even if the agent turns out not to be better than placebo, with the current practice as it is, it still may be of benefit to our patients. That's what I think is the main issue here.

DR. CRIM: I think there's circumstantial evidence to suggest that caffeine may be beneficial in patients with this problem. Because of the way the studies

that were reviewed in the literature were conducted, I don't think that's convincing but I think it's indeed suggestive of it. Likewise, I think that the current study that we're reviewing is also suggestive of it although not convincing, and that's because I think the biggest concern I have is the small size of the groups and particularly the dropout rate and the concern I have about the biases of the investigators both in enrolling patients into the study, as well as keeping the patients in the study.

So, I think there's circumstantial evidence to suggest that it's probably effective, but I'm not convinced that it really is. I would have liked to have seen the primary efficacy variables met.

DR. OSBORNE: I think there is sufficient evidence of efficacy. My only comment would be that my guess is there is a number of responders, which is not the entire population, but that will be sorted out in the marketplace.

DR. CRIM: The one thing I'd like to add is that the circumstantial evidence is for short-term use, as far as I'm concerned, definitely not long-term.

DR. JENNE: Well, I would come down on the side of efficacy. I'm particularly affected, although we should probably think independently of this, but the comparison with theophylline, which is in wide use, is a reason to not

dally further I think. When it was decided to study this drug, it was a number of years ago, and these studies take a long time. I think there's a down side to continuing to do studies like this.

I think we need to give credit to the practitioners, many of them who have personal experience, and it's likely that many of these finer points that have been brought up will be solved with this drug in smaller studies that focus on some particular issue.

So, that's what I have.

DR. JOBE: I find the evidence for efficacy in these trials and in the historical review to be basically circumstantial, as pointed out by the other people.

I think there's a large safety issue with having caffeine available.

I think everyone needs to realize that this is really a unique population of patients that cannot be generalized to other folks.

There's one thing that really hasn't been talked about today and that's the clinical evidence for this which is very common where infants are put on theophylline or caffeine and their apnea resolves, and as they get older, it's withdrawn. Very often they have apnea again and the drug is restarted, and that's a very common clinical observation which sort of demonstrates efficacy to

me.

DR. KELLY: I think just so I can say something different than everybody else said, I've spent 20 years teaching people, residents, students that use of a drug in and by itself does not indicate appropriate use.

Then having said that, I think the primary endpoint or the primary goal of therapy is to end apnea episodes. In that endpoint, the double-blind, placebo-controlled trial was successful in terms of showing more patients got rid of their apnea. So, I think there is sufficient evidence, although not a lot -- sufficient evidence -- of efficacy.

DR. HENDELES: Well, I think there's sufficient evidence of efficacy. I think hindsight is always 20/20. If the sponsor and the agency knew what they knew today, they probably would have designated a different endpoint and this may have been less of an issue.

I'm comfortable that the drug is both safe and effective. I think there needs to be some precautions. The association with NEC needs to be included as a precaution in the package insert, and I think the indications need to be explicitly limited because I can see where anesthesiologists might use caffeine to reverse medazolam sedation and other things because it's an adenosine receptor antagonist. So, it may be used for many

other purposes, and so I think there needs to be an effort to restrict it to this indication unless the company is willing to conduct other studies.

DR. LI: Thanks for everybody's comments. We can still stay open.

Dr. Bilstad?

DR. BILSTAD: I just wanted to make a comment to the comment that was made earlier that the FDA's usual standard is two randomized placebo-controlled studies. In fact, we talk about adequate and well-controlled studies, but we very definitely do not say that these need to be randomized placebo-controlled studies. In fact, there are a number of controls that are mentioned in the regulations as possible controls, and one is even the historical control where a study may not have a concomitant control group but the results might be compared to historical experience with the drug. So, I just wanted to make clear the usual standard is not necessarily two placebo-controlled randomized studies.

DR. LI: Right. Thank you for that clarification.

We can still stay open for discussion if anyone wants to make comments or question any one of the other panel members based on comments that you've heard already.

What I might suggest is a question for our

panel and that is whether we want to modify the question to include the short-term qualifier that I've heard at least a couple of the panel members raise as an issue. For example, as an example only, we could slightly alter the question to address the question of whether the evidence constitutes sufficient evidence on the efficacy of the short-term use of caffeine in the treatment of apnea. Is there any favor toward that issue? Yes?

DR. ROTHSTEIN: I don't want to restrict or remove the drug for use in the population that Dr. Jobe has described or withdrawn from the drug, the drug is stopped, and then have a recurrence of their apnea and are started treated again. So, I'm not sure where this short-term stops and long-term begins.

DR. LI: That's a good point. On the other hand, the data that we're basing our decision on really -- at least the study data -- ends at 10 days, does it not?

DR. ROTHSTEIN: I understand that, but the 26- or 27-weeker who's born hasn't read the insert yet.

(Laughter.)

DR. ROTHSTEIN: And his apnea is not going to resolve necessarily in 10 days, and it may be possible to reduce the episodes from 7 to 2 in that infant. He may get treated for 3 or 4 weeks.

DR. CRIM: But I guess caffeine is not FDA

approved for apnea of prematurity now, is it?

DR. ROTHSTEIN: No.

DR. CRIM: So, physicians are using it how they want to use it anyway. So, if we approve it for short-term use, it's still not going to stop physicians from doing what they're going to do anyway. Correct?

DR. JOBE: The way it's worded I think is good because it's not treatment of apnea, but it's apnea of prematurity, which be definition means that as the child approaches term, they ought to be bringing the babies off the drug.

DR. GOLDSMITH: I would agree with Dr. Jobe. Peter, I'm not as concerned about babies being treated up till 36 even 38 weeks post-conceptual age. What I'm concerned about is being treated for a year while they're on home monitors with virtually no other kind of monitoring because it's the easiest way out and they got sent home on it or discharged on it. As we're starting to discharge children now at 34 to 36 weeks post-conceptual age, many of them are going home on methylxanthines, and very honestly, the practicing pediatrician may be a little different from the practicing neonatologist and doesn't know when to stop. So, the easiest thing to do is not to stop, just continue on.

So, I think we have to be very careful about

opening the doors too wide.

DR. LI: What would be your recommendation for indication?

DR. GOLDSMITH: I think short-term use and some caveat about treatment beyond 38 weeks post-conceptual age has not been studied or is beyond the scope of the information available, or something along that line.

DR. JOBE: Yes, or prolonged apnea beyond the newborn period or something like that.

DR. ROTHSTEIN: What about apnea of prematurity?

DR. JOBE: That says it all I think.

DR. GOLDSMITH: But when does apnea of prematurity stop? The problem is for the practicing pediatrician who gets handed these babies post-discharge. Apnea of prematurity on the discharge summary he may think continues on 52 to 56 weeks post-conceptual age.

DR. ROTHSTEIN: But then that's something that the neonatology community needs to communicate to the pediatricians. I don't want to incorporate that into a restriction or start writing science into the package insert that doesn't exist.

DR. HENDELES: As I understand it, the labeling guideline really regulates what the manufacturer can promote this for, not what a physician -- any approved drug

just regulates the manufacturer's promotion. It does not regulate the physician's practice.

DR. GOLDSMITH: I would agree but I think physicians are more aware of the medical-legal consequences of using drugs for non-approved uses and that some indication in there would be helpful in terms of not having the drug continued for months and months after discharge, which I think is very common, extremely common.

DR. HENDELES: It sounds like an educational problem.

DR. LI: Courtney, then Molly.

DR. CRIM: I guess the viewpoint I take of that is because I'm not concerned about the safety issue, at least the long-term safety issue, since we don't have that kind of data and the data we do have is for the short-term use up to 12 days, I guess I would go along with the recommendation in terms of short-term use because to me we're talking about circumstantial evidence.

My sense is that I'm concerned about the clinician -- again, not being a pediatrician, I guess my concern would be about the pediatrician who would keep this person on it for months or a year. And whether or not the clinician should know about those medical-legal ramifications doesn't help that baby that dies because of he or she was kept on it for a prolonged period of time;

whereas if you put a short-term limitation on it, then neonatologists or the person who's experienced with it will know the ramifications in terms of when they can or can't. But for the person who is relatively ignorant of it, at least perhaps having that short-term use will cause that person to pause and think and if they have this patient on it for longer than what it's approved for will seek consultation to say, what can we do with this particular type of medication as opposed to leaving it on them willy-nilly.

DR. LI: I'll add that it may be possible for us to recommend that some limitation or a caveat be included in the directions for use whether or not the actual words "short-term" are used. For example, it's possible to put into the indication or the labeling that controlled studies beyond 10 days of use have not been performed. That already would be a warning or a caveat. So, we probably don't have to decide on the wording but I think the concept is important since it's raised by several.

Molly.

DR. OSBORNE: Yes. My opinion would be that the way number 1 is worded, for me personally, is adequate to make a decision, and that on 5a about the dosing period, which has to do with the labeling specifically, my opinion

would be that we discuss that fully. My opinion would be that there be something in there about it being reevaluated around the time of birth, or whatever the best wording is, and that reevaluation is warning signal to a pediatrician that something needs to be done. If they don't know what it is, they might actually ask for help.

DR. JENNE: In fact, Dr. Jobe really was talking about repeated short-term use I think. In other words, it could be stated that one should evaluate before further short-term use is necessary or further trial is necessary.

DR. LI: Stan or Peter, any final thoughts on either this issue or any other issue?

(No response.)

DR. LI: I think I'll take Dr. Osborne's suggestion and let's address the question as it is written, and we discuss approvability on item 5, then we can again more specifically outline what our concerns are about warning or duration or use.

So, in fact, now I will ask for a vote, and the question is, do the effects shown in study OPR-001 and the published literature constitute sufficient evidence of the efficacy of caffeine citrate for the treatment of apnea of prematurity? So, all in favor, raise your hand.

(A show of hands.)

MR. MADOO: How about all who are not in favor?

DR. LI: All opposed?

(A show of hands.)

MR. MADOO: So, do we have two opposed? We have 14 who are eligible to vote, so I would suggest that we have 12 in favor --

DR. LI: Any abstentions?

(No response.)

MR. MADOO: So, the vote outcome is 12 in favor, efficacy demonstrated; 2 opposed.

DR. LI: So, Courtney, was your vote opposed?

DR. CRIM: No. I agree with that statement.

MR. MADOO: Okay, so it's 13 --

DR. LI: Let me rephrase the question. Do the effects shown in study OPR-001 and the published literature constitute sufficient evidence of the efficacy of caffeine citrate for the treatment of apnea of prematurity? So, all agreed, all in favor of this statement in the affirmative, please raise your hand.

(A show of hands.)

MR. MADOO: I'm seeing 12 hands.

DR. LI: All opposed?

(A show of hands.)

MR. MADOO: I'm seeing one opposed.

(Laughter.)

DR. SESSLER: I'm between an opposed and an abstain.

(Laughter.)

DR. SESSLER: I am unhappy with the scientific evidence. I respect the neonatologists' observations at the bedside and opinions. I don't believe that there's sufficient evidence. What I'd like to do is abstain because I think this is an important drug perhaps to that group.

DR. LI: Twelve in favor, one opposed, one abstention.

MR. MADOO: Duly noted for the record.

DR. LI: Let us now address in an open fashion the second question which deals with safety, and I'll read the question. Does the NDA database, together with the data available from published literature and the spontaneous reporting system experience, demonstrate the safety of the short-term use of caffeine citrate in patients with apnea of prematurity?

I'll open this for any comment. Yes.

DR. CHINCHILLI: Yes. I have a question for our colleagues. Was the incidence of sepsis a surprise? I take it with the NEC, that wasn't a surprise because that's obviously a complication with the pre-term infant, but with the sepsis, was that a surprise or is it out of the range

that you would expect for these neonates? I guess the range was 6 out of 6 or 8. Dr. Pina, you had the numbers. I can't remember what they were.

DR. PINA: Eight patients, all of them exposed to caffeine.

DR. LI: Right, and none in placebo.

Stan?

DR. SZEFLER: But I think as we talked about before, having had experience in the past but not recently, sepsis is a diagnostic suspicion and then the confirmation -- in this case, it sounded like there was only one case that had bacterial confirmation. To my knowledge, whenever it's suspected, blood cultures are obtained. So, it's not as if it wouldn't be found if it wouldn't be there unless the cultures weren't sensitive enough. So, it's actually one out of eight cases, and the seven cases were suspected sepsis and suspected sepsis is considered rule out sepsis. So, again, I kind of like --

DR. LI: Is it concerning that all eight that were suspected or had sepsis were in the treatment -- received the caffeine?

DR. ROTHSTEIN: The study set up criteria for inclusion in the study -- to my reading, the study did not define sepsis, and so it did not define a positive blood culture or a regaining of ability to maintain temperature

or a rise in the platelet count following institution of antibiotics. So, I don't know how to define or then interpret what sepsis is.

DR. GOLDSMITH: That's a big problem. The nosocomial infection rate for VLBW babies can approach 20 percent and be within the norm and prolonged hospitalizations. The problem is that sepsis is a diagnosis that's difficult to make. We draw very small blood cultures and we generally do them once before antibiotics are initiated. In some literature, you see where babies who truly have supportive evidence of sepsis, all kinds of white blood cell counts, abnormalities and clinical deterioration, et cetera, and 30 percent of those infants have negative blood cultures. So, it's very difficult to interpret the data.

I'm not uncomfortable with the data to that point where I would believe that caffeine offers a disadvantage towards babies to getting sepsis.

DR. LI: What about the issue of the necrotizing enterocolitis? Are you concerned that there may be an increased risk with caffeine?

DR. GOLDSMITH: Not on the basis of the information we have, not in my personal information. I still remain very, very concerned about the interaction with other drugs and causing NEC specifically the H2

blockers. I'm concerned that that's an issue that many of these babies will be on histamine blockers, as well as methylxanthines of some sort, and that interaction will be a new interaction, and possibly in a stage 4 time that these things should be reported back. I don't know how we could know that now, but I am concerned about it.

DR. LI: Yes, Curtis.

DR. SESSLER: I'm particularly struck by the one-sided nature of the exposure data. I don't know how good it is and that relates back to the question that I had earlier about severity of illness and if there were other explanations for this. But one might argue that the best drug now to avoid the onset of sepsis, necrotizing enterocolitis, and death is avoidance of caffeine, because it was 0, 22 in all three categories.

The concern I have I guess about approval, based on the safety data or in light of the safety data, is that we've already heard that there is a lot of variation in management of this condition and that there's little good science so far. A lot of it is observational. Without a doubt, this would become the drug of choice and would become very widely used.

If we guess wrong about the safety data, I think there's potentially significant damage that can be done. So, I disagree with some of the earlier statements

that if we do approve it, there's no loss. It's either a gain or it's not going to be harmful. So, I have concerns about the safety information there. It's far more one-sided I guess when one looks at the exposure data than the randomized data.

DR. CROSS: You preempted my statement. I was going to say the same thing, that the way to get at the safety issue is to approve it. It's being very widely used, and perhaps the stage 4 surveillance will produce better data than what we have now. I think approval probably is safer than nonapproval and 70 percent use.

DR. OSBORNE: I'll tease Curtis a minute and just point out in the adult ICU with your logic, we wouldn't be giving oxygen either.

(Laughter.)

DR. OSBORNE: Let me go on to point out as a person who works with --

DR. SESSLER: We need to go back 20 years and do those studies again.

DR. OSBORNE: It's a deal.

I'd just make my opinion which is that certainly the FDA recommendation was for safety. At least on the basis of the information we have, the concept was that caffeine was well tolerated by patients in the population studied.

DR. LI: Dr. Jobe?

DR. JOBE: The issue of safety I think is something that we all have to be worried about. It turns out that in the neonatal business now, there are two very large networks, the NICHD network that has approximately 20,000 infants registered less than 1,500 grams, and the Vermont Oxford trial network. A lot of that database has been mined for a lot of different things. One is for sepsis, and I'm not aware that there's an association with methylxanthines. But I'm not sure it has been looked at that way. That's information that could be probably requested by either the FDA or the sponsor to better flush out that sort of an issue.

I am aware that H2 blockers are associated with increased infection in babies looking at a database from a recent glucocorticoid trial that's unpublished presently, but that interaction has turned up as well.

The point is I think that in neonatology, in contrast to a lot of other diseases, we have very large databases that are out there that can be looked at.

DR. LI: For those who have a concern about the safety regarding in particular the necrotizing enterocolitis, would a label warning and a surveillance study be adequate to allay some of those concerns?

DR. SESSLER: I guess you're looking at me,

aren't you, Jim?

(Laughter.)

DR. LI: You don't have to respond.

DR. SESSLER: It's interesting because in thinking about this, you wonder if it one includes the exposure to caffeine data in the labeling, it might bring up more healthy questions actually to its automatic use. That is, if you are getting ready to prescribe this drug to your patient and see data that the likelihood of death is 0 percent without it and 4 and a half percent with it, and sepsis, 0 percent versus 13 percent, and on down the line, it may perhaps appropriately bring questions about making sure the indications are correct. So, without a doubt, appropriate labeling would have to include extensive data I think about this potential side effect.

The concern I have I think is not just that it's something that doesn't make sense. It's a random finding, but there's potential rationale for that in terms of whether it's neonatal models or adult models in terms of GI mucosal injury and the potential for bacterial contamination or bacterial products, quote, translocation.

So, the rationale is there and it's something that I have significant concerns about that we may be missing something given the striking nature of the data. So, it definitely does need to be prominently displayed I

think.

DR. JENNE: I don't think the data is very striking. That's my problem. The exposure to caffeine in one of the open labels, the person had a small bowel resection almost simultaneously with his beginning caffeine. At autopsy the diagnosis was made. So, I don't consider that a case -- I think that's very questionable as exposure being associated. That's two cases in the placebo versus four in the caffeine exposure.

You're starting from a different total sufficiently between those two denominators in those cases, that you end up with worthless statistics. It's so close to being random, I can't take it seriously.

DR. SESSLER: It's very strikingly one-sided I guess would be the thing that catches my eye. You have a bunch of zeroes in the not-exposed column and significant numbers in the other.

DR. JENNE: Well, how about the statisticians discussing this?

DR. KELLY: I agree with John Jenne. The thing that increases it really is the exposure data which is the sicker patients getting put on caffeine, the bias there in terms of who do you enter and who gets left off of caffeine altogether, those patients that are doing fine and not sick and doing well. That's one of the problems that you have

with a study like this. When you take people off, your placebo group keeps getting better and better and better all the time. But if you just look at the very baseline in terms of who got randomized, you don't see that difference.

I agree with you. There is that striking difference, but that's after things have been unblinded to the clinicians.

DR. HENDELES: I'm wondering if Dr. Jenkins can clarify whether the agency can even require the company to do some type of surveillance after it's approved. Is that logical?

DR. JENKINS: I'm not sure what type of surveillance you're exactly talking about.

DR. HENDELES: To see whether there's an increased risk of NEC with the use of caffeine.

DR. JENKINS: Well, we certainly can enter into agreements to do phase IV studies which could be controlled trials or they could be some sort of looking at epidemiologic databases.

—We're interested in hearing your ideas or your suggestions on what would be useful to either better clarify the safety or efficacy of caffeine, if it were to be approved, in the post-approval phase or also any epidemiologic studies you might suggest.

But we could require a phase IV commitment for

that type of study.

DR. HENDELES: Given that, then I think I'll make my comment when we get to item number 6.

DR. LI: Stan?

DR. SZEFLER: John, by the post-marketing, you wouldn't be able to require another placebo-controlled trial. Is that right or is that within the purview?

DR. JENKINS: I think that goes to what the question is you're trying to answer.

DR. SZEFLER: Because I think in order to answer Les' question, you have to have a database to compare to to say whether it's increased or not unless it's a striking number like 70 percent of the infants all of a sudden.

DR. JENKINS: Well, phase IV commitments can be placebo-controlled trials, but they should not be placebo-controlled trials to answer the question of whether the drug is safe and effective because we need to answer that before we approve the drug. But they could be placebo-controlled trials to better ferret out various areas that are still left questioned such as dosing regimens in different subpopulations, that type of information. But we certainly should not go into this with the thought that we could require a phase IV commitment to do another placebo-controlled trial to determine whether this is really safe

and effective. That we need to do before we approve the drug.

DR. SZEFLER: Because in order to get those population differences, it would beg the question to the neonatologists to come up with figures to say what's the incidence of necrotizing enterocolitis, say, at certain age groups in the absence of methylxanthine. I don't know if that data is out there.

DR. JENKINS: Also keep in mind that the ability to do placebo-controlled trials, if this drug is approved, may even be more hampered than if the drug is not approved.

DR. SZEFLER: Right. It was hard enough to get it to an IRB without its approval. It's going to be even harder with an approval.

DR. JENKINS: Well, this study had to be designed with a very strong open-label rescue component, and in order to do another placebo-controlled trial, that may even have to be increased. You saw the effect of the very rapid dropout rate on this study of that open-label rescue provision. If it's an approved drug, even if you could get people to randomize to drug versus placebo, they may only do that in the scenario where the open-label rescue was very liberal, which may compromise severely what you could learn.

But there may be designs that could be useful, such as dose titration studies or parallel group differing dosing regimens looking to see if there is incremental benefit. You could have targeted plasma concentration studies to see whether there is really a therapeutic range that makes a difference. So, you could do studies where you could have different dosing groups. Placebo may be difficult.

DR. LI: Dr. Crim, did you have a comment?

DR. CRIM: It's more a comment/question. It's regarding the concern about NEC, and maybe, Dr. Rothstein, you found this when you reviewed the literature.

Recognizing the problem with historical controls, was there any sense what the incidence of NEC was in the pre-caffeine days compared to the caffeine days?

DR. ROTHSTEIN: Caffeine has been around and used in newborn units before I even started practicing.

DR. SZEFLER: I think that's part of the problem because NEC I think just became a diagnostic disorder --

DR. ROTHSTEIN: But again, looking historically caffeine sodium benzoate was used as a respiratory stimulant. Until the institution use of continuous positive airway pressure, newborns didn't survive long enough to have NEC. So, NEC only becomes apparent once

these kids are living long enough for this disease to take its toll.

DR. SESSLER: Are there any preclinical data related to that at all as far as the effects of caffeine on an NEC equivalent in an animal model or anything?

DR. LI: Yes, Dr. Pina.

DR. PINA: I mentioned one study, but it was not used -- they did not use caffeine. It was aminophylline. There is one animal study where they did show that aminophylline increased the risk of NEC when there was an injured GI mucosa.

DR. HENDELES: But that could be from the ethylenediamine. We don't know that it's from the theophylline component.

DR. JOBE: Just a comment for perspective. Methylxanthines became common for apnea of prematurity about 1975, so they've been used for a very long time.

DR. SZEFLER: That's about the time NEC was popularized.

DR. ROTHSTEIN: The use of positive pressure was introduced in 1970, so it's shortly thereafter.

DR. SZEFLER: Let me ask another question in terms of this area because I think what seems to be emerging is that this is an interesting drug that needs refinement, and what is the potential for that? I know in

my area in terms of asthma, there's been networks developed. NIH has supported networks in terms of doing studies on questions that may not be taken up by industry because of the type of question or because of financial. Is there that type of network available in neonatology?

Second, are there guidelines that are published in terms of management of the newborn like we have now guidelines in terms of management of asthma, and if there are these guidelines, what do the authorities recommend in terms of the management of this disorder?

DR. JOBE: I guess you asked the right person. I'm actually the chair of the Neonatal Network for NICHD.

Interestingly, of all the things we've considered studying, caffeine or theophylline has not been one of them because it's considered by everybody I think standard of care, accepted, and in all the manuals for neonatal care, there are recipes for how you give theophylline or caffeine. So, if you look at Neofax or any of these other drug delivery studies or the textbooks of neonatology, this is considered a non-issue.

DR. SZEFLER: After hearing this discussion --

DR. JOBE: Yes, I think after hearing this discussion, there are a lot of issues about dosing, about duration.

DR. SZEFLER: Could your network benefit by

some interest in terms of --

DR. JOBE: The network could benefit. Again, these are the kinds of studies that industry perhaps could be encouraged to do in terms of dosing and so on. Sure.

DR. SZEFLER: Because I guess I see what is emerging out of here is this drug is provocative in terms of its effect. It's convincing in terms of some of its application, but there's a lot of room for improvement in terms of its application and safety. Perhaps the marriage of the Network and the FDA and industry support to do these kinds of studies would help refine the guidelines and make everybody feel a little bit more comfortable.

DR. JOBE: I think that's true.

DR. LI: Dr. Sessler.

DR. SESSLER: Sorry about getting back to the NEC question and the sepsis. If there are well-established risk factors from previous studies, is it possible -- and I guess this is directed to the sponsors -- to query the databases to try to determine whether in fact this observation is explained and is that data available? Can one do that without having to conduct prospective studies? I guess that's a question for the sponsors.

I think this is still an unknown and there may very well be good alternative explanations. That would be marvelous if there is.

DR. LI: Would anyone from Roxane like to address that? Dr. Wynne?

DR. WYNNE: Yes. Those data are not available in our database. As Dr. Erenberg previously said, we often don't have culture-proven sepsis. So, we could maybe expand the information a little bit to give you a little bit more, but I don't think we have the information -- well, in fact, I know we don't -- that you're looking for because we just don't have that culture-proven bacteremia.

DR. JOBE: Just as a comment, there is the NIH-sponsored IVIG randomized controlled trial which was published about four or five years ago. That data has just been released to the public sector by NICHD, and that is in fact a sepsis study. I assume they coded in methylxanthines, but I don't know that for sure. So, that is in the public sector now and it's a very large database of approximately 2,000 infants.

DR. GOLDSMITH: Part of the problem was mentioned this morning by Dr. Jobe was that NEC in various nurseries is very episodic. So, although generally the practices of giving methylxanthines is not episodic, although it might vary from attending to attending, it's generally pretty consistent. You may go a year or two in a very large nursery with no cases of NEC and then have an epidemic. So, the numbers here are going to have to be

quite large and the time frame over which it's looked at is going to have to be relatively long.

DR. LI: Yes, Dr. Osborne.

DR. OSBORNE: I must say my opinion for question number 2 for using this drug, is it safe for the short-term use of caffeine citrate in patients with apnea of prematurity, I would say yes.

I would say when we get to talking about number 6, there are several ways we could go about it. For example, the two papers on necrotizing enterocolitis point out it's about 1 in 1,000, and certainly the frequency in this study is within keeping of what has been described in many other studies. If it's possible to have a registry database mined, what you do is you could set up a case-controlled study with multiple controls, so you might have one case where NEC is infrequent and then three or four controls. Then you can do a sophisticated analysis of several kinds of variables that you think might be important in particularly not only the single medication, but medication regimens and multiple effects, such as the H2 blockers, and aminophylline and theophylline and caffeine might come into play in that kind of setting. But I think that's a question I'll address in number 6.

DR. LI: I think we're ready to take number 2 to a vote. Does the NDA database, together with the data

available from published literature and the spontaneous reporting system experience, demonstrate the safety of the short-term use of caffeine citrate in patients with apnea of prematurity?

So, all in favor, raise your hand please.

(A show of hands.)

DR. LI: Did you get that, Leander?

MR. MADOO: Who was against?

DR. LI: All against?

(A show of hands.)

DR. LI: Abstentions?

(No response.)

MR. MADOO: We have 13 in favor of that statement and 1 opposed.

DR. LI: All right. Let's take item 3 as a question. Taking into consideration the overall benefits and risks of using caffeine citrate for the treatment of apnea of prematurity, do you recommend that this drug be approved for marketing?

Discussion? Yes, Les.

DR. HENDELES: I thought you were calling for a vote.

DR. LI: We will in a minute.

(Laughter.)

DR. LI: So, this question of course has to do

with approvability. I guess the key word in this question is "overall" taking into account the efficacy and the safety evidence that we reviewed.

Again, before the vote, are there any comments, any questions? Yes, Dr. Szefler.

DR. SZEFLER: I have a question back to the other one that I should have asked before the vote. But there's no drug that's completely safe and is there a liberal definition of safety or is that just kind of gestalt?

DR. LI: My interpretation is safety based on the opinion of the committee, but perhaps Dr. Jenkins would like to comment on that.

DR. JENKINS: Well, I think you're correct in pointing out that there is probably no drug that's completely safe, or if there is such a drug, it's probably not effective.

(Laughter.)

DR. JENKINS: Usually safety becomes a question of a risk-benefit analysis, so you're analyzing the risk to the patient populations who may be receiving the drug versus the benefit they may be receiving by having the drug administered. So, there is no absolute definition of safety because what may be a safe drug for patients with ARDS where there's no approved therapy would not be

considered safe for use as an antihistamine for allergic rhinitis, for example. So, you have to take in the indication, the available treatment option, as well as the actual data and do a risk-benefit type of analysis.

DR. LI: That's a good question. That's the essence of this question number 3.

All right. Let's go ahead and vote on the question. I guess I won't read it again. All in favor, raise your hand.

(A show of hands.)

MR. MADOO: Is there anyone opposed? That makes it easier.

(A show of hands.)

MR. MADOO: Okay, so there are 13 in favor of approval of this agent and 1 who's not in favor of approval.

DR. LI: Number 4 we will skip.

Number 5 has to do with labeling. We'll take part a separate from part b. If caffeine citrate were to be approved for the treatment of apnea of prematurity, in the labeling would you recommend that the dosing period be restricted to 10 to 12 days?

DR. SZEFLER: I don't know who the one opposed was, but I was interested, if that person was opposed, is number 4 applicable? Because we're a recommending panel.

We're not a confirmatory panel, and if there is useful information for number 4, maybe it should come from that question.

DR. LI: That's an invitation, Curt. What additional studies, if any, would be useful to you?

DR. SESSLER: I think additional studies would be problematic certainly. I guess part of my questions that I asked before, without going too far down the field, is we had nine centers that enrolled over 18 months and trying to get a grasp on overall issues of the difficulty in actually performing a second clinical trial. I understand the feelings around the room that that would be very difficult to undertake, and given that this is kind of standard therapy. In my mind, there are some uncertainties in both safety and efficacy, and that would clarify it.

My concern I guess is that by going into the acceptance of this as the state of the art and the gold standard, that the important thing is that we don't become complacent about readdressing safety and efficacy.

DR. SZEFLER: I guess my question is one of extent because if you have kind of like one vote standing out there, it's useful to kind of know is that because you're convinced it has no effect, or you're just not convinced that there's enough data to make a conviction?

DR. SESSLER: Right. I think that there is --

well, there are a couple things.

I think that there are clearly some indications that this is likely to be effective. Thus, I move to an abstention on the first question.

Having said that, the evidence is weak in my view. I guess I'm tainted by being exposed to a lot of negative clinical trials in adult medicine, adult critical care, where similar a sort of findings would not have been borne out by large scale, randomized clinical trials. I cite the several different sepsis studies where the phase II studies looked very promising and where subsequent pivotal clinical trials were performed and proved that the drug had no value.

None of them were based on the clinical opinions and bedside experience. Thus, that's why that weighed in in terms of the neonatologists' opinions in my decision there.

I still have questions. I think this is unsettled and I feel bad that if in five years we discover that there is some clear-cut relationship between this drug and sepsis and necrotizing enterocolitis, that we perhaps have not been rigorous enough today in apply the standard of actually determining that.

DR. LI: Do you have a comment, Dr. Rothstein?

DR. ROTHSTEIN: Just that the agents that have

been first used by the community and then eventually submitted to randomized studies for ARDS I believe are a lot more toxic than the drug we're talking about here. The numbers of infants who would have to have induced sepsis on the basis of caffeine would have to be elevated quite high in order to start matching some of the drugs that we've been throwing around the adult ICU's.

DR. SESSLER: The other factor, I guess, in that decision that I'm made to vote as I did was the fact that this is already approved. It's something that by not approving it, the standard remains.

DR. HENDELES: It's not an approved drug.

DR. SESSLER: No, it's not an approved drug. I'm sorry. It's in use.

So, the advantage of course is that we now have a very standardized preparation and that is clearly worth something, but it is not the same as perhaps denying something that may be a lifesaving drug since it is available. My opinion.

DR. LI: Yes, Dr. Crim.

DR. CRIM: I would just comment since I was one who also voted -- well, did not support the efficacy question. Again, my not supporting that question is because I considered it was more the circumstantial evidence.

In terms of number 4, again what Curtis mentioned, if the technology is now available in neonatal ICU's to objectively measure these parameters better, then I think it may be possible to do that type of a study. That is, if the neonatologists in the unit have better monitoring equipment, then it may in fact be possible to do those types of studies, but you can do a controlled placebo type of a study with larger numbers.

DR. LI: Say, Courtney, did you vote affirmative for approvability?

DR. CRIM: Yes, I voted affirmative for approvability, but I voted negative for the efficacy question.

DR. LI: Would you like to elaborate on the --

(Laughter.)

DR. CRIM: No. Because number 3 was taking into consideration the overall benefits.

DR. LI: No, absolutely.

DR. CRIM: And that's why I voted for approval overall, but getting back to the question that was raised in terms of number 4, if you do not recommend approval, I did not support the first question about the efficacy. That's once again my reasons for voting overall but not for the efficacy in terms of what I would like to see. Ideally what I would like to see would be if the technology is now

available to do a better efficacy which will also include safety studies.

So, I think there are still questions about the safety in terms of the data that was presented both in terms of the literature and in terms of this pilot study here in terms of the numbers and the way the study was controlled. I don't think the data is good, but I don't think the data suggests that the safety of the caffeine is worse than placebo.

DR. LI: I understand. Thank you.

Let us address as a discussion the question on labeling. A, would you recommend that the dosing period be restricted to 10 to 12 days? We had discuss this briefly and deferred it until now.

Yes, Alan.

DR. JOBE: I realize the study was designed as a 10- to 12-day study for practical reasons. I think the difficulty here is in clinical practice. Again, the clinical practice is to initiate caffeine or methylxanthines or whatever they're using when a baby presents with apnea of prematurity once the baby is off the ventilator, and then therapy should be discontinued at a point when you anticipate that the baby is mature enough to no longer have apnea of prematurity. That's usually in the 32- to 34-week window.

In terms of clinical practice, if one has a 26-week infant that you've just extubated, and you treat him for 2 weeks, he'll be 28 weeks gestation and it's unlikely that anybody would stop caffeine at that point. So, I think it's a practical issue of the physiology of apnea of prematurity in that it's a developmental disease and it tends to resolve by 32 to 34 weeks.

So, I don't know how to deal with that because the study design wasn't intended to answer that question.

DR. LI: Yes, Peter?

DR. ROTHSTEIN: I think you've in fact just dealt with that, that the labeling state that this study lasted 10 to 12 days, that this is a developmental issue, that infants born at earlier gestational ages may in fact not have resolution of their apnea until they are 32 or 34 weeks, and just leave it at that.

DR. HENDELES: I like that.

DR. GOLDSMITH: I think you need to take out the word "restricted" from that phrase from a, that you recommend that the dosing period be restricted. If you recommend that the dosing period -- only that 10 to 12 days has been adequately studied or has been studied and that evaluation should come sometime at 34 to 36 weeks post-conceptual age, I think that handles the problem. I don't think I would restrict it to use because that really does

lead to problems for clinicians.

DR. LI: So, I'm not hearing a lot of support for actually including a restriction as it's written in this particular question. So, the indication, for example, can be apnea of prematurity as the indication. Since there is primarily this one study which is the basis for most of the information that we have, we can recommend that a synopsis or a table or information from that study indicating that the study itself was limited to 10 days. That can be in labeling without writing in a restriction, as Dr. Goldsmith indicated.

DR. JOBE: But I think Dr. Goldsmith is recommending putting in the indication that the baby should be tested for need after the period he's likely to have apnea of prematurity, sometime between 32 and 36 weeks. The recommendation would be then that the baby be assessed for need rather than put on continuous drug.

DR. ROTHSTEIN: And to answer some of Jay's other concerns, efficacy for other causes of apnea other than prematurity has not been demonstrated.

DR. GOLDSMITH: That's right, specifically ALTEs and for weaning from ventilators which I think, although we haven't discussed that today, most children in our unit get started before they demonstrate apnea. They get started while they're still on the ventilator in order

to enhance rapid weaning.

DR. CRIM: So, if I understand what's being proposed is that we take out the restriction but include in the package insert that the drug has only been studied for 10 to 12 days?

DR. LI: Yes, something to that effect.

Is there an opposing view? John.

DR. JENKINS: Dr. Li, I was just going to suggest that since you all have modified the question so much, it's really not entirely necessary that you try to take a vote. I think we've heard a lot of different ideas and we can incorporate those. But if you want to try to write the question in your own words and then take a vote, that's fine also.

DR. LI: Thank you.

Yes.

DR. SZEFLER: I was just going to mention there's kind of another soft area in there that probably requires some looking at right up front. In terms of description, it mentions bronchodilator activity and then it kind of pops up later on. That is distant from the apnea aspect and again kind of creates potentials for creative application. John?

DR. JENKINS: Yes, if I could comment on that also. The label that you have in your briefing package is

simply the label that was written by the sponsor and submitted. The sponsor generally submits their proposed labeling and that will undergo a rather extensive review. So, that has not been reviewed and modified by the agency as yet. So, if that helps to allay some of your concerns. You can be guaranteed that the labeling will be substantially revised because we always substantially revise what the sponsor sends in.

(Laughter.)

DR. SZEFLER: That part caught my attention. I don't want to have everybody running around that this is a new bronchodilator that was approved.

DR. LI: Rather than take a vote on the 10- to 12-day restriction, I would like to have the panel address three items that I had jotted down from our previous discussions earlier this afternoon and this morning that had to do with labeling.

One had to do with whether we wanted to recommend drug levels be performed, and if so, at what intervals?

The second had to do with whether the importance of the patient's renal function should be taken into account.

And the third was whether there was a therapeutic level or a therapeutic range that we wanted to

include.

Again, these are items that came up from our discussion earlier, and I just wanted to revisit them at this point because it is appropriate to address those.

Yes, Dr. Hendeles.

DR. HENDELES: I think what prompted those comments was reading the sponsor's labeling, and just letting the FDA know that we're concerned about that they be taken into account is really all that I feel the need to do.

DR. LI: So, for example, with the issue of drug levels, is there any opinion or any proposal for including anything about drug levels in the labeling?

DR. ROTHSTEIN: I think that's one of the wealth of phase IV studies. Some fellows can have a career over this.

(Laughter.)

DR. HENDELES: I think there's information in the literature, and the way I would deal with that issue is simply to recommend that there be a section on when they should be drawn and what should be done with the results and leave it to the agency.

DR. LI: Do you have an opinion about that, about when it should be drawn and how the results should be used?

DR. HENDELES: Yes, but I don't feel it's appropriate here.

DR. LI: All right.

Dr. Cross.

DR. CROSS: At the levels they're suggesting to use, they didn't find any really high levels that looked inappropriately high, at least from what I saw.

DR. HENDELES: Dr. Pina's review had indicated that there were some levels above 30.

DR. CROSS: But not any that were really concerning.

DR. HENDELES: I don't know.

DR. CROSS: I mean, one option is just to say if higher dose -- I'm sure we'd all agree if higher than recommended doses are used, blood levels should probably be checked.

DR. HENDELES: Or what if the patient doesn't respond to therapy? They are giving a loading dose. It might be because their level is too low. We don't know if there's a relationship, and under item number 6, I would recommend that since they have that data, that they examine it with that intent, to look and see whether those patients who failed to respond to the initial loading dose of caffeine had lower levels than the patients who did respond.

DR. SZEFLER: Just to follow up on your point, it's hard to kind of write that levels should be obtained, but levels are the only safety valve that you have with the restrictions of the study. The study was done in a certain age group, certain population, numerous exclusion factors. The levels are something you can use to kind of individualize the dose for your children less than 1,000 or less than 28 or on concomitant therapy. But I don't know exactly, without getting into the details you're referring to, Les, how to write those statements in there, but it's something that it would be nice to have some information around it.

DR. LI: Dr. Crim first.

DR. CRIM: I guess I'm of the opinion that as far as levels, I don't see a great need to have that in the package labeling as far as the company is concerned. That's because since we don't have any type of pharmacodynamic data, I don't know what to recommend or that the company should recommend since the company doesn't have the data. I think what has been done is what the clinicians have been doing over the years. They'll just titrate the dose up until they get a response or a side effect. If one wanted to just put a general statement that perhaps monitoring may be warranted, to me I think it should be left as nebulous as that because we don't have

any pharmacodynamic data.

DR. KELLY: Yes. It's like digoxin. You dose till they throw up, and then you back off.

When you do therapeutic drug monitoring, what you usually aim at is efficacy. So, you would load the patient. If they don't respond, you would probably reload them. If they then responded, you would get a serum concentration at that point to determine what that patient's therapeutic level was because it's that patient's therapeutic level. You can't write that into a package insert that I can see. Then you want to maintain that therapeutic level and it may take any number of different dosages.

People like me have made entire careers out of doing that on a daily basis in other types of patients. So, I don't want to take that away and put it in a package insert.

(Laughter.)

DR. LI: All right. Well, I don't hear a lot of support for including a very specific directive toward measurement of drug levels nor implicitly for a stated therapeutic range.

DR. JENNE: My first comment was that we shouldn't specify these levels so precisely, but I still think that they're worth doing. The question of they're a

check, for example, on renal elimination problems. They may be accumulating. I've got in this pharmacokinetic paper they happen to be going up over 12 days or so. They're continuing to go up.

But I don't think we should be so dogmatic about the upper level as if anything over that is a disaster because there should be some flexibility in the package insert, it seems to me.

DR. LI: So, perhaps a vote for a more general inclusion of a statement on drug levels rather than something specific. Fine.

On the issue of renal function, Les, did you think that a comment or a mention of that in the labeling is important?

DR. HENDELES: I think in general there needs to be more specific dosing guidelines than what's in that package insert, including an adjustment for patients who have decreased renal function.

DR. LI: Do others agree with that suggestion from Dr. Hendeles? Carroll nodding. Okay.

Let's now move on to 5b which is one of the important issues that is before us today. Would you recommend a warning considering the concern of necrotizing enterocolitis and caffeine? We did touch on this earlier, but we need to revisit the idea. Yes.

DR. HENDELES: I think there should be a precaution or some statement in there that reviews what the animal and human data is in a few sentences so that it informs the clinician of that information but not a warning which to me implies a black box.

DR. LI: Is there agreement or dissention? Yes.

DR. ROTHSTEIN: I've just got a follow-up question. If an infant develops enterocolitis or abdominal distention, should treatment be stopped?

DR. HENDELES: Well, if you stop the treatment, it's still going to go on for five days.

DR. ROTHSTEIN: Oh, yes.

DR. KELLY: What do you do now?

VOICE: Keep going.

DR. ROTHSTEIN: So, that's my question. One can say that sicker infants will have more severe apnea. There may be an increased incidence of sepsis in infants with increased apnea, but there is no firm association between the treatment of the apnea and exacerbation of enterocolitis or sepsis. Somehow acknowledging that these two conditions may run together and therefore, people have raised the issue, well, but caffeine or theophylline was used, therefore it's associated. It may or may not.

DR. LI: Right. So, you would propose or

recommend some indication of a potential association with acknowledgement that that association hasn't been proven.

DR. HENDELES: Right, a just a disclosure of the problem.

DR. SESSLER: I think I'm comfortable with that, for whatever that matters, in the sense that unfortunately we don't have definitive data. What we have is worrisome findings that may be easily explained somewhere else. Obviously it doesn't require something that's a very high level proven association type of warning, but it certainly does need to be mentioned that that was an area of concern in my opinion.

DR. LI: That would satisfy you, Dr. Sessler?

MR. MADOO: Couched as a warning or as a precaution? How are you are you going to couch this?

DR. LI: Well, we heard from Dr. Hendeles a suggestion for more of a comment. I'm not sure you even used the word "precaution."

DR. HENDELES: I probably did.

DR. ROTHSTEIN: I don't think it merits a boxed warning.

DR. LI: So, no support for the warning.

Yes.

DR. OSBORNE: I would agree, if I read the numbers correctly, that is, the FDA document pointed out

there was no statistical difference between the groups whether the caffeine group or placebo or by original randomization or adverse events of all patients. In none of those cases was there a statistical difference. We've talked about the small sample size extensively and this certainly could be a type 2 error.

But I'd also point out that in the literature, with all the problems that the literature has, there are huge ranges of either prevalence or incidence of NEC, but they range easily within the percentages we're seeing here, which are less than 10 percent. They're often much higher in the kind of population that seems similar to this one. So, at least if it is occurring by association, the numbers are not dramatic, and so I would agree with no warning.

DR. LI: Curtis.

DR. SESSLER: I would ask that someone look at the statistics again just to clarify that in terms of this garbage area, the exposure area. Granted, it's an unknown but before we categorically state that patients by randomization or by exposure had no statistical difference in these, 0 percent versus 13 percent looks to me by a Fisher's Exact Test that it might be significant, and the same for the sepsis and for the NEC. So, I would just do that before we make the statements that we know.

DR. LI: Were those studies done, Dr. Jenkins

or Dr. Pina?

DR. JENKINS: I'll let Dr. Pina answer that question. Then I have a clarification I'd like to make for the committee.

DR. PINA: I think I will defer that question to Dr. Gebert.

DR. GEBERT: Yes. I did a Fisher's Exact Test on those data and they were not significant.

DR. SESSLER: Thank you.

DR. JENKINS: The clarification I'd like to offer for the committee is a boxed warning and a warning are not the same things. You can have warnings and they will not be in black boxes. A black box warning is a much higher level of a warning that are reserved for certain circumstances and have the desired impact of conveying the severity of the warning but also they have impacts with regards to how the sponsor may promote the product without providing the entire package insert for the physician.

So, just to clarify, there was some discussion earlier that it didn't merit a black box. Other people seemed to equate black box and warning being the same. Almost all drugs have a warning section in their labeling, and often things such as patients who are hypersensitive to the drug, it's contraindicated. That may be in the contraindications or it may be in the warnings.

But I just wanted to clarify a warning is not necessarily a black box warning. A black box warning is usually reserved for much more significant definite associations and more severe potential adverse effects.

DR. HENDELES: How does a precaution differ from a warning?

DR. JENKINS: I don't have the regulatory definitions of those sections here with me, but warnings are generally viewed as things where if the adverse event occurs, it could be serious or life-threatening, whereas precaution is a little bit lower standard. There are specific definitions of those in the CFR, and I don't know if Dr. Bilstad knows the definitions. He's indicating that he doesn't.

DR. BILSTAD: Well, it's really just a matter of degree of how strong we think that the message should get to health care providers. If there's concern about a safety problem, the milder concern is to put it into precautions, draw it to health care providers' attention. If the concern is stronger, it may warrant going into the warnings section, and as John indicated, if we have a great deal of concern about it and it's potentially life-threatening or has been demonstrated to cause mortality, then it may merit a boxed warning which again can be in the warnings section, or if we're really concerned, we'll put

it up front at the beginning of the labeling. So, there's sort of a spectrum of ways in which we can get across the concern in the labeling.

DR. LI: Well, John, would it be useful to get a sense from the group how concerned the panelists are about the risk of NEC?

DR. JENKINS: Yes, I think that would be useful because it's clear that we've gotten the feeling that there should be something in there stating what is known about the association between methylxanthines and NEC, and it would be useful to hear from this panel what your level of concern is. I think Dr. Bilstad almost laid out a hierarchy of no concern, therefore no statements; precaution; a warning; a black box warning in the warnings sections; a black box warning in the front of the labeling. So, it would be useful to know what your level of concern is and how much you'd like to convey that information to the prescribing clinician.

DR. LI: Why don't we go around the table? Actually, Les, you had your hand up, so you'd like to make some comments.

DR. HENDELES: I have a precaution level concern.

DR. LI: Thank you.

DR. KELLY: Precaution.

DR. JOBE: I would just like to see that clinicians know that there's a potential association so that that could be followed up if necessary.

DR. JENNE: I'd just say that we're uncertain and at least it should be mentioned.

DR. OSBORNE: I'm somewhere between precaution and warning. I don't have the clinical experience, but I'm certainly concerned there's an association. I'll say precaution.

DR. CRIM: Precaution.

DR. LI: Precaution for myself.

DR. ROTHSTEIN: I'll leave it for the discussions between the FDA and the sponsor to work out.

DR. CHINCHILLI: Yes, I agree. I think the FDA needs to make that judgment, based on the fact that it's not clear-cut, whether or not there is an association.

DR. SZEFLER: I lean towards precaution.

DR. CROSS: I'm leaving it to the FDA but note that their indication of the difference between precaution and warning is the severity of the complication, not the certainty of the complication or uncertainty.

DR. SESSLER: I agree. I think precaution is about right, but it is a very severe thing. We're hampered by a lack of clear-cut data unfortunately.

MS. CONNER: Precaution.

DR. GOLDSMITH: I would agree with precaution. One or two other comments.

I know Dr. Sessler has been concerned about the adverse events, and those babies who were exposed -- I don't know how many of them because I didn't take notes on this -- were rescued. So, I wonder whether they truly had apnea of prematurity by that point or whether they were suffering from NEC or sepsis when somebody switched them out from their possibly being in the not-exposed category, in the placebo category, because they weren't responding and they already had the beginnings of sepsis. So, one of the things that might be put in the precaution is that nonresponders should be looked at for other causes such as sepsis and necrotizing enterocolitis.

The second thing I would add would be that again drug interactions -- the use of caffeine in association with other drugs as potential causes for NEC or sepsis has not been investigated so that it's not just caffeine in itself, but in association with other drugs.

MR. MADOO: It looks like we had eight at the precaution level and seven at the let FDA take care of it.

DR. LI: Thank you, Mr. Madoo.

Let's tackle question number 6. If caffeine citrate were to be approved for this indication, what, if any, post-marketing studies would you recommend be

completed by the sponsor? We did actually tackle this to a limited extent. Let's try to give as much assistance as possible.

Yes.

DR. JENKINS: Jim, if I could just ask the committee, it would be very useful to us if we could hear a discussion of what studies you think should be a condition of approval, in other words, a required phase IV study, a phase IV commitment, versus studies that might be nice if someone would do them. So, it's kind of what's needed as a condition for approval, given that the committee has recommended approval, versus what would be nice in the broad spectra of things which you really wouldn't put it at the level that it had to be agreed to before you would recommend approval.

DR. GOLDSMITH: Maybe as an introduction to this -- and I'm not exactly sure of my numbers, but the neonatologists here are very familiar with working with other people's drugs. We get to use all the drugs that have been approved for adults and for children, but never looked at for neonates. I think, if I'm not right -- Alan may correct me on this, but surfactant probably is the only drug that has been approved specifically for neonates, and this may be the second.

DR. JOBE: Indomethacin for PDA is another one.

DR. GOLDSMITH: Okay. So, two or three drugs. So, what we wind up with is giving all kinds of drugs. We gave indomethacin for a long time before it was approved. I remember back in 1976 that discussion at the SPR's on giving it and what the consequences were.

In surfactant, there were 10,000 children looked at before it was approved by the FDA or some huge number in trials before we got a chance to use it clinically in 1990 I guess.

Several people said that this is a very important step because we're beginning to take some drugs, orphan drugs and other drugs, and say they have neonatal indications for use and they should be looked at, but we're beginning to see, as this committee has heard all day, what the tremendous difficulties of this are when you have drugs that are already in clinical use, that people won't take to an IRB that physicians want an easy opt-out. So, we have, I think, some real considerations here that we should have some definite stage 4 studies required.

Now, I don't know whether you can do any more stage 4 efficacy studies, but certainly safety has to be required and some way of monitoring safety over the next 12 to 24 months at a minimum, if we have 20,000, 30,000, 40,000 kids a year treated with this, has got to be done so that as we approach these drugs that are now being offered,

to compare 10,000 children treated with surfactant and I don't know how many thousand with indomethacin versus the small numbers here, I think we do have tremendous safety concerns in going forward.

DR. LI: Dr. Rothstein?

DR. ROTHSTEIN: The two areas that I would like to see commitments to is, one, the developmental pharmacology of this drug, the blood concentrations and the accumulation of this drug in the 27-weeker versus the 32-weeker, and then anticipating what's going to go on in the community, what happens when the dose is increased? Is there some sort of pharmacodynamic effect that we're going to see when the loading dose, instead of 10, becomes 15, when the maintenance dose is increased by 50 or 100 percent? Do we see a change either in the efficacy of the drug or do we see a change in the side effects?

DR. LI: Would those suggestions be under the required or nice-to-know categories?

DR. ROTHSTEIN: Well, I think the company is going to very much like to know about how their approved drug is now being used. I think the FDA might want it also, but I think the company has a vested interest in knowing what's going on with the drug.

DR. KELLY: Like the neonatologists who believe this drug works, I believe that there is a concentration-

effect relationship, and I think there should be dose ranging studies. I don't know the design of those, but I think that's one area that we really need to know more about. I think there's evidence in the literature that there are differences in response rate, and so I think a dose ranging study is necessary.

DR. HENDELES: In response to Dr. Jenkins' question, I think before the drug is approved, that the available literature needs to be analyzed and a lot of these questions can be answered, such as the relationship between renal function and half-life of the drug so that one could scale down the maintenance dose.

I think that through the network, there ought to be after approval some attempt to see whether there's an increased incidence of NEC in association with the use of this drug as opposed to CPAP or something else. If there is, I do support what Dr. Kelly said about looking at the relationship between concentration and effect. If there is no strong relationship, it may be that you can give a smaller dose of the drug and decrease any risks from it. So, I think that would be nice to know afterwards.

But right now I think that we have sufficient information to approve it and I think the dosing that's in the package insert could be adjusted based upon the knowledge of the biopharmaceutics and pharmacokinetics that

is available.

DR. LI: Curt, did you have a comment you'd like to make about this?

DR. SESSLER: I think the safety part is certainly key. I would include sepsis with NEC just because of the observation in the database that we have before us. Even though this may not have received attention so much in the past, I think we're obligated to look at that along with the NEC question in terms of follow-up safety.

DR. LI: Vernon, do you have any thoughts about whether any additional studies should be required as a condition for approval?

DR. CHINCHILLI: No. My main concern is the safety. So, I have similar concerns as Curtis.

DR. CROSS: Yes, mine is safety. I'm unclear, though, how one would handle sepsis because sepsis syndrome and suspected sepsis and bacterial proven sepsis and how you do the blood cultures, et cetera gets to be pretty complicated to deal with even in the adult ICU. So, I'm certainly interested in my own feeling on the safety in terms of the enterocolitis aspect, but in terms of the septic part, I'm not too sure without a stronger theoretical construct that I would make the company start recording sepsis and proved sepsis and maybe sepsis and

sepsis syndrome and hemodynamic over-reactivity and whatever.

DR. SESSLER: I would make it simple and do bacteremia. In adults we know that only 30 or 40 percent of septic patients have bacteremia, but if bacteremia is the only hard definition that could be utilized, then that would be better than nothing.

DR. LI: Dr. Jenkins.

DR. JENKINS: Assuming the drug is approved, it's very likely that it will become standard of care even more so than it is now. So, some of these questions that you're suggesting about follow-up issues on NEC and sepsis -- I'd be interested if you have any ideas how those studies would be conducted. In other words, what would the control groups be if nearly all of the patients with this disease were receiving caffeine citrate? Would we limit ourselves to historical controls, or how would you get some handle on whether the incidence of NEC is higher? What would your control group be?

DR. LI: Dr. Rothstein has the answer.

(Laughter.)

DR. ROTHSTEIN: We've heard that in some units this drug is started while children are still being ventilated in preparation for discontinuation of mechanical ventilation. You can very easily double-arm that. So,

some kids are not started on it until mechanical ventilation is discontinued, and they demonstrate disorders of respiratory control. The practice already is established of starting it earlier. So, you have a way of perhaps getting a double-arm study there.

DR. LI: Molly?

DR. OSBORNE: I think it depends a lot on what kind of database is available. If there's a database through the NICHD that would have enough information, certainly one simple way to do it would be to identify NEC which, first of all, is going to need a longer study than this anyway. The articles suggest 25 percent occur 30 days after birth. So, we're missing a lot of them perhaps in the study. And look at dose response. I mean, at least dose response so you can get some information on dose, some information on weight, and get some information, but doing it that way without having to get a placebo group, although controls would be great.

DR. SZEFLER: Correct me if I'm wrong, but I would think NEC is a complication that you monitor in a unit, and so good units that have good data would be places to go to see what happens to the incidence before and after approval. So, I think historical controls in a controlled setting would be a good place to start in terms of looking at changing incidence.

DR. JOBE: I think again the NICHD Neonatal Network database and the Vermont Oxford databases are published every year or two with incidences versus birth weight for NEC, IVH, all the alphabet soup of neonatology. One can at least get that sort of epidemiologic data with the introduction of a drug. That was done very effectively for surfactant and its introduction.

DR. CRIM: Who reports to those databases? Is it just major university centers or is it even community hospitals that have a pediatric --

DR. JOBE: There are two different databases. The NICHD network is 14 university centers. The Vermont Oxford is about 100 non-university centers by and large. So, they have different flavors to them.

DR. CRIM: Yes, that's what I was wondering because if you have a sicker population in the university setting, then the incidence may be higher than, let's say, some pediatric hospital out in the communities.

DR. LI: Dr. Goldsmith, did you have an additional comment?

DR. GOLDSMITH: Maybe Alan can comment on this in terms of what the NICHD did, but obviously the same problems that you have with sepsis, we have in NEC. There are stages, the Bell's modified criteria, and what level does it have to rise to, to what stage in the Bell's

criteria before NICHD listed it as a complication of NEC? Do you have information on that?

DR. JOBE: I don't know the definitions being used right now.

DR. GOLDSMITH: We have similar kinds of issues in terms of sepsis, and that obviously has to be looked at carefully.

DR. LI: So, do I sort of hear, as a summary of what was recommended, that a safety post-marketing study be conducted primarily again looking at NEC and perhaps sepsis too as a follow-up of safety and that this recommendation would be required as a condition for approval? I see Dr. Goldsmith nodding.

Curt, what's your feeling about the requirement of this type of study for safety?

DR. SESSLER: Just as you stated it.

DR. LI: Is there anyone in disagreement?

DR. JENNE: I don't understand the definitions here. You say a post-marketing study. In other words, it would be marketed.

DR. LI: Yes.

DR. JENNE: And this would be a requirement for the company to continue studying along certain lines.

DR. LI: Yes, as opposed to optional.

DR. JENNE: I would put a dose-response in the

same category frankly. Whether the company should do it or somebody else be commissioned to do it, I think there could be some ingenious ways of finding this information out.

DR. LI: So, I think the first issue is that there was agreement I believe on our recommendation for a post-marketing safety study looking, in particular, at NEC.

And the second issue that Dr. Jenne brought up and which we discussed is studies regarding dose ranging studies or concentration effects.

John, is it your opinion that you would recommend that this be a required activity that would be a condition for approval?

DR. JENNE: Yes, I think it should be done by reputable investigators. It doesn't take a large group to do this. It doesn't take controls necessarily to do a dose-response study. But I think the company should have the first chance to do this.

DR. LI: Dr. Kelly, I see you nodding. Does that mean you're in agreement?

DR. KELLY: I agree and I think there are ways to analyze sparse data now where you don't have to get large amounts of blood samples and stuff from the patients to do it. So, I don't think it's that difficult to do.

DR. LI: Any other comments from the group, either agreement or disagreement?

(No response.)

DR. LI: Okay, thank you.

That really concludes the six questions that we were asked to address. Let me ask Dr. Jenkins if he would like to make some comments before we adjourn for the day.

DR. JENKINS: I would just like to thank the committee. I think you've done an outstanding job of reviewing the data and really have a very good discussion today. Particularly I'd like to thank the neonatology consultants who joined us today: Dr. Goldsmith, Dr. Rothstein, and Dr. Jobe. I think they really added a lot to the discussion and brought a lot of information that maybe most of us who are not neonatologists don't have a very good feel for. I think it was a very productive and useful session, and we'll certainly take your recommendations under consideration very strongly.

DR. LI: Yes, Peter.

DR. ROTHSTEIN: Since the transcripts are available of this hearing, is the data that was presented here now in the public forum?

MR. MADOO: It has to go through FOI. We'll process it through FOI and then you can make a request for it.

DR. LI: Yes, Stan.

DR. SZEFLER: If I could make one other

suggestion. I don't know if it comes under here, but I would encourage a full publication of the study. I don't know if you can make that a requirement. At least you have some reference in terms of public access.

DR. ROTHSTEIN: That depends on the journals.

DR. SZEFLER: Yes, but I mean, I would encourage a smaller detailed summary.

DR. JENKINS: One thing I can say to that, if the drug is approved by the agency, the agency's reviews of the NDA become available to the public under the Freedom of Information Act. Those may be partially redacted to protect any proprietary information, but the FDA reviews are available. In fact, they're now available electronically on the World Wide Web very quickly after the approval. So, the medical officer review that you have, once it's finalized, if the application is approved, as well as the other discipline reviews, are available under the Freedom of Information Act which, if the drug is approved along its current time frame, might occur before publication could be out there also.

DR. LI: Dr. Osborne?

DR. OSBORNE: Is it also possible it would come out in the Medical Letter?

DR. JENKINS: The Medical Letter generally does review newly approved therapies, and the FDA does receive

pre-publication copies of those documents for review and comment. But I can't speculate on whether the Medical Letter will consider this to be a substantive enough approval that they'll put it in their publication, which is very widely distributed and not just to neonatologists. This is a pretty focused area of indication.

DR. LI: Okay. Thanks to the panelists. Thanks very much to Dr. Jenkins, Dr. Pina, the FDA. Thank you to the sponsor.

The meeting is adjourned.

(Whereupon, at 3:47 p.m., the committee was adjourned.)

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SIGN-OFF CLEARANCE RECORD
CENTER FOR DRUG EVALUATION AND RESEARCH
FEDERAL REGISTER NOTICE OF ADVISORY COMMITTEE MEETING

NAME OF MEETING: Pulmonary-Allergy Drugs Advisory Committee

DATE OF MEETING: December 15, 1997

CONTACT PERSON: Leander B. Madoo
CENTER/OFFICE: CDER/ACS/HFD-21
PHONE: 301/443-5455

TO: Committee Management Officer, HFA-306

THRU: Director, Division of Pulmonary Drug Products, HFD-570 /S/ 10/29/97

Director, Office of Drug Evaluation II, HFD-102 /S/ 10/29/97

APPEARS THIS WAY
ON ORIGINAL

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

Advisory Committee; Notice of Meeting

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

This notice announces a forthcoming meeting of a public advisory committee of the Food and Drug Administration (FDA). The meeting will be open to the public.

Name of Committee: Pulmonary-Allergy Drugs Advisory Committee.

General Function of the Committee: To provide advice and recommendations to the agency on FDA regulatory issues.

Date and Time: The meeting will be held on December 15, 1997, 8 a.m. to 5 p.m.

Location: Ramada Inn, Embassy Ballroom, 8400 Wisconsin Avenue, Bethesda, MD.

Contact Person: Leander B. Madoo, Food and Drug Administration, CDER/ACS/HFD-21, 5600 Fishers Lane, Rockville, MD, 301/443-5455, or FDA Advisory Committee Information Line, 1-800-741-8138 (301-443-0572 in the Washington, DC area), code 12545. Please call the Information Line for up-to-date information on this meeting.

Agenda: The Committee will discuss the safety and efficacy of new drug application (NDA) 20-793 Cafcit™ (caffeine citrate

injection, 10 mg/mL), Roxane Laboratories, Inc., for intravenous or oral use in the treatment of apnea of prematurity.

Procedure: Interested persons may present data, information, or views, orally or in writing, on issues pending before the committee. Written submissions may be made to the contact person by December 5, 1997. Oral presentations from the public will be scheduled between approximately 8:30 a.m. and 9:30 a.m. Time allotted for each presentation may be limited. Those desiring to make formal oral presentations should notify the contact person before December 5, 1997, and submit a brief statement of the general nature of the evidence or arguments they wish to present, the names and addresses of proposed participants, and an indication of the approximate time requested to make their presentation.

Notice of this meeting is given under the Federal Advisory Committee Act (5 U.S.C., app. 2).

Dated_____

/S/

Leander B. Madoo

Roxane Laboratories, Inc.

P.O. Box 16532 • Columbus, Ohio 43216-6532 • Phone 614/276-4000 • Fax 614/274-0974

Post-it® Fax Note 7671	Date 20 Oct 97	# of pages ▶ 1
To MR. LEANDER MADOO	From READE	
Co./Dept. FDA	Co. ROXANE	
Phone # 301-443-5455	Phone # 614-276-4000 x2345	
Fax # 301-443-0699	Fax # 614-276-0321	

20 October 1997

Leander Madoo
Advisors and Consultant Staff
Food and Drug Administration

Subject: **NDA 20-793 (Cafcit™)**
Caffeine Citrate Injection, 10 mg/mL (Caffeine Base Equivalent)
User Fee ID No. 3293

Mr. Madoo:

The proposed Trade Name for the drug product (caffeine citrate Injection, 10 mg/mL) is Cafcit™. Cafcit™ is intended for use intravenously or orally for the treatment of apnea of prematurity.

Your primary contact will be me. I can be reached by telephone at 614-276-4000, x2345 and by telefax at 614-276-0321. You call also reach my Coordinator, Ms. Sheila Campbell at 614-276-4000, ext. 2344. In my absence, your secondary contact will be Beverly Wynne, Ph.D., Director of Medical Affairs. She can be reached by telephone at 614-276-4000, ext. 2188 and by telefax at 614-276-8061.

Please send to us information concerning your title and address.

Respectfully,

Sean Alan F.X. Reade, M.A.
Director, Regulatory Affairs