

**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 51 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 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

REQUEST FOR CONSULTATION

51
12-12-97

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

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

DATE: December 12, 1997	IND NO.:	NDA NO.: 20-793	TYPE OF DOCUMENT : NDA	DATE OF DOCUMENT: August 22, 1997
NAME OF DRUG: Cafcit (caffeine citrate)		PRIORITY CONSIDERATION: Priority	CLASSIFICATION OF DRUG: 2P	DESIRED COMPLETION DATE: January 12, 1997
NAME OF FIRM: O.P.R. Development, L.P./Roxane (US Agent)				

REASON FOR REQUEST

I. GENERAL

- | | | |
|--|--|--|
| ☐ NEW PROTOCOL | ☐ PRE-NDA MEETING | ☐ RESPONSE TO DEFICIENCY LETTER |
| ☐ PROGRESS REPORT | ☐ END OF PHASE II MEETING | ☐ FINAL PRINTED LABELING |
| ☐ NEW CORRESPONDENCE | ☐ RESUBMISSION | ☐ LABELING REVISION |
| ☐ DRUG ADVERTISING | ☐ SAFETY/EFFICACY | ☐ ORIGINAL NEW CORRESPONDENCE |
| ☐ ADVERSE REACTION REPORT | ☐ PAPER NDA | ☒ FORMULATIVE REVIEW |
| ☐ MANUFACTURING CHANGE/ADDITION | ☐ CONTROL SUPPLEMENT | ☐ OTHER (SPECIFY BELOW): |
| ☐ MEETING PLANNED BY | | |

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH

- ☐ TYPE A OR B NDA REVIEW
☐ END OF PHASE II MEETING
☐ CONTROLLED STUDIES
☐ PROTOCOL REVIEW
OTHER:

STATISTICAL APPLICATION BRANCH

- ☐ CHEMISTRY REVIEW
☐ PHARMACOLOGY
☐ BIOPHARMACEUTICS
☐ OTHER:

III. BIOPHARMACEUTICS

- | | |
|--|---|
| ☐ DISSOLUTION | ☐ DEFICIENCY LETTER RESPONSE |
| ☐ BIOAVAILABILITY STUDIES | ☐ PROTOCOL-BIOPHARMACEUTICS |
| ☐ PHASE IV STUDIES | ☐ IN-VIVO WAIVER REQUEST |

IV. DRUG EXPERIENCE

- | | |
|--|--|
| ☐ PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL | ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY |
| ☐ DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES | ☐ SUMMARY OF ADVERSE EXPERIENCE |
| ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below) | ☐ POISON RISK ANALYSIS |
| ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP | |

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 not completed yet.*

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

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

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.
Peer Reviewer: Douglas Kramer, M.D.
Date of Document: June 30, 1999
Date Received: July 23, 1999
Date Reviewed: September 1, 1999

9/9/99
/S/ /S/ 9/10/99

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: [] 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.

EC: Original HDA 20-743

Division File

HFD-570 / Cdbhs

APPEARS THIS WAY
ON ORIGINAL

MEMORANDUM

To: Division file
NDA 20-793

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

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

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 than 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

APPEARS THIS WAY
ON ORIGINAL

MEMORANDUM

DATE: February 12, 1998

TO: NDA 20-793

FROM: John K. Jenkins, M.D.
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 ml of a 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

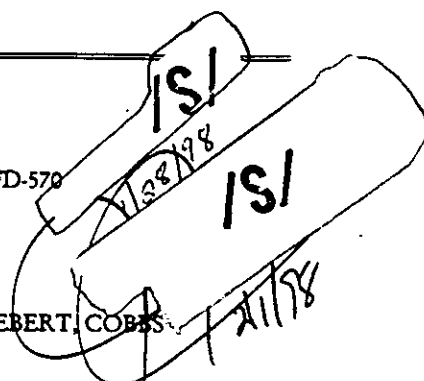
HFD-570/Cobbs

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, COBBES



Handwritten notes in the top right corner include "1/31/98" and "1/31/98" written vertically, and "1/31/98" written horizontally. There are also some illegible initials and a signature.

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 their 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.

APPEARS THIS WAY
ON ORIGINAL

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 / Statistical: 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 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 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 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.

Cafcit Injection
NDA 20-793
Page 2

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:	Lindsay Cobbs		Catck 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

REQUEST FOR CONSULTATION

C 151
5-21-99

TO (Division/Office): Labeling and Nomenclature Comm. Attn:
Dan Boring

FROM: HPD-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

- ☐ TYPE A OR B NDA REVIEW
- ☐ END OF PHASE II MEETING
- ☐ CONTROLLED STUDIES
- ☐ PROTOCOL REVIEW
- ☐ OTHER:

STATISTICAL APPLICATION BRANCH

- ☐ CHEMISTRY REVIEW
- ☐ PHARMACOLOGY
- ☐ BIOPHARMACEUTICS
- ☐ OTHER:

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILITY STUDIES
- ☐ PHASE IV STUDIES

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

IV. DRUG EXPERIENCE

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

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

151
5-21-99

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

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
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NAME OF DRUG: Cafcit(cafeine citrate) Injection	PRIORITY CONSIDERATION: Priority	CLASSIFICATION OF DRUG: 2P	DESIRED COMPLETION DATE: November 1, 1997
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NAME OF FIRM: O.P.R. Development, L.P. (Agent: Roxane Laboratories, Inc.)

REASON FOR REQUEST

I. GENERAL

- | | | |
|--|--|--|
| ☐ NEW PROTOCOL | ☐ PRE-NDA MEETING | ☐ RESPONSE TO DEFICIENCY LETTER |
| ☐ PROGRESS REPORT | ☐ END OF PHASE II MEETING | ☐ FINAL PRINTED LABELING |
| ☐ NEW CORRESPONDENCE | ☐ RESUBMISSION | ☐ LABELING REVISION |
| ☐ DRUG ADVERTISING | ☐ SAFETY/EFFICACY | ☐ ORIGINAL NEW CORRESPONDENCE |
| ☐ ADVERSE REACTION REPORT | ☐ PAPER NDA | ☐ FORMULATIVE REVIEW |
| ☐ MANUFACTURING CHANGE/ADDITION | ☐ CONTROL SUPPLEMENT | ☒ OTHER (SPECIFY BELOW): |
| ☐ MEETING PLANNED BY | | 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
☐ BIOAVAILABILITY STUDIES
☐ PHASE IV STUDIES | ☐ DEFICIENCY LETTER RESPONSE
☐ PROTOCOL-BIOPHARMACEUTICS
☐ IN-VIVO WAIVER REQUEST |
|---|--|

IV. DRUG EXPERIENCE

- | | |
|--|---|
| ☐ PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
☐ DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP | ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
☐ SUMMARY OF ADVERSE EXPERIENCE
☐ POISON RISK ANALYSIS |
|--|---|

V. SCIENTIFIC INVESTIGATIONS

- | | |
|-----------------------------------|--------------------------------------|
| ☐ CLINICAL | ☐ PRECLINICAL |
|-----------------------------------|--------------------------------------|

COMMENTS/SPECIAL INSTRUCTIONS: Please evaluate the proposed 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: [redacted] /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 with a concentration of 10 mg of caffeine base/mL. It is intended for either intravenous 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: NOA#
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.

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

APPEARS THIS WAY
ON ORIGINAL

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 CAF CIT. 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]

The information contained in this facsimile is **CONFIDENTIAL** and is intended only for use by the individual(s) and/or entity(s) to whom addressed. Copying or distributing this transmission is strictly prohibited except by the intended recipient, or their employee, or agent. If this communication is received in error, please notify us immediately by telephone.

REQUEST FOR CONSULTATION

KUZMIK
6/5/95
12-596

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

REASON FOR REQUEST

I. GENERAL

- | | | |
|--|--|--|
| ☐ NEW PROTOCOL | ☐ PRE-NDA MEETING | ☐ RESPONSE TO DEFICIENCY LETTER |
| ☐ PROGRESS REPORT | ☐ END OF PHASE II MEETING | ☐ FINAL PRINTED LABELING |
| ☐ NEW CORRESPONDENCE | ☐ RESUBMISSION | ☐ LABELING REVISION |
| ☐ DRUG ADVERTISING | ☐ SAFETY/EFFICACY | ☐ ORIGINAL NEW CORRESPONDENCE |
| ☐ ADVERSE REACTION REPORT | ☐ PAPER NDA | ☐ FORMULATIVE REVIEW |
| ☐ MANUFACTURING CHANGE/ADDITION | ☐ CONTROL SUPPLEMENT | ☐ OTHER (SPECIFY BELOW) |
| ☐ MEETING PLANNED BY | | |

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 | ☐ DEFICIENCY LETTER RESPONSE |
| ☐ BIOAVAILABILITY STUDIES | ☐ PROTOCOL-BIOPHARMACEUTICS |
| ☐ PHASE IV STUDIES | ☐ IN-VIVO WAIVER REQUEST |

IV. DRUG EXPERIENCE

- | | |
|--|--|
| ☐ PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL | ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY |
| ☐ DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES | ☐ SUMMARY OF ADVERSE EXPERIENCE |
| ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below) | ☐ POISON RISK ANALYSIS |
| ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP | |

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 [redacted] and NDA 20-793/Div File HFD-570/Bertha/Schumaker/Kuzmik

SIGNATURE OF REQUESTER [redacted] 12/8/96	METHOD OF DELIVERY (Check one) ☒ MAIL ☐ HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

REQUEST FOR TRADEMARK REVIEW

ISI

To: Labeling and Nomenclature Committee

Attention: Dan Boring, Chair (HFD-530), 9201 Corporate Blvd, Room N401

From: 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

C-166

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

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.

- 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)

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 [] 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 [] 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 [] to read "For single use only, discard unused portion" and move from left panel to right panel below CAUTION statement.
 - h. Revise [] on right panel to read "Control Room Temperature 15° [] (59° - [])".

- i. Revise the product composition statement as follows:

Each mL of CAFKIT™ Injection contains: 10 mg caffeine base equivalent prepared in solution by the addition of 10 mg caffeine anhydrous to [] mg citric acid, monohydrate, [] 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 [] 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

NDA 20-793

Page 8

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

APPEARS THIS WAY
ON ORIGINAL

18 Page(s) Redacted

Draft

Labeling

Cobbs

NDA 20-793

APR 30 1999

O.P.R. Development, L.P.

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

pages of trade

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.

APPEARS THIS WAY
ON ORIGINAL

NDA 20-793
Page 5

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.

Redacted 5

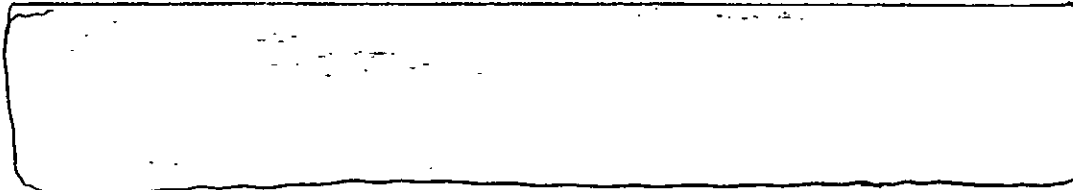
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information



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: Pratima 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 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 [] 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 [] and the 3 mL injection are identical in the manufacturing, filling, sealing, [] 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 [] vial is the imprinted information. The material of the seal is identical to the [] vial. The specifications and analytical methods of the 3 mL are identical to the [] except for the unique specification and method numbers.

5. Roxane and Ben Venue agreed to amend the specifications for particulate matter provided for the [] 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.

NDA 20-793

April 19, 1999

Page 4

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 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.

Chemistry, Manufacturing & Controls Telecon

Cafcit (caffeine citrate) Injection

January 8, 1998

Page 3

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

**APPEARS THIS WAY
ON ORIGINAL**



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.

ROXANE • PAIN • INSTITUTE



...making smart and safe pain relief through their research...
1 • 8 0 0 • 3 3 5 • 9 1 0 0

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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

APPEARS THIS WAY
ON ORIGINAL

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.

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW.

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Thank you.

/S/

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

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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 marketed 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.

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NDA 20-793

Page 3

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

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ON ORIGINAL

DEPARTMENT OF HEALTH AND HUMAN SERVICES FOOD AND DRUG ADMINISTRATION APPLICATION TO MARKET A NEW DRUG, BIOLOGIC, OR AN ANTIBIOTIC DRUG FOR HUMAN USE <i>(Title 21, Code of Federal Regulations, 314 & 601)</i>		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: Areas 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: _____	
Ds: _____	

FORM FDA 356h (4/97)

BEST POSSIBLE COPY

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 knowledge 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

Sean Alan F. X. Reade, M.A.
Director of Regulatory Affairs.

15 April 1999

ADDRESS (Street, City, State, and ZIP Code)
P.O. Box 16532
Columbus, Ohio 43216-6532

Telephone Number
(614) 276-4000

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

TELECONFERENCE

Representing Roxane:

Jonathan Donalek, Manager Regulatory Affairs
Ed Gunn, Manager 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, Biostatistics 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 [] vial are for the [] and not the 3 mL vial for injection. Roxane also stated that the drug product for the [] is identical to the drug product for the injection.
 - The Agency requested that the data supporting the [] 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 [] 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 [] at this time. The [] 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 [] 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.

Cafcit (caffeine citrate) Injection

June 5, 1998

Page 3

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

APPEARS THIS WAY
ON ORIGINAL

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

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/ *irritation & 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. Upoor 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 associated with O₂ desaturations (and to what percent) or with changes (decelerations) in heart rate. They also documented the degree of intervention required 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.


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

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.

APPEARS THIS WAY
ON ORIGINAL

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.

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ON ORIGINAL

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.

APPEARS THIS WAY
ON ORIGINAL

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

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 #

Applicant:

O.P.R. Development, L.P.

(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 amendments).
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 all 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 : 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

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ELECTRONIC MAIL MESSAGE

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
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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 d application (NDA) 20-793, Cafcit (caffeine citrate injection, 10 mg/ml (10 milligram/milliliter) for intravenous or oral use in the treatment of apnea of prematurity. The sponsor was Roxane Laboratories.

Results on the vote for approvability of caffeine 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 caffeine 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, caffeine had a similar safety profile, but milder and less frequent adverse events. In terms 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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This transcript has not been edited
or corrected, but appears as received
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service. Accordingly the Food and
Drug Administration makes no
representation as to its accuracy.

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5

CONTENTS

NDA 30-793, Ceficit (caffeine citrate injection)
for Intravenous or Oral Use in the Treatment of
Apnea of Prematurity

AGENDA ITEM	PAGE
CONFLICT OF INTEREST STATEMENT	
by Leander Madoo	12
OPEN PUBLIC HEARING	13
ROCHE LABORATORIES PRESENTATION	
Introduction - by Dr. Dean Alan Bonds	14
History of Caffeine Development -	
by Dr. Kirk V. Shepard	15
Apnea of Prematurity - by Dr. Allen Hembury	16
Literature Overview: Efficacy and Safety -	
by Dr. Kristen Woodell	17
Clinical Data Presentation -	
by Dr. Beverly A. Wynne	26
COMMITTEE DISCUSSION RE SPONSOR'S PRESENTATION	43
FOOD AND DRUG ADMINISTRATION PRESENTATION	
by Dr. L. Miriam Fine	82
COMMITTEE DISCUSSION RE FDA'S PRESENTATION	101

6

PROCEEDINGS

- 1
- 2 DR. LI: Good morning, ladies and gentlemen.
- 3 My name is James Li. I'm the Chair of today's Pulmonary
- 4 Allergy Drug Advisory Committee, and welcome to everybody
- 5 here. Thank you for coming.
- 6 I would like to start by having the panelists
- 7 and the committee members introduce themselves. I'm an
- 8 allergist at the Mayo Clinic. I've been on the committee
- 9 for about three or four years.
- 10 Perhaps we could go around the table and have
- 11 each individual just introduce themselves and where they
- 12 are from, perhaps what their specialty is.
- 13 DR. GOLDSMITH: I'm Jay Goldsmith from the
- 14 Ochsner Clinic in New Orleans. I'm a neonatologist.
- 15 MS. CONNER: Good morning, I'm Brenda Conner.
- 16 I'm a nurse with 20 years pediatric asthma and allergy
- 17 experience. I'm from Atlanta, Georgia. I'm the consumer
- 18 representative to the committee.
- 19 DR. SESSLER: Good morning, I'm Curt Sessler.
- 20 I'm an adult pulmonary and critical care specialist at the
- 21 Medical College of Virginia, at Virginia Commonwealth
- 22 University in Richmond.
- 23 DR. CROSS: I'm Carroll Cross, University of
- 24 California, Davis, adult pulmonologist-intensivist.
- 25 DR. SZEFLER: I'm Stan Szeffler from Denver,

8

CONTENTS (Continued)

AGENDA ITEM	PAGE
FADAC PRIMARY REVIEWERS' PRESENTATIONS	
by Dr. Peter Rothstein	131
by Dr. Vernon Chinchilli	136
by Dr. Stanley Sessler	150
COMMITTEE DISCUSSION	170

7

- 1 Colorado, Director of Clinical Pharmacology at the National
- 2 Jewish Medical and Research Center.
- 3 DR. CHINCHILLI: Vern Chinchilli,
- 4 biostatistics, Penn State, Hershey Medical Center.
- 5 DR. ROTHSTEIN: Peter Rothstein, Columbia
- 6 Presbyterian Medical Center, Babies and Children's
- 7 Hospital. I'm a pediatric anesthesiologist and was a
- 8 neonatologist in my previous life.
- 9 MR. MADOO: Leander Madoo, FDA, by way of Yale
- 10 University.
- 11 DR. OSBORNE: Molly Osborne, pulmonary and
- 12 critical care, Oregon Health Sciences University, in
- 13 Portland.
- 14 DR. JENNE: John Jenne, adult pulmonary
- 15 medicine, formerly Hines VA in Loyola, Chicago.
- 16 DR. JOBE: Alan Jobe. I'm a neonatologist and
- 17 I'm from Cincinnati Children's Hospital.
- 18 DR. KELLY: Bill Kelly from the University of
- 19 New Mexico Health Sciences Center. I'm pediatric pulmonary
- 20 and critical care.
- 21 DR. HENDELES: Leslie Hendeles, University of
- 22 Florida. I'm a clinical pharmacist in the pediatric
- 23 pulmonary division.
- 24 DR. HIMMEL: Marty Himmel. I'm Deputy Division
- 25 Director of the Division of Pulmonary Drugs.

9

1 DR. PINA: Miriam Pina, medical reviewer,
2 Division of Pulmonary Drug Products.
3 DR. JENKINS: I'm John Jenkins. I'm the
4 Director of the Division of Pulmonary Drug Products, FDA.
5 DR. BILSTAD: Jim Bilstad, Office of Drug
6 Evaluation II.
7 DR. LI: Thank you. Dr. Jenkins, would you or
8 any of the members of the FDA like to make some
9 introductory comments?
10 DR. JENKINS: Thank you, Dr. Li. I'd first
11 like to just start by thanking the members of the advisory
12 committee, the sponsor, my FDA colleagues, and the members
13 of the audience for attending today's meeting, which should
14 be very interesting.
15 First I'd like to make several acknowledgments
16 for members of the panel, to make it known what their new
17 positions may be or to acknowledge their presence.
18 First I'd like to thank you, Dr. Li, for
19 agreeing to serve as chair of the advisory committee for
20 the remainder of your term. We look forward to working
21 with you on the issues that come to the committee over the
22 next six to seven months.
23 We also have a couple of members joining us
24 today as consultants who will be official committee members
25 as soon as the paperwork is finalized. First is Brenda

10

1 Conner. She's is currently the acting consumer
2 representative, but will be in that position permanently
3 soon, we hope. Also Dr. Bill Kelly from University of New
4 Mexico will be joining us on the committee as well. We
5 look forward to working with you over the next several
6 years as you continue your service on the committee.
7 Finally, given the nature of today's topic, we
8 have asked several consultants to join the committee to
9 bring their unique expertise to this issue. First, Dr.
10 Jobe, who is a former member of our advisory committee who
11 is joining us, as well as Dr. Goldsmith and Dr. Rothstein.
12 We appreciate your willingness to review the materials and
13 join us today in our discussion. And also Dr. Les
14 Hendeles, who is also a former member of our advisory
15 committee. Thanks, Les, for agreeing to attend today also.
16 I think today's meeting will be very
17 interesting. It is an indication for which this committee,
18 to my knowledge, has never had an advisory committee
19 discussion, that being apnea of prematurity. It is also a
20 unique situation for our committee because I don't recall
21 in the last several years a situation where the drug
22 product being brought before the committee was one for
23 which we have essentially one adequate and well-controlled
24 study prepared by the sponsor, as well as numerous reports
25 from the literature, and the widespread common use of ad

11

1 hoc compounded versions of caffeine citrate for this
2 indication.
3 So, we look forward to the committee's
4 discussion of this new indication and also this new type of
5 data set. Thanks.
6 DR. LI: Thanks, John. Next Mr. Madoo will
7 read the conflict of interest statement.
8 MR. MADOO: Yes, and I also have some general
9 announcements. The committee will see in front of them
10 desk copies of today's slide presentations. The black
11 folder pertains to the sponsor, Roxane's presentation.
12 Feel free to take any notation you require on these. Then
13 we have FDA's slide presentation, Dr. Pina's presentation,
14 and that's clipped here.
15 Also I would like to reiterate that Brenda
16 Conner and Dr. Kelly will shortly be on board. In fact, I
17 think their formal appointment is in fact signed off and it
18 is just a formality and they will be with us very shortly
19 as full-fledged members.
20 I'd also like to note that all of our invited
21 consultants have been granted, from Dr. Woodcock, voting
22 status at this meeting, so everyone around the table will
23 be in a voting mode.
24 Let me proceed on to the conflict of interest
25 statement.

12

1 The following announcement addresses the
2 conflict of interest with regard to this meeting and is
3 made part of the record to preclude even the appearance of
4 such at this meeting.
5 Based on the submitted agenda and the
6 information provided by the participants, the agency has
7 determined that all reported interests in firms regulated
8 by the Center for Drug Evaluation and Research present no
9 potential for a conflict of interest at this meeting.
10 In the event the discussions involve any other
11 products or firms not already on the agenda for which an
12 FDA participant has a financial interest, the participants
13 are aware of the need to exclude themselves from such
14 involvement, and their exclusion will be noted for the
15 record.
16 With respect to all other participants, we ask
17 in the interest of fairness that they address any current
18 or previous financial involvements with any firms whose
19 products they may wish to comment upon.
20 Thank you.
21 Dr. LI?
22 DR. LI: Thank you, Mr. Madoo. We will move on
23 to the open public hearing phase of today's meeting. My
24 understanding, Mr. Madoo, is that we have not heard from
25 anyone who requested time to speak to us this morning.

13

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

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

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

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

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

14

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

4 DR. SHEPARD: Thank you, Sean. Good morning.
5 Regarding the history, in 1985 the FDA
6 contracted the University of Iowa to perform a literature
7 search and review and provide a summary of published data
8 concerning the use of selected drugs used to treat
9 newborns. Caffeine was one of the seven drugs selected for
10 review.

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

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

25 The FDA contract report concluded that it would

16

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

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

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

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

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

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

15

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

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

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

17

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

7 DR. ERENBURG: Thank you, Kirk.

8 Apnea of prematurity is one of the most common
9 problems that is identified in the neonatal intensive care
10 unit. Apnea is defined as respiratory pauses varying
11 between 10 and 20 seconds in duration and associated with
12 bradycardia, which is defined as a heart rate of less than
13 80 beats per minute.

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

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

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

18

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

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

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

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

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

25 DR. MOSDELL: Good morning. The following is a

19

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

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

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

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

20

1 addition, 11 uncontrolled clinical trials were published.

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

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

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

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

21 Studies also demonstrated a decrease in apnea
22 index, which is defined as the average number of apnea
23 episodes per 100 minutes. Studies also showed a decrease
24 in the number of episodes of bradycardia, a decrease in
25 oxygen desaturation, decrease in pCO₂, and a decrease in

21

1 periodic breathing and percent periodic breathing.
2 Studies also demonstrated a significant
3 increase in respiratory rate and a normalization of
4 pneumocardiograms.

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

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

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

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

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

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

22

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

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

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

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

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

23

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

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

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

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

24

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

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

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

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

25

1 the last caffeine dose.

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

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

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

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

24 DR. WYNNE: Thank you, Kristen.

25 Also, Dr. Dennis Haack, our consultant

— 26 —

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

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

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

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

21 The population were preterm infants, age 28 to
22 32 weeks post-conception at the time of study, and had
23 apnea of prematurity.

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

— 27 —

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

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

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

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

— 28 —

1 less than 1 milliliter per kilogram per hour.

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

5 Previous treatment with methylxanthines within
6 7 days prior to study enrollment or previous treatment with
7 H2 antagonists were also exclusionary factors.

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

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

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

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

— 29 —

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

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

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

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

30

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

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

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

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

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

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

31

1 attention to the right-hand side of the slide and you will
2 note that there are no significant differences in any of
3 these baseline parameters. So, the two groups were
4 similar. There were no significant differences between
5 caffeine and placebo in the double-blind trial at baseline.
6 We wanted to look at what was the disposition
7 of these patients. It becomes very important because as
8 you'll see, a lot of patients were discontinued from the
9 study or transferred to open-label. I think this really
10 bears special attention.

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

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

32

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

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

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

19 I'd like to draw your attention to those 14 and
20 16 patients that were transferred to open-label caffeine.
21 We can see that on day 1 there were 2 in the caffeine
22 group. However, at the time of transfer, 1 of these
23 patients had at least a 50 percent decrease in apnea
24 episodes, so at the time of transferring was actually a
25 success as defined by the protocol.

33

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

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

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

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

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

34

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

3 Now I'd like to talk about success or efficacy
4 as we previously defined it, at least a 50 percent
5 reduction in apnea events. First of all, I'd like to draw
6 your attention to a scale to 24 hours. What we did,
7 because we had different time periods, if there were 6
8 apnea events reported in 12 hours, that would be scaled to
9 12 in 24 hours or any fraction of the 24-hour day they were
10 all scaled so that there would be uniformity across.

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

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

35

1 10.

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

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

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

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

36

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

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

9 If we compile this data, we look at the
10 caffeine and the placebo in the double-blind, and we look
11 at just 7 to 10 days. We chose that. We thought it was a
12 strict criterion among the 10 days. How many babies
13 actually had success based on this? We find that 69
14 percent had at least a 50 percent reduction apnea in the
15 caffeine as compared to 43. There you see the approximate
16 20 percent difference again. This was highly significant
17 in favor of caffeine.

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

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

37

1 We looked at daily weight.
2 Laboratory parameters in the double-blind were
3 taken at baseline and when the infant was discontinued from
4 the double-blind, and you can see the parameters which are
5 listed.

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

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

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

38

1 attributed some association with caffeine.

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

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

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

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

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

39

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

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

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

14 Lung edema and anemia, mild, was also reported.
15 So, these were 10 AE's in 8 patients.

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

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

40

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

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

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

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

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

41

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

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

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

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

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

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

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

42

1 there is a comprehensive roster of both consultants and
2 members.

3 Thank you.

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

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

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

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

21 DR. EREBERG: The actual percentage?

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

25 DR. EREBERG: The 1,000 infants were the

43

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

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

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

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

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

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

24 DR. LI: Dr. Goldsmith.

25 DR. GOLDSMITH: I have a whole series of

44

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

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

6 Secondly --

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

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

14 Dr. Erenberg has something to add.

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

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

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

45

1 DR. EREBERG: Yes, that is correct.
2 DR. GOLDSMITH: All right.
3 Secondly, most apneic episodes have been shown
4 in most nurseries to be missed by nurses. Were hard copies
5 done of printouts for apnea, bradycardia and oxygen
6 saturation so that these could be looked at in a scientific
7 way rather than just on clinical observation?

8 DR. EREBERG: This was not done. This was not
9 required in our protocol.

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

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

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

25 DR. GOLDSMITH: There was one child that was

46

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

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

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

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

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

47

1 prolonged treatment -- the treatment here only went 10 to
2 12 days, but after prolonged treatment with theophylline
3 and caffeine, significantly in babies less than 1,000 grams
4 a very significant hyponatremia. That was reported here in
5 one infant. Both theophylline and caffeine are diuretics
6 and natureses.

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

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

14 DR. GOLDSMITH: Thank you.

15 DR. LI: Les.

16 DR. HENDELES: I was wondering if you could
17 provide some additional information on the relationship
18 between caffeine drug level and treatment failure, and also
19 what kind of range of levels resulted from the loading dose
20 and how that contrasted with the levels from the
21 maintenance dose, and how many patients were greater than
22 20 micrograms per milliliter.

23 DR. WYNNE: Sorry for the delay.

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

48

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

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

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

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

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

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

49

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

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

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

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

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

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

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

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

50

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

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

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

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

51

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

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

9 DR. WYNNE: No, we did not.

10 Did you want to add anything to that, Dr.

11 Haack? No. No, we did not.

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

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

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

52

1 Dr. Haack would like to --

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

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

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

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

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

53

1 that had 7 days or 8 days.

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

11 Did I answer your question?

12 DR. ROTHSTEIN: Somewhat.

13 DR. JENNE: According to the literature in one
14 fairly recent paper on a large population, mean half-life
15 was 144 hours. There is such a tremendous spread in half-
16 life. I was wondering if you had the data. Were you
17 satisfied when you looked at the 2-hour versus the 12-hour
18 levels, that there were not some levels that were really
19 climbing up? I don't have a feeling of the spread of those
20 12-hour levels.

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

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

54

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

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

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

15 DR. LI: Thank you.

16 Dr. Szeffler?

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

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

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

55

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

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

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

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

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

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

22 If we look at the open-label, and we'll go on
23 to that, again, here you see now the open-label, so you see
24 4 patients in open-label that had sepsis. That's for a
25 total of 6. And actually the 2 in the placebo -- placebo

56

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

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

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

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

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

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

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

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

57

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

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

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

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

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

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

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

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

58

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

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

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

15 DR. LI: Dr. Chinchilli?

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

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

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

59

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

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

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

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

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

60

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

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

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

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

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

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

18 DR. ERENBERG: We have faith in caffeine.
(Laughter.)

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

61

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

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

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

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

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

25 DR. LI: But the variable then of the 50

62

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

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

7 DR. WYNNE: This was based on the literature
8 and discussing with experts. If you look into the
9 literature, most of the literature assesses success with a
10 50 percent reduction in apnea, so that's where we based
11 ours. It's my understanding. I wasn't there at the
12 earlier part of this trial either.

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

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

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

25 DR. ERENBURG: At the initial meetings, the

63

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

5 DR. LI: Dr. Rothstein.

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

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

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

64

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

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

6 DR. LI: Dr. Cross.

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

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

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

65

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

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

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

14 DR. LI: Dr. Crim?

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

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

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

66

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

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

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

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

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

19 One, as far as the review of the literature,
20 although the duration of the studies range from 24 hours to
21 3 months, do you have a sense of how long the infants were
22 treated in this study? I know your study was approximately
23 10 to 12 days. How long were these babies treated in the
24 studies that were reviewed in the literature?

25 DR. MOSDELL: It is very difficult from the

67

1 literature to say that there is an average duration. The
2 24-hour study was just trying to -- it was one particular
3 trial that was trying to evaluate the effects within the
4 first 24 hours.

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

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

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

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

25 Then if the apnea recurs, the baby is put back

68

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

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

7 DR. CRIM: Is it initiated at birth?

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

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

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

69

1 times, so it really is very variable.

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

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

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

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

23 DR. ERENBURG: It was about between 7 and 10
24 days, approximately.

25 DR. CRIM: Would these babies have been

70

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

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

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

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

20 DR. LI: Dr. Sessler.

21 DR. SESSLER: I have two unrelated questions.

22 The first is in regards to the study itself.

23 What was the duration of enrollment for the nine centers to
24 get these 80 patients enrolled?

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

71

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

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

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

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

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

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

25 Certainly there is a large body of evidence

72

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

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

16 DR. LI: Dr. Jenne?

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

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

73

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

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

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

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

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

17 DR. JENNE: I see.

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

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

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

74

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

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

6 DR. LI: Les?

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

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

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

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

75

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

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

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

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

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

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

25 I can if you wish go through the data with

76

1 cerebral blood flow if you are interested in those studies.

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

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

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

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

17 DR. SZEFLER: And these are all neonatal
18 subjects?

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

21 DR. LI: Yes, Molly?

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

77

1 was included in your documents, Clinics in Perinatology,
2 1994. So, I'm going to say, is this a reasonable
3 hypothesis, and then help you give me feedback to see if
4 this is a way to think about it.

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

14 Is that a reasonable hypothesis? Is that how
15 to best put this information together that in some patients
16 with underlying mucosal injury, caffeine could then have an
17 exacerbating effect?

18 DR. ERENBERG: I think that is a potential.
19 There is no data to substantiate it. One of the proposed
20 etiologies for necrotizing enterocolitis is hyperosmolar
21 ether formula or medications. Caffeine is hypo-osmolar,
22 compared to theophylline, which is hyperosmolar. If the
23 mucosal injury has already occurred then I think that is a
24 potential. Does the oral administration of caffeine cause
25 the mucosal injury, which would then go on, I don't think

78

1 is.

2 Unfortunately, infants with necrotizing
3 enterocolitis, before they are clinically recognized, may
4 present with apnea, without the abdominal distention and
5 other signs and symptoms of necrotizing enterocolitis. So,
6 therefore, the potential does exist that the clinician may
7 initiate methylxanthine therapy prior to the full-blown
8 picture or the ability to make the diagnosis of necrotizing
9 enterocolitis.

10 DR. OSBORNE: Thank you. I'm just trying to
11 address how we're going to put together a warning.

12 DR. LI: Yes. Maybe the last question for
13 right now. Stan?

14 DR. SZEFLER: Just one question because I'm not
15 sure if we're going to be able to come back to Roxane
16 later.

17 DR. LI: We can.

18 DR. SZEFLER: Okay, good.

19 The quick question is, in the documentation
20 that we have, I didn't get a feel for what the study sites
21 were like. Were these clinical research sites that
22 participated in this study, or were they clinical sites
23 that had the opportunity to participate in research? What
24 was the distribution of the nine sites?

25 DR. ERENBERG: There were nine study sites.

79

1 All of them were affiliated with universities. None of
2 them had CRC's per se, but all had experience in clinical
3 research, and Dr. Wynne could list her study sites.

4 DR. WYNNE: I would like to refer you to your
5 briefing document. I don't know if you all have it or not.
6 It's actually page 8-19. I'll just go through these for
7 you very briefly.

8 The University of Kansas enrolled 3 patients.
9 Cooper Hospital enrolled 5. Medical College of Virginia,
10 14. Denver, Colorado Children's Hospital, 19. Women and
11 Infants Hospital of Rhode Island, 5. Oakwood Hospital, 3.
12 University of Texas Health Science Center, 12. University
13 of California, Irvine Medical Center, 17. And 4 at the
14 Carolinas Medical Center.

15 So, you can see there are three that enrolled
16 quite a few patients. The others enrolled a few.

17 DR. LI: I'd like to thank the sponsor for
18 their very forthright answers to the questions from the
19 committee.

20 Let's take a 15 minute break and we'll have the
21 FDA presentation at 10:15.

22 (Recess.)

23 DR. LI: Ladies and gentlemen, the sponsor and
24 Dr. Wynne have asked for just one or two minutes to have
25 the opportunity to answer some of the questions that came

80

1 up earlier this morning. They have been able to find some
2 additional information that might be helpful to us.

3 Dr. Wynne, before Dr. Pina's presentation, if
4 you would go ahead.

5 DR. WYNNE: Yes, thank you very much. One of
6 the questions that you raised earlier was, why were these
7 approximate 1,000 patients excluded from entry into the
8 trial? I do have that information for you.

9 The exact number of patients screened was
10 1,029, 87 of whom were enrolled. The patients excluded
11 then were 942. Reasons for exclusion were, 482 patients
12 did not meet the age requirement or apnea event
13 requirement. 248 were already receiving theophylline or
14 they were on ventilation. Parents refused or were unable
15 to give consent, 63 of the patients. Underlying disease,
16 CNS, cardiovascular, sepsis, 55. Death, 52; patient
17 transferred, 17; other, 13; and then there were 12 patients
18 with no reason stated. I think that will give you an
19 overview of the approximate 1,000 patients that were
20 screened.

21 A second question that came up earlier was the
22 incidence of PDA during the study. Actually there were two
23 reports -- I'm talking now about the double-blind -- in the
24 caffeine group and two in the placebo group. An additional
25 2 patients that were transferred from the placebo into the

81

1 caffeine open-label also were reported to have PDA.

2 I hope that answers the questions that you
3 asked earlier. Thank you very much.

4 DR. LI: Thank you, Dr. Wynne.

5 I'd now like to invite Dr. Pina, who is the FDA
6 medical reviewer, to give the FDA's presentation. Dr.
7 Pina.

8 DR. PINA: Good morning. I am Miriam Pina, the
9 medical reviewer from the Division of Pulmonary Drug
10 Products. I thank the members of the pulmonary committee
11 and consultants for being here today to discuss this
12 important drug, caffeine citrate injection, for the
13 treatment of apnea of prematurity.

14 I also would like to publicly acknowledge the
15 hard work of the other members of my review team: Dr. Jim
16 Gebert, statistical reviewer; Vibhakar Shah, our chemistry
17 reviewer; Misoon Chun from pharmacology-toxicology; Albert
18 Chen from biopharmacology; and our tireless project
19 manager, Lindsay Cobbs. Thank you very much for your help.

20 We heard a detailed presentation of what apnea
21 of prematurity is all about, and the data that the studies
22 with caffeine citrate have generated from the sponsor.
23 Thus, I would like to focus only on some issues that are
24 either complementary for the understanding of the data or
25 of concern from the regulatory point of view regarding the

82

1 study design and the results of trial OPR-001, and from the
2 data available from the literature. I will end my
3 presentation with a summary of the issues for discussion.

4 I will start with trial OPR-001.

5 As the sponsor explained, trial OPR-001 was a
6 multi-center randomized double-blind placebo-controlled
7 parallel study with an open-label rescue phase.

8 The target population was premature babies
9 between 28 and less than 33 weeks of gestational age, with
10 at least 6 apnea episodes in 24 hours or less. Apnea for
11 this trial was defined as a respiratory pause of 20 seconds
12 or more, with or without bradycardia. These events were to
13 be observed and recorded by the attending personnel.

14 As presented by Dr. Wynne, patients with
15 underlying causes of apnea were excluded from the trial. I
16 would like to explain here that the 2 patients in the
17 placebo group who were excluded because they were not
18 treated, they did not receive any treatment because they
19 were advanced from CPAP to mechanical ventilation before
20 they even started the treatment.

21 During the double-blind phase, the patients
22 received either caffeine citrate or an equivalent volume of
23 placebo. A patient could be rescued with open-label
24 caffeine citrate if the number of apnea events did not
25 remain less than 50 percent of the baseline rate and the

83

1 investigator felt that continuing double-blind treatment
2 placed the patient at unacceptable risk.

3 The original maximum duration of treatment was
4 10 days, but the treatment period was extended to 12 days
5 in the last amendment, and only 16 patients were enrolled
6 under this provision. As Dr. Wynne explained, only 4
7 patients completed the treatment to 12 days.

8 I should point out here that the primary
9 endpoint defined in the original protocol was the success
10 rate defined as having a 50 percent reduction of the
11 baseline number of episodes of apnea during hours 24 to 48
12 after the double-blind loading dose. But this primary
13 endpoint was revised, was amended to apnea rate on day 2
14 during amendment number 5. So, the final version of the
15 protocol has the primary efficacy endpoint, apnea rate on
16 day 2.

17 As we will see shortly after, both definitions
18 failed to show a statistically significant difference
19 between the treatment groups.

20 Secondary analyses of the apnea rate, the
21 primary endpoint, were number one, the reduction in apnea
22 episodes by at least 50 percent and, number two, the
23 elimination of apnea events, that is, no apnea events
24 reported for that day by treatment day or by total number
25 of days reported without apnea.

84

1 The secondary efficacy endpoints were, for
2 those patients who continued to have apnea events, they
3 analyzed the lowest heart rate, lowest oxygen saturation,
4 and the duration of apnea events. A sample size of 78
5 patients was chosen based on the original primary endpoint.
6 The sponsor assumed that a 50 percent reduction of apnea
7 events during hours 24 to 48 after the double-blind loading
8 dose would be seen in 70 percent of the caffeine-treated
9 patients and only 20 percent or less in the placebo-treated
10 patients.

11 The difference in success rates was lower than
12 the sponsor had predicted. It was about 20 percent, as we
13 have seen. According to our statistical reviewer's
14 calculations, the study was estimated to have only 44
15 percent power to pick up the observed difference in success
16 rates.

17 Before discussing the study results, let's look
18 at the number of patients receiving double-blind therapy by
19 treatment day as a result of the design of the study.
20 Let's remember that the study allowed for patients to be
21 transferred to open-label caffeine treatment if the
22 investigator considered it necessary.

23 From this light we note the marked reduction in
24 sample size in both groups after treatment day number 2.
25 Here we have study days baseline to day 10, and the number

85

1 of patients who completed that study day on baseline we
2 have 100 percent of patients in the caffeine and in the
3 placebo group. As you see, there is almost half of the
4 patients by the end of day number 2.

5 The number of patients who were transferred to
6 open-label caffeine or were permanently discontinued from
7 the trial was similar in the caffeine and in the placebo
8 groups, 53 percent in the caffeine group versus 65 percent
9 in the placebo group.

10 As explained before, the protocol-specified
11 primary efficacy endpoint was apnea rate on day 2. The
12 sponsor did not submit this analysis. Therefore, the
13 statistical reviewer performed the primary analysis of the
14 primary protocol-specified efficacy endpoint. For this
15 analysis he used scaling of the duration of baseline and of
16 the study days to 24 hours and the last value carried over
17 method.

18 Here we have the number of apneas in 24 hours
19 and the results on day 2. As we can see, the caffeine
20 group has an apnea rate of about 4.95 apneas in 24 hours.
21 In the placebo group, the apnea rate was 7.2. The
22 difference was not statistically significant.

23 The sponsor analyzed the apnea rate on day 2 by
24 identifying those patients who had a reduction in apnea
25 events equal to or greater than 50 percent of the baseline

86

1 apnea rate. In this chart we have the percent of patients
2 and the results on day 2.

3 From the total of patients, about 76 percent of
4 the patients had a reduction of 50 percent or more of the
5 apnea rates on day 2, and in the placebo group, 57 percent
6 of the patients met this endpoint on day 2. The difference
7 was not statistically significant.

8 Analyzing the 50 percent reduction of apnea
9 events by treatment days, we have here the percent of
10 patients and the number of treatment days. Each treatment
11 day up to day number 10. We see that on day 2 there was no
12 statistically significant difference, but the difference
13 was significant for days 4, 5, 7, 8, 9 and 10.

14 We should note, however, that this is a post
15 hoc analysis. In addition, it carries forward the apnea
16 rate value of 10 on the last day of double-blind treatment
17 for those patients who were transferred to open-label
18 caffeine or were discontinued from the trial.

19 I would like to explain that 10 patients in the
20 caffeine group, that is, 28 percent, and 6 patients in the
21 placebo group, 25 percent, had a reduction of 50 percent in
22 their apnea rate the day that they were transferred to
23 open-label caffeine or that they were discontinued from the
24 trial.

25 There were several reasons why they were

87

1 transferred from the trial. These were frequent
2 bradycardic events without apnea, persistent apnea events,
3 although the rate was still less than 50 percent of the
4 baseline period, or the patient was referred to another
5 hospital.

6 Keeping in mind that these are post hoc
7 analyses, we wanted to know how many patients in the
8 double-blind phase maintain the beneficial effect of the
9 drug until the end of the study period, how many patients
10 that had a 50 percent reduction of their apnea events, once
11 they reached the endpoint, how many maintained that effect.
12 Here is the graphic.

13 Here we have percent of patients. This y axis
14 uses as a denominator only the patients who achieved at
15 least once this endpoint. Here we have those patients who
16 maintained the drug effect, and those who did not maintain
17 the effect. That is, some days they had a reduction of 50
18 percent and some others did not reach this endpoint.

19 These two columns do not add to 100 percent
20 because we excluded those patients who reached this
21 endpoint but were transferred to open-label or were
22 discontinued from the trial.

23 The difference between the patients who
24 maintained the effect and those who did not plus those who
25 were discontinued is statistically significant.

88

1 Another way of analyzing the apnea rate was the
2 percent of patients with zero apnea events reported for 24-
3 hour periods. This table shows the percentage of patients
4 with no apnea events at each treatment day. Here we have
5 on the y axis the percent of patients who reached this
6 endpoint on treatment day number 1 up to day number 10. As
7 we can see, those with the asterisks, the difference was
8 statistically significant in favor of caffeine.

9 I would like to point out at this point that on
10 day 2 the difference was statistically significant. Day 2
11 was the day chosen by the sponsor to measure the primary
12 endpoint.

13 This graphic shows the analysis of the number
14 of patients by the total number of days spent without
15 apneas. That is, on the y axis we have how many patients
16 remained apnea-free for how many days. Here we don't have
17 treatment days, but total number of days with no apneas.

18 I would like to focus your attention on these
19 days, where about 10 patients in the caffeine group remain
20 apnea-free for 8 or more days. No patients in the placebo
21 group remained apnea-free for this long.

22 To answer one of Dr. Rothstein's questions,
23 regarding once the patients remained with no apneas for 24
24 hours, how many patients remained without apnea for the
25 rest of the period, I should say that from these 10

89

1 patients, 6 of them remained apnea-free continuously from
2 the first time they reached that endpoint.

3 We've also wanted to see how many patients
4 remained apnea-free once they reached that endpoint, and
5 that's what I said before. On the y axis we have those
6 patients who at least once -- is the percent of patients
7 who at least once presented no apneas for 24 hours, and how
8 many of those were able to maintain that effect until the
9 end of the study period.

10 Again, we see at 29 percent of the patients in
11 the caffeine group maintained that effect versus 1 patient,
12 which is 7.6 percent, in the placebo group. This patient,
13 1 patient in the placebo group, achieved this endpoint on
14 the last 2 days of the study period. Really, no patient
15 was in the placebo group apnea-free for more than 5 days,
16 and neither one in a row. There were some days yes and
17 some days no.

18 This table shows some of the characteristics
19 that you were asking before of those patients in the
20 caffeine group who met different efficacy endpoints, and
21 those who never met any of the efficacy endpoints. Here we
22 have some of the characteristics, gestational age, what was
23 the baseline apnea rate, the weight at entry, and the
24 caffeine plasma levels.

25 For those patients, 12, who had a reduction of

90

1 50 percent for more than 7 days, who had 0 apneas for more
2 than 7 days, and this is the failure group who never had a
3 greater than 50 percent reduction of their apnea rates. We
4 have 9 patients here.

5 As you can see, there is not a particular
6 subset of characteristics other than maybe weight at entry,
7 where those patients who had no apneas for greater than 7
8 days after the treatment was started were slightly heavier
9 than the other two groups.

10 Other secondary efficacy endpoints were lowest
11 heart rate associated with apneas. The mean values between
12 the caffeine and placebo groups were similar and not
13 statistically significantly different. They were between
14 67 to 78 beats per minute.

15 The lowest oxygen saturation associated with
16 apneas. The values were similar in both groups, 78 to 84
17 in the caffeine group and 77 to 87 in the placebo group.

18 The duration of apnea events was another
19 secondary efficacy endpoint. The durations were recorded
20 by the attending nurse once the apnea alarm went off.
21 Because the nurse was not always at bedside at the time the
22 apnea alarm went off, the manner of recording of the
23 duration of the apnea events can be considered unreliable.

24 The sponsor presented the duration of the apnea
25 events by day for the double-blind and the open-label

91

1 treatment periods for each treatment group, but did not
2 provide the analysis of the data for this endpoint.

3 According to the statistical reviewer's
4 calculations, the overall analysis of the summarization of
5 duration of the apnea events submitted by the sponsor did
6 not show a significant effect of caffeine on the duration
7 of apnea events.

8 From the safety point of view, the sponsor has
9 already presented a detailed description of the results in
10 OPR-001 trial. I would like to focus my discussion on two
11 issues only: some main adverse events and deaths.

12 The assessment of adverse events between the
13 treatment groups in this trial was difficult. Firstly, the
14 complex design of the trial allowed some patients in the
15 placebo group to be exposed to open-label caffeine at
16 different times, and secondly, the high frequency of
17 complications encountered in this population did not help
18 in many cases.

19 We tried to assess the main adverse events in
20 several ways to overcome some of these difficulties. I
21 will present to you the data by analyzing the incidence of
22 adverse events by exposure to caffeine and by
23 randomization.

24 The first analysis assessed the incidence of
25 adverse events by exposure to caffeine. The exposed group

92

1 includes all the patients randomized to the caffeine group
2 plus those patients in the placebo group who were
3 transferred to open-label caffeine. The not exposed group
4 includes the patients in the placebo group who were not
5 transferred to the open-label caffeine.

6 As you can see, no significant differences were
7 noted in the incidence of adverse events analyzed between
8 the treatment groups. It is clear, however, that the small
9 sample size could have made it difficult to pick up
10 significant differences in safety parameters, had there
11 been any. However, it is of note the numerical increase of
12 necrotizing enterocolitis, 5 versus 1; sepsis, 8 patients
13 versus 0; and death, 3 patients versus 0.

14 Another analysis studied the adverse events
15 that occurred to patients by their randomization,
16 regardless of their exposure to caffeine. We did this
17 analysis to overcome the time factor, where some patients
18 in the placebo group were transferred to open-label
19 caffeine quite early, with the possibility that they did
20 not have enough time to develop some complications that may
21 have occurred had they been allowed to continue in the same
22 treatment group for a longer time period. Again, no
23 significant differences were noted between the treatment
24 groups.

25 About mortality, there were 3 deaths reported

93

1 and all of them had been exposed to caffeine. Again, very
2 small numbers are difficult to interpret the meaning of
3 this.

4 I would like to discuss the data in the
5 literature for efficacy. The database consisted of 27
6 articles to provide data on efficacy, and we have 59
7 articles to provide data on safety. We have more safety
8 articles than the sponsor reported because we did our own
9 search.

10 From the efficacy point of view, 10 controlled
11 and 17 uncontrolled trials were submitted and reviewed. In
12 our review, we noted that no study was placebo-controlled,
13 all were open-label, and several different clinical
14 endpoints were studied. Except for one study, there were
15 no follow-up data after caffeine was discontinued.

16 However, all the investigators concluded that
17 caffeine improved the patients' apnea endpoints, when
18 compared to the patients' own baseline. However, we should
19 note here that apnea of prematurity tends to improve
20 simultaneously over time.

21 At this point I would like to bring your
22 attention to a particular study conducted by Murat, et al.,
23 in 1991. This is perhaps the best designed trial that
24 supports efficacy of caffeine in the literature. 18
25 premature infants were studied in this prospective

94

1 randomized parallel controlled trial. The dosage regimen
2 was similar to that used in trial OPR-001. Its primary
3 endpoint was apnea index on days 1, 5 and 15. Apnea index
4 was defined as the average number of apneic events per 100
5 minutes, obtained from the total number of events recorded
6 within a 24-hour period.

7 24-hour cardiorespiratory recordings were
8 performed to monitor apnea events on days 1, 5, 15 and on
9 day 8 after the therapy was discontinued.

10 The study by Murat, et al. showed a
11 statistically significant improvement of the apnea index in
12 the treated group on day 1 and day 5. I will show you
13 later the numbers obtained.

14 A substantial dropout of patients in the
15 control group made the analysis not significant at day 15.
16 This study also showed that apnea did not recur on day 8
17 after the discontinuation of caffeine.

18 Here we have the results on day 1, 5, and 15.
19 The apnea index was .24 versus .74 in the untreated
20 controls, and on day 5 we have .11 versus .57. This apnea
21 index of .24 would be an equivalent of about 3 apneas in 24
22 hours versus 10.6 apneas in 24 hours in the control group.
23 and the difference was statistically significant.

24 On day 5 we have an apnea rate of about 1.6 in
25 the caffeine group versus about 8 apneas in 24 hours in the

95

1 control group. Again, the difference was statistically
2 significant.

3 On day 15 the control group from 9 patients had
4 dropped to 3 patients only. The others had to be treated
5 with caffeine or were intubated. This apnea index is about
6 .5 apnea rate in 24 hours, and this is about 1.7, and the
7 difference was not statistically significant.

8 Regarding safety, the database from published
9 clinical trials and from our own search included over 800
10 premature infants exposed to caffeine. Instead of going
11 over the data on safety that the sponsor has already
12 presented, I would like to emphasize two particular issues.
13 The association of methylxanthines with the incidence of
14 necrotizing enterocolitis and the information currently
15 available on drug-drug interactions.

16 In general, the adverse events reported in the
17 literature for caffeine are similar to those reported for
18 trial OPR-001, and when caffeine was compared to
19 theophylline, the adverse events were usually less
20 frequent.

21 Because of its morbidity and high mortality,
22 and the question raised in the literature regarding its
23 association with the use of methylxanthines, I would like
24 now to focus your attention on necrotizing enterocolitis.

25 As the sponsor has explained, NEC is a major

96

1 cause of morbidity and mortality in premature infants. Its
2 reported incidence ranges from 2 to about 15 percent, with
3 the highest incidence seen in the lowest birth weight
4 groups.

5 The reported mortality varies from 20 to 50
6 percent according to other medical factors involved.
7 Factors like the use of umbilical artery catheters, some
8 pharmacological agents like aminophylline, theophylline,
9 caffeine and vitamin E, in high density formulas have all
10 been implicated with the incidence of NEC and infant
11 survival.

12 Some of the issues obtained from the literature
13 are as follows. Robinson, et al., in 1980 was one of the
14 first ones to suggest the association of xanthine treatment
15 with the development of NEC. The others published three
16 cases of NEC in premature infants after treatment with
17 aminophylline, and postulated that in these cases NEC was
18 related to bacteria overgrowth due to decreased GI motility
19 which followed the use of xanthines.

20 Grosfeld, et al., in 1983 studied the effect of
21 aminophylline in an experimental bowel ischemia model and
22 suggested that aminophylline had an adverse effect in
23 animals with ischemic bowel insults.

24 After these reports, several other studies
25 tried to address this question. In most cases theophylline

97

1 was the xanthine studied, probably because theophylline was
2 the most widely used methylxanthine.

3 A retrospective analysis by Davis, et al., in
4 1986 demonstrated that 124 infants treated with
5 theophylline had a similar incidence of NEC as did 151
6 infants who were not treated with theophylline.

7 In other papers, theophylline was compared to
8 caffeine. Bairam, et al., in 1986 studied the effect of
9 caffeine in 10 babies compared to those of 10 babies on
10 theophylline. In this trial, 4 infants in the theophylline
11 group were stopped for GI intolerance. 2 of them were
12 reported to have developed signs of NEC.

13 The caffeine group did not develop significant
14 GI symptoms. These results were not compared to a placebo-
15 or untreated arm for a background incidence of NEC.

16 Larsen, et al., in 1995 reported no differences
17 in the incidents of necrotizing enterocolitis between the
18 caffeine group -- 82 patients were treated with caffeine --
19 and theophylline, 98 patients. However, the actual
20 incidence of NEC in each group was not published.

21 I will close this section by stating that
22 overall the findings in the literature are not conclusive.
23 Whether the exposure to methylxanthines in general and to
24 caffeine in particular is associated with an increased
25 incidence of NEC, nor if there is a subset of patients at

98

1 higher risk of developing this disease if exposed to
2 caffeine. One of my personal goals for today is to hear
3 your opinion regarding this issue.

4 The second issue on safety derived from the
5 literature is the drug interactions with caffeine. The
6 biopharmacology data base consisted of 71 studies, mainly
7 from adult healthy volunteers or patients. Only 1
8 pediatric patient was submitted for a discussion of drug-
9 drug interactions. This paper reported three cases of
10 increased clearance of caffeine within co-administration of
11 phenobarbital.

12 The data provided very limited information on
13 caffeine dose adjustments that may be needed following the
14 coadministration of drugs prescribed to preterm neonates.
15 Lower or higher doses may be needed following
16 coadministration of drugs like cimetidine, ketoconazole,
17 and phenobarbital. But the manager of the adjustment is
18 not yet known.

19 In summary, study OPR-001 is the only
20 randomized double-blind placebo-controlled trial in which
21 caffeine was studied for the treatment of apnea of
22 prematurity. It failed to show a statistically significant
23 difference in the primary endpoint apnea rate on day 2
24 after the loading dose in favor of caffeine. But it showed
25 a statistically significant effect in reducing or

99

1 eliminating apnea events in the target population. These
2 calculations, however, were not protocol-specified.

3 Most trials in the literature were small and
4 not adequate and well-controlled. However, caffeine was
5 consistently shown to improve the patients' endpoint
6 studied when compared to the patients on baseline.

7 Based on the results from study OPR-001 and the
8 data available in the literature, do you consider that
9 there is enough evidence to support efficacy of caffeine
10 citrate for the treatment of apnea of prematurity? That's
11 our question.

12 Regarding safety, study OPR-001 had a complex
13 design with a high rate of dropouts early in the study that
14 made difficult the interpretation of the data. It showed
15 no clinically significant differences in adverse events by
16 body system between caffeine and placebo-treated patients.

17 The numerical increase in the incidence of
18 necrotizing enterocolitis found in the caffeine-treated
19 group is of concern, admitting that the association of
20 methylxanthines with an increased risk of NEC has
21 previously been questioned in the literature.

22 The data in the literature were consistent with
23 the findings in the clinical trial.

24 Regarding the association of NEC with the use
25 of xanthines, the findings are not conclusive in either

100

1 direction.

2 And regarding the drug-drug interactions, no
3 data are available to adjust caffeine dose with the
4 coadministration of other drugs.

5 We would like to hear the opinion of the panel
6 whether the effects shown to you today constitute
7 sufficient evidence of the safety of caffeine citrate for
8 the treatment of apnea of prematurity.

9 Thank you very much.

10 DR. LI: Thank you, Dr. Pina.

11 I'd like to ask the committee if they have any
12 questions for Dr. Pina.

13 DR. CRIM: I have a question relating to both
14 the efficacy and the safety from the literature review. I
15 think it would help in terms of my question on the efficacy
16 if you can pull back up your slide 36 that gave the results
17 of that Murat study.

18 The question I had was in terms of the number
19 or frequency in which patients would get better over time
20 anyway. My question as far as this efficacy is, it looks
21 like there's a decrease in this apnea index for both groups
22 over time. Although you don't have either standard error
23 or standard deviation data for day 5, just looking at the
24 control group, is it possible to glean from that study as
25 to whether the difference between day 1 and day 5 for the

101

1 control group, or between day 5 and day 15 is improving
2 statistically within groups?

3 DR. PINA: Yes, they did check that in the
4 study and it was statistically significant from here to
5 here.

6 DR. CRIM: And what about for the control,
7 between the .74 and the .57, and .57 to .12 for the
8 control? That statistically improved?

9 DR. PINA: It was, yes.

10 DR. CRIM: And then the other thing regarding
11 the safety, which I guess you have on slide 41, was the
12 study by Davis that saw similar incidents of NEC between
13 the theophylline-treated and the non-theophylline infants.

14 I guess my question for that, was there any
15 statement in that study as to the duration of exposure to
16 theophylline in 124 infants? In other words, was this any
17 exposure, or 10-day exposure, or 2-week exposure and an
18 effect not being found, or was this, for instance, 1 day of
19 exposure in the theophylline?

20 DR. PINA: I don't know if the sponsor has that
21 article with you, but this is a retrospective study. This
22 was a study for something else. So, inside of the study
23 they looked for the patients who were treated with
24 theophylline and those who were not treated with
25 theophylline with apnea events.

102

1 I'm not sure if they evaluated duration of
2 treatment of theophylline.

3 DR. SZEFLER: I'd like to congratulate you and
4 also Roxane for some excellent presentations and
5 interaction on the evaluation of the data.

6 The one question I had was, these primary
7 efficacy variables are very hard to choose and they are so
8 important. In the development of this protocol and the FDA
9 involvement, how much discussion was there around the
10 primary efficacy variable?

11 Is the Murat study the study that was kind of
12 counted on for these estimates of 70 percent efficacy and
13 20 percent placebo? Did you have general agreement or
14 disagreement on the primary efficacy variable?

15 DR. PINA: I know from the sponsor's point of
16 view, nobody there was at the preliminary discussion of the
17 original protocol. From our side, I was not here when this
18 was started.

19 DR. SZEFLER: Because I believe these start
20 from the IND phase.

21 DR. PINA: Yes. We had discussed with them
22 from the beginning the design of this protocol and we went
23 through a lot of arrangements trying to find the ideal
24 design for this trial.

25 I think the sponsor has something to add.

103

1 DR. LI: Does the sponsor want to make a brief
2 comment?

3 DR. ERENBURG: I guess I have the historical
4 memory because I was at all of those. You are absolutely
5 correct. We did go through what we could glean from the
6 literature, looked at the various endpoints, apnea density,
7 number of apneic events. We tried to come to a conclusion
8 as to what would be reasonable estimates, and we came to
9 the protocol as it is designed here.

10 DR. PINA: The original protocol-specified
11 primary endpoint was the 50 percent reduction, and then it
12 was changed to apnea rate on day 2.

13 What I can say is that even no apneas on day 2
14 are all different analyses of the same event, which is the
15 number of apnea events on day 2 and just a 50 percent
16 reduction or no apneas, or apnea rate per se on day 2.
17 They are just different analyses of the same clinical
18 endpoint.

19 DR. LI: Dr. Goldsmith?

20 DR. GOLDSMITH: If we look at safety as well as
21 drug-drug interaction, I want to come back to a comment by
22 Dr. Osborne before looking at potential causes of
23 necrotizing enterocolitis. If we say that there is mucosal
24 injury and ischemia, and then the potential for something
25 that might cause a change in blood flow, some drug that

104

1 might cause a change in blood flow, and then in addition a
2 bacterial aspect to this or an invasion of an organism,
3 then I'm concerned about the interaction between
4 methylxanthines and any H2 blockers, any H2 antagonists,
5 where we change the flora in the gastrointestinal system.
6 So, the combination of caffeine and cimetidine, or any of
7 the other H2 blockers would be very important.

8 Is there any information with regards to NEC on
9 that combination drug-drug interaction or safety that you
10 know about or that the sponsor knows about?

11 DR. PINA: Not from our point of view.

12 DR. WYNNE: I think I'm going to address this
13 question to Dr. Mosdell, who just returned. Could you
14 repeat the question please?

15 DR. GOLDSMITH: The question was, is there any
16 information regarding incidence of NEC in combination with
17 H2 blockers, methylxanthines with H2 blockers, since the H2
18 blockers may change the bacterial flora by changing the pH
19 of the gastrointestinal tract?

20 DR. MOSDELL: The primary focus that we did in
21 our literature search involved caffeine and its association
22 with NEC, and also an additional analysis that looked at
23 theophylline and its association with NEC. In none of
24 those trials was it mentioned that histamine blockers could
25 be associated with an increased incidence of NEC, or the

105

1 combination of the two increased the incidence of NEC.
2 Although our literature search did not focus on histamine
3 blockers, so we may not have collected all the articles.

4 In specifically looking at caffeine or
5 theophylline literature, what I could read didn't have any
6 type of association that was described.

7 DR. HENDELES: To Dr. Pina. You commented on a
8 study on drug interactions involving premature infants, but
9 I don't recall, what were the drugs and what were the
10 findings of that study?

11 DR. PINA: There was only one paper submitted
12 addressing drug interactions. One paper in premature
13 infants. This paper was just a report of three cases of
14 phenobarbital interaction with caffeine, where they didn't
15 find caffeine levels. They had to increase the caffeine
16 dose.

17 DR. HENDELES: The reason why I bring that up
18 is there were all these other papers on interactions in
19 adults. I don't see the relationship. If the premature
20 infant lacks cytochrome P450 1A2, which is the primary site
21 of interaction in adults, I don't know that any of those
22 have any relationship to this population at all.

23 DR. LI: Curt?

24 DR. SESSLER: The high rate of sepsis and NEC
25 in the caffeine-exposed patients may be concerning, but it

106

1 also might be related to other factors, including severity
2 of illness. Was there any severity adjustment considered
3 in that analysis or other comments you might make in that
4 regard?

5 DR. PINA: I'm sorry. Can you repeat your
6 question?

7 DR. HENDELES: I'm struck by the fact that the
8 sepsis rate was 13 percent in the caffeine-exposed patients
9 and 0 percent in the not exposed patients. But it may be
10 that the not exposed patients were less premature and had
11 less in the way of other medical illness.

12 Did you attempt to adjust for severity in any
13 way in your analysis?

14 DR. PINA: No, we didn't. What I see is that
15 sepsis could be one of these cases where you start having
16 apneas before the child is diagnosed with sepsis. We
17 thought that these patients could have the apnea and then
18 be enrolled in the trial and then start having the culture
19 positive or the other signs of sepsis.

20 It's one of these cases where it is also common
21 to find sepsis in this population and not in the study.

22 DR. SESSLER: If I may follow, I'd be
23 interested in any thoughts really from the sponsor or other
24 members of the committee or others in this room along those
25 lines as far as experience with severity of illness and its

107

1 relationship to this condition.

2 DR. ERENBURG: I think the neonatologists on
3 the panel would also agree that many infants are labeled as
4 suspect sepsis as soon as they develop any form of
5 symptomatology. We know of only one infant who was culture
6 proven. The question is, of these increased number, how
7 many of them were culture proven and how many of them were
8 suspect sepsis because of just development of apnea, were
9 treated for a very limited time period, and then
10 discontinued.

11 I think you're correct in that if a child does
12 become symptomatic, you automatically list certain
13 potential disease processes, and sepsis is always very
14 high.

15 The key is what happens 48 to 72 hours later
16 after you get your blood cultures back, what was the
17 response of the child to your therapeutic interventions.

18 DR. PINA: What is difficult to know here is
19 that in many cases even when the culture was not positive,
20 the patient did receive complete treatment with
21 antibiotics. I don't know what to say in those cases.

22 DR. SESSLER: May I follow up with further on
23 that?

24 DR. LI: Yes.

25 DR. SESSLER: Let me ask, perhaps to the

108

1 sponsor again, was any severity of illness scoring system
2 used to further define the population? Typically in adult
3 ICU populations you routinely will use an Apache score or
4 something akin to that.

5 DR. ERENBURG: No, we did not use that. The
6 only thing we used were the number of apneic spells at the
7 baseline for enrollment.

8 DR. LI: Dr. Goldsmith?

9 DR. GOLDSMITH: Throughout this discussion I
10 have not heard any distinguishing features of the apnea,
11 whether it was obstructive or central. In many of the
12 extremely premature infants, obstructive apnea can merely
13 be from body position in an incubator.

14 Were any differentiations made by the sponsor?
15 Did you see anything, Dr. Pina, in any of the literature
16 that would distinguish between the types of apnea as the
17 studies were done?

18 DR. PINA: Mainly they were addressed as
19 central apneas and that was the entry criteria.

20 DR. GOLDSMITH: Defined as what, and proven by
21 what?

22 DR. PINA: It was clinically assessed.

23 I think that you do have some pneumograms at
24 the beginning but we found so many technical problems that
25 at the end it was decided not to continue doing

109

1 pneumocardiogram recordings.

2 DR. LI: I think based on some of the
3 differences that were found between the treatment and the
4 placebo group, you came to the conclusion that the study
5 was under-powered. Do you have an estimate of how large a
6 study would have been necessary to increase the power of
7 the study from the 44 percent to about 80 percent or so?

8 DR. PINA: Do you want to answer that question?

9 DR. GEBERT: Jim Gebert, Division of
10 Biometrics. I did not do any calculations to see what size
11 study would have been needed to have, let's say, 80 percent
12 power.

13 DR. LI: Dr. Osborne.

14 DR. OSBORNE: Along those lines, just to make a
15 comment and then ask Dr. Pina if I'm off base or this is a
16 correct kind of comment. It strikes me that looking at
17 table 7, which is a very nice way of looking at the
18 patients and the caffeine group and the placebo group, this
19 is page 13 in the document that we got. I actually don't
20 know if you have something comparable for the sponsors.

21 It nicely goes through both the patients who
22 got caffeine and placebo, and as a reminder, the sample
23 size estimates had hoped for a 70 percent reduction, 70
24 percent of the patients having greater than 50 percent
25 reduction in the caffeine group, 20 percent having greater

110

1 than 50 percent in the placebo group.

2 Although we certainly don't see those numbers,
3 what I see are very consistent numbers for both the
4 caffeine group and the placebo group and they are
5 different. We've talked about two sources of problems that
6 might give us a type 2 error that we might not see a
7 difference that's really there: number one, the small
8 sample size, which has been alluded to, which I think is a
9 crucial factor, and number two, the possibility that in
10 fact the group that got caffeine was sicker.

11 One might think with the open-label modeling of
12 the design that we might actually be incorporating in the
13 caffeine group those that have a higher severity of illness
14 score. Certainly they were, at least by numbers, more
15 patients with sepsis.

16 Those kinds of problems in a small sample size
17 and perhaps a difference in severity in the two groups
18 would actually argue that we would not expect to see an
19 effect. So, I'm actually impressed that we've seen
20 consistent numbers in the two columns, even though it's not
21 quite 70 percent for caffeine, and it's certainly not 20 in
22 placebo. That's my comment.

23 The question is, is that on base? And if it is
24 on base, were any trend analyses done for the very nice
25 data that you did show, the post hoc analyses that did show

111

1 significant differences in the two groups and zero apneas
2 and so forth because the trend analyses might help with
3 putting together these day-by-day comparisons.

4 DR. PINA: Yes, your analysis of this is
5 correct except that the part of the sicker patients -- this
6 is analysis of-only the double-blind phase, where both
7 groups were exactly the same by randomization. When they
8 were transferred to open-label, the value of that day was
9 carried forward. So, it doesn't take into account what
10 happened to those transferred to open-label from the
11 placebo group.

12 DR. OSBORNE: Do you do trend analyses on the
13 data that you showed this morning or just pair-wise
14 comparison?

15 DR. PINA: No, we did not do that analysis.

16 DR. LI: Dr. Kelly?

17 DR. KELLY: It seems to me with the way the
18 study was designed that you can go to an open-label
19 caffeine that sort of a survival analysis would have been a
20 nice thing to look at in terms of separation of the groups.
21 Did you do Kaplan-Meier survival type analysis?

22 DR. PINA: I think we did try to do that but it
23 was not possible due to this design also. It's not one
24 event. The first time you have the event is the event on
25 each day so it was not possible to do that design. I think

112

1 Dr. Chinchilli will talk about that.

2 DR. CHINCHILLI: Yes, I did an analysis like
3 that which I'll present this afternoon.

4 DR. KELLY: Okay.

5 DR. LI: Dr. Osborne.

6 DR. OSBORNE: One more quick question. In all
7 fairness again, asking if I'm on base here. It sounds like
8 the FDA and the sponsor did agree on these endpoints, at
9 least at some point during the development of this study.
10 Although we might all look back and do it differently, this
11 was something that was agreed upon over several iterations
12 -- is that correct -- over the last few years.

13 DR. PINA: Yes, we did agree on the design.

14 DR. LI: And to follow up on Molly's point, the
15 conclusion of the presentation is that the agreed-upon
16 primary efficacy variables endpoints in fact were negative
17 in result in that there was no statistically significant
18 difference between the treatment group and the placebo on
19 those agreed-upon primary efficacy variables, although the
20 post hoc analysis of various sorts with multiple
21 comparisons did show certainly trends, perhaps even strong
22 trends toward support of the idea that the treatment was
23 more effective than the placebo.

24 Is that a fair characterization?

25 DR. PINA: Yes.

113

1 DR. SZEFLER: Jim, just to follow up on that
2 line of thought, are there enough variables that you see
3 because if you take enough tests, you're going to find
4 something that works. But in here there seemed to be, at
5 least to me, a pretty large proportion of those kind of
6 numbers. Maybe you looked at larger numbers and this
7 represents a small population of those numbers. Are you
8 pretty convinced that clinically meaningful parameters,
9 that a large proportion of those numbers seem to go in the
10 right direction?

11 DR. PINA: Well, I hope Dr. Chinchilli will
12 talk about that analysis this afternoon, but that's one of
13 the puzzles we have that we are asking you to help us with.
14 If there's really enough evidence, can we extrapolate this
15 small number to a larger number of patients?

16 DR. LI: I think to follow up, I think that's
17 probably the crucial question. For example, with the
18 multiple comparisons that were performed, I see that
19 statistical analyses were done and generally p less than
20 0.05 was used as a cutoff for significance, arbitrarily of
21 course. Is there any reason to think, I guess based on
22 what Stan just said, whether we ought to be using a more
23 stringent criteria for statistical significance based on
24 the multiple comparisons that were done?

25 DR. PINA: Exactly. That's one of our questions.

114

1 Actually sample size is one of the things that
2 we asked the sponsor if they were sure the sample size was
3 calculated correctly because that was one of our concerns.
4 Is the sample size enough to show the efficacy of caffeine?
5 Now it's one of the things that see is a problem that maybe
6 is the problem.

7 DR. SZEFLER: I think your approach was
8 excellent. Where the lack was was in past data. That's
9 what Vern was asking the question about previously is what
10 literature do you have to make those kind of estimates
11 because I think what we need to hone down on is what was
12 that past literature and what are clinically meaningful
13 results that bear some risk. I'll kind of address those
14 comments later on.

15 DR. LI: Again, along those lines, how much
16 confidence do you have in the data from the Murat study
17 given the analysis is based on published information and I
18 take it you haven't had a chance to analyze the data and
19 certainly didn't proctor the study.

20 DR. PINA: I think that the Murat trial -- one
21 of them, it was an open-label, so it is a negative point.
22 But the recording of the apnea events not only observed by
23 the nurse, which is not always at the bedside -- that's I
24 think one of the deficiencies of the trial OPR-001. But in
25 the Murat trial, they did a 24-hour recording of apnea

115

1 events. So, that makes an objective evaluation of the
2 primary endpoint. So, even though it was an open-label, we
3 have a reasonable objective primary endpoint that we can
4 talk about.

5 DR. LI: As a follow-up, would it be feasible
6 currently to conduct a study using an apnea monitor rather
7 than counting apnea episodes on nurses' observations? Is
8 that practical and feasible or not?

9 DR. PINA: I would let the neonatologists, but
10 I think that it would have been the ideal if we had a
11 monitor with a recording capability.

12 DR. GOLDSMITH: Absolutely possible now because
13 most of the monitors have memory and you can go back for
14 several days. Probably to prove it, you'd have to hook
15 some sort of printout mechanism to it, but most of the
16 monitors in use now in NICU's all over this country have
17 memory that goes --

18 DR. LI: But was that technology not available
19 a year or two ago?

20 DR. GOLDSMITH: I think that has been changing
21 over the last five years or so. The other neonatologists
22 can comment, but as people have been upgrading their
23 monitoring systems, all the new ones now have memory.

24 DR. PINA: And many babies go home with these
25 type of monitors.

116

1 DR. GOLDSMITH: Which also has memory.

2 DR. PINA: Right.

3 DR. LI: Dr. Crim.

4 DR. CRIM: My question may have been addressed
5 when the sponsor presented their data. Maybe you can
6 comment upon it.

7 Just take an observation of the high dropout
8 rate over the course of the study such that, for instance,
9 by day 10 there were only 11 in the placebo group, and
10 recognizing that apparently there was a great deal of
11 reluctance of the various study centers to enroll patients
12 just because of the fact it appeared that they felt that
13 the caffeine was standard treatment.

14 Do you have a sense of -- and maybe it was
15 again presented. The subjects who were taken out of the
16 double-blind and put into an open-label -- I'm just
17 wondering whether or not there was some degree of bias on
18 the part of the investigators, since they were not
19 enthusiastic about giving their patients placebo in the
20 first place, to what degree they were inclined to take
21 their patients out of the blinded and put them in the open-
22 label in terms of the number of apnea events prior to them
23 being taken out of the blinded and placed into the open-
24 label. Were there any major differences between the
25 placebo --

117

1 DR. PINA: I think there was some kind of bias,
2 that investigators felt not sure that this patient is on
3 caffeine because in many cases I could see a drop of the
4 apnea rate below 50 percent of the baseline and this
5 patient was still transferred to open-label caffeine. So,
6 it at least tells me the investigator was blind but was not
7 sure that it was in the right drug, and so many patients
8 were transferred to open-label caffeine even though they
9 were responding, not meeting the endpoint criteria but some
10 of them were meeting a 50 percent reduction.

11 DR. CRIM: In even some of the placebos?

12 DR. PINA: In some of the placebos.

13 DR. LI: It shows the power of the placebo
14 design of the study, as Dr. Rothstein said I think.
15 Clearly the response in the placebo group was greater than
16 one might have anticipated.

17 Stan?

18 DR. SZEFLER: Just to follow up, I think you
19 have an important question. As I was going through the
20 literature, I was asking myself questions on the
21 pharmacodynamics because I hadn't had a chance to look
22 through all the articles, but what doesn't kind of come out
23 is the pharmacodynamics. My understanding, in talking to
24 several people, is the onset of effect is immediate, like
25 within minutes and certainly within hours. So, that time

118

1 of 24 hours would certainly be an area where you could
2 characterize whether somebody was a responder or
3 nonresponder.

4 I think that gets to be critical because in my
5 understanding of this population -- we'll probably talk
6 about it more later -- there are dramatic responders and
7 there are nonresponders and then there are responders who
8 then become nonresponders later on. This probably is the
9 most detailed observation period in terms of the effect of
10 the drug versus placebo that would be published I think.

11 DR. CRIM: I guess I'll say, along the same
12 lines, were there individuals who responded one day, didn't
13 respond the next, and then responded again a subsequent
14 day?

15 DR. SZEFLER: I think without that kind of
16 monitoring that was mentioned previously, the dynamics
17 wouldn't be as clearly elucidated as you would like.

18 DR. PINA: I think those who responded with no
19 apneas, those who responded well to the treatment,
20 maintained that effect, and 50 percent reduction, we see a
21 little more variability from day to day. I don't think we
22 have data as to onset of effect after the double-blind
23 loading dose.

24 There is one article in the literature where
25 two different doses of caffeine -- if you please look at

119

1 table 21 from the medical review of the NDA, table 21 and
2 the author is Scanlon, et al., 1992. Two different doses
3 of caffeine were studied versus theophylline, and the
4 higher dose of caffeine seemed to have had a better
5 response earlier than the lower dose, but at the end, the
6 effect was about the same in both groups. The higher dose
7 was similar to the theophylline group. The lower dose, it
8 seemed that it took a little longer to hit in, and then the
9 response was about the same in both groups. That's about
10 what we have regarding onset of effect.

11 DR. LI: Are there any other questions for Dr.
12 Pina?

13 (No response.)

14 DR. LI: Well, we remain ahead of schedule.
15 Let's break for lunch and return at 12:20. That will give
16 us an extra 10 minutes that we can recapture for this
17 afternoon. So, we'll plan to reconvene and begin promptly
18 at 12:20.

19 (Whereupon, at 11:30 a.m., the committee was
20 recessed, to reconvene at 12:20 p.m., this same day.)

120

AFTERNOON SESSION

(12:30 p.m.)

1 DR. LI: Welcome back. I'd like to reconvene
2 our meeting this afternoon.

3 We've taken the liberty of asking three of our
4 committee members to prepare some comments and thoughts for
5 us. So, we will begin our open discussion with
6 presentations, first from Dr. Rothstein. Then we've
7 already had a tantalizing preview from Dr. Chinchilli, and
8 he'll be able to fill us in on the meat of his presentation
9 secondly. Last but certainly not least, Dr. Szeffler will
10 give us some comments, perhaps give us the big picture on
11 the issues before us today.

12 I think we will also have time for questions or
13 discussions after each presentation.

14 So, Dr. Rothstein, do you have some comments
15 and some slides for us?

16 DR. ROTHSTEIN: Dr. LI asked me to make some
17 comments about the topic, and given some of the questions
18 today, as the expression goes at meetings, I just happen to
19 have a few slides with me.

20 (Laughter.)

21 DR. ROTHSTEIN: For those of you who spend most
22 of your life with the 3,000-week old infants --

23 (Laughter.)

121

1 DR. ROTHSTEIN: -- newborn encompasses a
2 tremendous range in terms of development and function, and
3 those infants who are born without the benefit of the last
4 trimester, when there are tremendous changes in organ
5 function and development, are working at a disadvantage.
6 But it is very difficult to lump a 28-weeker together with
7 a 37-weeker and come up with any sort of coherent
8 conclusions.

9 The questions were raised about incidence of
10 various diseases. The younger you are, the more likely
11 you're to have any of these afflictions: RDS, patent
12 ductus, enterocolitis, retrolental fibroplasia,
13 bronchopulmonary dysplasia, intraventricular hemorrhage.

14 As you can see, the numbers go up the younger the infant.
15 I've got a couple slides just on sort of
16 developmental pharmacokinetics and dynamics in terms of
17 looking at various parameters. This happens to be response
18 to the drug isoflurane, which most of you do not use but is
19 common in the operating room. I use it only to show that
20 -- these are term newborns here. These are 32-37-weekers.
21 These are less than 32-weekers. And there's not great data
22 on 27-, 26-, 28-weekers in terms of various drugs. But the
23 y axis can represent any drug effect you want, ED50, ED95.
24 There is going to be a markedly different response the
25 younger the infant.

122

1 This happens to show the development in term
2 infants of the neuromuscular junction. A term infant, when
3 born, does not have the same level of development that you
4 or I do.

5 In terms of variation of response, this happens
6 to be a response to curare, one of my favorite drugs, but
7 looking at the difference in response to a given dose to
8 produce a uniform endpoint, the variation response between
9 newborns is about three times what it is in older kids and
10 adults.

11 What causes some of these differences in
12 response? Drugs that are distributed through the
13 extracellular fluid space -- again, these are neonates.
14 These are term neonates, not even including some of the
15 micro-beings that we're discussing this morning and this
16 afternoon. But the extracellular fluid space is
17 significantly larger than it is in adults.

18 This is steady state distribution volume again
19 for curare which mirrors the extracellular fluid space.

20 People have raised the issue of renal function.
21 Again, GFR is about a third to a quarter of what it is in
22 adults in term newborns. I notice one of the exclusion
23 criteria for this study was a creatinine I believe greater
24 than 1.7. By the time your creatinine is 1 as a newborn,
25 you're essentially approaching renal failure in terms of

123

1 clearance.

2 Again, 24-hour excretion. Given the low GFR,
3 any drug that depends on renal excretion, there will be
4 accumulation in the young infants.

5 Variability of response. This happens to be
6 elimination half-lives of morphine in a population of
7 newborns, essentially almost a six-fold difference in half-
8 life. So, the differences that are being seen with
9 caffeine or theophylline are no different than seen with
10 any other drug. What it's going to depend on is a given
11 28-weeker or 32-weeker, what was the development of the
12 kidney?

13 And it can vary tremendously. All 32-weekers
14 are not the same. All volumes of distribution are not
15 equal in any given population of 31-weekers. Then you
16 start mixing and matching all these various factors, and
17 one comes up with some parameters with tremendously wide
18 standard deviations.

19 Let's skip these last two and we'll go to the
20 overheads.

21 One of the difficulties in the literature in
22 apnea of prematurity starts with the definition. Even this
23 morning, we heard two definitions of apnea of prematurity.
24 As one goes through the older literature, people introduce
25 concepts of short apnea, apnea defined as 10 seconds, 15

124

1 seconds, 20 seconds. So, there may be either different
2 processes going on that are being looked at or there's a
3 tremendously broad range of the problem that people have
4 examined.

5 The incidence of the problem, depending on what
6 series and how the study was conducted, in infants under
7 1,000 grams, the incidence of apnea, anywhere between 84 or
8 85 percent and 100 percent. In infants below 2,500 grams,
9 it's quoted as about 25 percent.

10 The peak frequency of apnea occurs by day 7.
11 It's influenced, as was mentioned this morning, by the
12 sleep state or the awake state that the child is in.
13 That's increased in REM states.

14 Another area that impacts on apnea is the
15 tremendously different responses to carbon dioxide and
16 hypoxia in the newborn compared to you and I.

17 This data is from the classic studies of Henry
18 Gaye Rigatto looking at responses to carbon dioxide
19 depending on gestational age. The 32-weeker, as the
20 inhaled CO₂ is increased, has less of a response than does
21 a 37-weeker. One would normally think that one doesn't
22 give CO₂ in the newborn unit, but any process that may
23 increase CO₂ in the newborn, whether it's fever, whether
24 it's hypoventilation from any cause, the response to that
25 is diminished the younger the infant.

125

1 Looking at it another way, at day of life 2
2 versus day of life 27, there is an increasing response to a
3 given stimulus with chronologic age. One of the problems
4 we're dealing with in looking at apnea is we saw in the
5 data that in the control population there is a decrease in
6 apnea from whenever time 0 is chosen for that infant, but
7 there will also be changes in response to hypoxia or
8 hypercarbia depending on the chronologic age of the child
9 and it will change as one goes farther into the study.

10 This is a composite looking at changes in
11 minute ventilation at 32 weeks versus 37 weeks versus CO2
12 and then again looking at it with advancing chronologic
13 age.

14 A significant difference in newborns compared
15 to us is the response to hypoxia. Hypoxemia in you or I is
16 a respiratory stimulant. Otherwise no one would have ever
17 climbed Mount Everest. They all would have dropped off
18 when they hit the first base camp. In a premature neonate,
19 there is initially an increase in ventilation in response
20 to decreased oxygen, and then hypoxia becomes a respiratory
21 depressant. This response, as you can see -- with
22 advancing chronologic age, there is an increase in
23 ventilation initially, but there is still then a decrease
24 in ventilation very shortly after the institution of a
25 hypoxic event.

126

1 The interaction of levels of oxygenation,
2 hypoxia with increase in carbon dioxide, again as one sees
3 with a 15 percent oxygen stimulus, there is a depression of
4 the CO2 response curve.

5 As we do the entire newborn physiology state in
6 10 minutes, this is looking at ventilatory responses in
7 various sleep states given a hypoxic challenge, and one can
8 see in the awake and REM state that hypoxia is a
9 respiratory depressant. It's only in non-REM state that
10 hypoxia is a respiratory stimulant.

11 Finally just to sum up the various treatments
12 that are available and that have been used to treat apnea,
13 one is just having someone standing there flicking the
14 infant's foot every time they slow down. One of the things
15 I did not hear today is with the apnea events, what was the
16 treatment of these events. Was stimulation instituted when
17 the saturation hit 70, when it hit 60, or when the heart
18 rate hit 90 or 80? That I'm not clear about.

19 We've heard a lot about the drug treatment.

20 The use of continuous positive airway pressure
21 as a respiratory stimulant is used in many units.

22 In some cases increasing the inspired oxygen
23 has been used from room air up to 25 percent.

24 Finally, as one increases the hematocrit, one
25 can decrease the incidence of apnea in these kids.

127

1 In summary, what we're dealing with is a
2 problem where these kids have multiple medical problems,
3 multiple interventions, and whose organ development and
4 responses is changing, and possibly rapidly changing, over
5 a period of time that the infants are exposed to the drug.
6 Thank you.

7 DR. LI: Thank you very much, Dr. Rothstein.
8 What I'd like to do is maybe spend 5 or 10
9 minutes now to open the floor for questions from the
10 committee for Dr. Rothstein. There may be a lot of
11 questions. I'll probably just cut it off and move on to
12 Dr. Chinchilli since we will have time for general
13 discussion. But right now I'd like to open the floor for
14 questions.

15 Dr. Jobe.

16 DR. JOBE: Just as a comment, one of the issues
17 this morning was this issue of the placebo effect, the
18 large effect of the placebo. I think you hit on the
19 probable explanation for most of that, and that was other
20 interventions. Perhaps the sponsors could comment about
21 the use of higher oxygen or CPAP or other kinds of things
22 in these babies because clearly the physicians didn't just
23 give methylxanthines and then sit back and watch, but they
24 intervened. And those interventions are known to be
25 effective ways of decreasing the amount of apnea. So,

128

1 that's probably the placebo effect we're seeing.

2 DR. LI: If you could put up your last
3 overhead, Peter, maybe if I could ask the question in a
4 slightly different way. How effective are these other
5 nonpharmacologic modalities in treating neonatal apnea?

6 And another question is, just in general what
7 is the standard of care nowadays for this disorder?

8 DR. ROTHSTEIN: In answer to the first
9 question, someone can correct me, but I'm not sure that
10 there are any random controlled trials of any of the other
11 therapies. There are series with small numbers of
12 patients, three in one group, four in another, but there
13 are not numbers to make any coherent --

14 DR. LI: So, that would be true of the
15 stimulation, the CPAP, oxygen, and increasing the
16 hematocrit. Okay.

17 So, the second question, just in your view,
18 what is the standard of care? What is the range of the
19 standard of care for neonatal apnea?

20 DR. ROTHSTEIN: A lot. Since medicine is like
21 religion, it depends which church you believe and pray at,
22 there are some units that will use stimulation. We've
23 heard a lot about the use of methylxanthines in units.
24 People will use multiple modalities in the treatment. I
25 don't know of units that use a single modality in a pure

129

1 approach, that they will only use methylxanthines or they
2 will only use CPAP. Everyone is constantly kicking the
3 Isolettes to get the kids to breathe.

4 DR. LI: Do you have questions, Dr. Goldsmith?

5 DR. GOLDSMITH: I don't want to be a wet dish
6 rag here. We started with the premise, or at least it's
7 mentioned in the materials sent to the committee, that
8 apnea of prematurity causes brain injury. I don't think
9 that has ever been proven in modern neonatal intensive care
10 units.

11 When that statement was made, probably back in
12 the late 1960's and early 1970's, we didn't have continuous
13 monitoring of babies available, and babies often went for a
14 prolonged period of time with apnea and bradycardia before
15 it was recognized based on the nurse-to-patient care
16 ratios.

17 In modern intensive care units, babies would
18 not be allowed to go past 15 or 20 seconds, wherever you
19 set your alarm, and assuming appropriate care ratios, which
20 most states require in their neonatal intensive care units,
21 babies would respond just by stimulation.

22 So, the question is, what are we treating? And
23 if we are treating it, is it going to make a difference?

24 I assume, although that I didn't hear it this
25 morning, also that there was exclusion criteria of brain

130

1 injury such as an intraventricular hemorrhage prior to
2 putting these patients into the study.

3 However, without long-term follow-up for
4 injuries such as periventricular leukomalacia, which there
5 is a correlation between apnea of prematurity and PVL later
6 that takes two to three weeks to show up, how do we know
7 the babies who didn't respond didn't have a brain injury
8 associated with an injury that does not show up as an
9 intraventricular hemorrhage or something visible on day 1
10 or 2 or up to day 10 of life?

11 Peter, do you want to comment on those?

12 DR. ROTHSTEIN: There is so much going on in
13 the unit with these kids, and the endpoint may not be even
14 at 3 weeks, as you state. It may be much farther out.
15 Given the I spend most of my time working with kids, we
16 sometimes deal with endpoints that are 1 year or 10 years
17 out from the treatment, and until you start looking, one
18 doesn't know.

19 Case in point. And I know it's going farther
20 afield than this. Back in the 1970's and 1980's, the
21 treatment for transposition of the great vessels was
22 something called a mustard procedure. It was only on 10-
23 year follow-up that people found out that none of these
24 kids were in sinus rhythm 10 years out and all required
25 pacemakers.

131

1 So, we're looking at endpoints that need to be
2 defined and may not even be known at the present time. I
3 think that, if anything, what's coming out today is there
4 is a tremendous opportunity for long-term, well-constructed
5 trials to try to look at some of these issues, but I can't
6 tell you where one starts and stops.

7 I certainly agree with you. I do not accept,
8 you know, if you don't treat this, the kid is going be
9 brain damaged, which comes up a lot. I don't accept that
10 premise.

11 DR. LI: Molly.

12 DR. OSBORNE: Another obvious question. We're
13 going to be asked to recommend the dosing period and
14 whether it be restricted. That's one of our questions.

15 But just to ask you in terms of a clinical
16 comment, once people are put on methylxanthines, can you
17 comment on duration of treatment just for our edification?

18 DR. ROTHSTEIN: To go way out on the limb, I
19 suspect the treatment and treatment times will bear no
20 relationship to the kinetics or the dynamics of the drug.
21 There is really no data looking at higher dosing, looking
22 at kinetics, looking at the questions that were asked this
23 morning. Is there a correlation between blood
24 concentration and effect? Is there an ED50 or an ED95 at a
25 given blood concentration? I suspect that will not be

132

1 looked at. I suspect that very few units have ever looked
2 at renal excretion or maturation of renal function versus
3 the dose of drug they're giving.

4 DR. OSBORNE: So, there's nothing like the
5 dose-response curve that we often see in adults.

6 DR. ROTHSTEIN: No.

7 DR. LI: Okay, last question for right now.
8 Dr. Jobe.

9 DR. JOBE: Just as a comment, I don't want
10 people to leave this thinking that apnea isn't a problem
11 because apnea is actually a severe problem in preterm
12 infants and the selection of the therapies is at least
13 clinically driven by least intervention. It turns out that
14 if a small preterm infant gets significant amounts of
15 apnea, the consequences of that are continual stimulation,
16 continual bagging, interference with feeding, and
17 ultimately going on a ventilator. What that gets the baby
18 is basically chronic lung disease. So, there are a lot of
19 down sides to having apnea independent of if it caused
20 brain damage or not.

21 -- And I would agree that these babies don't end
22 up with brain damage because people intervene. On the
23 other hand, the interventions are not benign.

24 I would think that most people would accept as
25 a standard of practice, that once one thinks that one has

133

1 apnea of prematurity, the first thing you give is
2 methylxanthines because it's less invasive than continually
3 stimulating the baby and it's less invasive than using CPAP
4 which then can cause stomach inflation and then you can't
5 feed the baby and so on and so forth.

6 So, in general, I think what most people do is
7 assess the baby. If they think it's apnea, they start with
8 methylxanthines. If it doesn't work, then they up the ante
9 with more stimulation or with CPAP or with increasing
10 oxygen or those sorts of things. Again, I think that's why
11 so many of these babies that were in the placebo group got
12 better, is presumably because these other things were being
13 done.

14 DR. ROTHSTEIN: I'm not claiming that any of
15 the other interventions are more or less invasive, and
16 certainly I can tell you about major complications with any
17 of them. If in fact decreasing the incidence of apnea
18 decreases the amount of -- instead of having a nurse
19 assigned to an infant around the clock because he stops
20 breathing every 10 minutes, you can free up personnel, then
21 that may be a major endpoint in terms of treatment also.

22 DR. LI: Okay. Thank you.

23 Next we'll have Dr. Chinchilli give us some
24 comments about his views on the subject.

25 DR. CHINCHILLI: As we know, this was a

134

1 randomized, double-blind study comparing caffeine citrate
2 injection and placebo with respect to treatment of apnea of
3 prematurity.

4 Because of safety concerns, the patient could
5 be transferred to open-label caffeine citrate rescue
6 between day 1 and day 8 of the randomized treatment phase
7 under two different scenarios: one, if the number of apnea
8 episodes in a 24-hour period exceeded 50 percent of the
9 number of baseline apnea episodes, or the investigator
10 suspected that the randomized treatment placed the patient
11 at risk. And we saw with the data that were presented this
12 morning by the sponsor and the FDA, that there was quite a
13 bit of investigator discretion.

14 Also, the patients in the double-blind,
15 randomized phase could be permanently discontinued from
16 participation due to adverse event, apnea recurrence, or
17 investigator discretion. I've just reproduced here one of
18 the tables that the sponsor provided in terms of how the
19 two randomized groups compared in that regard, again
20 looking at just the numbers they used for the efficacy
21 analysis with 37 randomized to placebo and 45 to caffeine.
22 You can see that there was a higher percentage of caffeine
23 babies that completed the study and a slightly less rescue
24 rate when compared to the placebo.

25 Now, this major feature of the design I feel

135

1 yields a natural primary outcome variable which should be
2 considered and that's mainly the number of days until
3 rescue or discontinuation. It was I thought a very ethical
4 design. You're worried about placebo in this instance
5 putting the neonates at risk, and so this is an ethical
6 procedure in terms of designing the study. You monitor
7 them very carefully and as soon as there's a problem, you
8 immediately come to their rescue.

9 This is not unprecedented. In some of the
10 asthma studies with which I'm involved, we do that with
11 adult asthmatics, take them off their inhaled steroids,
12 monitor them closely, as soon as they run into a problem,
13 we immediately come rescue them with prednisone or
14 something else. So, it's not unusual to have this type of
15 a design in this type of a situation, but if you do, it
16 seems to me that a natural variable to analyze and what we
17 do with our asthma studies is look at time until rescue or
18 discontinuation.

19 So, that's the analysis I'm going to present
20 right now very quickly. I just got the data on Wednesday
21 from the agency, so I completed this on Friday. So, I
22 don't have a lot of detailed analyses but just some
23 straightforward things.

24 First, if we just look at some descriptive
25 statistics, the median number of days until rescue or

136

1 discontinuation, you can see there was an advantage to the
2 caffeine group. The median number of days until rescue or
3 discontinuation was 6 for the caffeine group and 3 days for
4 the placebo group.

5 I have the Kaplan-Meier survival plots, as Bill
6 Kelly asked this morning. Again, there's not a big
7 difference here between the two groups, but you notice then
8 later on, as you get out to, say, 3, 4, 5, and 6 -- say
9 days 4 through 8 of the study, you can distinguish a
10 difference here in the survival curve. Remember, survival
11 is surviving the study. You survive being rescued or
12 discontinued. That doesn't happen to you. So, you can see
13 that the caffeine group is doing slightly better in terms
14 of the Kaplan-Meier survival curves.

15 So, the question naturally arises, well, is it
16 statistically significantly better? Obviously, the
17 descriptive statistics indicate there's an advantage to
18 caffeine, but is it statistically significant?

19 That did not turn out to be the case. You
20 probably saw this when I had this up there earlier. I did
21 the usual, the logrank test and the generalized Wilcoxon
22 test, and the p values, you can see, are on the order of .2
23 and .23 in both cases.

24 One more overhead. So, I thought, well, maybe
25 I could get a little bit more precision because -- this is

137

1 a small sample size, by the way, for doing this type of
2 analysis. I thought maybe I could get a little bit more
3 precision by accounting for investigator site and baseline
4 number of apnea attacks. So, I tried to do a more
5 sophisticated analysis to account for them.

6 So, I did a proportional hazards regression
7 where I had 8 degrees of freedom for the covariates for
8 site and 1 degree of freedom for the baseline number of
9 apnea attacks. I did use the scale baseline number of
10 apnea attacks, the way the sponsor did.

11 The estimated hazard ratio or relative risk of
12 caffeine to placebo in this case is .73. A risk of 1 means
13 there's no difference in terms of the hazard risk for the
14 group when you compare caffeine to placebo. In this case,
15 there's a reduced risk. We saw that with the Kaplan-Meier
16 curves. Numerically that comes out to a relative risk of
17 .73. I did not get increased precision here, getting a p
18 value along the same lines, .28. The 95 percent confidence
19 interval for the relative risk was .41 to 1.30, and you can
20 see that it coincides with the p value because a relative
21 risk of 1 can be embedded within the confidence interval.

22 So, although there seems to be a numerical
23 advantage to the caffeine in terms of this type of
24 analysis, again it wasn't statistically significant, as the
25 other analyses with the primary variables that the FDA

138

1 considered this morning.

2 So, I did do a calculation if you designed the
3 study in this way and planned to do this type of primary
4 analysis, what sample size would be necessary to have 80
5 percent statistical power. My calculations were that we
6 would need a sample size of 210 patients, which is sort of
7 like two and a half times the size that the current study
8 was done.

9 Just one other comment about the analyses that
10 were done. There was some question this morning about
11 whether or not multiple comparison adjustments should be
12 made since the sponsor and the FDA both looked at analyses,
13 say, at day 2, day 3, et cetera, all the way up through day
14 10.

15 My feeling is that that's not really critical
16 in this instance simply because the analyses that were done
17 used this last value carried forward approach. That
18 approach works relatively well when you don't have a lot of
19 dropouts as we did here. When you have 5 percent, 10
20 percent dropouts, that type of data imputation of missing
21 values works reasonably well.

22 In this case, since we had such a high
23 percentage of dropouts, I wouldn't recommend that type of
24 analysis anyway. So, I think it's interesting to look at
25 the results in terms of descriptive statistics, but I

139

1 wouldn't rely on that type of analysis looking at what
2 happens, say, at day 8, 9, 10, when so many values are
3 being carried forward. I think this is a natural approach
4 to take in terms of the way to analyze this particular
5 study simply because of the design, but again it was a
6 little bit -- well, quite a bit under-powered to detect a
7 difference, although it did show a numerical advantage to
8 the caffeine group. So, I think it's supportive and gives
9 similar results as the analyses we've seen this morning,
10 but again there wasn't a statistical significance.

11 DR. LI: Thank you very much, Vernon.

12 Any questions from our committee? Yes, Dr.
13 Hendeles.

14 DR. HENDELES: Could you help me understand why
15 there was such a large placebo response? Was that an
16 artifact of how the data was analyzed?

17 DR. CHINCHILLI: No. I think one of the
18 reasons this happened -- I don't know obviously all the
19 physiology here, but I think there's a regression to the
20 mean effect, and I've mentioned that to a couple of people
21 on the board already this morning. A lot of these infants
22 are detected to have high levels of apnea episodes early on
23 at their peak. You get to the point where they're having a
24 lot of episodes, and so naturally they're going to fall and
25 come back down. So, I think that's what's happening. Part

140

1 of the placebo response could be that there's a regression
2 to the mean effect. You're catching these infants when
3 they have a high number of episodes, and then they're going
4 to naturally going to start coming back down.

5 DR. HENDELES: What do you think of just
6 analyzing the number of apneic episodes right at the early
7 period right after the loading dose and not carrying that
8 data forward?

9 DR. CHINCHILLI: Well, I think that's why the
10 FDA was focusing on that primary analysis of, say, the
11 number of episodes at day 2 or a 50 percent reduction, how
12 many infants had a 50 percent reduction in number of
13 episodes at day 2. I think that's why the sponsor
14 indicated that was the primary response as well.

15 DR. LI: Vernon, it would seem to me that there
16 would be at least two ways to interpret the data that you
17 presented, which is the same data, of course, that we heard
18 from the sponsor and the FDA. That's actually almost
19 easier to think about it in the way that you presented it
20 to us.

21 -- So, one interpretation would be that, indeed,
22 the caffeine is effective and more effective than placebo
23 in reducing apneic episodes but that the study was in some
24 way under-powered to show that, 80 patients instead of
25 perhaps a necessary 210 or so.

141

1 The other hypothesis would be that the drug in
2 fact is no different from placebo, and the small
3 differences that we do see that fail to reach a statistical
4 significance is simply because there is no effect or the
5 effect itself is minuscule.

6 Do you have any sense of which one of those
7 hypotheses may be correct?

8 (Laughter.)

9 DR. LI: Or is there a way to think that
10 through from a study design or statistical point of view?

11 DR. CHINCHILLI: Well, we laugh when
12 statisticians always get asked that particular question.
13 There's incomplete observations. A study, it turns out,
14 either had a design flaw or was under-powered, and so
15 you're asked to make a determination based on incomplete
16 information. It's easy for me to stand up here and
17 criticize this issue and that issue because I'm not the
18 ones doing the study. But still, it comes down to the
19 point, as we have to today. We have to come to some kind
20 of recommendation and decision.

21 I think given the amount of consistent results
22 in the literature, even though most of the studies, if not
23 all of them, were uncontrolled studies or not double-blind
24 or placebo-controlled type of studies, I think there are
25 indications in the literature that this is effective.

142

1 DR. LI: That it is or isn't?

2 DR. CHINCHILLI: That it is effective. I think
3 there's indications of that. I'm not saying it's
4 convincing, but I'm saying there are indications that it's
5 effective.

6 So, I think given that this study too -- given
7 that this is double-blind and randomized and placebo-
8 controlled, showing similar types of results, maybe not as
9 strong an effect as we had anticipated seeing, but given
10 that there is this effect that's consistent with the
11 literature, I'd say, yes, there is very good evidence that
12 this is effective.

13 However, I could be wrong too. Again, I'm
14 using my subjective judgment based on incomplete
15 information, just as the rest of you will be asked to do.

16 DR. LI: If I can put the question in a
17 slightly different way. We look at the post hoc analyses,
18 which are very much more convincing.

19 DR. CHINCHILLI: Right.

20 DR. LI: To what extent is that analysis flawed
21 by the very basis of the post hoc nature of it?

22 DR. CHINCHILLI: Well, just the way you've
23 indicated. Given that it's post hoc, that there's a chance
24 to look at the data and decide are there other things we
25 could identify -- now, some were identified as secondary

143

1 variables by the sponsor and they weren't. I wouldn't say,
2 entirely post hoc. They were identified as secondary
3 variables, and they did come out to be significant.

4 This is really a judgment call. I don't think
5 here is a situation where a statistician is much help.

6 (Laughter.)

7 DR. LI: Well, you have helped us so far.

8 Thank you.

9 Peter.

10 DR. ROTHSTEIN: In response to some of your
11 comments, if you have a treatment that's being widely used
12 for a condition that is widely present, but where there are
13 other interventions going on or the natural history of the
14 course of the disease is to get better on its own, then
15 many of these previous studies will come up with a
16 positive effect.

17 DR. CHINCHILLI: That's true.

18 DR. ROTHSTEIN: But we are over-estimating the
19 effectiveness of a particular treatment, in this case the
20 caffeine or the theophylline or whatever.

21 DR. CHINCHILLI: Yes. I think the one study
22 I'm really relying on too is that Murat study that was
23 discussed this morning by the FDA.

24 DR. ROTHSTEIN: Who, I should point out, went
25 on also to be a pediatric anesthesiologist.

144

1 (Laughter.)

2 DR. CHINCHILLI: So, I think although that was
3 open-label and it's a small study size, much smaller even
4 than this study we're discussing, it did show a significant
5 effect. You have to wonder how much bias there is given
6 that it was open-label, but there was something there.

7 DR. LI: If you look at the Murat study, that
8 study might have been judged as under-powered too. There
9 were only, what, 18 patients or so, and yet they were able
10 to find a fairly sizable effect with good statistical
11 significance.

12 DR. CHINCHILLI: You have to wonder how much is
13 due to bias. Given it's open-label, it's hard to really
14 quantify how much of this was really due to some bias.

15 DR. LI: Courtesy.

16 DR. CRIM: Just from a statistical standpoint
17 you mentioned about the median days before they went to the
18 open-label. I think it was 3 and 6 for the two groups.

19 DR. CHINCHILLI: Right, either rescue or
20 discontinuation.

21 DR. CRIM: With the number of subjects from the
22 nine institutions ranging from, I think, 3 to 17 max, to
23 what degree could that difference or any of the other
24 differences be related to, let's say, a bias at one
25 institution, thinking that they should be in an open-label,

145

1 basically moving the bulk of their patients to an open-
2 label, and therefore that would affect -- see, I don't know
3 to what degree these outliers in terms of a hospital moving
4 their three or four patients to an open-label would make
5 those differences.

6 DR. CHINCHILLI: Right. I didn't do those
7 kinds of sensitivity analyses to see, well, let's eliminate
8 this site or that site and see if the results change in any
9 way.

10 They're going to be very sensitive doing that
11 simply because the overall sample size is small. So,
12 typically the types of multi-center trials you see here
13 where you have a couple of hundred subjects or even close
14 to a thousand subjects in a trial, you do those types of
15 sensitivity analyses to see if one or two or a cluster of
16 centers has that type of impact.

17 Here I'd expect that, yes, one or two centers
18 do have a big impact. I think there were three centers
19 that had, say, more than 15 subjects or close to that.
20 You're going to see that. You remove those three and
21 obviously things will change. Or if you remove a couple of
22 the smaller ones. Given that the overall sample size is so
23 small, I think that's probably why I didn't pursue that
24 endeavor because I would be able to find things along that
25 line.

146

1 DR. LI: Yes, Dr. Osborne.

2 DR. OSBORNE: Certainly sometimes when there
3 are small sample sizes, in many studies meta-analyses are
4 done. Are there obvious reasons why a meta-analysis would
5 not be helpful in this case?

6 DR. CHINCHILLI: Well, you have the precursor
7 to a meta-analysis. You have both the sponsor and the FDA
8 doing sort of a very thorough literature review. But I
9 think the studies were so different. You have to decide
10 which studies you're going to use in the meta-analysis.
11 Are you just going to use randomized studies? Well, that's
12 going to eliminate most of them. Are you going to use
13 placebo-controlled studies? Well, then we've got a
14 problem. We've got one. So, I think that's probably why
15 they didn't pursue that, and that was prudent on both the
16 sponsor's and the FDA's part not to try to do a meta-
17 analysis.

18 DR. LI: Yes, Curtis.

19 DR. SESSLER: Vern, did you look at any of the
20 safety data in terms of reworking the statistics?

21 DR. CHINCHILLI: I didn't do that. Obviously I
22 noticed the -- I forget it now. What is the --

23 DR. OSBORNE: Necrotizing enterocolitis.

24 DR. CHINCHILLI: Yes, that thing.

25 (Laughter.)

147

1 DR. CHINCHILLI: Yes. I had some concerns
2 about that as well, and I realize the analysis that was
3 presented this morning -- I'm trying to remember now. I
4 guess there were five or six in the caffeine group. If you
5 looked at safety in terms of whether or not they received
6 caffeine at all, even if they had been switched, I think
7 the percentages gave you something that wasn't
8 statistically significant. But again, given the small
9 sample size, that probably is the reason why.

10 I don't know enough about this to know if this
11 is a cause-effect relationship or if this is something
12 concurrent that happens with these neonates. I think
13 there's reason for concern, and my recommendation would be,
14 obviously, this needs to be closely monitored. If this is
15 approved and gets on the market, I think in the phase IV
16 type of studies I think this really would have to be
17 monitored very closely as to sepsis and this side effect as
18 well. So, I didn't analyze them just because the numbers
19 were small, but there is concern about the proportions.

20 DR. LI: Dr. Kelly?

21 DR. KELLY: In the Murat study, their entry
22 criteria was three apnea episodes in a 24-hour period
23 versus the six in this. I know that we heard previously
24 that there was not a relationship or predictive phenomenon
25 of baseline apnea levels or severity. I guess my question

148

1 is, is there a more sensitive way of looking at that in
2 terms of controlling for the level of the baseline apnea
3 episodes or number than was looked at by the groups here?

4 DR. CHINCHILLI: Well, the FDA did an analysis
5 where they used that as a covariate, and that's mentioned
6 in the biostatistical report. I did something similar here
7 with the proportional hazards regression to try to adjust
8 for the baseline level, and it wasn't significant. When I
9 looked at the p value for the covariate, it was well above
10 .5. So, it's not to say that it's not an important factor,
11 but I think there was a good balance between the placebo
12 and caffeine groups in terms of the baseline levels.

13 DR. KELLY: But if you just looked at the
14 patients who got caffeine and looked at who responded and
15 who didn't respond, would that be a better way of doing it
16 than just comparing the two groups the way they did? It
17 just seems like the dramatic effect of the Murat study was
18 -- they took in potentially significantly less severe
19 patients than they did in this study.

20 DR. CHINCHILLI: I mean, that could be the
21 case. I don't know. I'm still concerned about the bias
22 too with an open-label study of the Murat as well.

23 DR. LI: Dr. Pina?

24 DR. PINA: I just would like to clarify that
25 the entrance criteria for the Murat study was three

149

1 episodes of apnea associated with bradycardia less than
2 100. So, the definition is not exactly the same as in this
3 trial which was just apneic events with or without
4 bradycardia. So, that was the difference.

5 DR. LI: Okay. Thank you very much, Vernon,
6 for that helpful discussion.

7 Next on our agenda is Dr. Szefer who I've
8 asked to give some comments on his view of the evidence
9 presented before us. Dr. Szefer is Director of Clinical
10 Pharmacology at a major medical center.

11 DR. SZEFLER: Thank you, Dr. Li.

12 I received a package in the mail about 10 days
13 ago. It was about this thick with all the information, and
14 I said, well, I'll get through this before the meeting.
15 Then I think the following Monday, Dr. Li called me and
16 said, I've got a challenge for you here and I want you to
17 be the primary reviewer. It was a little shocking for me,
18 and I asked him, well, why? He said, well, you're a
19 pediatrician. You're a clinical pharmacologist. You've
20 published on theophylline and you're in a respiratory
21 center. I said, well, let me clarify a few things here.

22 (Laughter.)

23 DR. SZEFLER: Theophylline is not caffeine and
24 the respiratory center I deal with works with asthma and
25 not neonates.

150

1 But, nevertheless, I really enjoyed the
2 experience because one of the other things that I do in my
3 spare time is I'm on the Committee on Drugs for the Academy
4 of Pediatrics. I've been on this committee for a year and
5 a half and I've seen several areas discussed. I'm
6 beginning to associate Dr. Jenkins with landmark
7 discussions in pulmonary medicine.

8 I think this one here is a landmark because
9 this is an area that has been largely -- I would not say
10 neglected, but poorly defined, the neonates and the young
11 children in product information. So, I really congratulate
12 them on taking the challenge to discuss this issue because
13 it has great impact for the future.

14 As you all know, the legislation has been
15 moving to get better information on medicine in children,
16 and on that ground, I'd like to congratulate Roxane for
17 taking on this challenge because, as you heard this
18 morning, it's really a challenging area with a lot of new
19 information to be identified.

20 Having not touched a neonate for about 20
21 years, the approach that I took was to look at the
22 literature and to call two people that I respect very much
23 in terms of their opinions in this area. To this point
24 their names haven't been mentioned.

25 One is Jacob Aranda, who's in Montreal, who has

151

1 published more extensively in the area of caffeine than
2 anybody else that's listed there. I would recommend that
3 his opinion be solicited, if this is approved and if
4 guidelines are developed for its use, if it hasn't already.

5 The second person is Robert Ward who's the
6 chair of the Committee on Drugs in the Academy of
7 Pediatrics and also is a neonatologist at the University of
8 Utah.

9 Both of them gave me the impression that if
10 this preparation was available, one, they would feel it's
11 important and, two, they would use it if it was FDA
12 approved.

13 So, what I'd like to do is take you through
14 some steps in approaching this issue.

15 I got the impression from reading this
16 literature that the incidence is, indeed, high in terms of
17 this problem. It occurs in 25 percent of preterm infants
18 with a birth weight under 2,500 grams, and there does seem
19 to be a relationship to the extent of prematurity in that
20 it occurs in approximately 84 percent of those with a birth
21 weight less than 1,000 grams. So, I think this is a
22 significant medical problem that deserves attention because
23 of its high prevalence in this population.

24 Risk. I got the impression from reading the
25 literature that there was significant risk in terms of

152

1 morbidity, that this can lead to irreversible neurological
2 damage secondary to hypoxia and acidosis.

3 Mortality also is mentioned in the literature
4 and that it may lead to death if it's untreated, for
5 example, in 23 percent of cases where no treatment is
6 administered or postponed due to mild apnea, and about 34
7 percent required mechanical ventilation. Again, these are
8 points that can be discussed because this is a population
9 of patients at risk for a number of disorders that kind of
10 tie together.

11 What are the available methods of management?
12 Some of these were discussed, but I don't think they were
13 really compared. There's monitoring, physical stimulation,
14 bagging which would also include use of CPAP. I think this
15 study is an excellent format for doing a pharmaco-economic
16 analysis if the data is there in terms of looking at
17 comparative care because, as physicians, we're all being
18 faced with cost effective management.

19 The treatments available are theophylline for
20 those who want to use an approved drug in an unapproved
21 application. It has the disadvantage of a narrow
22 therapeutic range, significant forms of toxicity with
23 overdose, including mortality.

24 Caffeine sodium benzoate was another choice,
25 but Les said it's not on the market, plus it's not an

153

1 applicable preparation here because it interferes with
2 bilirubin binding which in and of itself can result in
3 neurological damage if it's not recognized and controlled.

4 What is being used in this patient population
5 -- and it's used quite extensively, and perhaps a fact
6 analysis should be conducted. Caffeine citrate by
7 extemporaneous formulation seems to be the medication of
8 choice. This is fraught with problems in terms of it's
9 prepared in the pharmacy. It has poor stability. I'm told
10 that it only is stable for about 24 hours, and the quality
11 control can be poor. There are reports of toxicity in the
12 literature with overdose due to errors in extemporaneous
13 formulation. So, that in itself highlights a problem.

14 What are the potential benefits of this type of
15 preparation? If this is approved, it will come under FDA
16 guidance in terms of application of safety principles for
17 the commercial preparation, and it will also come under the
18 guidance that would facilitate better information and
19 better stability of the product, a better quality
20 controlled type product.

21 Continued monitoring of the use of this
22 medication would improve its application. I think today --
23 I've been away from it, but I've heard the best discussion
24 of this type of problem and the medical management of this
25 problem focused on a specific drug that I've heard in a

154

1 very long time and probably in this area of management.
2 So, I think it opens the door for continued improvement and
3 continued evaluation of this medical disorder.

4 What are the benefits over available
5 preparations? I touched on that, but the long half-life of
6 this drug facilitates once-daily administration and reduces
7 day-to-day and within-day variability of serum caffeine
8 concentrations. That in itself is an advantage over
9 theophylline.

10 The stability and quality control would be an
11 advantage.

12 Caffeine is a medication of choice based on the
13 communication of several opinion leaders. I asked Jack
14 Aranda and Bob what their feeling would be if this
15 medication was approved, and both of them indicated to me
16 that if this preparation was available, this would be the
17 one that they would use in their nursery. So, I think it
18 would have application.

19 There was another point that I mentioned
20 earlier that caffeine has no effect on cerebral blood flow,
21 whereas theophylline appears to have that effect.

22 What's the information that's there to support
23 the application? Extensive past literature and I think
24 very nice analyses were done both by the company and by the
25 FDA showing some pretty strong evidence that it does have

155

1 some effect. However, there was no placebo-controlled
2 trial with caffeine in the past literature.

3 It appears, from reading the literature, that
4 both the sponsor and the FDA worked pretty closely to
5 develop a plan to look at this drug very carefully. It
6 followed some of the initiatives that have been proposed in
7 looking at medications in a small population in an area of
8 need and also seems to support the movement in terms of
9 getting better medications in children. So, I think the
10 steps were taken and it seemed like it was a friendly
11 exchange of knowledge to get us where we are today. It
12 followed the orphan drug step, carefully reviewed the
13 supportive literature, and a single study was conducted was
14 recommended in the design that was also recommended.

15 As a result of that, the overall efficacy, even
16 though the key variables didn't work out, seemed to support
17 the past literature.

18 The adverse effect profile for this medication
19 seemed to be pretty reasonable. The central nervous system
20 effects -- again, these are objective findings. We have no
21 way of assessing subjective findings unless adult studies
22 were done in terms of this preparation. But the objective
23 findings were irritability, jitteriness, restlessness which
24 appears in the literature, and it's also indicated that
25 tolerance to these adverse effects can develop. Again,

156

1 that comes from the literature.

2 The literature doesn't point to any long-term
3 effects on growth and neurological development. Seizures
4 can occur with overdose, but prior to this study, there
5 were no deaths reported. The literature with theophylline
6 indicates seizures can develop and there have also been
7 reports of death with theophylline.

8 The clinical experience shows that it also
9 seems to have a very good profile. Rapid onset of effect.
10 It seems to be the drug of choice with the ones available.
11 It has a better safety profile than theophylline with
12 equivalent efficacy, the advantage of once-daily
13 administration, potential therapeutic advantages. Again, I
14 haven't looked at the pharmacology literature, but better
15 CNS preparation.

16 The extemporaneous preparations are widely used
17 indicating, at least to me, that a number of people feel
18 this drug is effective and they're using it whatever way
19 they can get their hands on it.

20 The area of concern, as we discussed, is that
21 the primary efficacy variable was not met. Maybe this was
22 just bad luck or poor study design, but I think Vern kind
23 of alluded to numbers of patients that would be required
24 and I think you alluded to the difficulties in obtaining
25 these kind of patients. So, I think the efforts were made,

157

1 but just the primary efficacy variable didn't come out.
 2 The risk of necrotizing enterocolitis. Reading
 3 the literature provided, this seems to be the second most
 4 common cause of neonatal death. So, it's not a side effect
 5 that we can ignore. However, it is a concomitant disorder
 6 in this patient population. It has about a 10 percent
 7 incidence. The patient population is at risk with or
 8 without the methylxanthines. Unfortunately, there are no
 9 good studies that show the relative prevalence.

10 I think based on your discussions and the IRB
 11 discussions, it would be hard-pressed to think in terms of
 12 doing a study that would give us the kind of numbers that
 13 would be needed and it would take a long time to design the
 14 study, get the approval, and if that was held back, we'd be
 15 holding back about two or three years before the drug could
 16 be approved. I don't know if there's anybody else that's
 17 ready to stand up to the plate with a product with the kind
 18 of studies that would be used to allay our anxieties about
 19 this.

20 It seems to be that caffeine has less risk than
 21 theophylline, the approved medication.

22 If indeed this drug was approved and could be
 23 available, what kind of information should be out there to
 24 the physicians to prevent any catastrophic episodes?
 25 That's where we get to the product information.

158

1 In terms of the dosage guidelines, the doses
 2 that were recommended and studied seem to be consistent
 3 with the past literature and seem to be adequate for the
 4 target population. However, I think the product
 5 information could benefit by some information on
 6 pharmacodynamics in relationship to the onset of effect,
 7 the time of maximum effect, the expected time of maximum
 8 effect, and the offset of effect when discontinued.

9 It should indicate that there are responders.
 10 In talking to Drs. Aranda and Ward, they seem to paint the
 11 picture that there are responders, dramatic responders,
 12 there are nonresponders, and then there are patients who
 13 respond initially but then kind of break through later on.
 14 I think that kind of discussion needs to come out so that
 15 there's some information on how to use the drug because you
 16 have to remember it will be used in academic centers, but
 17 then it will also be carried on in other types of centers.
 18 So, the more information available on how to use the drug
 19 safely, the better.

20 Also discussing the duration of treatment I
 21 think came up earlier. Dr. Jobe addressed the extent of
 22 use, that a 12-day limitation won't be realistic in terms
 23 of its application. So, some guidance in terms of
 24 discussing the duration of treatment, when to consider
 25 stopping and how to do it, whether a tapering schedule

159

1 should be used or just discontinuation when the time seems
 2 appropriate.

3 There are some precautions in terms of
 4 approving this drug that should be considered. It is a
 5 limited study population. There is an absence of data in
 6 adults. As I mentioned before, I think there are
 7 situations -- and maybe Dr. Jenne can address this that in
 8 some of the patients on respirators, apnea in adults, that
 9 preparations like this may be used, and if there is
 10 anticipated use, studies should be programmed.

11 There is an absence of data in premature
 12 newborns. Dr. Aranda pointed out to me that the literature
 13 has been very scarce in the population less than 1,000
 14 grams, and I think this study has that population in it and
 15 maybe some analysis to see what kind of efficacy it has in
 16 that young group would be helpful. There's a Scandinavian
 17 study that he alluded to that I think is in our information
 18 in 1995 that also includes some information on these
 19 younger patients.

20 There was mention that there are some subset
 21 differences, and this needs to be explored a little bit
 22 more in terms of some of the populations. The Hispanic
 23 population has higher volume of distribution, and patients
 24 with higher frequency of apnea have higher clearance. It
 25 would be interesting in the future to explore this in terms

160

1 of its pharmacodynamic implications.

2 Also I think there needs to be some better
 3 information on guidelines for monitoring levels. I forget
 4 the term that's in the product information now but it's
 5 kind of loose in terms of being recommended to obtain it,
 6 but some kind of general knowledgeable guidelines like
 7 obtaining a serum concentration once a week would be
 8 useful.

9 In terms of this issue about tolerance, Dr.
 10 Aranda mentioned that in some of the patients who initially
 11 respond and then break through that an increase in dose is
 12 helpful. That doesn't come through in the product
 13 information and potentially needs to be addressed.

14 If it was approved and the product information
 15 was developed, what would be the considerations in terms of
 16 post-marketing surveillance? Information to date does not
 17 indicate long-term adverse effects, but this needs to be
 18 followed, particularly for the drug and for the
 19 preparation. I think a new drug out there in a new
 20 population would recommend cautions in terms of some
 21 surveillance systems being set up. I don't know how to do
 22 them but that would be useful.

23 Limited use of product to date. The extent has
 24 been only in these 46 patients in terms of the clinical
 25 experience. So, that in itself would merit some long-term

161

1 follow-up.

2 The product would be used if available and
3 would likely become preparation of choice for the
4 management of apnea of prematurity. I think monitoring its
5 use would be very helpful in setting up some kind of system
6 to see if it is being used in populations. I would hate to
7 have this kind of legislation kind of be the way of getting
8 drugs approved for the future, to take the simple way out,
9 get a drug approved for the simplest indication, and then
10 have more extensive use. So, I think the FDA should watch
11 out for that kind of application. I'm not sure, based on
12 the discussion here, that it has application in older
13 patient populations.

14 It would be useful, as I said before, to assess
15 the pharmacodynamic implication of the patient subsets with
16 varying pharmacokinetics.

17 I think this particular drug, if it's approved
18 and the nature that it's approved, is a landmark
19 initiative. It seems to fulfill the intention of the new
20 and emerging initiatives in better medication guidelines
21 for children. As such, this application and potential
22 approval needs to be monitored in terms of its application
23 and use to develop principles for other medications that
24 will be coming along in the same direction. So, I think
25 there are a lot of lessons to be learned in terms of this

162

1 particular process.

2 DR. LI: Thank you very much, Dr. Szeffler, for
3 those thoughtful comments.

4 Are there any questions for Dr. Szeffler? Yes,
5 Brenda?

6 MS. CONNER: This one really isn't for Dr.
7 Szeffler as much as maybe the neonatologists in the group.
8 If you would clarify for me -- we've talked about
9 management methods, and we've seen that methylxanthines are
10 used regularly. What percentage of the time would someone
11 choose an extemporaneous formulation of caffeine over a
12 standardized theophylline product, and does that change on
13 discharge when you're sending a patient home?

14 DR. JOBE: I can try to address that only
15 because I recently moved from UCLA to Cincinnati where
16 there are two different practice styles.

17 In many institutions, a theophylline
18 preparation is used not because people like it but because
19 it's easier to get plasma levels, and that's what happened
20 at UCLA. Basically we used theophylline because we didn't
21 have a caffeine assay.

22 In Cincinnati all the babies for a 50-mile
23 radius are on caffeine. It's made up extemporaneously and
24 they have an in-house assay. So, it's used there because
25 it's felt to be less toxic, more effective, and because

163

1 there's an assay for measuring drug level.

2 MS. CONNER: Are those formulations available
3 for discharge?

4 DR. JOBE: Actually the pharmacy makes them and
5 they're prescribed as outpatient medication.

6 DR. GOLDSMITH: It really depends on the
7 institution. There are a lot of institutions that will not
8 make up caffeine because it has to be made on site, and
9 stability and the problems.

10 Dr. Szeffler, Alan touched on a problem and that
11 is most institutions have the ability to do levels in house
12 because they are monitoring theophylline levels for older
13 people and asthma, et cetera. I would dare say less than
14 20 percent -- maybe less than 10 percent -- of hospitals in
15 this country have the ability to do caffeine. Is that our
16 concern or will that naturally follow if this drug gets
17 approved and everybody will put those procedures in place?

18 DR. SZEFLER: Les will address this but I think
19 they have the availability. It's just a matter of getting
20 the right kit.

21 DR. HENDELES: Yes. The Abbott TDX method of
22 measuring drug levels and drugs of abuse in the urine is
23 the most common. It's a fluorescence polarization
24 immunoassay, and there is a caffeine kit for it that can be
25 obtained. It's expensive to do that if you only have one

164

1 level a month and labs may not be willing to do it unless
2 you can increase the number of levels. But it is
3 commercially available.

4 DR. LI: Stan, did you come across any evidence
5 that the homemade preparations of caffeine have actually
6 caused clinical problems?

7 DR. SZEFLER: As I read through the literature,
8 there was reference to a couple of publications on that. I
9 didn't get a chance to read them to see exactly what was
10 going on there and tease them apart, but it's mentioned
11 several times in the document.

12 Perhaps the company would want to comment on
13 that.

14 DR. MOSDELL: These are two cases of overdoses
15 which resulted from errors in extemporaneous compounding.
16 You can see that some of the errors were fairly
17 significant.

18 The first error was actually a tenfold
19 calculation error made by the pharmacy which was discovered
20 66 hours after the end of the overdose. The level was 160
21 milligrams per liter.

22 The second level -- it didn't say the amount of
23 an overdose it was. However, at the time that the error
24 was recognized, the caffeine levels were 346 milligrams per
25 liter.

165

1 In both of these cases, the infants had
2 significant adverse events during the course of the
3 overdose.

4 DR. LI: Thank you.

5 Any other questions for Dr. Szefer? John?

6 DR. JENNE: Well, I just wanted to mention in
7 regard to caffeine in adults and respiratory failure that
8 Dr. Szefer mentioned in his comments.

9 I know that about 10 years ago Supinski -- I
10 forget his first name -- in Cleveland published some
11 studies in dogs in which caffeine was considerably superior
12 to theophylline as far as increasing force of contraction.
13 When I was at Hines, theophylline was not the most popular
14 drug in patients being ventilated, despite my efforts,
15 although we did have some patients on it.

16 But it seems to me that this would be an ideal
17 population to study not only in ventilated patients, but
18 patients with severe COPD such as Obay has done with
19 theophylline to see what effects it has on pCO₂ and so
20 forth. There may be others that have some better
21 understanding of the literature to date than I do.

22 DR. LI: Thank you, Dr. Szefer, for those
23 thoughtful comments. I know you took a lot of time
24 preparing this for us.

25 I'd like to continue our open discussion of the

166

1 use of caffeine citrate. Rather than just right at this
2 moment focusing exclusively on the questions that we would
3 like to address for the FDA, let's see if we can just focus
4 just somewhat on the broader areas of efficacy and safety,
5 and keep the discussion open, not necessarily exclude
6 comments. Then maybe in another 20 minutes or so we can
7 address in a very much more focused way the questions that
8 we have on our handout.

9 Yes, Dr. Cross.

10 DR. CROSS: I'd just like to mention something
11 that hasn't been discussed probably. Many intensive care
12 units -- and our hospital is among them -- do review and
13 keep a record of their problems with drugs or drug
14 reactions and complications. In our neonatology unit, on
15 many occasions the number one drug problem has been
16 calculation errors in dosing the drug being administered,
17 and number two has been methylxanthines often.

18 I think that this is one thing that has to be
19 taken into consideration as quality control measures are
20 more rigorously reviewed in intensive care units. We meet
21 once a month and discuss such things as the aggregate total
22 of reported drug complications in the patients, units,
23 deaths, et cetera.

24 This is a possible retrieval of information,
25 and I'm sure our hospital wouldn't be the only one where

167

1 methylxanthines continue to be high on the list of drug
2 complications in hospitalized patients.

3 DR. LI: So, how do you see that as
4 impacting --

5 DR. CROSS: I would see both of those issues
6 impacting the neonatology unit. The methylxanthines are
7 tremendously hard to dose. I'm sure that the young neonate
8 is sort of like the very aged patient. It's hard to know
9 what dose to give a 90-year-old and it's hard to say what
10 dose to run the other way. We're all used to this 10 to 20
11 or 5 to 20 dose range, but 15 may be toxic to a 90-year-
12 old, and we see kids that have had no complications and
13 their theophylline level is 30.

14 Now we move down this slope, and we've seen it.
15 I have a problem with Dr. Szefer's wanting a lot of
16 monitoring in dosage in a range where there's tremendous
17 individual variability at one age, and now we're on that
18 steep neonate curve which is going down from 36 months
19 downward where not only are we dealing with individual
20 variability but tremendous variability. I suspect, on
21 gestational period in terms of the kinetics of a drug that
22 most of our hospitals, including UCLA, aren't even
23 monitoring the drug level.

24 So, I think it would be very, very difficult,
25 and I think it probably points to the complications of

168

1 theophylline administration in this same age group. I
2 suspect if one looked at neonatology intensive care units,
3 they'd find that methylxanthines were pretty high up on the
4 list of drug complications.

5 DR. LI: So, is the basic idea that if caffeine
6 is available, it would reduce the use and therefore the
7 errors associated with theophylline or aminophylline?

8 DR. CROSS: Yes, I think that would be a very
9 important point and that you would have the data because I
10 think it's probably collected.

11 DR. LI: Dr. Rothstein.

12 DR. ROTHSTEIN: A question for our pharmacology
13 friends. If you had a hospital that's got, say, 40
14 newborns and 10 or 15 of them are on caffeine, and so the
15 lab is being sent 5 or 10 assays every couple days, how
16 easy would it be to set up those assays?

17 DR. HENDELES: It would be real easy. Again,
18 if they use the TDX machine, it's just buying the kit, and
19 if they don't, it's a very simple, cheap HPLC assay.

20 DR. GOLDSMITH: With regard to the
21 complications of theophylline, I also sit on a drug review
22 committee. Most of the ones we see are minor overdoses
23 without tremendous clinical significance, but because in
24 assay it was greater than what our limit is, if it's 15 or
25 20 for theophylline and the child has a symptom, which

169

1 could be tachycardia alone which will resolve over a few
2 hours, it gets brought to the committee.

3 The ones that are devastating -- at least the
4 ones that we've reviewed -- had to do with packaging in
5 that the packaging of the product in different
6 concentrations is very similar. I don't know if that has
7 been changed or not recently, but it can vary by 25-fold in
8 the amount of drug per unit volume. If that's done
9 incorrectly, then you have a disaster.

10 So, we're not here to discuss theophylline, but
11 obviously if you're going to do different packaging with
12 different concentrations per unit volume, that's an
13 extremely difficult problem for the neonates who have,
14 obviously, limited ways of excreting the drug.

15 DR. HENDELES: I think what Dr. Goldsmith is
16 referring to is the fact that aminophylline is a 25
17 milligram per cc solution. So, if you want to use it in a
18 neonate, you really have to dilute it down to 1 milligram
19 per cc. You increase the risk of errors when you
20 extemporaneously prepare a preparation as opposed to
21 getting it commercially from a company.

22 I think that's just one of the many reasons why
23 bringing a product like caffeine on the market will really
24 reduce the risks to this patient population for serious and
25 potentially fatal toxicity because it's very clear that

170

1 caffeine at levels of 50 micrograms per milliliter seem to
2 not cause any serious neurologic problems, whereas
3 theophylline at that same level can cause very devastating
4 effects.

5 DR. GOLDSMITH: What I'm suggesting is that if
6 we're approving this or moving towards approval for a
7 neonatal indication, then it should be packaged in a
8 neonatal volume that's appropriate, not to be put into an
9 adult volume that has to then be diluted on site by the
10 pharmacist.

11 DR. HENDELES: Well, it's 10 milligrams per cc,
12 and the dose for an adult would be in the 300 milligram
13 range. So, you'd have to use many vials.

14 DR. LI: I have a question on a slightly
15 different topic and that has to do with looking at the
16 information that's available to us now and maybe just
17 looking at one of the future questions having to do with
18 future studies.

19 My question really to the panel would be, what
20 is the feasibility and how realistic is it to expect or
21 request a study involving 200 patients using computerized
22 monitoring in order to at least get a chance of getting
23 additional data that would perhaps make this decision
24 easier? The question would be, what is the feasibility
25 given the difficulties with the study that was already

171

1 conducted? I just want to maybe have a guess or an opinion
2 from some of our panelists. We'll start with Stan.

3 DR. SZEFLER: It sounded like it would be
4 difficult. It sounded like the study design was
5 reasonable. It just feel short in terms of the efficacy
6 variable and the number of patients. It sounded like you
7 lost sites, one because of their IRB's.

8 I guess the other question would be how long
9 did it take to recruit because if the nine centers
10 fulfilled their quota in one month, then I would say
11 there's a lot of population available, but if the deadlines
12 were extended, then it sounds like recruitment was very
13 difficult in some very good centers.

14 DR. LI: Dr. Sessler.

15 DR. SESSLER: I had similar questions. I guess
16 I'd like to ask in a fashion that gets to some of the data
17 that might help us come to conclusions. If we had
18 somewhere between 16 and 18 months at nine centers, that's
19 what? 15 center-years or something. How many centers are
20 there that are out in the United States that are capable of
21 doing this sort of work, looking specifically at the
22 neonatologists here who might be in the know as to how many
23 more than nine? Are there 100? Are there 50? Are there
24 12?

25 DR. GOLDSMITH: Well, it depends on who you

172

1 ask. Because the protocol was written so narrowly and with
2 great constraints, it was very difficult to sign up
3 patients. Roxane did the best they could and I
4 congratulate them on it, but it's a very difficult
5 protocol.

6 If we're looking at babies per year, 1.1
7 percent of babies in this country are born less than 1,500
8 grams and fall into what we call the very low birth weight
9 group. I would imagine 50 to 70 percent of those babies --
10 let's say 50 conservatively -- are going to get on some
11 sort of methylxanthine at some point in time. That's
12 20,000 babies a year. So, if we're looking only at safety
13 issues, how many of these babies versus another population
14 are going to get NEC or any other kind of safety issues,
15 that information should be easy to come by.

16 To get the kinds of effects that Roxane tried
17 to get, in terms of a very narrow protocol with so much
18 methylxanthine already being used and with all the other
19 problems and all the exclusion criteria, that's very
20 difficult.

21 There are probably 1,200, 1,300, 1,400 neonatal
22 intensive care units in this country. I would imagine
23 probably 1 in 5 to 1 in 10 is capable of doing this kind of
24 study or wants to do this kind of study, to be involved.

25 They are now beginning to have some consortiums

173

1 like groups of institutions looking at problems together
2 like the Vermont Oxford group and the NIH group, but it's
3 difficult to get a study like this to get the power that
4 you need, the numbers of patients that you need.

5 DR. SESSLER: May I ask the sponsors how many
6 centers they approached to get their nine centers that
7 agreed to participate?

8 DR. ERENBURG: I don't remember exactly, but I
9 think it was somewhere in the 2 to 1 range. I think we had
10 approached 15 to 18 different centers looking for people
11 who would be willing to follow the narrow protocol with all
12 the various constraints that have been cited.

13 DR. GOLDSMITH: Has the company made an
14 estimate of the amount of use that this would have if it
15 were approved in terms of manufacturing and how many babies
16 a year would get this? I mean, is 20,000 unreasonable?

17 DR. ERENBURG: Mr. Gunn?

18 MR. GUNN: My name is Ed Gunn. I'm Marketing
19 Manager for Roxane Laboratories.

20 The potential patient base for methylxanthine
21 therapy right now currently, looking at babies that would
22 be actually available to treat, would be around the 70,000
23 patient range a year. Of that, obviously there would be a
24 portion that would go to caffeine. Looking at how many
25 neonatal intensive care units out there that are currently

174

1 using caffeine to treat, we predict of those 70,000 in NICU
2 units, approximately 10,000 of those patients are receiving
3 caffeine now.

4 DR. ERENBURG: As Mr. Gunn did focus groups,
5 one of the major problems has been availability of caffeine
6 levels, and if this were resolved, I think people would
7 look at the data and look at dosing, the cost of getting
8 multiple theophylline levels versus one caffeine level a
9 week and look at the medical economics, as has been stated
10 before.

11 DR. HENDELES: Dr. Erenberg, it's not clear
12 that you'd need to do that if the patient was responding
13 and had normal renal function. Would there be any
14 rationale for doing a caffeine level under that
15 circumstance?

16 DR. ERENBURG: I think those of us who have
17 used caffeine for a long time feel very comfortable with
18 it. I think people who are going to be switching from
19 theophylline, where it is required to do levels to know on
20 an individual baby, especially when you first start, where
21 they are -- I think people will probably want to do a level
22 until they get comfortable with the use of the drug and
23 know what the clinical response is.

24 DR. LI: Yes, Molly?

25 DR. OSBORNE: I have a question actually about

175

1 the labeling since this seems to be just a open period of
2 discussion here just because I don't know very much about
3 the cytochrome P450 1A2 system in neonates, let alone in
4 adults. I'm ashamed to say. I'm confused about how the
5 drug interactions will actually work. I certainly know
6 them for adults, but it seems that for the neonate it might
7 be different. I know that there were exclusion criteria in
8 the studies that Roxane performed, the sponsor performed,
9 and so I'm wondering how to best approach what should be in
10 the package insert since it might be different depending on
11 a neonate or somebody -- I don't know -- early-life infant,
12 et cetera.

13 DR. KELLY: The major problem is that caffeine
14 is excreted primarily unchanged in the kidney, and so most
15 of the drug interactions that are related to both
16 theophylline and methylxanthines in adults aren't going to
17 happen because all of those are metabolic in nature. You
18 can see from the literature search that they did that you
19 don't achieve adult levels till about 6 months of age, at
20 which time, if it's apnea of prematurity, you're not going
21 to have any more apnea of prematurity.
22 So, it's unclear to me as well how they're
23 going to address these interactions because in the patient
24 population that they're using the drug in, it's very
25 unlikely that these drug interactions may occur except for

176

1 in patients whose mothers got phenobarbital and they have
2 then some enzymes in their liver and are metabolizing. But
3 other than that, it's very unclear.

4 Just to list them all I think would actually
5 create some false information that these actually even have
6 a potential for occurring.

7 DR. LI: Yes, Les?

8 DR. HENDELES: On the other hand, the package
9 insert doesn't contain any advice on how to adjust the
10 dosage if a patient has renal dysfunction. Since in your
11 study you eliminated all of those patients, there's a huge
12 population of these patients that have varying degrees of
13 renal dysfunction and are going to get the drug once it
14 becomes commercially available.

15 So, I think it's really essential that both a
16 dosage guideline be provided for reduced renal function
17 since that's a major way of getting rid of the drug, and
18 then secondly, some advice on when to measure levels and
19 how to use that information to adjust dosage, similar to
20 what we have in the theophylline package insert.

21 DR. JENNE: We're talking about the package
22 insert now, and one of my impressions is that it comes down
23 a little too strongly that the therapeutic range is 8 to
24 20. I think this may have real legal ramifications -- I
25 mean, to state it as positively as it is stated. There

177

1 should be some buffer there or some reference to higher
2 levels being relatively safe in certain series and so
3 forth.

4 The other thing in regard to the necrotic
5 enterocolitis, there was one study mentioned here in the
6 review where there was a comparison between theophylline
7 and caffeine on enterocolitis I believe. It seems to me
8 that a better way to state the caffeine situation is to say
9 that there is no evidence at this time that it's associated
10 with enterocolitis, whereas there is a question whether
11 theophylline is associated with enterocolitis. In other
12 words, I think we're tending to condemn the drug a little
13 prematurely here on the basis of what we know right now.

14 DR. LI: I think it's a reasonable time now to
15 proceed to the very specific questions that the committee
16 has before them, and we'll start with the first question on
17 efficacy and again open with just a discussion but
18 discussion now focused on this particular question, which I
19 will read.

20 Do the effects shown in study OPR-001 and the
21 published literature constitute sufficient evidence of the
22 efficacy of caffeine citrate for the treatment of apnea of
23 prematurity? I suppose the key word here is "sufficient."

24 I'll again open it up for discussion. Then
25 maybe we'll have a comment or an opinion from each of our

178

1 committee members, and then finally we'll actually take a
2 vote. Dr. Chinchilli.

3 DR. CHINCHILLI: Yes. I have a question for
4 Dr. Jenkins which I warned him about at lunchtime.

5 (Laughter.)

6 DR. CHINCHILLI: And that is, what are the
7 ramifications of something like this? If the committee
8 recommends approval in terms of efficacy and safety based
9 on one multi-center trial where there wasn't statistical
10 significance for efficacy with the primary response
11 variable, is this going to set a precedent for the FDA, and
12 is it going to cause ramifications for other drug products
13 and biological products that's going to cause problems for
14 the agency?

15 DR. JENKINS: I think that is a very important
16 question and it's one that we have debated internally quite
17 a bit. Since you provided me warning at lunch that you
18 were going to ask me this, I provided my boss warning that
19 I was going to defer the question to him --

20 (Laughter.)

21 DR. JENKINS: -- because he has so many more
22 years of experience in the area than I do.

23 But before I let Dr. Bilstad address some of
24 those issues, we should go back and look historically. The
25 sponsor presented this morning that there was a literature

179

1 review conducted in the mid-1980's for the agency. The
2 agency concluded that the data at that time based on the
3 literature were not adequate to support the efficacy of
4 caffeine in this indication, and that's why we requested
5 that adequate and well-controlled trials be conducted.

6 We actually did take some heat for that
7 recommendation because some people thought it was unethical
8 to have a placebo-controlled trial in this disease because
9 they were so convinced that caffeine was effective and was
10 standard of care.

11 To Roxane's credit, they did take on the task
12 and complete the study we've heard about today.

13 The agency did agree at that time that given
14 the literature-based evidence of efficacy, that one
15 adequate and well-controlled trial could potentially serve
16 as the basis for an approval action if the data were
17 favorable for the effectiveness of caffeine.

18 It's correct that generally we focus on the
19 primary endpoint that's specified by the sponsor and
20 hopefully agreed to by the agency in advance in the
21 protocol before the data are unblinded in making our
22 determinations of efficacy in clinical trials. We usually
23 expect that there will be prespecified analyses plans also
24 in place before the data are unblinded.

25 However, that does not mean that the agency

180

1 doesn't have some flexibility in how we can interpret the
2 overall results of clinical trials. We're not bound to
3 limiting ourselves just to the prespecified primary
4 endpoint/primary analysis.

5 Finally, in anticipation that this question
6 would come up, you'll notice that in our package to the
7 committee from the agency, we included a draft guidance
8 document that the agency issued recently which tries to
9 spell out some information for the industry about what the
10 effectiveness standard is for the approval of drugs.
11 Hopefully you had a chance to look that over and see some
12 of the legal and scientific bases for the standard that has
13 generally been two adequate and well-controlled trials, but
14 also there was a lot of detailed descriptions in there of
15 situations where the agency could or has made
16 determinations based on a data set of less than two
17 adequate and well-controlled trials which met the primary
18 effectiveness endpoint.

19 Dr. Bilstad has had a lot more experience in
20 this area than I have, and I think he has been thinking
21 about this most of the day and I'll let him give you some
22 of his thoughts on what level of flexibility there is in
23 the effectiveness standard and also what, if any, precedent
24 an action favorable to caffeine might have on the agency
25 and the industry.

181

1 DR. BILSTAD: Well, there currently are some
2 weaknesses in the efficacy database provided for this drug,
3 and we see that as a regulatory challenge. Is there enough
4 evidence to be able to say that the drug is effective for
5 approval for marketing?

6 At the same time, I think it's fair to say that
7 we don't view the data on its face as being completely
8 inadequate. If we viewed it that way, we would not have
9 presented it to the committee for review. We believe this
10 falls into a gray area where judgment really is needed.

11 The Food, Drug and Cosmetic Act, which provides
12 the framework under which we operate, refers to substantial
13 evidence consisting of adequate and well-controlled trials.
14 As Dr. Jenkins mentioned, we have interpreted that in most
15 circumstances to mean that there needs to be some sort of
16 independent substantiation of the results, data from more
17 than one source.

18 At the same time, we believe that we have some
19 flexibility in how we can interpret that legislative
20 standard, and we believe that we can take into
21 consideration expert judgment that the studies and the
22 database, taken as a whole, do provide substantial evidence
23 of effectiveness.

24 There are some factors that can be taken into
25 consideration in this situation, factors of multiple

182

1 sources of data, looking at the data as a whole. To some
2 extent, feasibility can be addressed, although that's a
3 difficult one. Feasibility is a factor in all drug
4 development programs to some extent, somewhat more in
5 programs that deal with orphan drugs, and sometimes there
6 is the ethical question on the feasibility of conducting
7 studies which can be taken into consideration.

8 So, I guess I would say in summary we believe
9 that we, from a regulatory standpoint, have some
10 flexibility in this situation, but we certainly would like
11 your expert judgment, taking all the data as a whole,
12 whether there really is in your view substantial evidence
13 of effectiveness.

14 DR. LI: Thank you for those comments, Dr.
15 Bilstad.

16 Yes, Dr. Osborne.

17 DR. OSBORNE: Specifically I'd just like to say
18 that the attachment that we received, the draft guidance on
19 level of evidence, I thought was absolutely outstanding.
20 It helped me. It clarified certainly in my own mind
21 exactly how the FDA does look towards drugs in terms of
22 safety and efficacy and would also, of course, point out
23 that for me it was very helpful to read that our expert
24 judgment could conclude that studies together represent
25 substantial evidence of effectiveness. This leaves us a

183

1 tremendous amount of flexibility, in the case where there's
2 substantial evidence in the literature, to help make a
3 recommendation here. Somehow it doesn't mention statistics
4 at all.

5 (Laughter.)

6 DR. LI: What I think we'll do next is go
7 around the table, and I'll ask for an opinion and thoughts
8 about the issue that's before us on evidence. Is there
9 substantial evidence or sufficient evidence of efficacy in
10 order to move forward toward a possible vote toward
11 approval or approvability?

12 If you feel strongly, feel free to actually
13 voice what your vote will be. I'm not asking for a vote
14 right now. I'm just asking for thoughts and impressions
15 and what you think the major issues are. Perhaps we'll go
16 around the table and hear from everyone, starting with Dr.
17 Goldsmith.

18 DR. GOLDSMITH: You would make me start.
19 (Laughter.)

20 DR. GOLDSMITH: I just want to point out that
21 there's a substantial difference between question number 1
22 and question number 2. I know we're not at question number
23 2. But it says in question number 2, short-term use. It
24 doesn't say short-term use in question number 1, and I
25 think that needs to be added because that's basically what

184

1 we're looking at. I am concerned that once the drug is
2 there, it will be used for months rather than days.

3 But I think given the literature review, my
4 tendency at this point is to say that the published
5 literature in conjunction with the one study, despite the
6 flaws of the study and the lack of power, is adequate
7 information at this point.

8 DR. LI: Brenda?

9 MS. CONNER: I think the literature review that
10 we have with us, as well as the post hoc evaluation after
11 the study, and the anecdotal information that Dr. Szeffler
12 provided us from his other experts that he talked with, as
13 well as who I consider the experts on the panel, the
14 general consensus that it would be used and that it is
15 needed, I think that helps substantiate the efficacy.

16 DR. SESSLER: I have some difficulties with it.
17 I think the "sufficient evidence" is the key phrase there,
18 and we're bending two rules. I think we're moving away
19 from using two randomized controlled trials to one, and I
20 think in order for that to work frankly, that the one
21 randomized controlled trial should be of sufficient
22 strength to stand pretty firmly on its own.

23 I think there are serious questions about the
24 powering of this current study. Some of the other
25 literature is consistent, but again it's almost entirely

185

1 open-label.

2 If we went with these criteria, I think we
3 would have several monoclonal antibodies or similar such
4 agents available for adult critical care in treatment of
5 sepsis. I know we'd have interleukin-1 receptor
6 antagonist, for example, and probably many others. So, I
7 think we need to look clearly at whether bending both rules
8 is the right thing to do.

9 DR. CROSS: I, like Molly, read parts of the
10 document that the FDA prepared as their draft on the way
11 out here from the coast, and I thought it was outstanding
12 and was amazed at the flexibility. I thought that was
13 great.

14 I also appreciate Dr. Goldsmith's proviso that
15 we should maybe consider short-term on this first question.
16 I still have problems of mechanism, general CNS stimulant,
17 tolerance, et cetera, et cetera on the longer-term studies.

18 It's interesting that their electrolytes didn't
19 show any changes in CO₂ which I might have expected if it
20 was a long-term stimulant driving respiration.

21 I feel much more comfortable with the short-
22 term use approval rather than long-term use.

23 And that's all my comments.

24 DR. SZEFLER: I reviewed my comments there, and
25 what I was alluding to is the literature seems to support

186

1 its efficacy and seems to support the need for a product
2 out there that could be used safer than what's being used
3 right now.

4 DR. CHINCHILLI: Well, I definitely think
5 there's evidence and whether or not it's sufficient is what
6 I'm debating internally right now. I guess if I had to put
7 a probability on it, I'd probably say there's a 65 percent
8 chance I'll vote yes.

9 (Laughter.)

10 DR. LI: Spoken like a true statistician.

11 (Laughter.)

12 DR. ROTHSTEIN: I like waffles for breakfast.

13 (Laughter.)

14 DR. ROTHSTEIN: I think there's evidence for
15 some efficacy of this drug.

16 I'd also throw out a problem with drugs and
17 with kids. Let's say you have two drugs, both of which
18 have absolutely no effect at all but are used widely
19 because of the belief that the drug has some effect, but
20 one of those two drugs is safer than the other. If
21 approving a second drug will drive the first less safe drug
22 off the market, then there may be a rationale for approving
23 the drug.

24 But going back to the efficacy, I think there's
25 some efficacy. I think it's overrated but there is an

187

1 indication of efficacy.

2 DR. LI: I'll just voice my own opinion. I
3 think it's again a tremendous asset that we have this
4 placebo-controlled trial before us so at least we have some
5 evidence on which to base a decision.

6 I do share some of the concerns that were
7 voiced earlier, and as I looked through the FDA guidelines
8 on what constitutes sufficient evidence, again I'm struck
9 that the usual standard is two well-controlled, placebo-
10 controlled trials and in certain cases a single trial can
11 be considered sufficient generally when that single trial
12 is especially strong or the results are especially strong.

13 I'll add that more likely than not I would
14 support the idea of having the indication include some
15 duration of treatment, be it, say, 10 to 12 days or 10 days
16 or so. My opinion there is based on the evidence that's
17 available to us that was presented which goes up to about
18 10 days or so. So, it would be to me difficult for us
19 later on to advocate an indication for longer than 10 days.
20 So, I support the idea of including the short-term caveat.

21 I think our decision today is going to be based
22 on the particulars with this drug in this setting. So,
23 there are extenuating circumstances in this case that are
24 in some ways unique in terms of the orphan drug, the
25 difficulty in conducting this trial and future trials. As

188

1 Dr. Rothstein said, we need to consider the risk of,
2 approval, as well as risk perhaps of not recommending
3 approval.

4 I think the theoretical down side perhaps would
5 be that, if we recommend approval and actually eventually
6 the drug becomes available on the market, the drug in fact
7 is not effective because that's certainly a possibility
8 that we have to entertain whether that's true or not.

9 But even theoretically, even just as Dr.
10 Rothstein said -- I think my rationale is the same. Even
11 in a worst case scenario, so to speak, if the drug turns
12 out to be no better than placebo, in some ways we're still
13 better off. So, I guess my own view is --

14 DR. ROTHSTEIN: Excuse me. I didn't say no
15 better than placebo. No better than theophylline, and if
16 this replaces theophylline and the attendant problems with
17 theophylline, then --

18 DR. LI: Right, fair enough.

19 Actually my own view would be even if the agent
20 turns out not to be better than placebo, with the current
21 practice as it is, it still may be of benefit to our
22 patients. That's what I think is the main issue here.

23 DR. CRIM: I think there's circumstantial
24 evidence to suggest that caffeine may be beneficial in
25 patients with this problem. Because of the way the studies

189

1 that were reviewed in the literature were conducted, I
2 don't think that's convincing but I think it's indeed
3 suggestive of it. Likewise, I think that the current study
4 that we're reviewing is also suggestive of it although not
5 convincing, and that's because I think the biggest concern
6 I have is the small size of the groups and particularly the
7 dropout rate and the concern I have about the biases of the
8 investigators both in enrolling patients into the study, as
9 well as keeping the patients in the study.

10 So, I think there's circumstantial evidence to
11 suggest that it's probably effective, but I'm not convinced
12 that it really is. I would have liked to have seen the
13 primary efficacy variables met.

14 DR. OSBORNE: I think there is sufficient
15 evidence of efficacy. My only comment would be that my
16 guess is there is a number of responders, which is not the
17 entire population, but that will be sorted out in the
18 marketplace.

19 DR. CRIM: The one thing I'd like to add is
20 that the circumstantial evidence is for short-term use, as
21 far as I'm concerned, definitely not long-term.

22 DR. JENNE: Well, I would come down on the side
23 of efficacy. I'm particularly affected, although we should
24 probably think independently of this, but the comparison
25 with theophylline, which is in wide use, is a reason to not

190

1 daily further I think. When it was decided to study this
2 drug, it was a number of years ago, and these studies take
3 a long time. I think there's a down side to continuing to
4 do studies like this.

5 I think we need to give credit to the
6 practitioners, many of them who have personal experience,
7 and it's likely that many of these finer points that have
8 been brought up will be solved with this drug in smaller
9 studies that focus on some particular issue.

10 So, that's what I have.

11 DR. JOBE: I find the evidence for efficacy in
12 these trials and in the historical review to be basically
13 circumstantial, as pointed out by the other people.

14 I think there's a large safety issue with
15 having caffeine available.

16 I think everyone needs to realize that this is
17 really a unique population of patients that cannot be
18 generalized to other folks.

19 There's one thing that really hasn't been
20 talked about today and that's the clinical evidence for
21 this which is very common where infants are put on
22 theophylline or caffeine and their apnea resolves, and as
23 they get older, it's withdrawn. Very often they have apnea
24 again and the drug is restarted, and that's a very common
25 clinical observation which sort of demonstrates efficacy to

191

1 me.

2 DR. KELLY: I think just so I can say something
3 different than everybody else said, I've spent 20 years
4 teaching people, residents, students that use of a drug in
5 and by itself does not indicate appropriate use.

6 Then having said that, I think the primary
7 endpoint or the primary goal of therapy is to end apnea
8 episodes. In that endpoint, the double-blind, placebo-
9 controlled trial was successful in terms of showing more
10 patients got rid of their apnea. So, I think there is
11 sufficient evidence, although not a lot -- sufficient
12 evidence -- of efficacy.

13 DR. HENDELES: Well, I think there's sufficient
14 evidence of efficacy. I think hindsight is always 20/20.
15 If the sponsor and the agency knew what they knew today,
16 they probably would have designated a different endpoint
17 and this may have been less of an issue.

18 I'm comfortable that the drug is both safe and
19 effective. I think there needs to be some precautions.
20 The association with NEC needs to be included as a
21 precaution in the package insert, and I think the
22 indications need to be explicitly limited because I can see
23 where anesthesiologists might use caffeine to reverse
24 medazolam sedation and other things because it's an
25 adenosine receptor antagonist. So, it may be used for many

192

1 other purposes, and so I think there needs to be an effort
2 to restrict it to this indication unless the company is
3 willing to conduct other studies.

4 DR. LI: Thanks for everybody's comments. We
5 can still stay open.

6 Dr. Bilstad?

7 DR. BILSTAD: I just wanted to make a comment
8 to the comment that was made earlier that the FDA's usual
9 standard is two randomized placebo-controlled studies. In
10 fact, we talk about adequate and well-controlled studies,
11 but we very definitely do not say that these need to be
12 randomized placebo-controlled studies. In fact, there are
13 a number of controls that are mentioned in the regulations
14 as possible controls, and one is even the historical
15 control where a study may not have a concomitant control
16 group but the results might be compared to historical
17 experience with the drug. So, I just wanted to make clear
18 the usual standard is not necessarily two placebo-
19 controlled randomized studies.

20 DR. LI: Right. Thank you for that
21 clarification.

22 We can still stay open for discussion if anyone
23 wants to make comments or question any one of the other
24 panel members based on comments that you've heard already.

25 What I might suggest is a question for our

193

1 panel and that is whether we want to modify the question to
2 include the short-term qualifier that I've heard at least a
3 couple of the panel members raise as an issue. For
4 example, as an example only, we could slightly alter the
5 question to address the question of whether the evidence
6 constitutes sufficient evidence on the efficacy of the
7 short-term use of caffeine in the treatment of apnea. Is
8 there any favor toward that issue? Yes?

9 DR. ROTHSTEIN: I don't want to restrict or
10 remove the drug for use in the population that Dr. Jobe has
11 described or withdrawn from the drug, the drug is stopped,
12 and then have a recurrence of their apnea and are started
13 treated again. So, I'm not sure where this short-term
14 stops and long-term begins.

15 DR. LI: That's a good point. On the other
16 hand, the data that we're basing our decision on really --
17 at least the study data -- ends at 10 days, does it not?

18 DR. ROTHSTEIN: I understand that, but the 26-
19 or 27-weeker who's born hasn't read the insert yet.

20 (Laughter.)

21 DR. ROTHSTEIN: And his apnea is not going to
22 resolve necessarily in 10 days, and it may be possible to
23 reduce the episodes from 7 to 2 in that infant. He may get
24 treated for 3 or 4 weeks.

25 DR. CRIM: But I guess caffeine is not FDA

194

1 approved for apnea of prematurity now, is it?

2 DR. ROTHSTEIN: No.

3 DR. CRIM: So, physicians are using it how they
4 want to use it anyway. So, if we approve it for short-term
5 use, it's still not going to stop physicians from doing
6 what they're going to do anyway. Correct?

7 DR. JOBE: The way it's worded I think is good
8 because it's not treatment of apnea, but it's apnea of
9 prematurity, which by definition means that as the child
10 approaches term, they ought to be bringing the babies off
11 the drug.

12 DR. GOLDSMITH: I would agree with Dr. Jobe.
13 Peter, I'm not as concerned about babies being treated up
14 till 36 even 38 weeks post-conceptual age. What I'm
15 concerned about is being treated for a year while they're
16 on home monitors with virtually no other kind of monitoring
17 because it's the easiest way out and they got sent home on
18 it or discharged on it. As we're starting to discharge
19 children now at 34 to 36 weeks post-conceptual age, many of
20 them are going home on methylxanthines, and very honestly,
21 the practicing pediatrician may be a little different from
22 the practicing neonatologist and doesn't know when to stop.
23 So, the easiest thing to do is not to stop, just continue
24 on.

25 So, I think we have to be very careful about

195

1 opening the doors too wide.

2 DR. LI: What would be your recommendation for
3 indication?

4 DR. GOLDSMITH: I think short-term use and some
5 caveat about treatment beyond 38 weeks post-conceptual age
6 has not been studied or is beyond the scope of the
7 information available, or something along that line.

8 DR. JOBE: Yes, or prolonged apnea beyond the
9 newborn period or something like that.

10 DR. ROTHSTEIN: What about apnea of
11 prematurity?

12 DR. JOBE: That says it all I think.

13 DR. GOLDSMITH: But when does apnea of
14 prematurity stop? The problem is for the practicing
15 pediatrician who gets handed these babies post-discharge.
16 Apnea of prematurity on the discharge summary he may think
17 continues on 52 to 56 weeks post-conceptual age.

18 DR. ROTHSTEIN: But then that's something that
19 the neonatology community needs to communicate to the
20 pediatricians. I don't want to incorporate that into a
21 restriction or start writing science into the package
22 insert that doesn't exist.

23 DR. HENDELES: As I understand it, the labeling
24 guideline really regulates what the manufacturer can
25 promote this for, not what a physician -- any approved drug

196

1 just regulates the manufacturer's promotion. It does not
2 regulate the physician's practice.

3 DR. GOLDSMITH: I would agree but I think
4 physicians are more aware of the medical-legal consequences
5 of using drugs for non-approved uses and that some
6 indication in there would be helpful in terms of not having
7 the drug continued for months and months after discharge,
8 which I think is very common, extremely common.

9 DR. HENDELES: It sounds like an educational
10 problem.

11 DR. LI: Courtney, then Molly.

12 DR. CRIM: I guess the viewpoint I take of that
13 is because I'm not concerned about the safety issue, at
14 least the long-term safety issue, since we don't have that
15 kind of data and the data we do have is for the short-term
16 use up to 12 days. I guess I would go along with the
17 recommendation in terms of short-term use because to me
18 we're talking about circumstantial evidence.

19 My sense is that I'm concerned about the
20 clinician -- again, not being a pediatrician, I guess my
21 concern would be about the pediatrician who would keep this
22 person on it for months or a year. And whether or not the
23 clinician should know about those medical-legal
24 ramifications doesn't help that baby that dies because of
25 he or she was kept on it for a prolonged period of time;

197

1 whereas if you put a short-term limitation on it, then
2 neonatologists or the person who's experienced with it will
3 know the ramifications in terms of when they can or can't.
4 But for the person who is relatively ignorant of it, at
5 least perhaps having that short-term use will cause that
6 person to pause and think and if they have this patient on
7 it for longer than what it's approved for will seek
8 consultation to say, what can we do with this particular
9 type of medication as opposed to leaving it on them willy-
10 nilly.

11 DR. LI: I'll add that it may be possible for
12 us to recommend that some limitation or a caveat be
13 included in the directions for use whether or not the
14 actual words "short-term" are used. For example, it's
15 possible to put into the indication or the labeling that
16 controlled studies beyond 10 days of use have not been
17 performed. That already would be a warning or a caveat.
18 So, we probably don't have to decide on the wording but I
19 think the concept is important since it's raised by
20 several.

21 Molly.

22 DR. OSBORNE: Yes. My opinion would be that
23 the way number 1 is worded, for me personally, is adequate
24 to make a decision, and that on 5a about the dosing period,
25 which has to do with the labeling specifically, my opinion

198

1 would be that we discuss that fully. My opinion would be
2 that there be something in there about it being reevaluated
3 around the time of birth, or whatever the best wording is,
4 and that reevaluation is warning signal to a pediatrician
5 that something needs to be done. If they don't know what
6 it is, they might actually ask for help.

7 DR. JENNE: In fact, Dr. Jobe really was
8 talking about repeated short-term use I think. In other
9 words, it could be stated that one should evaluate before
10 further short-term use is necessary or further trial is
11 necessary.

12 DR. LI: Stan or Peter, any final thoughts on
13 either this issue or any other issue?

14 (No response.)

15 DR. LI: I think I'll take Dr. Osborne's
16 suggestion and let's address the question as it is written,
17 and we discuss approvability on item 5, then we can again
18 more specifically outline what our concerns are about
19 warning or duration or use.

20 So, in fact, now I will ask for a vote, and the
21 question is, do the effects shown in study OPR-001 and the
22 published literature constitute sufficient evidence of the
23 efficacy of caffeine citrate for the treatment of apnea of
24 prematurity? So, all in favor, raise your hand.

25 (A show of hands.)

199

1 MR. MADOO: How about all who are not in favor?
2 DR. LI: All opposed?
3 (A show of hands.)

4 MR. MADOO: So, do we have two opposed? We
5 have 14 who are eligible to vote, so I would suggest that
6 we have 12 in favor --

7 DR. LI: Any abstentions?

8 (No response.)

9 MR. MADOO: So, the vote outcome is 12 in
10 favor, efficacy demonstrated; 2 opposed.

11 DR. LI: So, Courtney, was your vote opposed?

12 DR. CRIM: No. I agree with that statement.

13 MR. MADOO: Okay, so it's 13 --

14 DR. LI: Let me rephrase the question. Do the
15 effects shown in study OPR-001 and the published literature
16 constitute sufficient evidence of the efficacy of caffeine
17 citrate for the treatment of apnea of prematurity? So, all
18 agreed, all in favor of this statement in the affirmative,
19 please raise your hand.

20 (A show of hands.)

21 MR. MADOO: I'm seeing 12 hands.

22 DR. LI: All opposed?

23 (A show of hands.)

24 MR. MADOO: I'm seeing one opposed.

25 (Laughter.)

200

1 DR. SESSLER: I'm between an opposed and an
2 abstain.

3 (Laughter.)

4 DR. SESSLER: I am unhappy with the scientific
5 evidence. I respect the neonatologists' observations at
6 the bedside and opinions. I don't believe that there's
7 sufficient evidence. What I'd like to do is abstain
8 because I think this is an important drug perhaps to that
9 group.

10 DR. LI: Twelve in favor, one opposed, one
11 abstention.

12 MR. MADOO: Duly noted for the record.

13 DR. LI: Let us now address in an open fashion
14 the second question which deals with safety, and I'll read
15 the question. Does the NDA database, together with the
16 data available from published literature and the
17 spontaneous reporting system experience, demonstrate the
18 safety of the short-term use of caffeine citrate in
19 patients with apnea of prematurity?

20 I'll open this for any comment. Yes.

21 DR. CHINCHILLI: Yes. I have a question for
22 our colleagues. Was the incidence of sepsis a surprise? I
23 take it with the NEC, that wasn't a surprise because that's
24 obviously a complication with the pre-term infant, but with
25 the sepsis, was that a surprise or is it out of the range

201

1 that you would expect for these neonates? I guess the
2 range was 6 out of 6 or 8. Dr. Pina, you had the number.
3 I can't remember what they were.

4 DR. PINA: Eight patients, all of them exposed
5 to caffeine.

6 DR. LI: Right, and none in placebo.

7 Stan?

8 DR. SZEFLER: But I think as we talked about
9 before, having had experience in the past but not recently,
10 sepsis is a diagnostic suspicion and then the confirmation
11 -- in this case, it sounded like there was only one case
12 that had bacterial confirmation. To my knowledge, whenever
13 it's suspected, blood cultures are obtained. So, it's not
14 as if it wouldn't be found if it wouldn't be there unless
15 the cultures weren't sensitive enough. So, it's actually
16 one out of eight cases, and the seven cases were suspected
17 sepsis and suspected sepsis is considered rule out sepsis.
18 So, again, I kind of like --

19 DR. LI: Is it concerning that all eight that
20 were suspected or had sepsis were in the treatment --
21 received the caffeine?

22 DR. ROTHSTEIN: The study set up criteria for
23 inclusion in the study -- to my reading, the study did not
24 define sepsis, and so it did not define a positive blood
25 culture or a regaining of ability to maintain temperature

202

1 or a rise in the platelet count following institution of
2 antibiotics. So, I don't know how to define or then
3 interpret what sepsis is.

4 DR. GOLDSMITH: That's a big problem. The
5 nosocomial infection rate for VLBW babies can approach 20
6 percent and be within the norm and prolonged
7 hospitalizations. The problem is that sepsis is a
8 diagnosis that's difficult to make. We draw very small
9 blood cultures and we generally do them once before
10 antibiotics are initiated. In some literature, you see
11 where babies who truly have supportive evidence of sepsis,
12 all kinds of white blood cell counts, abnormalities and
13 clinical deterioration, et cetera, and 30 percent of those
14 infants have negative blood cultures. So, it's very
15 difficult to interpret the data.

16 I'm not uncomfortable with the data to that
17 point where I would believe that caffeine offers a
18 disadvantage towards babies to getting sepsis.

19 DR. LI: What about the issue of the
20 necrotizing enterocolitis? Are you concerned that there
21 may be an increased risk with caffeine?

22 DR. GOLDSMITH: Not on the basis of the
23 information we have, not in my personal information. I
24 still remain very, very concerned about the interaction
25 with other drugs and causing NEC specifically the H2

203

1 blockers. I'm concerned that that's an issue that many of
2 these babies will be on histamine blockers, as well as
3 methylxanthines of some sort, and that interaction will be
4 a new interaction, and possibly in a stage 4 time that
5 these things should be reported back. I don't know how we
6 could know that now, but I am concerned about it.

7 DR. LI: Yes, Curtis.

8 DR. SESSLER: I'm particularly struck by the
9 one-sided nature of the exposure data. I don't know how
10 good it is and that relates back to the question that I had
11 earlier about severity of illness and if there were other
12 explanations for this. But one might argue that the best
13 drug now to avoid the onset of sepsis, necrotizing
14 enterocolitis, and death is avoidance of caffeine, because
15 it was 0, 22 in all three categories.

16 The concern I have I guess about approval,
17 based on the safety data or in light of the safety data, is
18 that we've already heard that there is a lot of variation
19 in management of this condition and that there's little
20 good science so far. A lot of it is observational.
21 Without a doubt, this would become the drug of choice and
22 would become very widely used.

23 If we guess wrong about the safety data, I
24 think there's potentially significant damage that can be
25 done. So, I disagree with some of the earlier statements

204

1 that if we do approve it, there's no loss. It's either a
2 gain or it's not going to be harmful. So, I have concerns
3 about the safety information there. It's far more one-
4 sided I guess when one looks at the exposure data than the
5 randomized data.

6 DR. CROSS: You preempted my statement. I was
7 going to say the same thing, that the way to get at the
8 safety issue is to approve it. It's being very widely
9 used, and perhaps the stage 4 surveillance will produce
10 better data than what we have now. I think approval
11 probably is safer than nonapproval and 70 percent use.

12 DR. OSBORNE: I'll tease Curtis a minute and
13 just point out in the adult ICU with your logic, we
14 wouldn't be giving oxygen either.

15 (Laughter.)

16 DR. OSBORNE: Let me go on to point out as a
17 person who works with --

18 DR. SESSLER: We need to go back 20 years and
19 do those studies again.

20 DR. OSBORNE: It's a deal.

21 I'd just make my opinion which is that
22 certainly the FDA recommendation was for safety. At least
23 on the basis of the information we have, the concept was
24 that caffeine was well tolerated by patients in the
25 population studied.

205

1 DR. LI: Dr. Jobe?

2 DR. JOBE: The issue of safety I think is
3 something that we all have to be worried about. It turns
4 out that in the neonatal business now, there are two very
5 large networks, the NICHD network that has approximately
6 20,000 infants registered less than 1,500 grams, and the
7 Vermont Oxford trial network. A lot of that database has
8 been mined for a lot of different things. One is for
9 sepsis, and I'm not aware that there's an association with
10 methylxanthines. But I'm not sure it has been looked at
11 that way. That's information that could be probably
12 requested by either the FDA or the sponsor to better flush
13 out that sort of an issue.

14 I am aware that H2 blockers are associated with
15 increased infection in babies looking at a database from a
16 recent glucocorticoid trial that's unpublished presently,
17 but that interaction has turned up as well.

18 The point is I think that in neonatology, in
19 contrast to a lot of other diseases, we have very large
20 databases that are out there that can be looked at.

21 DR. LI: For those who have a concern about the
22 safety regarding in particular the necrotizing
23 enterocolitis, would a label warning and a surveillance
24 study be adequate to allay some of those concerns?

25 DR. SESSLER: I guess you're looking at me.

206

1 aren't you, Jim?

2 (Laughter.)

3 DR. LI: You don't have to respond.

4 DR. SESSLER: It's interesting because in
5 thinking about this, you wonder if it one includes the
6 exposure to caffeine data in the labeling, it might bring
7 up more healthy questions actually to its automatic use.
8 That is, if you are getting ready to prescribe this drug to
9 your patient and see data that the likelihood of death is 0
10 percent without it and 4 and a half percent with it, and
11 sepsis, 0 percent versus 13 percent, and on down the line,
12 it may perhaps appropriately bring questions about making
13 sure the indications are correct. So, without a doubt,
14 appropriate labeling would have to include extensive data I
15 think about this potential side effect.

16 The concern I have I think is not just that
17 it's something that doesn't make sense. It's a random
18 finding, but there's potential rationale for that in terms
19 of whether it's neonatal models or adult models in terms of
20 GI mucosal injury and the potential for bacterial
21 contamination or bacterial products, quote, translocation.

22 So, the rationale is there and it's something
23 that I have significant concerns about that we may be
24 missing something given the striking nature of the data.
25 So, it definitely does need to be prominently displayed I

207

1 think

2 DR. JENNE: I don't think the data is very
3 striking. That's my problem. The exposure to caffeine in
4 one of the open labels, the person had a small bowel
5 resection almost simultaneously with his beginning
6 caffeine. At autopsy the diagnosis was made. So, I don't
7 consider that a case -- I think that's very questionable as
8 exposure being associated. That's two cases in the placebo
9 versus four in the caffeine exposure.

10 You're starting from a different total
11 sufficiently between those two denominators in those cases,
12 that you end up with worthless statistics. It's so close
13 to being random, I can't take it seriously.

14 DR. SESSLER: It's very strikingly one-sided I
15 guess would be the thing that catches my eye. You have a
16 bunch of zeroes in the not-exposed column and significant
17 numbers in the other.

18 DR. JENNE: Well, how about the statisticians
19 discussing this?

20 DR. KELLY: I agree with John Jenne. The thing
21 that increases it really is the exposure data which is the
22 sicker patients getting put on caffeine, the bias there in
23 terms of who do you enter and who gets left off of caffeine
24 altogether, those patients that are doing fine and not sick
25 and doing well. That's one of the problems that you have

208

1 with a study like this. When you take people off, your
2 placebo group keeps getting better and better and better
3 all the time. But if you just look at the very baseline in
4 terms of who got randomized, you don't see that difference.

5 I agree with you. There is that striking
6 difference, but that's after things have been unblinded to
7 the clinicians.

8 DR. HENDELES: I'm wondering if Dr. Jenkins can
9 clarify whether the agency can even require the company to
10 do some type of surveillance after it's approved. Is that
11 logical?

12 DR. JENKINS: I'm not sure what type of
13 surveillance you're exactly talking about.

14 DR. HENDELES: To see whether there's an
15 increased risk of NEC with the use of caffeine.

16 DR. JENKINS: Well, we certainly can enter into
17 agreements to do phase IV studies which could be controlled
18 trials or they could be some sort of looking at
19 epidemiologic databases.

20 --We're interested in hearing your ideas or your
21 suggestions on what would be useful to either better
22 clarify the safety or efficacy of caffeine, if it were to
23 be approved, in the post-approval phase or also any
24 epidemiologic studies you might suggest.

25 But we could require a phase IV commitment for

209

1 that type of study.

2 DR. HENDELES: Given that, then I think I'll
3 make my comment when we get to item number 6.

4 DR. LI: Stan?

5 DR. SZEFLER: John, by the post-marketing, you
6 wouldn't be able to require another placebo-controlled
7 trial. Is that right or is that within the purview?

8 DR. JENKINS: I think that goes to what the
9 question is you're trying to answer.

10 DR. SZEFLER: Because I think in order to
11 answer Les' question, you have to have a database to
12 compare to to say whether it's increased or not unless it's
13 a striking number like 70 percent of the infants all of a
14 sudden.

15 DR. JENKINS: Well, phase IV commitments can be
16 placebo-controlled trials, but they should not be placebo-
17 controlled trials to answer the question of whether the
18 drug is safe and effective because we need to answer that
19 before we approve the drug. But they could be placebo-
20 controlled trials to better ferret out various areas that
21 are still left questioned such as dosing regimens in
22 different subpopulations, that type of information. But we
23 certainly should not go into this with the thought that we
24 could require a phase IV commitment to do another placebo-
25 controlled trial to determine whether this is really safe

210

1 and effective. That we need to do before we approve the
2 drug.

3 DR. SZEFLER: Because in order to get those
4 population differences, it would beg the question to the
5 neonatologists to come up with figures to say what's the
6 incidence of necrotizing enterocolitis, say, at certain age
7 groups in the absence of methylxanthine. I don't know if
8 that data is out there.

9 DR. JENKINS: Also keep in mind that the
10 ability to do placebo-controlled trials, if this drug is
11 approved, may even be more hampered than if the drug is not
12 approved.

13 DR. SZEFLER: Right. It was hard enough to get
14 it to an IRB without its approval. It's going to be even
15 harder with an approval.

16 DR. JENKINS: Well, this study had to be
17 designed with a very strong open-label rescue component,
18 and in order to do another placebo-controlled trial, that
19 may even have to be increased. You saw the effect of the
20 very rapid dropout rate on this study of that open-label
21 rescue provision. If it's an approved drug, even if you
22 could get people to randomize to drug versus placebo, they
23 may only do that in the scenario where the open-label
24 rescue was very liberal, which may compromise severely what
25 you could learn.

211

1 But there may be designs that could be useful,
2 such as dose titration studies or parallel group differing
3 dosing regimens looking to see if there is incremental
4 benefit. You could have targeted plasma concentration
5 studies to see whether there is really a therapeutic range
6 that makes a difference. So, you could do studies where
7 you could have different dosing groups. Placebo may be
8 difficult.

9 DR. LI: Dr. Crim, did you have a comment?

10 DR. CRIM: It's more a comment/question. It's
11 regarding the concern about NEC, and maybe, Dr. Rothstein,
12 you found this when you reviewed the literature.

13 Recognizing the problem with historical
14 controls, was there any sense what the incidence of NEC was
15 in the pre-caffeine days compared to the caffeine days?

16 DR. ROTHSTEIN: Caffeine has been around and
17 used in newborn units before I even started practicing.

18 DR. SZEFLER: I think that's part of the
19 problem because NEC I think just became a diagnostic
20 disorder --

21 DR. ROTHSTEIN: But again, looking historically
22 caffeine sodium benzoate was used as a respiratory
23 stimulant. Until the institution use of continuous
24 positive airway pressure, newborns didn't survive long
25 enough to have NEC. So, NEC only becomes apparent once

212

1 these kids are living long enough for this disease to take
2 its toll.

3 DR. SESSLER: Are there any preclinical data
4 related to that at all as far as the effects of caffeine on
5 an NEC equivalent in an animal model or anything?

6 DR. LI: Yes, Dr. Pina.

7 DR. PINA: I mentioned one study, but it was
8 not used -- they did not use caffeine. It was
9 aminophylline. There is one animal study where they did
10 show that aminophylline increased the risk of NEC when
11 there was an injured GI mucosa.

12 DR. HENDELES: But that could be from the
13 ethylenediamine. We don't know that it's from the
14 theophylline component.

15 DR. JOBE: Just a comment for perspective.
16 Methylxanthines became common for apnea of prematurity
17 about 1975, so they've been used for a very long time.

18 DR. SZEFLER: That's about the time NEC was
19 popularized.

20 DR. ROTHSTEIN: The use of positive pressure
21 was introduced in 1970, so it's shortly thereafter.

22 DR. SZEFLER: Let me ask another question in
23 terms of this area because I think what seems to be
24 emerging is that this is an interesting drug that needs
25 refinement, and what is the potential for that? I know in

213

1 my area in terms of asthma, there's been networks
2 developed. NIH has supported networks in terms of doing
3 studies on questions that may not be taken up by industry
4 because of the type of question or because of financial.
5 Is there that type of network available in neonatology?

6 Second, are there guidelines that are published
7 in terms of management of the newborn like we have now
8 guidelines in terms of management of asthma, and if there
9 are these guidelines, what do the authorities recommend in
10 terms of the management of this disorder?

11 DR. JOBE: I guess you asked the right person.
12 I'm actually the chair of the Neonatal Network for NICHD.

13 Interestingly, of all the things we've
14 considered studying, caffeine or theophylline has not been
15 one of them because it's considered by everybody I think
16 standard of care, accepted, and in all the manuals for
17 neonatal care, there are recipes for how you give
18 theophylline or caffeine. So, if you look at Neofax or any
19 of these other drug delivery studies or the textbooks of
20 neonatology, this is considered a non-issue.

21 DR. SZEFLER: After hearing this discussion --

22 DR. JOBE: Yes, I think after hearing this
23 discussion, there are a lot of issues about dosing, about
24 duration.

25 DR. SZEFLER: Could your network benefit by

214

1 some interest in terms of --

2 DR. JOBE: The network could benefit. Again,
3 these are the kinds of studies that industry perhaps could
4 be encouraged to do in terms of dosing and so on. Sure.

5 DR. SZEFLER: Because I guess I see what is
6 emerging out of here is this drug is provocative in terms
7 of its effect. It's convincing in terms of some of its
8 application, but there's a lot of room for improvement in
9 terms of its application and safety. Perhaps the marriage
10 of the Network and the FDA and industry support to do these
11 kinds of studies would help refine the guidelines and make
12 everybody feel a little bit more comfortable.

13 DR. JOBE: I think that's true.

14 DR. LI: Dr. Sessler.

15 DR. SESSLER: Sorry about getting back to the
16 NEC question and the sepsis. If there are well-established
17 risk factors from previous studies, is it possible -- and I
18 guess this is directed to the sponsors -- to query the
19 databases to try to determine whether in fact this
20 observation is explained and is that data available? Can
21 one do that without having to conduct prospective studies?
22 I guess that's a question for the sponsors.

23 I think this is still an unknown and there may
24 very well be good alternative explanations. That would be
25 marvelous if there is.

215

1 DR. LI: Would anyone from Roxane like to
2 address that? Dr. Wynne?

3 DR. WYNNE: Yes. Those data are not available
4 in our database. As Dr. Erenberg previously said, we often
5 don't have culture-proven sepsis. So, we could maybe
6 expand the information a little bit to give you a little
7 bit more, but I don't think we have the information --
8 well, in fact, I know we don't -- that you're looking for
9 because we just don't have that culture-proven bacteremia.

10 DR. JOBE: Just as a comment, there is the NIH-
11 sponsored IVIG randomized controlled trial which was
12 published about four or five years ago. That data has just
13 been released to the public sector by NICHD, and that is in
14 fact a sepsis study. I assume they coded in
15 methylxanthines, but I don't know that for sure. So, that
16 is in the public sector now and it's a very large database
17 of approximately 2,000 infants.

18 DR. GOLDSMITH: Part of the problem was
19 mentioned this morning by Dr. Jobe was that NEC in various
20 nurseries is very episodic. So, although generally the
21 practices of giving methylxanthines is not episodic,
22 although it might vary from attending to attending, it's
23 generally pretty consistent. You may go a year or two in a
24 very large nursery with no cases of NEC and then have an
25 epidemic. So, the numbers here are going to have to be

216

1 quite large and the time frame over which it's looked at is
2 going to have to be relatively long.

3 DR. LI: Yes, Dr. Osborne.

4 DR. OSBORNE: I must say my opinion for
5 question number 2 for using this drug, is it safe for the
6 short-term use of caffeine citrate in patients with apnea
7 of prematurity, I would say yes.

8 I would say when we get to talking about number
9 6, there are several ways we could go about it. For
10 example, the two papers on necrotizing enterocolitis point
11 out it's about 1 in 1,000, and certainly the frequency in
12 this study is within keeping of what has been described in
13 many other studies. If it's possible to have a registry
14 database mined, what you do is you could set up a case-
15 controlled study with multiple controls, so you might have
16 one case where NEC is infrequent and then three or four
17 controls. Then you can do a sophisticated analysis of
18 several kinds of variables that you think might be
19 important in particularly not only the single medication,
20 but medication regimens and multiple effects, such as the
21 H2 blockers, and aminophylline and theophylline and
22 caffeine might come into play in that kind of setting. But
23 I think that's a question I'll address in number 6.

24 DR. LI: I think we're ready to take number 2
25 to a vote. Does the NDA database, together with the data

217

1 available from published literature and the spontaneous
2 reporting system experience, demonstrate the safety of the
3 short-term use of caffeine citrate in patients with apnea
4 of prematurity?

5 So, all in favor, raise your hand please.

6 (A show of hands.)

7 DR. LI: Did you get that, Leander?

8 MR. MADOO: Who was against?

9 DR. LI: All against?

10 (A show of hands.)

11 DR. LI: Abstentions?

12 (No response.)

13 MR. MADOO: We have 13 in favor of that
14 statement and 1 opposed.

15 DR. LI: All right. Let's take item 3 as a
16 question. Taking into consideration the overall benefits
17 and risks of using caffeine citrate for the treatment of
18 apnea of prematurity, do you recommend that this drug be
19 approved for marketing?

20 Discussion? Yes, Les.

21 DR. HENDELES: I thought you were calling for a
22 vote.

23 DR. LI: We will in a minute.

24 (Laughter.)

25 DR. LI: So, this question of course has to do

218

1 with approvability. I guess the key word in this question
2 is "overall" taking into account the efficacy and the
3 safety evidence that we reviewed.

4 Again, before the vote, are there any comments,
5 any questions? Yes, Dr. Szeffler.

6 DR. SZEFLER: I have a question back to the
7 other one that I should have asked before the vote. But
8 there's no drug that's completely safe and is there a
9 liberal definition of safety or is that just kind of
10 gestalt?

11 DR. LI: My interpretation is safety based on
12 the opinion of the committee, but perhaps Dr. Jenkins would
13 like to comment on that.

14 DR. JENKINS: Well, I think you're correct in
15 pointing out that there is probably no drug that's
16 completely safe, or if there is such a drug, it's probably
17 not effective.

18 (Laughter.)

19 DR. JENKINS: Usually safety becomes a question
20 of a risk-benefit analysis, so you're analyzing the risk to
21 the patient populations who may be receiving the drug
22 versus the benefit they may be receiving by having the drug
23 administered. So, there is no absolute definition of
24 safety because what may be a safe drug for patients with
25 ARDS where there's no approved therapy would not be

219

1 considered safe for use as an antihistamine for allergic
2 rhinitis, for example. So, you have to take in the
3 indication, the available treatment option, as well as the
4 actual data and do a risk-benefit type of analysis.

5 DR. LI: That's a good question. That's the
6 essence of this question number 3.

7 All right. Let's go ahead and vote on the
8 question. I guess I won't read it again. All in favor,
9 raise your hand.

10 (A show of hands.)

11 MR. MADOO: Is there anyone opposed? That
12 makes it easier.

13 (A show of hands.)

14 MR. MADOO: Okay, so there are 13 in favor of
15 approval of this agent and 1 who's not in favor of
16 approval.

17 DR. LI: Number 4 we will skip.

18 Number 5 has to do with labeling. We'll take
19 part a separate from part b. If caffeine citrate were to
20 be approved for the treatment of apnea of prematurity, in
21 the labeling would you recommend that the dosing period be
22 restricted to 10 to 12 days?

23 DR. SZEFLER: I don't know who the one opposed
24 was, but I was interested, if that person was opposed, is
25 number 4 applicable? Because we're a recommending panel.

220

1 We're not a confirmatory panel, and if there is useful
2 information for number 4, maybe it should come from that
3 question.

4 DR. LI: That's an invitation, Curt. What
5 additional studies, if any, would be useful to you?

6 DR. SESSLER: I think additional studies would
7 be problematic certainly. I guess part of my questions
8 that I asked before, without going too far down the field,
9 is we had nine centers that enrolled over 18 months and
10 trying to get a grasp on overall issues of the difficulty

11 in actually performing a second clinical trial. I
12 understand the feelings around the room that that would be
13 very difficult to undertake, and given that this is kind of
14 standard therapy. In my mind, there are some uncertainties

15 in both safety and efficacy, and that would clarify it.
16 My concern I guess is that by going into the
17 acceptance of this as the state of the art and the gold
18 standard, that the important thing is that we don't become
19 complacent about readdressing safety and efficacy.

20 DR. SZEFLER: I guess my question is one of
21 extent because if you have kind of like one vote standing
22 out there, it's useful to kind of know is that because
23 you're convinced it has no effect, or you're just not
24 convinced that there's enough data to make a conviction?

25 DR. SESSLER: Right. I think that there is --

221

1 well, there are a couple things.

2 I think that there are clearly some indications
3 that this is likely to be effective. Thus, I move to an
4 abstention on the first question.

5 Having said that, the evidence is weak in my
6 view. I guess I'm tainted by being exposed to a lot of
7 negative clinical trials in adult medicine, adult critical
8 care, where similar a sort of findings would not have been
9 borne out by large scale, randomized clinical trials. I
10 cite the several different sepsis studies where the phase
11 II studies looked very promising and where subsequent
12 pivotal clinical trials were performed and proved that the
13 drug had no value.

14 None of them were based on the clinical
15 opinions and bedside experience. Thus, that's why that
16 weighed in in terms of the neonatologists' opinions in my
17 decision there.

18 I still have questions. I think this is
19 unsettled and I feel bad that if in five years we discover
20 that there is some clear-cut relationship between this drug
21 and sepsis and necrotizing enterocolitis, that we perhaps
22 have not been rigorous enough today in apply the standard
23 of actually determining that.

24 DR. LI: Do you have a comment, Dr. Rothstein?

25 DR. ROTHSTEIN: Just that the agents that have

222

1 been first used by the community and then eventually
2 submitted to randomized studies for ARDS I believe are a
3 lot more toxic than the drug we're talking about here. The
4 numbers of infants who would have to have induced sepsis on
5 the basis of caffeine would have to be elevated quite high
6 in order to start matching some of the drugs that we've
7 been throwing around the adult ICU's.

8 DR. SESSLER: The other factor, I guess, in
9 that decision that I'm made to vote as I did was the fact
10 that this is already approved. It's something that by not
11 approving it, the standard remains.

12 DR. HENDELES: It's not an approved drug.

13 DR. SESSLER: No, it's not an approved drug.
14 I'm sorry. It's in use.

15 So, the advantage of course is that we now have
16 a very standardized preparation and that is clearly worth
17 something, but it is not the same as perhaps denying
18 something that may be a lifesaving drug since it is
19 available. My opinion.

20 DR. LI: Yes, Dr. Crim.

21 DR. CRIM: I would just comment since I was one
22 who also voted -- well, did not support the efficacy
23 question. Again, my not supporting that question is
24 because I considered it was more the circumstantial
25 evidence.

223

1 In terms of number 4, again what Curtis
2 mentioned, if the technology is now available in neonatal
3 ICU's to objectively measure these parameters better, then
4 I think it may be possible to do that type of a study.
5 That is, if the neonatologists in the unit have better
6 monitoring equipment, then it may in fact be possible to do
7 those types of studies, but you can do a controlled placebo
8 type of a study with larger numbers.

9 DR. LI: Say, Courtney, did you vote
10 affirmative for approvability?

11 DR. CRIM: Yes, I voted affirmative for
12 approvability, but I voted negative for the efficacy
13 question.

14 DR. LI: Would you like to elaborate on the --
15 (Laughter.)

16 DR. CRIM: No. Because number 3 was taking
17 into consideration the overall benefits.

18 DR. LI: No, absolutely.

19 DR. CRIM: And that's why I voted for approval
20 overall, but getting back to the question that was raised
21 in terms of number 4, if you do not recommend approval, I
22 did not support the first question about the efficacy.
23 That's once again my reasons for voting overall but not for
24 the efficacy in terms of what I would like to see. Ideally
25 what I would like to see would be if the technology is now

224

1 available to do a better efficacy which will also include
2 safety studies.

3 So, I think there are still questions about the
4 safety in terms of the data that was presented both in
5 terms of the literature and in terms of this pilot study
6 here in terms of the numbers and the way the study was
7 controlled. I don't think the data is good, but I don't
8 think the data suggests that the safety of the caffeine is
9 worse than placebo.

10 DR. LI: I understand. Thank you.

11 Let us address as a discussion the question on
12 labeling. A, would you recommend that the dosing period be
13 restricted to 10 to 12 days? We had discuss this briefly
14 and deferred it until now.

15 Yes, Alan.

16 DR. JOBE: I realize the study was designed as
17 a 10- to 12-day study for practical reasons. I think the
18 difficulty here is in clinical practice. Again, the
19 clinical practice is to initiate caffeine or
20 methylxanthines or whatever they're using when a baby
21 presents with apnea of prematurity once the baby is off the
22 ventilator, and then therapy should be discontinued at a
23 point when you anticipate that the baby is mature enough to
24 no longer have apnea of prematurity. That's usually in the
25 32- to 34-week window.

225

1 In terms of clinical practice, if one has a 26-
2 week infant that you've just extubated, and you treat him
3 for 2 weeks, he'll be 28 weeks gestation and it's unlikely
4 that anybody would stop caffeine at that point. So, I
5 think it's a practical issue of the physiology of apnea of
6 prematurity in that it's a developmental disease and it
7 tends to resolve by 32 to 34 weeks.

8 So, I don't know how to deal with that because
9 the study design wasn't intended to answer that question.

10 DR. LI: Yes, Peter?

11 DR. ROTHSTEIN: I think you've in fact just
12 dealt with that, that the labeling state that this study
13 lasted 10 to 12 days, that this is a developmental issue,
14 that infants born at earlier gestational ages may in fact
15 not have resolution of their apnea until they are 32 or 34
16 weeks, and just leave it at that.

17 DR. HENDELES: I like that.

18 DR. GOLDSMITH: I think you need to take out
19 the word "restricted" from that phrase from a, that you
20 recommend that the dosing period be restricted. If you
21 recommend that the dosing period -- only that 10 to 12 days
22 has been adequately studied or has been studied and that
23 evaluation should come sometime at 34 to 36 weeks post-
24 conceptual age, I think that handles the problem. I don't
25 think I would restrict it to use because that really does

226

1 lead to problems for clinicians.

2 DR. LI: So, I'm not hearing a lot of support
3 for actually including a restriction as it's written in
4 this particular question. So, the indication, for example,
5 can be apnea of prematurity as the indication. Since there
6 is primarily this one study which is the basis for most of
7 the information that we have, we can recommend that a
8 synopsis or a table of information from that study
9 indicating that the study itself was limited to 10 days.
10 That can be in labeling without writing in a restriction,
11 as Dr. Goldsmith indicated.

12 DR. JOBE: But I think Dr. Goldsmith is
13 recommending putting in the indication that the baby should
14 be tested for need after the period he's likely to have
15 apnea of prematurity, sometime between 32 and 36 weeks.
16 The recommendation would be then that the baby be assessed
17 for need rather than put on continuous drug.

18 DR. ROTHSTEIN: And to answer some of Jay's
19 other concerns, efficacy for other causes of apnea other
20 than prematurity has not been demonstrated.

21 DR. GOLDSMITH: That's right, specifically
22 ALTEs and for weaning from ventilators which I think,
23 although we haven't discussed that today, most children in
24 our unit get started before they demonstrate apnea. They
25 get started while they're still on the ventilator in order

227

1 to enhance rapid weaning.

2 DR. CRIM: So, if I understand what's being
3 proposed is that we take out the restriction but include in
4 the package insert that the drug has only been studied for
5 10 to 12 days?

6 DR. LI: Yes, something to that effect.
7 Is there an opposing view? John.

8 DR. JENKINS: Dr. LI, I was just going to
9 suggest that since you all have modified the question so
10 much, it's really not entirely necessary that you try to
11 take a vote. I think we've heard a lot of different ideas
12 and we can incorporate those. But if you want to try to
13 write the question in your own words and then take a vote,
14 that's fine also.

15 DR. LI: Thank you.

16 Yes.

17 DR. SZEFLER: I was just going to mention
18 there's kind of another soft area in there that probably
19 requires some looking at right up front. In terms of
20 description, it mentions bronchodilator activity and then
21 it kind of pops up later on. That is distant from the
22 apnea aspect and again kind of creates potentials for
23 creative application. John?

24 DR. JENKINS: Yes, if I could comment on that
25 also. The label that you have in your briefing package is

228

1 simply the label that was written by the sponsor and
2 submitted. The sponsor generally submits their proposed
3 labeling and that will undergo a rather extensive review.
4 So, that has not been reviewed and modified by the agency
5 as yet. So, if that helps to allay some of your concerns.
6 You can be guaranteed that the labeling will be
7 substantially revised because we always substantially
8 revise what the sponsor sends in.

9 (Laughter.)

10 DR. SZEFLER: That part caught my attention. I
11 don't want to have everybody running around that this is a
12 new bronchodilator that was approved.

13 DR. LI: Rather than take a vote on the 10- to
14 12-day restriction, I would like to have the panel address
15 three items that I had jotted down from our previous
16 discussions earlier this afternoon and this morning that
17 had to do with labeling.

18 One had to do with whether we wanted to
19 recommend drug levels be performed, and if so, at what
20 intervals?

21 The second had to do with whether the
22 importance of the patient's renal function should be taken
23 into account.

24 And the third was whether there was a
25 therapeutic level or a therapeutic range that we wanted to

229

1 include.

2 Again, these are items that came up from our
3 discussion earlier, and I just wanted to revisit them at
4 this point because it is appropriate to address those.

5 Yes, Dr. Hendeles.

6 DR. HENDELES: I think what prompted those
7 comments was reading the sponsor's labeling, and just
8 letting the FDA know that we're concerned about that they
9 be taken into account is really all that I feel the need to
10 do.

11 DR. LI: So, for example, with the issue of
12 drug levels, is there any opinion or any proposal for
13 including anything about drug levels in the labeling?

14 DR. ROTHSTEIN: I think that's one of the
15 wealth of phase IV studies. Some fellows can have a career
16 over this.

17 (Laughter.)

18 DR. HENDELES: I think there's information in
19 the literature, and the way I would deal with that issue is
20 simply to recommend that there be a section on when they
21 should be drawn and what should be done with the results
22 and leave it to the agency.

23 DR. LI: Do you have an opinion about that,
24 about when it should be drawn and how the results should be
25 used?

230

1 DR. SZEFLER: Just to follow up on your point,
2 it's hard to kind of write that levels should be obtained,
3 but levels are the only safety valve that you have with the
4 restrictions of the study. The study was done in a certain
5 age group, certain population, numerous exclusion factors.
6 The levels are something you can use to kind of
7 individualize the dose for your children less than 1,000 or
8 less than 28 or on concomitant therapy. But I don't know
9 exactly, without getting into the details you're referring
10 to, Les, how to write those statements in there, but it's
11 something that it would be nice to have some information
12 around it.

13 DR. LI: Dr. Crim first.

14 DR. CRIM: I guess I'm of the opinion that as
15 far as levels, I don't see a great need to have that in the
16 package labeling as far as the company is concerned.
17 That's because since we don't have any type of
18 pharmacodynamic data, I don't know what to recommend or
19 that the company should recommend since the company doesn't
20 have the data. I think what has been done is what the
21 clinicians have been doing over the years. They'll just
22 titrate the dose up until they get a response or a side
23 effect. If one wanted to just put a general statement that
24 perhaps monitoring may be warranted, to me I think it
25 should be left as nebulous as that because we don't have

232

1 DR. HENDELES: Yes, but I don't feel it's
2 appropriate here.

3 DR. LI: All right.

4 Dr. Cross.

5 DR. CROSS: At the levels they're suggesting to
6 use, they didn't find any really high levels that looked
7 inappropriately high, at least from what I saw.

8 DR. HENDELES: Dr. Pina's review had indicated
9 that there were some levels above 30.

10 DR. CROSS: But not any that were really
11 concerning.

12 DR. HENDELES: I don't know.

13 DR. CROSS: I mean, one option is just to say
14 if higher dose -- I'm sure we'd all agree if higher than
15 recommended doses are used, blood levels should probably be
16 checked.

17 DR. HENDELES: Or what if the patient doesn't
18 respond to therapy? They are giving a loading dose. It
19 might be because their level is too low. We don't know if
20 there's a relationship, and under item number 6, I would
21 recommend that since they have that data, that they examine
22 it with that intent, to look and see whether those patients
23 who failed to respond to the initial loading dose of
24 caffeine had lower levels than the patients who did
25 respond.

231

1 any pharmacodynamic data.

2 DR. KELLY: Yes. It's like digoxin. You dose
3 till they throw up, and then you back off.

4 When you do therapeutic drug monitoring, what
5 you usually aim at is efficacy. So, you would load the
6 patient. If they don't respond, you would probably reload
7 them. If they then responded, you would get a serum
8 concentration at that point to determine what that
9 patient's therapeutic level was because it's that patient's
10 therapeutic level. You can't write that into a package
11 insert that I can see. Then you want to maintain that
12 therapeutic level and it may take any number of different
13 dosages.

14 People like me have made entire careers out of
15 doing that on a daily basis in other types of patients.
16 So, I don't want to take that away and put it in a package
17 insert.

18 (Laughter.)

19 DR. LI: All right. Well, I don't hear a lot
20 of support for including a very specific directive toward
21 measurement of drug levels nor implicitly for a stated
22 therapeutic range.

23 DR. JENNE: My first comment was that we
24 shouldn't specify these levels so precisely, but I still
25 think that they're worth doing. The question of they're a

233

1 check, for example, on renal elimination problems. They
2 may be accumulating. I've got in this pharmacokinetic
3 paper they happen to be going up over 12 days or so.
4 They're continuing to go up.

5 But I don't think we should be so dogmatic
6 about the upper level as if anything over that is a
7 disaster because there should be some flexibility in the
8 package insert, it seems to me.

9 DR. LI: So, perhaps a vote for a more general
10 inclusion of a statement on drug levels rather than
11 something specific. Fine.

12 On the issue of renal function, Les, did you
13 think that a comment or a mention of that in the labeling
14 is important?

15 DR. HENDELES: I think in general there needs
16 to be more specific dosing guidelines than what's in that
17 package insert, including an adjustment for patients who
18 have decreased renal function.

19 DR. LI: Do others agree with that suggestion
20 from Dr. Hendeles? Carroll nodding. Okay.

21 Let's now move on to 5b which is one of the
22 important issues that is before us today. Would you
23 recommend a warning considering the concern of necrotizing
24 enterocolitis and caffeine? We did touch on this earlier,
25 but we need to revisit the idea. Yes.

234

1 DR. HENDELES: I think there should be a
2 precaution or some statement in there that reviews what the
3 animal and human data is in a few sentences so that it
4 informs the clinician of that information but not a warning
5 which to me implies a black box.

6 DR. LI: Is there agreement or dissent?
7 Yes.

8 DR. ROTHSTEIN: I've just got a follow-up
9 question. If an infant develops enterocolitis or abdominal
10 distention, should treatment be stopped?

11 DR. HENDELES: Well, if you stop the treatment,
12 it's still going to go on for five days.

13 DR. ROTHSTEIN: Oh, yes.

14 DR. KELLY: What do you do now?

15 VOICE: Keep going.

16 DR. ROTHSTEIN: So, that's my question. One
17 can say that sicker infants will have more severe apnea.
18 There may be an increased incidence of sepsis in infants
19 with increased apnea, but there is no firm association
20 between the treatment of the apnea and exacerbation of
21 enterocolitis or sepsis. Somehow acknowledging that these
22 two conditions may run together and therefore, people have
23 raised the issue, well, but caffeine or theophylline was
24 used, therefore it's associated. It may or may not.

25 DR. LI: Right. So, you would propose or

235

1 recommend some indication of a potential association with
2 acknowledgement that that association hasn't been proven.

3 DR. HENDELES: Right, a just a disclosure of
4 the problem.

5 DR. SESSLER: I think I'm comfortable with
6 that, for whatever that matters, in the sense that
7 unfortunately we don't have definitive data. What we have
8 is worrisome findings that may be easily explained
9 somewhere else. Obviously it doesn't require something
10 that's a very high level proven association type of
11 warning, but it certainly does need to be mentioned that
12 that was an area of concern in my opinion.

13 DR. LI: That would satisfy you, Dr. Sessler?

14 MR. MADOO: Couched as a warning or as a
15 precaution? How are you are you going to couch this?

16 DR. LI: Well, we heard from Dr. Hendeles a
17 suggestion for more of a comment. I'm not sure you even
18 used the word "precaution."

19 DR. HENDELES: I probably did.

20 DR. ROTHSTEIN: I don't think it merits a boxed
21 warning.

22 DR. LI: So, no support for the warning.
23 Yes.

24 DR. OSBORNE: I would agree, if I read the
25 numbers correctly, that is, the FDA document pointed out

236

1 there was no statistical difference between the groups
2 whether the caffeine group or placebo or by original
3 randomization or adverse events of all patients. In none
4 of those cases was there a statistical difference. We've
5 talked about the small sample size extensively and this
6 certainly could be a type 2 error.

7 But I'd also point out that in the literature,
8 with all the problems that the literature has, there are
9 huge ranges of either prevalence or incidence of NEC, but
10 they range easily within the percentages we're seeing here,
11 which are less than 10 percent. They're often much higher
12 in the kind of population that seems similar to this one.
13 So, at least if it is occurring by association, the numbers
14 are not dramatic, and so I would agree with no warning.

15 DR. LI: Curtis.

16 DR. SESSLER: I would ask that someone look at
17 the statistics again just to clarify that in terms of this
18 garbage area, the exposure area. Granted, it's an unknown
19 but before we categorically state that patients by
20 randomization or by exposure had no statistical difference
21 in these, 0 percent versus 13 percent looks to me by a
22 Fisher's Exact Test that it might be significant, and the
23 same for the sepsis and for the NEC. So, I would just do
24 that before we make the statements that we know.

25 DR. LI: Were those studies done, Dr. Jenkins

237

1 or Dr. Pina?

2 DR. JENKINS: I'll let Dr. Pina answer that
3 question. Then I have a clarification I'd like to make for
4 the committee.

5 DR. PINA: I think I will defer that question
6 to Dr. Gebert.

7 DR. GEBERT: Yes. I did a Fisher's Exact Test
8 on those data and they were not significant.

9 DR. SESSLER: Thank you.

10 DR. JENKINS: The clarification I'd like to
11 offer for the committee is a boxed warning and a warning
12 are not the same things. You can have warnings and they
13 will not be in black boxes. A black box warning is a much
14 higher level of a warning that are reserved for certain
15 circumstances and have the desired impact of conveying the
16 severity of the warning but also they have impacts with
17 regards to how the sponsor may promote the product without
18 providing the entire package insert for the physician.

19 So, just to clarify, there was some discussion
20 earlier that it didn't merit a black box. Other people
21 seemed to equate black box and warning being the same.
22 Almost all drugs have a warning section in their labeling,
23 and often things such as patients who are hypersensitive to
24 the drug, it's contraindicated. That may be in the
25 contraindications or it may be in the warnings.

238

1 it up front at the beginning of the labeling. So, there's
2 sort of a spectrum of ways in which we can get across the
3 concern in the labeling.

4 DR. LI: Well, John, would it be useful to get
5 a sense from the group how concerned the panelists are
6 about the risk of NEC?

7 DR. JENKINS: Yes. I think that would be useful
8 because it's clear that we've gotten the feeling that there
9 should be something in there stating what is known about
10 the association between methylxanthines and NEC, and it
11 would be useful to hear from this panel what your level of
12 concern is. I think Dr. Bilstad almost laid out a
13 hierarchy of no concern, therefore no statements;
14 precaution; a warning; a black box warning in the warnings
15 sections; a black box warning in the front of the labeling.
16 So, it would be useful to know what your level of concern
17 is and how much you'd like to convey that information to
18 the prescribing clinician.

19 DR. LI: Why don't we go around the table?
20 Actually, Les, you had your hand up, so you'd like to make
21 some comments.

22 DR. HENDELES: I have a precaution level
23 concern.

24 DR. LI: Thank you.

25 DR. KELLY: Precaution.

240

1 But I just wanted to clarify a warning is not
2 necessarily a black box warning. A black box warning is
3 usually reserved for much more significant definite
4 associations and more severe potential adverse effects.

5 DR. HENDELES: How does a precaution differ
6 from a warning?

7 DR. JENKINS: I don't have the regulatory
8 definitions of those sections here with me, but warnings
9 are generally viewed as things where if the adverse event
10 occurs, it could be serious or life-threatening, whereas
11 precaution is a little bit lower standard. There are
12 specific definitions of those in the CFR, and I don't know
13 if Dr. Bilstad knows the definitions. He's indicating that
14 he doesn't.

15 DR. BILSTAD: Well, it's really just a matter
16 of degree of how strong we think that the message should
17 get to health care providers. If there's concern about a
18 safety problem, the milder concern is to put it into
19 precautions, draw it to health care providers' attention.
20 If the concern is stronger, it may warrant going into the
21 warnings section, and as John indicated, if we have a great
22 deal of concern about it and it's potentially life-
23 threatening or has been demonstrated to cause mortality,
24 then it may merit a boxed warning which again can be in the
25 warnings section, or if we're really concerned, we'll put

239

1 DR. JOBE: I would just like to see that
2 clinicians know that there's a potential association so
3 that that could be followed up if necessary.

4 DR. JENNE: I'd just say that we're uncertain
5 and at least it should be mentioned.

6 DR. OSBORNE: I'm somewhere between precaution
7 and warning. I don't have the clinical experience, but I'm
8 certainly concerned there's an association. I'll say
9 precaution.

10 DR. CRIM: Precaution.

11 DR. LI: Precaution for myself.

12 DR. ROTHSTEIN: I'll leave it for the
13 discussions between the FDA and the sponsor to work out.

14 DR. CHINCHILLI: Yes, I agree. I think the FDA
15 needs to make that judgment, based on the fact that it's
16 not clear-cut, whether or not there is an association.

17 DR. SZEFLER: I lean towards precaution.

18 DR. CROSS: I'm leaving it to the FDA but note
19 that their indication of the difference between precaution
20 and warning is the severity of the complication, not the
21 certainty of the complication or uncertainty.

22 DR. SESSLER: I agree. I think precaution is
23 about right, but it is a very severe thing. We're hampered
24 by a lack of clear-cut data unfortunately.

25 MS. CONNER: Precaution.

241

1 DR. GOLDSMITH: I would agree with precaution.
2 One or two other comments.
3 I know Dr. Sessler has been concerned about the
4 adverse events, and those babies who were exposed -- I
5 don't know how many of them because I didn't take notes on
6 this -- were rescued. So, I wonder whether they truly had
7 apnea of prematurity by that point or whether they were
8 suffering from NEC or sepsis when somebody switched them
9 out from their possibly being in the not-exposed category,
10 in the placebo category, because they weren't responding
11 and they already had the beginnings of sepsis. So, one of
12 the things that might be put in the precaution is that
13 nonresponders should be looked at for other causes such as
14 sepsis and necrotizing enterocolitis.

15 The second thing I would add would be that
16 again drug interactions -- the use of caffeine in
17 association with other drugs as potential causes for NEC or
18 sepsis has not been investigated so that it's not just
19 caffeine in itself, but in association with other drugs.

20 MR. MADOO: It looks like we had eight at the
21 precaution level and seven at the let FDA take care of it.

22 DR. LI: Thank you, Mr. Madoo.

23 Let's tackle question number 6. If caffeine
24 citrate were to be approved for this indication, what, if
25 any, post-marketing studies would you recommend be

242

1 completed by the sponsor? We did actually tackle this to a
2 limited extent. Let's try to give as much assistance as
3 possible.

4 Yes.

5 DR. JENKINS: Jim, if I could just ask the
6 committee, it would be very useful to us if we could hear a
7 discussion of what studies you think should be a condition
8 of approval, in other words, a required phase IV study, a
9 phase IV commitment, versus studies that might be nice if
10 someone would do them. So, it's kind of what's needed as a
11 condition for approval, given that the committee has
12 recommended approval, versus what would be nice in the
13 broad spectra of things which you really wouldn't put it at
14 the level that it had to be agreed to before you would
15 recommend approval.

16 DR. GOLDSMITH: Maybe as an introduction to
17 this -- and I'm not exactly sure of my numbers, but the
18 neonatologists here are very familiar with working with
19 other people's drugs. We get to use all the drugs that
20 have been approved for adults and for children, but never
21 looked at for neonates. I think, if I'm not right -- Alan
22 may correct me on this, but surfactant probably is the only
23 drug that has been approved specifically for neonates, and
24 this may be the second.

25 DR. JOBE: Indomethacin for FDA is another one.

243

1 DR. GOLDSMITH: Okay. So, two or three drugs.
2 So, what we wind up with is giving all kinds of
3 drugs. We gave indomethacin for a long time before it was
4 approved. I remember back in 1976 that discussion at the
5 SPR's on giving it and what the consequences were.

6 In surfactant, there were 10,000 children
7 looked at before it was approved by the FDA or some huge
8 number in trials before we got a chance to use it
9 clinically in 1990 I guess.

10 Several people said that this is a very
11 important step because we're beginning to take some drugs,
12 orphan drugs and other drugs, and say they have neonatal
13 indications for use and they should be looked at, but we're
14 beginning to see, as this committee has heard all day, what
15 the tremendous difficulties of this are when you have drugs
16 that are already in clinical use, that people won't take to
17 an IRB that physicians want an easy opt-out. So, we have,
18 I think, some real considerations here that we should have
19 some definite stage 4 studies required.

20 Now, I don't know whether you can do any more
21 stage 4 efficacy studies, but certainly safety has to be
22 required and some way of monitoring safety over the next 12
23 to 24 months at a minimum, if we have 20,000, 30,000,
24 40,000 kids a year treated with this, has got to be done so
25 that as we approach these drugs that are now being offered,

244

1 to compare 10,000 children treated with surfactant and I
2 don't know how many thousand with indomethacin versus the
3 small numbers here, I think we do have tremendous safety
4 concerns in going forward.

5 DR. LI: Dr. Rothstein?

6 DR. ROTHSTEIN: The two areas that I would like
7 to see commitments to is, one, the developmental
8 pharmacology of this drug, the blood concentrations and the
9 accumulation of this drug in the 27-weeker versus the 32-
10 weeker, and then anticipating what's going to go on in the
11 community, what happens when the dose is increased? Is
12 there some sort of pharmacodynamic effect that we're going
13 to see when the loading dose, instead of 10, becomes 15,
14 when the maintenance dose is increased by 50 or 100
15 percent? Do we see a change either in the efficacy of the
16 drug or do we see a change in the side effects?

17 DR. LI: Would those suggestions be under the
18 required or nice-to-know categories?

19 DR. ROTHSTEIN: Well, I think the company is
20 going to very much like to know about how their approved
21 drug is now being used. I think the FDA might want it
22 also, but I think the company has a vested interest in
23 knowing what's going on with the drug.

24 DR. KELLY: Like the neonatologists who believe
25 this drug works, I believe that there is a concentration-

245

1 effect relationship, and I think there should be dose
2 ranging studies. I don't know the design of those, but I
3 think that's one area that we really need to know more
4 about. I think there's evidence in the literature that
5 there are differences in response rate, and so I think a
6 dose ranging study is necessary.

7 DR. HENDELES: In response to Dr. Jenkins'
8 question, I think before the drug is approved, that the
9 available literature needs to be analyzed and a lot of
10 these questions can be answered, such as the relationship
11 between renal function and half-life of the drug so that
12 one could scale down the maintenance dose.

13 I think that through the network, there ought
14 to be after approval some attempt to see whether there's an
15 increased incidence of NEC in association with the use of
16 this drug as opposed to CPAP or something else. If there
17 is, I do support what Dr. Kelly said about looking at the
18 relationship between concentration and effect. If there is
19 no strong relationship, it may be that you can give a
20 smaller dose of the drug and decrease any risks from it.
21 So, I think that would be nice to know afterwards.

22 But right now I think that we have sufficient
23 information to approve it and I think the dosing that's in
24 the package insert could be adjusted based upon the
25 knowledge of the biopharmaceutics and pharmacokinetics that

246

1 is available.

2 DR. LI: Curt, did you have a comment you'd
3 like to make about this?

4 DR. SESSLER: I think the safety part is
5 certainly key. I would include sepsis with NEC just
6 because of the observation in the database that we have
7 before us. Even though this may not have received
8 attention so much in the past, I think we're obligated to
9 look at that along with the NEC question in terms of
10 follow-up safety.

11 DR. LI: Vernon, do you have any thoughts about
12 whether any additional studies should be required as a
13 condition for approval?

14 DR. CHINCHILLI: No. My main concern is the
15 safety. So, I have similar concerns as Curtis.

16 DR. CROSS: Yes, mine is safety. I'm unclear,
17 though, how one would handle sepsis because sepsis syndrome
18 and suspected sepsis and bacterial proven sepsis and how
19 you do the blood cultures, et cetera gets to be pretty
20 complicated to deal with even in the adult ICU. So, I'm
21 certainly interested in my own feeling on the safety in
22 terms of the enterocolitis aspect, but in terms of the
23 septic part, I'm not too sure without a stronger
24 theoretical construct that I would make the company start
25 recording sepsis and proved sepsis and maybe sepsis and

247

1 sepsis syndrome and hemodynamic over-reactivity and
2 whatever.

3 DR. SESSLER: I would make it simple and do
4 bacteremia. In adults we know that only 30 or 40 percent
5 of septic patients have bacteremia, but if bacteremia is
6 the only hard definition that could be utilized, then that
7 would be better than nothing.

8 DR. LI: Dr. Jenkins.

9 DR. JENKINS: Assuming the drug is approved,
10 it's very likely that it will become standard of care even
11 more so than it is now. So, some of these questions that
12 you're suggesting about follow-up issues on NEC and sepsis
13 -- I'd be interested if you have any ideas how those
14 studies would be conducted. In other words, what would the
15 control groups be if nearly all of the patients with this
16 disease were receiving caffeine citrate? Would we limit
17 ourselves to historical controls, or how would you get some
18 handle on whether the incidence of NEC is higher? What
19 would your control group be?

20 DR. LI: Dr. Rothstein has the answer.
21 (Laughter.)

22 DR. ROTHSTEIN: We've heard that in some units
23 this drug is started while children are still being
24 ventilated in preparation for discontinuation of mechanical
25 ventilation. You can very easily double-arm that. So,

248

1 some kids are not started on it until mechanical
2 ventilation is discontinued, and they demonstrate disorders
3 of respiratory control. The practice already is
4 established of starting it earlier. So, you have a way of
5 perhaps getting a double-arm study there.

6 DR. LI: Molly?

7 DR. OSBORNE: I think it depends a lot on what
8 kind of database is available. If there's a database
9 through the NICHD that would have enough information,
10 certainly one simple way to do it would be to identify NEC
11 which, first of all, is going to need a longer study than
12 this anyway. The articles suggest 25 percent occur 30 days
13 after birth. So, we're missing a lot of them perhaps in
14 the study. And look at dose response. I mean, at least
15 dose response so you can get some information on dose, some
16 information on weight, and get some information, but doing
17 it that way without having to get a placebo group, although
18 controls would be great.

19 DR. SZEFLER: Correct me if I'm wrong, but I
20 would think NEC is a complication that you monitor in a
21 unit, and so good units that have good data would be places
22 to go to see what happens to the incidence before and after
23 approval. So, I think historical controls in a controlled
24 setting would be a good place to start in terms of looking
25 at changing incidence.

249

1 DR. JOBE: I think again the NICHD Neonatal
2 Network database and the Vermont Oxford databases are
3 published every year or two with incidences versus birth
4 weight for NEC, IVH, all the alphabet soup of neonatology.
5 One can at least get that sort of epidemiologic data with
6 the introduction of a drug. That was done very effectively
7 for surfactant and its introduction.

8 DR. CRIM: Who reports to those databases? Is
9 it just major university centers or is it even community
10 hospitals that have a pediatric --

11 DR. JOBE: There are two different databases.
12 The NICHD network is 14 university centers. The Vermont
13 Oxford is about 100 non-university centers by and large.
14 So, they have different flavors to them.

15 DR. CRIM: Yes, that's what I was wondering
16 because if you have a sicker population in the university
17 setting, then the incidence may be higher than, let's say,
18 some pediatric hospital out in the communities.

19 DR. LI: Dr. Goldsmith, did you have an
20 additional comment?

21 DR. GOLDSMITH: Maybe Alan can comment on this
22 in terms of what the NICHD did, but obviously the same
23 problems that you have with sepsis, we have in NEC. There
24 are stages, the Bell's modified criteria, and what level
25 does it have to rise to, to what stage in the Bell's

250

1 criteria before NICHD listed it as a complication of NEC?
2 Do you have information on that?

3 DR. JOBE: I don't know the definitions being
4 used right now.

5 DR. GOLDSMITH: We have similar kinds of issues
6 in terms of sepsis, and that obviously has to be looked at
7 carefully.

8 DR. LI: So, do I sort of hear, as a summary of
9 what was recommended, that a safety post-marketing study be
10 conducted primarily again looking at NEC and perhaps sepsis
11 too as a follow-up of safety and that this recommendation
12 would be required as a condition for approval? I see Dr.
13 Goldsmith nodding.

14 Curt, what's your feeling about the requirement
15 of this type of study for safety?

16 DR. SESSLER: Just as you stated it.

17 DR. LI: Is there anyone in disagreement?

18 DR. JENNE: I don't understand the definitions
19 here. You say a post-marketing study. In other words, it
20 would be marketed.

21 DR. LI: Yes.

22 DR. JENNE: And this would be a requirement for
23 the company to continue studying along certain lines.

24 DR. LI: Yes, as opposed to optional.

25 DR. JENNE: I would put a dose-response in the

251

1 same category frankly. Whether the company should do it or
2 somebody else be commissioned to do it, I think there could
3 be some ingenious ways of finding this information out.

4 DR. LI: So, I think the first issue is that
5 there was agreement I believe on our recommendation for a
6 post-marketing safety study looking, in particular, at NEC.

7 And the second issue that Dr. Jenne brought up
8 and which we discussed is studies regarding dose ranging
9 studies or concentration effects.

10 John, is it your opinion that you would
11 recommend that this be a required activity that would be a
12 condition for approval?

13 DR. JENNE: Yes, I think it should be done by
14 reputable investigators. It doesn't take a large group to
15 do this. It doesn't take controls necessarily to do a
16 dose-response study. But I think the company should have
17 the first chance to do this.

18 DR. LI: Dr. Kelly, I see you nodding. Does
19 that mean you're in agreement?

20 DR. KELLY: I agree and I think there are ways
21 to analyze sparse data now where you don't have to get
22 large amounts of blood samples and stuff from the patients
23 to do it. So, I don't think it's that difficult to do.

24 DR. LI: Any other comments from the group,
25 either agreement or disagreement?

252

1 (No response.)

2 DR. LI: Okay, thank you.

3 That really concludes the six questions that we
4 were asked to address. Let me ask Dr. Jenkins if he would
5 like to make some comments before we adjourn for the day.

6 DR. JENKINS: I would just like to thank the
7 committee. I think you've done an outstanding job of
8 reviewing the data and really have a very good discussion
9 today. Particularly I'd like to thank the neonatology
10 consultants who joined us today: Dr. Goldsmith, Dr.
11 Rothstein, and Dr. Jobe. I think they really added a lot
12 to the discussion and brought a lot of information that
13 maybe most of us who are not neonatologists don't have a
14 very good feel for. I think it was a very productive and
15 useful session, and we'll certainly take your
16 recommendations under consideration very strongly.

17 DR. LI: Yes, Peter.

18 DR. ROTHSTEIN: Since the transcripts are
19 available of this hearing, is the data that was presented
20 here now in the public forum?

21 MR. MADDOO: It has to go through FOI. We'll
22 process it through FOI and then you can make a request for
23 it.

24 DR. LI: Yes, Stan.

25 DR. SZEFLER: If I could make one other

253

1 suggestion. I don't know if it comes under here, but I
2 would encourage a full publication of the study. I don't
3 know if you can make that a requirement. At least you have
4 some reference in terms of public access.

5 DR. ROTHSTEIN: That depends on the journals.

6 DR. SZEFLER: Yes, but I mean, I would
7 encourage a smaller detailed summary.

8 DR. JENKINS: One thing I can say to that, if
9 the drug is approved by the agency, the agency's reviews of
10 the NDA become available to the public under the Freedom of
11 Information Act. Those may be partially redacted to
12 protect any proprietary information, but the FDA reviews
13 are available. In fact, they're now available
14 electronically on the World Wide Web very quickly after the
15 approval. So, the medical officer review that you have,
16 once it's finalized, if the application is approved, as
17 well as the other discipline reviews, are available under
18 the Freedom of Information Act which, if the drug is
19 approved along its current time frame, might occur before
20 publication could be out there also.

21 DR. LI: Dr. Osborne?

22 DR. OSBORNE: Is it also possible it would come
23 out in the Medical Letter?

24 DR. JENKINS: The Medical Letter generally does
25 review newly approved therapies, and the FDA does receive

— 254 —

1 pre-publication copies of those documents for review and
2 comment. But I can't speculate on whether the Medical
3 Letter will consider this to be a substantive enough
4 approval that they'll put it in their publication, which is
5 very widely distributed and not just to neonatologists.
6 This is a pretty focused area of indication.

7 DR. LI: Okay. Thanks to the panelists.
8 Thanks very much to Dr. Jenkins, Dr. Pina, the FDA. Thank
9 you to the sponsor.

10 The meeting is adjourned.

11 (Whereupon, at 3:47 p.m., the committee was
12 adjourned.)

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— 255 —

- 0 -

0.05 114:20
0.7 21:4

- 1 -

1,000 20:14 29:12 43:22
43:25 48:3 65:8 81:7
81:19 125:7 152:21
160:13 217:11 232:7
1,029 81:10
1,200 173:21
1,300 173:21
1,400 173:21
1,500 60:9 60:18 173:7
206:6
1.1 173:6
1.30 138:19
1.5 28:24
1.6 95:24
1.7 96:6 123:24
1.89 21:4
10,000 175:2 244:6
10-day 102:17
10.1 41:6
10.6 95:22
100 21:20 21:23 55:11
86:2 88:19 95:4 125:8
150:2 172:23 245:14
250:13
10:15 80:21
11:30 120:19
11 32:13 34:4 95:20
117:9
12-day 159:22 225:17
229:14
12-hour 54:17 54:20
124 98:4 102:16
12:20 120:15 120:18
120:20
12:30 121:2
12 28:4 30:24 35:8
35:9 48:2 58:21 67:23
80:12 81:17 84:4 84:7
90:25 102:7 172:24
188:15 197:16 200:6
200:9 200:21 220:22
225:13 226:13 226:21
228:5 234:3 244:22
13 81:17 107:8 110:19
200:13 207:11 218:13
220:14 237:21
144 54:15
14 32:14 33:19 34:14
41:9 58:22 58:23 80:10
200:5 250:12
151 98:5
15 15:19 41:9 60:2
74:4 80:20 95:3 95:8
95:15 95:18 96:3 97:2

124:25 127:3 130:18
146:19 168:11 169:14
169:24 172:19 174:10
245:13
160 165:20
16 32:15 33:20 34:21
84:5 172:18
17 80:13 81:17 94:11
145:22
18.8 34:21
18 42:5 58:23 72:2
94:24 145:9 172:18
174:10 221:9
1960's 130:12
1970's 17:10 130:12
131:20
1970 213:21
1975 213:17
1976 244:4
1980's 17:10 131:20
1980 97:13
1983 97:20
1985 16:5
1986 16:12 72:13 98:4
98:8
1990 244:9
1991 15:5 41:7 94:23
1992 120:2
1993 15:7
1994 71:25 78:2
1995 98:16 160:18
1996 15:13
1997 73:25
19 34:22 80:10
1a2 106:20 176:3

- 2 -

2,000 216:17
2,500 125:8 152:18
2-hour 54:17
2-week 102:17
2.5 30:4 30:14
20,000 173:12 174:16
206:6 244:23
20/20 192:14
200 171:21
20 8:16 18:11 28:8
28:23 32:12 35:20 35:22
35:23 36:24 37:16 39:15
48:22 50:25 61:2 61:14
64:10 83:11 85:9 85:12
97:5 103:13 110:25
111:21 130:18 151:20
164:14 167:6 168:10
168:11 169:25 177:24
192:3 203:5 205:18
210 139:6 141:25
22 15:17 20:15 36:5
204:15
23 23:2 137:23 153:5
23rd 15:7
24-hour 35:9 68:2
71:11 95:6 95:7 115:25

124:2 135:8 148:22
24-hours 28:12
248 81:13
24 21:3 21:5 27:10
28:7 30:9 30:19 35:6
35:9 37:18 44:10 52:19
52:22 52:24 53:17 63:14
66:19 67:20 68:4 69:5
83:10 84:11 85:7 86:16
86:18 86:20 89:2 89:23
90:7 95:19 95:21 95:21
95:22 95:25 96:6 154:10
244:23
25-fold 170:7
25 15:18 30:5 39:15
87:21 125:9 127:23
152:17 170:16 249:12
26 122:22 194:18
27-weeker 194:19
245:9
275 72:14
27 94:5 122:22 126:2
28-weeker 122:6
124:11
28-weekers 122:22
28 15:13 27:21 28:10
43:10 44:5 44:9 44:10
60:4 65:9 65:14 83:9
87:20 138:18 226:3
232:8
29 90:10

- 3 -

3,000-week 121:24
3-day 47:9
30,000 244:23
30-minute 30:3
300 171:12
30 25:25 41:16 41:21
74:4 168:13 203:13
231:9 248:4 249:12
31-weekers 124:15
31.4 39:12
32-37-weekers 122:20
32-week 44:5
32-weeker 124:11
125:19
32-weekers 43:10
122:21 124:13
32 27:22 28:11 60:4
65:9 65:14 68:20 68:23
69:5 126:11 225:25
226:7 226:15 227:15
245:9
33 21:3 83:9
34-week 225:25
346 26:4 165:24
34 68:20 68:23 69:5
153:6 195:19 226:7
226:15 226:23
35 74:2
36 69:21 70:5 101:16
168:18 195:14 195:19

226:23 227:15
37-weeker 122:7
125:21
37 32:13 126:11 135:21
38 195:14 196:5
39 31:13
3:47 255:11

- 4 -

4.95 86:20
40,000 244:24
40 64:15 74:7 169:13
248:4
41 22:21 25:5 25:23
31:10 102:11 138:19
43 34:16 37:15
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45 32:11 135:21
46 31:9 31:13 161:24
48-hour 27:10 52:19
63:15
482 81:11
48 28:25 52:22 53:17
84:11 85:7 108:15

- 5 -

5.05 34:25
5.1 41:13
50-mile 163:22
52 81:16 196:17
53 86:8
55 81:16
56 196:17
57 87:5 95:20 102:7
102:7
59 94:6
5a 198:24
5b 234:21

- 6 -

6.13 34:24
60 127:17
63 81:15
65 86:8 187:7
66 165:20
67 91:14
69 37:13

- 7 -

7.2 86:21
7.6 90:12
70,000 174:22
70 43:12 44:5 85:8
103:12 110:23 110:23

111:21 127:17 173:9
205:11 210:13
71 99:6
72 108:15
73 138:12 138:17
74 95:19 102:7
76 87:3
77 91:17
78 85:4 91:14 91:16

- 8 -

8-19 80:6
8.9 41:12
800 96:9
80 18:13 19:4 43:23
71:24 110:7 110:11
127:18 139:4 141:24
82 98:18
84 91:16 125:7 152:20
85 31:12 31:15 125:8
86 75:21
87 31:9 31:11 81:10
91:17
887 22:22

- 9 -

90-year-old 168:9
90-year 168:11
90 127:18
942 81:11
95 138:18
98 98:19

- A -

a.m 120:19
Abbott 164:21
abdominal 79:4 235:9
ability 79:8 164:11
164:15 202:25 211:10
abnormal 28:18 69:25
abnormalities 28:18
203:12
absence 160:5 160:11
211:7
absolute 219:23
absolutely 52:23
104:4 116:12 183:19
187:18 224:18
abstain 201:2 201:7
abstention 201:11
222:4
abstentions 200:7
218:11
Abstracts 20:7
abuse 164:22
academic 159:16
Academy 151:3 152:6

accelerated 15:18
accept 132:7 132:9
133:24
acceptance 221:17
accepted 214:16
access 254:4
according 22:14 27:9
32:22 34:8 34:17 40:19
41:6 53:15 54:13 56:14
85:13 92:3 97:6
account 112:9 138:5
219:2 229:23 230:9
accounting 138:3
accumulating 234:2
accumulation 55:8
124:4 245:9
achieve 176:19
achieved 88:14 90:13
acidosis 41:2 153:2
acknowledge 10:17
82:14
acknowledgement
236:2
acknowledging 235:21
acknowledgments
10:15
acronym 15:11
across 35:10 51:16
54:25 55:8 165:4 240:2
Act 182:11 254:11
254:18
action 58:14 58:15
180:16 181:24
actions 19:7
active 15:24 19:6 29:9
activity 228:20 252:11
actual 43:21 63:14
63:19 63:21 63:23 98:19
198:14 220:4
acute 69:18 70:10
ad 11:25 62:23
add 45:14 52:10 73:12
88:19 103:25 188:13
190:19 198:11 242:15
added 184:25 253:11
addition 21:16 87:15
additional 20:17 25:9
25:20 41:24 48:17 77:10
81:2 81:24 105:22
171:23 221:5 221:6
247:12 250:20
address 13:17 14:7
45:9 54:21 60:22 62:17
63:17 79:11 97:25
105:12 115:13 160:7
163:14 164:18 167:3
167:7 176:23 179:23
194:5 199:16 201:13
216:2 217:23 225:11
229:14 230:4 253:4
addressed 76:13 109:18
117:4 159:21 161:13
183:2
addressing 106:12
adenosine 24:8 192:25
adequate 11:23 100:4

159:3 180:3-180:5
180:15 181:13 181:17
182:13 185:6 193:10
198:23 206:24
adequately 226:22
adjourn 253:5
adjourned 255:10
255:12
adjust 101:3 107:12
149:7 177:9 177:19
adjusted 246:24
adjusting 52:7 61:24
75:15
adjustment 99:17
107:2 234:17
adjustments 99:13
139:11
administered 30:2
30:7 30:8 30:9 30:13
30:18 30:24 42:5 78:8
153:6 167:16 219:23
administration 16:21
40:6 78:24 155:6 157:13
admitting 100:19
adult 8:20 8:24 9:14
58:3 99:7 109:2 136:11
156:21 171:9 171:12
176:19 186:4 205:13
207:19 222:7 222:7
223:7 247:20
adults 57:14 57:15
57:16 57:19 106:19
106:21 123:10 123:17
123:22 133:5 160:6
160:8 166:7 176:4
176:6 176:16 243:20
248:4
advance 180:20
Advanced 41:2 83:19
advancing 126:12
126:22
advantage 76:8 137:17
138:23 140:7 155:8
155:11 157:12 223:15
advantages 26:7 157:13
adverse 16:24 23:7
23:8 23:12 23:20 23:21
23:22 23:23 24:13 24:17
25:22 26:12 33:8 38:11
38:11 38:24 39:17 40:5
41:15 57:18 57:20 76:21
92:11 92:12 92:19 92:22
92:25 93:7 93:14 96:16
96:19 97:22 100:15
135:16 156:18 156:25
161:17 166:2 237:3
239:4 239:9 242:4
adversely 24:10 25:18
77:7
advice 177:9 177:18
Advisory 8:4 10:11
10:19 11:10 11:14 11:18
14:15
advocate 188:19
advocated 19:17
AE'S 38:25 40:15

AE 38:14
Affairs 14:16 15:22
26:21
affect 24:10 25:18
76:7 77:7 77:13 146:2
affected 190:23
affiliation 50:13
affirmative 200:18
224:10 224:11
afflictions 122:11
afield 131:20
afternoon 113:3 114:12
120:17 121:4 123:16
229:16
afterwards 246:21
aged 168:8
agency's 254:9
agency 13:6 16:12
136:21 179:14 180:2
180:13 180:20 180:25
181:7 181:8 181:15
181:24 192:15 209:9
229:4 230:22 254:9
agenda 13:5 13:11
42:21 42:22 150:7
agent 15:14 189:19
220:15
agents 97:8 186:4
222:25
ages 226:14
aggregate 167:21
agree 40:21 64:21
108:3 113:8 113:13
132:7 133:21 180:13
195:12 197:3 200:12
208:20 209:5 231:14
234:19 236:24 237:14
241:14 241:22 252:20
agreed-upon 113:15
113:19
agreed 113:11 174:7
180:20 200:18 243:14
agreeing 10:19 11:15
agreement 103:13
235:6 252:5 252:19
252:25
agreements 209:17
aim 233:5
air 127:23
airway 19:19 28:21
127:20 212:24
akn 109:4
al 72:13 94:22 95:10
97:13 97:20 98:3 98:8
98:16 120:2
Alan 9:16 14:15 164:10
225:15 243:21 250:21
alarm 91:20 91:22
130:19
Albert 82:17
alcohol 58:2
allay 158:18 206:24
229:5
Allen 14:21 69:23
allergist 8:8
Allergy 8:4 8:16 14:14

allow 50:7
 allowed 74:6 85:20
 92:14 93:21 130:18
 alluded 111:8 157:23
 157:24 160:17
 alluding 186:25
 alphabet 250:4
 ALT 29:2
 alter 194:4
 altered 19:9
 alternative 54:8 215:24
 ALTES 69:18 227:22
 altogether 208:24
 amazed 186:12
 ambitious 61:3 61:16
 amended 84:13
 amendment 30:25
 84:5 84:14
 aminophylline 19:21
 43:17 97:8 97:17 97:21
 97:22 169:7 170:16
 213:9 213:10 217:21
 amounts 75:18 133:14
 252:22
 analyses 61:25 62:2
 63:23 84:20 88:7 104:14
 104:17 111:24 111:25
 112:2 112:12 114:19
 136:22 138:25 139:9
 139:12 139:16 140:9
 143:17 146:7 146:15
 155:24 180:23
 analyze 115:18 136:16
 140:4 148:18 252:21
 analyzed 85:3 86:23
 93:7 140:16 246:9
 Analyzing 87:8 92:21
 141:6 219:20
 and/or 28:21
 anecdotal 185:11
 anemia 40:14
 anesthesiologist 9:7
 144:25
 anesthesiologists
 192:23
 animal 213:5 213:9
 235:3
 animals 97:23
 announcements 12:9
 answer 54:11 60:7
 61:9 61:21 64:4 65:19
 72:9 80:25 89:22 110:8
 129:8 210:9 210:11
 210:17 210:18 226:9
 227:18 238:2 248:20
 answered 58:6 246:10
 answers 53:20 80:18
 82:2
 antagonism 24:8
 antagonist 186:6
 192:25
 antagonists 29:7
 105:4
 ante 134:8
 antibiotics 108:21
 203:2 203:10

antibodies 186:3
 anticipate 57:15 225:23
 anticipated 118:16
 143:9 160:10
 anticipating 245:10
 anticipation 181:5
 anxieties 158:18
 anybody 152:2 158:16
 226:4
 anyway 66:25 101:20
 139:24 195:4 195:6
 249:12
 anywhere 61:23 125:7
 Apache 109:3
 apart 165:10
 apnea-free 53:23 89:16
 89:20 89:21 90:4 90:15
 apneas 86:18 86:20
 89:15 89:17 89:23 90:7
 91:7 91:11 91:16 95:21
 95:22 95:25 104:13
 104:16 107:16 109:19
 119:19
 apneic 46:3 46:12
 68:23 71:10 73:11 95:4
 104:7 109:6 141:6
 141:23 150:3
 apparent 59:10 212:25
 appearance 13:3
 appeared 49:22 117:12
 appears 26:3 49:24
 155:21 156:3 156:24
 appendages 38:20
 appended 42:21
 applicable 220:25
 application 27:5 153:21
 154:16 154:22 155:18
 155:23 159:23 162:11
 162:12 162:21 162:22
 215:8 215:9 228:23
 254:16
 apply 222:22
 appointed 15:14
 appointment 12:17
 appreciate 11:12
 186:14
 approach 14:4 115:7
 139:17 139:18 140:3
 151:21 176:9 203:5
 244:25
 approached 174:6
 174:10
 approaches 195:10
 approaching 123:25
 152:14
 appropriate 65:18
 75:8 130:19 160:2
 171:8 192:5 207:14
 230:4 231:2
 appropriately 207:12
 approvability 184:11
 199:17 224:10 224:12
 approval 158:14 162:22
 171:6 179:8 180:16
 181:10 182:5 184:11
 186:22 189:2 189:3

189:5 204:16 205:10
 211:14 211:15 220:15
 220:16 224:19 224:21
 243:8 243:11 243:12
 243:15 246:14 247:13
 249:23 251:12 252:12
 254:15 255:4
 approve 195:4 205:8
 210:19 246:23
 approved 17:3 19:20
 48:8 148:15 152:3
 152:12 153:20 154:15
 155:15 158:16 158:21
 158:22 161:14 162:8
 162:9 162:17 162:18
 164:17 174:15 196:25
 198:7 209:10 209:23
 211:11 211:12 211:21
 218:19 219:25 220:20
 223:10 223:12 223:13
 229:12 242:24 243:20
 243:23 244:4 244:7
 245:20 246:8 248:9
 254:9 254:16 254:19
 254:25
 approving 160:4 171:6
 187:21 187:22 223:11
 approximate 35:20
 36:24 37:15 60:10 81:7
 81:19
 approximately 34:16
 34:21 67:22 70:24 72:2
 152:20 175:2 206:5
 216:17
 April 16:12
 Aranda 40:19 151:25
 155:14 159:10 160:12
 161:10
 arbitrarily 114:20
 ARDS 219:25 223:2
 aren't 48:11 168:22
 176:16
 argue 111:18 204:12
 arises 137:15
 arm 30:18 98:15
 arrangements 103:23
 arrived 42:17
 arteriosis 46:11 47:2
 66:3
 artery 97:7
 article 102:21 119:24
 articles 20:14 20:19
 21:12 94:6 94:7 94:8
 106:3 118:22 249:12
 articulate 50:13
 artifact 140:16
 ashamed 176:4
 aside 53:7
 asking 90:19 113:7
 114:13 115:9 118:20
 121:5 184:13 184:14
 aspect 105:2 228:22
 247:22
 aspects 18:2
 aspirate 24:20
 assay 163:21 163:24

169:19 169:24
 assays 169:15 169:16
 assess 31:3 92:19
 134:7 162:14
 assessed 92:24 109:22
 227:16
 assesses 63:9
 assessing 156:21
 assessment 92:12
 asset 188:3
 assigned 27:5 31:10
 32:11 32:13 39:6 134:19
 assistance 243:2
 assistant 15:25
 assisted 14:24 29:4
 associate 151:6
 associated 17:19 18:11
 18:14 18:17 40:3 40:6
 40:10 78:3 76:24 91:11
 91:15 98:24 105:25
 131:8 169:7 178:9
 178:11 206:14 208:8
 235:24
 associating 25:6
 association 25:3 72:17
 72:24 73:6 96:13 96:23
 97:14 100:19 100:24
 105:21 105:23 106:6
 192:20 206:9 235:19
 236:2 236:10 237:13
 240:10 241:2 241:8
 241:16 242:17 242:19
 246:15
 associations 239:4
 assume 39:12 130:24
 216:14
 assumed 60:25 85:6
 assuming 130:19
 248:9
 assumption 30:16
 assumptions 64:18
 assurance 17:21
 AST 29:2
 asterisks 89:7
 asthma 8:16 136:10
 136:17 150:24 164:13
 214:8
 asthmatics 136:11
 Atlanta 8:17
 attachment 183:18
 attacks 21:18 51:19
 138:4 138:9 138:10
 attempt 107:12 246:14
 attend 11:15
 attendant 189:16
 attending 10:13 83:13
 91:20 216:22 216:22
 attention 27:11 32:10
 33:19 34:13 35:6 35:19
 36:4 36:23 37:22 38:23
 89:18 94:22 96:24
 152:22 229:10 239:19
 247:8
 attributed 39:17
 attributes 17:19
 audience 10:13 14:3

14:4 14:6
August 15:17 15:18
author 120:2
authorities 214:9
authors 40:21
automatic 207:7
automatically 108:12
autopsy 42:6 208:6
availability 164:19
175:5
average 21:22 58:19
58:21 68:6 70:21 95:4
avoid 204:13
avoidance 204:14
awake 125:12 127:8
aware 13:13 44:8
197:4 206:9 206:14
axis 88:13 89:5 89:15
90:5 122:23

- B -

baby 36:3 39:4 39:5
48:12 54:7 54:8 56:6
56:7 67:2 68:24 68:25
69:11 133:17 134:3
134:5 134:7 175:20
197:24 225:20 225:21
225:23 227:13 227:16
back 47:8 64:22 68:25
79:15 101:16 104:21
108:16 113:10 116:13
121:3 128:23 130:11
131:20 140:25 141:4
158:14 158:15 179:24
187:24 204:5 204:10
205:18 215:15 219:6
224:20 233:3 244:4
background 69:23
98:15
backup 51:7 55:23
bacteremia 41:3 216:9
248:4 248:5 248:5
bacteria 97:18
bacterial 105:2 105:18
202:12 207:20 207:21
247:18
bad 157:22 222:19
bagging 133:16 153:14
Bairam 98:8
balance 149:11
bar 36:9
bars 36:5
base 14:23 17:18 30:5
30:13 99:6 110:15
111:23 111:24 113:7
126:18 174:20 188:5
baseline 21:15 22:9
30:23 31:17 31:22 31:24
31:24 32:3 32:5 38:3
48:25 51:10 51:19 51:21
56:16 64:3 77:12 83:25
84:11 85:25 86:15 86:25
88:4 90:23 94:18 100:6

109:7 118:4 135:9
138:3 138:8 138:9
148:25 149:2 149:8
149:12 209:3
bases 181:12
basically 48:25 73:23
77:4 133:18 163:20
184:25 191:12
basing 194:16
bear 115:13 132:19
bears 32:10
beats 18:13 91:14
becomes 32:7 36:21
126:20 177:14 189:6
212:25 219:19 245:13
bedside 91:21 115:23
201:6 222:15
beg 211:4
begin 120:17 121:7
beginnings 242:11
begins 194:14
belief 187:19
Bell's 250:24 250:25
below 39:20 118:4
125:8
bending 185:18 186:7
beneficial 74:11 88:8
189:24
benefit 50:12 122:3
159:5 189:21 212:4
214:25 215:2 219:22
benefits 154:14 155:4
218:16 224:17
benign 133:23
benzoate 57:13 57:21
58:3 153:24 212:22
benzyl 58:2
Beverly 14:24 26:20
bias 117:17 145:5
145:13 145:14 145:24
149:21 208:22
biases 190:7
big 121:12 137:6 146:18
203:4
biggest 190:5
bilirubin 154:2
Bill 9:18 11:3 137:5
BILSTAD 10:5 10:5
179:23 181:19 183:15
193:6 193:7 239:13
239:15 240:12
binding 154:2
biological 179:13
Biometrics 110:10
biopharmaceutics
246:25
biopharmacology
82:18 99:6
Biosis 20:6
biostatistical 27:2
53:3 149:6
biostatistics 9:4
birth 21:3 41:5 67:7
67:9 67:14 69:7 70:15
97:3 152:18 152:20
173:8 199:3 249:13

250:3
bit 14:17 32:16 42:19
48:7 50:11 65:7 135:13
137:25 138:2 140:6
140:6 160:21 179:17
215:12 216:6 216:7
239:11
black 12:10 235:5
238:13 238:13 238:20
238:21 239:2 239:2
240:14 240:15
blind 17:24 32:13 56:21
118:6
blinded 64:16 117:21
117:23
blockers 105:4 105:7
105:17 105:17 105:18
105:24 106:3 204:2
206:14 217:21
blood 24:4 24:7 24:11
24:12 28:22 37:25 50:3
55:9 58:7 73:9 73:9
73:12 73:14 74:20 76:4
76:7 76:15 77:5 77:6
77:8 77:9 77:11 77:13
77:15 77:19 78:11
104:25 108:16 132:23
132:25 155:20 202:13
202:24 203:9 203:12
203:14 231:15 245:8
247:19 252:22
blue 42:21
board 12:16 16:2
140:21
Bob 155:14
body 20:8 26:17 38:13
38:17 38:17 49:23 72:25
75:21 100:16 109:13
borne 222:9
boss 179:18
bottom 34:13
bound 181:2
bowel 41:19 97:21
97:23 208:4
box 235:5 238:13
238:20 238:21 239:2
239:2 240:14 240:15
boxed 236:20 238:11
239:24
boxes 238:13
bradycardia 18:12
18:17 21:24 28:20 46:5
47:14 47:15 47:18 47:23
47:23 83:12 130:14
150:4
bradycardic 88:2
brain 130:8 130:25
131:7 132:9 133:20
133:22
break 39:10 74:6 80:20
120:15 159:13-161:11
breakdown 23:4
breakfast 187:12
breathe 69:9 130:3
breathing 18:19 28:8
134:20

Brenda 8:15 10:25
12:15 163:5 185:8
brief 75:18
briefing 80:5 228:25
briefly 80:7 225:13
bringing 170:23 195:10
broad 55:17 57:11
125:3 243:13
broader 167:4
bronchodilator 228:20
229:12
bronchopulmonary
122:13
bullet 24:23
bunch 208:16
business 206:4
buying 169:18

- C -

Cacit 14:13 14:25
15:14
caffeine's 14:23 16:15
16:20
caffeine-exposed
106:25 107:8
caffeine-treated 22:11
22:22 24:18 26:10 85:8
100:18
calculated 60:25 63:4
115:3
calculation 60:23 61:6
62:20 139:2 165:19
167:16
calculations 73:21
85:14 92:4 100:2 110:10
139:5
California 8:24 18:6
80:13
calling 218:21
camp 126:18
capability 116:11
capable 172:20 173:23
carbon 19:10 24:5
125:15 125:18 127:2
cardiorespiratory
95:7
cardiovascular 23:9
23:23 26:11 28:17 38:18
81:16
career 230:15
careers 233:14
careful 195:25
carefully 136:7 156:5
156:12 251:7
Carolinas 80:14
carries 87:15
Carroll 8:23 234:20
carry 53:14
carrying 141:7
catastrophic 158:24
catches 208:15
catching 141:2
categorically 237:19

categories 204:15
245:18
category 32:24 242:9
242:10
catheters 97:7
caught 229:10
cause-effect 148:11
caused 133:19 165:6
causes 18:21 41:20
52:7 73:9 83:15 104:22
123:11 130:8 227:19
242:13 242:17
causing 24:4 203:25
cautions 161:20
caveat 188:20 196:5
198:12 198:17
cc 170:17 170:19
171:11
cell 203:12
center-by-treatment
62:3
center-years 172:19
Center 9:2 9:4 9:6 9:19
13:8 16:2 18:6 19:10
50:18 61:22 61:24 62:2
62:3 62:6 62:6 80:12
80:13 80:14 150:10
150:21 150:24
centers 44:23 47:21
61:22 71:23 117:11
146:16 146:17 146:18
159:16 159:17 172:9
172:13 172:18 172:19
174:6 174:6 174:10
221:9 250:9 250:12
250:13
central 16:23 18:20
18:21 23:9 23:11 23:12
23:20 26:12 109:11
109:19 156:19
cerebral 16:22 19:2
24:3 24:7 24:9 24:11
24:12 76:7 76:15 77:5
77:6 77:8 77:9 77:11
77:13 77:15 77:19
155:20
cerebrovascular 24:6
certainty 241:21
certified 16:2
cessation 28:7
cetera 139:13 164:13
167:23 176:12 186:17
186:17 203:13 247:19
CFR 239:12
Chair 8:3 10:19 18:4
50:17 152:6 214:12
challenge 127:7 150:16
151:12 151:17 182:3
challenging 151:18
changed 104:12 170:7
changing 54:7 105:18
116:20 128:4 128:4
249:25
characteristics 31:22
51:10 90:18 90:22 91:6
characterization

113:24
characterize 119:2
characterized 40:25
chart 22:16
cheap 169:19
check 102:3
checked 53:24 231:16
chemistry 82:16
Chen 82:18
chest 28:19
chi-square 37:8
chi 36:12
Chicago 9:15
child 46:25 47:3 47:6
73:11 107:16 108:11
108:17 125:12 126:8
169:25 195:9
Children's 9:6 9:17
80:10
children 70:10 151:11
151:15 156:9 162:21
195:19 227:23 232:7
243:20 244:6 248:23
CHINCHILLI 9:3 9:3
59:15 59:16 60:21 61:7
61:15 61:20 62:9 113:2
114:11 121:9 128:12
134:23 134:25 140:17
141:9 142:11 143:2
143:19 143:22 144:17
144:21 145:2 145:12
145:19 146:6 147:6
147:21 147:24 149:4
149:20 179:2 179:3
179:6 187:4 201:21
241:14 247:14
choose 103:7 163:11
chose 37:11
chosen 85:5 89:11
126:6
chronic 133:18
chronologic 126:3
126:8 126:12 126:22
chronology 14:17
Chun 82:17
church 129:21
cimetidine 99:16
105:6
Cincinnati 9:17 163:15
163:22
circumstance 175:15
circumstances 182:15
188:23 238:15
circumstantial 189:23
190:10 190:20 191:13
197:18 223:24
cite 222:10
cited 16:16 174:12
citrate 15:3 17:16 20:2
26:19 27:6 31:10 31:13
40:3 42:8 73:21 82:12
82:22 83:22 83:24
100:10 101:7 135:5
154:6 178:22 199:23
200:17 201:18 217:6
218:3 218:17 220:19

242:24 248:16
claiming 134:14
clarification 193:21
238:3 238:10
clarified 183:20
clarify 70:20 149:24
150:21 163:8 209:9
209:22 221:15 237:17
238:19
classic 125:17
cleans 66:6
clear-cut 222:20 241:16
241:24
clear 42:13 93:8 127:18
170:25 175:11 193:17
240:8
clearance 49:23 50:3
58:20 58:22 99:10
160:24
Cleveland 166:10
climbed 126:17
climbing 54:19
Clinic 8:8 8:14
clinical 9:22 14:25
15:25 17:11 18:2 19:23
20:22 46:7 64:17 68:11
79:21 79:22 80:2 94:13
96:9 100:23 104:17
132:15 150:9 150:19
157:8 161:24 165:6
169:23 175:23 180:22
181:2 191:20 191:25
203:13 221:11 222:7
222:9 222:12 222:14
225:18 225:19 241:7
244:16
clinically 28:9 38:6
38:8 79:3 100:15 109:22
114:8 115:12 133:13
244:9
clinician 73:7 79:6
197:20 197:23 235:4
240:18
clinicians 47:16 209:7
232:21 241:2
clipped 12:14
clock 134:19
closely 136:12 148:14
148:17 156:4
closer 55:13
cluster 146:15
CMC 15:16
CNS 28:16 29:9 81:16
157:15 186:16
co-administration
99:10
CO2 125:20 125:22
125:23 126:11 127:4
186:19
coadministration 99:14
99:16 101:4
coast 186:11
Cobbs 82:19
Cochran's 36:12 37:7
coded 216:14
coffee 45:4

coherent 122:7 129:13
coincides 138:20
colleagues 10:12 42:25
201:22
collect 45:13
collected 106:3 169:10
College 8:21 80:9
Colorado 80:10
Columbia 9:5
column 51:19 208:16
columns 88:19 111:20
combination 105:6
105:9 105:16
comfortable 175:17
175:22 186:21 192:18
215:12 236:5
comment/question
212:10
comment 13:19 49:20
51:2 55:21 75:23 104:2
104:21 110:15 110:16
111:22 116:22 117:6
128:16 128:20 131:11
132:16 132:17 133:9
139:9 165:12 178:25
190:15 193:7 193:8
201:20 210:3 212:9
213:15 216:10 219:13
222:24 223:21 228:24
233:23 234:13 236:17
247:2 250:20 250:21
255:2
commented 106:7
comments 10:9 14:3
49:18 107:3 115:14
121:6 121:12 121:16
121:19 134:24 144:11
150:8 163:3 166:8
166:23 167:6 183:14
186:23 186:24 193:4
193:23 193:24 219:4
230:7 240:21 242:2
252:24 253:5
commercial 154:17
commercially 17:5
17:20 165:3 170:21
177:14
commissioned 252:2
commitment 209:25
210:24 243:9
commitments 210:15
245:7
committee's 12:3
Commonwealth 8:21
communicate 196:19
communication 155:13
communities 250:18
community 196:19
245:11 250:9
company 19:24 155:24
165:12 170:21 174:13
193:2 209:9 232:16
232:19 232:19 245:19
245:22 247:24 251:23
252:16
comparable 51:18

51:18 110:20
comparative 153:17
compare 138:14 210:12
compared 20:23 21:15
22:9 22:11 22:23 24:19
24:21 25:7 26:13 26:15
27:25 28:2 34:25 36:6
37:15 37:19 52:4 59:6
72:14 77:5 77:12 78:22
94:18 96:18 98:7 98:9
98:14 100:6 125:16
126:14 135:19 135:24
153:13 193:16 212:15
comparing 27:25
149:16
comparison 112:14
139:11 178:6 190:24
comparisons 112:3
113:21 114:18 114:24
compile 37:9
compiled 37:3
complacent 221:19
complementary 82:24
completed 16:11 17:11
32:12 32:14 84:7 135:23
136:21
completion 17:13
complex 92:14 100:12
complicated 247:20
complication 201:24
241:20 241:21 249:20
complications 41:20
92:17 93:20 134:16
167:14 167:22 168:2
168:12 168:25 169:4
169:21
component 18:21
211:17 213:14
composite 126:10
compound 24:8
compounded 20:22
41:23
compounding 165:15
comprehensive 20:4
comprise 77:14
compromise 211:24
computerized 171:21
concentrates 16:21
concentration 49:13
59:10 59:13 132:24
132:25 161:7 212:4
233:8 245:25 246:18
252:9
concentrations 26:15
26:16 28:3 48:25 49:4
49:8 49:11 50:6 58:10
155:8 170:6 170:12
245:8
concept 78:5 198:19
205:23
concepts 124:25
conceptual 226:24
concern 18:24 82:25
100:19 148:13 148:19
157:20 164:16 190:5
190:7 197:21 204:16

206:21 207:16 212:11
221:16 234:23 236:12
239:17 239:18 239:20
239:22 240:3 240:12
240:13 240:16 240:23
247:14
concerning 16:8 23:3
106:25 202:19 231:11
concerns 115:3 135:4
188:6 199:18 205:2
206:24 207:23 227:19
229:5 245:4 247:15
concise 42:13
conclude 52:14 183:24
concluded 16:13 16:25
94:16 180:2
concludes 37:21 42:10
253:3
conclusion 26:17 73:25
104:7 110:4 113:15
conclusions 21:12
22:5 25:20 122:8 172:17
conclusive 98:22
100:25
concomitant 158:5
193:15 232:8
concomitantly 65:25
66:4
concurrent 148:12
condemn 178:12
condition 56:14 66:16
144:12 204:19 243:7
243:11 247:13 251:12
252:12
conduct 27:15 29:18
116:6 193:3 215:21
conducted 20:13 27:4
29:19 35:11 94:22
125:6 154:6 156:13
180:5 248:14 251:10
conducting 183:6
188:25
confidence 115:16
138:18 138:21
confirmation 202:10
202:12
conflict 12:7 12:24
13:2 13:9
confounded 52:8
confused 176:4
confusion 69:18
congestive 46:18 66:3
congratulate 103:3
151:11 151:16 173:4
conjunction 185:5
CONNER 8:15 8:15
12:16 163:6 164:2
185:9 241:25
consensus 185:14
consent 28:13 81:15
consequence 18:24
consequences 133:15
197:4 244:5
conservatively 173:10
considerably 166:11
consideration 167:19

182:21 182:25 183:7
218:16 224:17 253:16
considerations 161:15
244:18
considering 20:11
234:23
consisted 94:5 99:6
consistent 49:3 49:15
100:22 111:3 111:20
142:21 143:10 159:2
185:25 216:23
consistently 100:5
consisting 182:13
consortiums 173:25
constantly 130:2
constipation 39:4
constitute 101:6 178:21
199:22 200:16
constitutes 188:8
194:6
constraints 173:2
174:12
construct 247:24
consultant 19:24 26:25
50:14 50:16 53:3
consultants 10:24
11:8 12:21 82:11 253:10
consultation 198:8
consults 19:16
consumer 8:17
contacted 14:2
contain 177:9
contamination 207:21
continual 133:15
133:16
continually 134:2
continue 11:6 69:20
93:21 109:25 166:25
195:23 251:23
continues 196:17
continuing 64:16
191:3 234:4
continuous 19:18
127:20 130:12 212:23
227:17
contract 16:11 16:25
17:14
contracted 16:6
contraction 166:12
contraindicated 238:24
contraindications
238:25
contrast 206:19
contrasted 48:20
control 17:21 64:11
95:15 95:22 96:3 101:24
102:6 102:8 126:5
154:11 155:10 167:19
193:15 193:15 248:15
248:19 249:3
controlled 17:11 17:22
20:22 64:17 69:16 72:20
94:10 129:10 143:8
154:3 154:20 185:19
185:21 188:10 192:9
193:19 198:16 209:17

210:17 210:20 210:25
216:11 217:15 224:7
225:7 249:23
controlling 66:3 149:2
controls 20:25 22:12
22:25 95:20 193:13
193:14 212:14 217:15
217:17 248:17 249:18
249:23 252:15
controversial 69:22
convey 240:17
conveyance 50:15
conveying 238:15
conviction 221:24
convinced 114:8 180:9
190:11 221:23 221:24
convincing 143:4
143:18 190:2 190:5
215:7
Cooper 80:9
COPD 166:18
copies 12:10 46:4
correct 45:24 63:16
70:22 104:5 108:11
110:16 112:5 113:12
129:9 142:7 180:18
195:6 207:13 219:14
243:22 249:19
corrected 73:22
correctly 115:3 236:25
correlate 51:12
correlation 47:13 49:25
50:10 52:2 131:5 132:23
correlations 49:20
Cosmetic 182:11
cost 153:18 175:7
COSTART 38:13 38:17
couch 236:15
Couched 236:14
counted 103:12
countered 72:19
counting 116:7
country 44:12 116:16
164:15 173:7 173:22
counts 203:12
couple 10:23 59:16
122:15 140:20 146:13
146:21 165:8 169:15
194:3
course 14:2 28:12
29:23 39:9 51:15 64:24
114:21 117:8 141:17
144:14 166:2 183:22
218:25 223:15
Courtney 145:15
197:11 200:11 224:9
covariate 149:5 149:9
covariates 138:7
CPAP 83:19 128:21
129:15 130:2 134:3
134:9 153:14 246:16
CRC'S 80:2
create 177:5
creates 228:22
creatinine 28:24 123:23
123:24

creative 228:23
credit 180:11 191:5
Crim 42:16 66:14 66:15
67:17 69:7 70:11 70:25
101:13 102:6 102:10
117:3 117:4 118:11
119:11 145:16 145:21
189:23 190:19 194:25
195:3 197:12 200:12
212:9 212:10 223:20
223:21 224:11 224:16
224:19 228:2 232:13
232:14 241:10 250:8
250:15
criteria 28:6 28:15
29:12 46:19 66:10 66:13
71:3 71:12 109:19
114:23 118:9 123:23
130:25 148:22 149:25
173:19 176:7 186:2
202:22 250:24
criterion 37:12
critical 8:20 9:12 9:20
119:4 139:15 186:4
222:7
criticize 142:17
CROSS 8:23 8:23 39:24
65:6 65:7 66:6 167:9
167:10 168:5 169:8
186:9 205:6 231:4
231:5 231:10 231:13
241:18 247:16
crucial 111:9 114:17
culture-proven 56:12
56:16 57:10 216:5
216:9
culture 107:18 108:5
108:7 108:19 202:25
cultures 108:16 202:13
202:15 203:9 203:14
247:19
curare 123:6 123:19
current 13:17 139:7
185:24 189:20 190:3
254:19
currently 18:5 20:12
25:2 96:14 116:6 174:21
174:25
Curt 8:19 106:23
221:4 247:2 251:14
Curtis 147:18 204:7
205:12 237:15 247:15
curve 127:4 133:5
137:10 168:18
curves 137:14 138:16
cutoff 114:20
cyanosis 28:20
cytochrome 106:20
176:3
cytomegalic 25:25

- D -

daily 37:24 37:25
233:15
damage 133:20 133:22
153:2 154:3 204:24
damaged 132:9
dare 164:13
database 20:15 31:12
94:5 96:8 182:2 182:22
201:15 206:7 206:15
210:11 216:4 216:16
217:14 217:25 247:6
249:8 249:8 250:2
databases 20:5 206:20
209:19 215:19 250:2
250:8 250:11
date 161:16 161:23
166:21
Davis 8:24 72:13 98:3
102:12
day-by-day 112:3
day-to-day 155:7
deadlines 172:11
dealing 126:4 168:19
deals 201:14
dealt 57:6 226:12
death 23:17 24:17
25:24 25:24 26:6 40:20
41:14 81:16 93:13
153:4 157:7 158:4
204:14 207:9
deaths 92:11 93:25
157:5 167:23
debated 179:16
debating 187:6
December 15:5 15:13
15:19
decide 143:24 147:9
198:18
decided 31:6 109:25
deciliter 28:23 28:24
45:17
decision 142:20 171:23
188:5 188:21 194:16
198:24 222:17 223:9
decrease 21:17 21:18
21:21 21:23 21:24 21:25
21:25 24:3 24:7 24:12
27:11 33:23 34:3 34:7
34:11 34:18 34:20 34:22
36:18 53:18 77:9 78:11
101:21 126:5 126:23
127:25 246:20
decreased 19:8 24:5
73:9 73:9 73:12 73:14
75:16 77:15 97:18
126:20 234:18
decreases 21:16 134:18
decreasing 128:25
134:17
defecation 18:15
defer 179:19 238:5
deferred 225:14
deficiencies 115:24
define 109:2 202:24
202:24 203:2
defined 18:10 18:12
21:19 21:22 28:7 28:19

33:25 35:4 64:2 83:11
84:9 84:10 95:4 109:20
124:25 132:2 151:10
definite 239:3 244:19
definitely 39:3 187:4
190:21 193:11 207:25
definition 34:8 34:17
62:10 62:11 66:8 124:22
150:2 195:9 219:9
219:23 248:6
definitions 84:17
124:23 239:8 239:12
239:13 251:3 251:18
definitive 54:23 236:7
degree 117:17 117:20
138:8 145:23 146:3
239:16
degrees 138:7 177:12
delay 48:23
delivery 214:19
demonstrate 201:17
218:2 227:24 249:2
demonstrated 21:21
22:2 24:20 26:9 98:4
200:10 227:20 239:23
demonstrates 191:25
Dennis 14:25 26:25
53:2 62:18 63:18
denominator 73:10
88:14
denominators 208:11
dense 68:18
density 21:19 97:9
104:6
Denver 8:25 80:10
denying 223:17
Department 26:21
depend 124:10
depending 125:5
125:19 126:8 176:10
depends 124:3 129:21
164:6 172:25 249:7
254:5
depressant 126:21
127:9
depression 127:3
Deputy 9:24
derived 15:12 49:16
99:4
desaturation 21:25
describe 29:14 48:11
describes 23:5
describing 20:2
description 92:9 228:20
descriptions 181:14
descriptive 136:24
137:17 139:25
deserves 152:22
designated 17:14
192:16
designation 15:2
designing 136:6
desired 238:15
desk 12:10
despite 166:14 185:5
detail 75:11

detailed 19:13 82:20
92:9 119:9 136:22
181:14 254:7
details 232:9
detect 140:6
detected 140:22
deterioration 203:13
determination 142:15
determinations 180:22
181:16
determine 27:24 28:2
51:11 60:12 60:15 64:24
210:25 215:19 233:8
determining 222:23
devastating 170:3
171:3
develop 93:20 98:13
108:4 156:5 156:25
157:6 162:23
developing 78:12
Development's 14:13
developmental 122:16
226:6 226:13 245:7
developments 24:16
develops 23:22 78:6
235:9
deviation 101:23
deviations 124:18
diagnosed 42:6 46:16
107:16
diagnosis 19:12 19:15
65:23 79:8 203:8 208:6
diagnostic 202:10
212:19
died 41:12 41:19 41:25
42:6
dies 197:24
differ 239:5
difference 25:10 34:22
35:21 35:23 35:25 36:24
37:6 37:16 37:19 38:16
76:18 84:18 85:11 85:15
86:22 87:6 87:12 87:12
88:23 89:7 89:10 95:23
96:7 99:23 101:25
111:7 111:17 113:18
123:7 124:7 126:14
130:23 137:7 137:10
138:13 140:7 145:23
150:4 184:21 209:4
209:6 212:6 237:4
237:20 241:19
differences 32:2 32:4
36:10 38:6 38:8 38:16
38:21 93:6 93:10 93:23
98:16 100:15 110:3
117:24 123:11 124:8
142:3 145:24 146:5
160:21 211:4 246:5
different 35:7 52:13
59:6 61:22 90:20 91:13
92:16 94:13 104:14
104:17 111:5 119:25
120:2 122:24 124:9
125:15 129:4 135:7
142:2 143:17 147:9

163:16 170:5 170:11
170:12 171:15 174:10
176:7 176:10 192:3
192:16 195:21 206:8
208:10 210:22 212:7
222:10 228:11 233:12
250:11 250:14
differentiating 47:17
differentiations 109:14
differently 113:10
differing 212:2
difficulties 92:20
124:21 157:24 171:25
185:16 244:15
difficulty 29:20 50:11
188:25 221:10 225:18
digestive 38:18
digoxin 233:2
dilute 170:18
diluted 171:9
diminished 125:25
dioxide 19:11 24:5
125:15 125:18 127:2
directed 215:18
directions 198:13
directive 233:20
Director 9:25 10:4
14:16 18:3 18:5 26:21
150:9
disadvantage 122:5
153:21 203:18
disagree 204:25
disagreement 103:14
251:17 252:25
disappears 60:16
disaster 170:9 234:7
discharge 69:2 163:13
164:3 195:18 196:16
197:7
discharged 195:18
discipline 254:17
disclosure 39:21 236:3
discontinuation 35:13
35:17 95:17 136:3
136:18 137:3 145:20
248:24
discontinuations 35:16
discontinue 54:8
discontinued 31:19
32:8 32:20 32:22 33:17
38:3 86:6 87:18 87:23
88:22 88:25 94:15 95:9
108:10 135:15 137:12
159:8 225:22 249:2
discontinuing 33:6
33:12 33:14
discover 222:19
discovered 165:19
discretion 33:13 135:13
135:17
discuss 18:2 24:22
26:22 76:15 82:11 94:4
151:12 167:21 170:10
199:17 225:13
discussed 22:18 22:19
23:2 103:21 144:23

151:5 153:8 153:12
157:20 167:11 227:23
252:8
discussing 63:8 75:11
85:17 123:15 145:4
159:20 159:24 208:19
discussion 11:13 11:19
12:4 42:23 83:3 92:10
99:8 103:9 103:16
109:9 121:7 128:13
150:6 154:23 159:14
162:12 166:25 167:5
176:2 178:17 178:18
178:24 193:22 214:21
214:23 218:20 225:11
230:3 238:19 243:7
244:4 253:8 253:12
discussions 13:10
17:23 121:15 151:7
158:10 158:11 229:16
241:13
disease 25:25 28:16
40:24 81:15 108:13
133:18 144:14 180:8
226:6 248:16
diseases 122:10 206:19
dish 130:5
disorder 24:25 39:25
73:6 129:7 155:3 158:5
212:20 214:10
disorders 28:16 38:19
153:9 249:2
displayed 207:25
disposition 32:6
dissent 235:6
distant 228:21
distention 79:4 235:10
distinguish 109:16
137:9
distinguished 18:18
distinguishing 109:10
distributed 123:12
255:5
distribution 79:24
123:18 124:14 160:23
disturbances 28:17
28:17
diuretics 48:5
division 9:23 9:24 9:25
10:2 10:4 82:9 110:9
document 56:9 80:5
110:19 165:11 181:8
186:10 236:25
documentation 55:18
79:19
documented 28:9 57:8
57:10 59:24
documents 63:13 63:22
dogmatic 234:5
dogs 166:11
dosage 168:16 177:10
177:16 177:19
dosages 233:13
dose-related 59:10
dose-response 133:5
251:25 252:16

doses 59:7 99:15
119:25 120:2 231:15
dosing 50:5 75:20
132:13 132:21-167:16
175:7 198:24 210:21
212:3 212:7 214:23
215:4 220:21 225:12
226:20 226:21 234:16
246:23
double-arm 248:25
249:5
double-blind 17:11
21:11 26:22 27:3 30:17
32:5 32:14 34:5 34:15
34:25 36:17 37:10 37:23
38:2 38:4 38:12 39:11
41:17 41:22 42:2 49:5
55:24 56:17 81:23 83:6
83:21 84:12 85:7 85:18
87:16 88:8 91:25 99:20
112:6 117:16 119:22
135:14 142:23 143:7
192:8
double-blinds 39:10
double 17:24 32:12
56:20 59:7
doubt 29:19 204:21
207:13
downward 168:19
draft 181:7 183:18
186:10
dramatic 55:7 119:6
149:17 159:11 237:14
draw 31:25 33:19 34:13
35:5 35:19 36:4 38:23
203:8 239:19
drawn 230:21 230:24
drift 58:10 58:10
driven 133:13
driving 186:20
drop 55:8 118:3
dropout 59:3 95:14
117:7 190:7 211:20
dropouts 100:13 139:19
139:20 139:23
dropped 96:4 126:17
Drs 159:10
drug-drug 96:15 101:2
104:21 105:9
drug-related 39:22
Drugs 9:25 16:8 16:9
17:4 39:9 99:14 99:16
101:4 106:9 122:22
123:6 123:12 151:3
152:6 162:8 164:22
167:13 181:10 183:5
183:21 187:16 187:17
187:20 197:5 203:25
223:6 238:22 242:17
242:19 243:19-243:19
244:3 244:11 244:12
244:12 244:15 244:25
ductus 46:11 47:2
47:5 47:9 66:2 122:12
Duly 201:12
duration 18:11 21:4

66:19 66:21 67:20 71:23
84:3 85:4 86:15 91:18
91:23 91:24 92:5 92:6
102:15 132:17 159:20
159:24 188:15 199:19
214:24
durations 68:9 68:12
91:19
dynamics 119:16
122:16 132:20
dysfunction 177:10
177:13
dysplasia 122:13
dyspnea 33:8

- E -

early-life 176:11
ease 70:7
easier 141:19 163:19
171:24 220:12
easiest 195:17 195:23
easily 236:8 237:10
248:25
echocardiographic
47:4
echoing 65:3
economics 175:9
ED50 122:23 132:24
ED95 122:23 132:24
Ed 174:18
edema 40:14
edification 132:17
educational 197:9
effectively 250:6
effectiveness 16:15
144:19 180:17 181:10
181:18 181:23 182:23
183:13 183:25
efficacious 21:14 22:8
22:14
elaborate 224:14
electrolytes 186:18
electronically 254:14
elevated 223:5
eligible 200:5
eliminate 62:5 66:4
146:7 147:12
eliminated 44:2 45:17
71:16 75:21 177:11
elimination 19:8 31:7
36:15 36:19 37:5 37:18
49:6 51:15 51:23 62:23
84:23 124:6
elucidated 119:17
embedded 138:21
emerging 162:20
213:24 215:6
emphasize 96:12
encountered 92:17
encourage 254:2
254:7
encouraged 215:4
endeavor 146:24

endpoint/primary
181:4
endpoint 84:9 84:13
84:15 84:21 85:5 86:11
86:14 87:6 88:11 88:15
88:18 88:21 89:6 89:12
90:2 90:4 90:13 91:19
92:2 95:3 99:23 100:5
104:11 104:18 116:2
116:3 118:9 123:8
131:13 134:21 180:19
181:18 192:7 192:8
192:16
endpoints 21:8 21:8
62:15 90:20 90:21 91:10
94:14 94:17 104:6
113:8 113:16 131:16
ends 194:17
enigmatic 40:25
enroll 29:13 117:11
enrolled 30:25 31:18
43:14 56:6 58:11 60:3
67:9 67:13 70:15 70:17
71:4 71:7 71:9 71:12
71:24 80:8 80:9 80:15
80:16 81:10 84:5 107:18
221:9
enrolling 190:8
enrollment 29:6 29:10
70:13 70:21 71:14 71:23
109:7
enter 208:23 209:16
enterocolitis 24:24
24:24 25:2 25:3 25:6
25:8 25:12 25:13 33:10
39:23 40:16 60:11 77:23
77:25 78:13 78:20 79:3
79:5 79:9 93:12 96:14
96:24 98:17 100:18
104:23 122:12 147:23
158:2 178:5 178:7
178:10 178:11 203:20
204:14 206:23 211:6
217:10 222:21 234:24
235:9 235:21 242:14
247:22
entertain 189:8
enthusiastic 117:19
entirely 144:2 185:25
228:10
entrance 149:25
entry 81:7 90:23 91:6
109:19 148:21
enzymes 177:2
epidemic 216:25
epidemiologic 209:19
209:24 250:5
epidemiology 77:25
episodes 19:8 21:15
21:23 21:24 22:9 27:11
28:7 30:22 31:17 31:24
33:24 34:11 34:23 46:3
46:13 62:12 63:14 65:14
68:24 73:11 83:10 84:11
84:22 116:7 135:8
135:9 140:22 140:24

141:3 141:6 141:11
141:13 141:23 148:22
149:3 158:24 192:8
194:23
episodic 60:12 216:20
216:21
equal 49:9 49:15 86:25
124:15
equally 21:14 22:8
equate 238:21
equipment 224:6
equivalent 83:22 95:21
157:12 213:5
Erenberg 14:21 18:3
18:7 43:13 43:21 43:25
44:22 45:14 45:15 45:25
46:8 46:16 47:6 47:20
60:7 60:8 61:10 61:11
61:18 63:25 65:19 65:21
66:11 68:10 70:23 71:10
74:13 74:18 74:23 78:18
79:25 104:3 108:2
109:5 174:8 174:17
175:4 175:11 175:16
216:4
error 101:22 111:6
165:18 165:19 165:23
237:6
errors 154:12 165:15
165:16 167:16 169:7
170:19
escalating 74:25
essence 220:6
essential 177:15
essentially 11:23
123:25 124:7
estimate 44:4 110:5
174:14
estimated 61:13 85:14
138:11
estimates 103:12
104:8 110:23 115:10
et 72:13 94:22 95:10
97:13 97:20 98:3 98:8
98:16 120:2 139:13
164:13 167:23 176:12
186:17 186:17 203:13
247:19
ether 78:21
ethical 136:3 136:5
183:6
ethylenediamine
213:13
etiologic 65:24
etiologies 78:20
etiology 60:15
evaluate 56:18 68:3
199:9
evaluated 31:21 72:6
72:23
evaluating 43:8 73:8
Evaluation 10:6 13:8
37:22 51:16 103:5
155:3 185:10 226:23
evaluations 37:25
event 13:10 23:7 23:12

23:20 39:17 47:15 47:17
47:18 49:15 76:21 81:12
104:14 112:24 112:24
112:24 126:25 135:16
239:9
eventually 53:14
189:5
Everest 126:17
everybody's 193:4
everybody 8:4 164:17
192:3 214:15 215:12
229:11
everyone 12:22 130:2
184:16 191:16
evolution 52:4
exacerbating 78:17
exacerbation 235:20
Exact 38:22 81:9
237:22 238:7
exactly 112:7 114:25
150:2 165:9 174:8
183:21 209:13 232:9
243:17
examination 19:14
examine 231:21
examined 77:10 125:4
example 65:16 114:17
153:5 186:6 194:4
194:4 198:14 217:10
220:2 227:4 230:11
exceeded 135:8
excellent 103:4 115:8
153:15
Excerptamedica 20:6
exchange 156:11
exclude 13:13 45:24
167:5
excluded 28:22 29:2
29:8 31:16 31:16 44:19
65:10 75:16 81:7 81:10
83:15 83:17 88:20
exclusion 13:14 28:6
28:15 44:3 46:19 66:12
71:3 71:12 81:11 123:22
130:25 173:19 176:7
232:5
exclusionary 29:7
exclusions 44:16 66:7
exclusively 167:2
excreted 176:14
excreting 170:14
excretion 75:22 124:2
124:3 133:2
Excuse 189:14
exist 79:6 196:22
exists 17:9
expand 216:6
expensive 164:25
experienced 198:2
experiencing 29:9
experimental 97:21
expert 182:21 183:11
183:23
expertise 11:9
experts 63:8 185:12
185:13

explain 83:16 87:19
explained 83:5 84:6
86:10 96:25 215:20
236:8
explanation 128:19
explanations 204:12
215:24
explicitly 192:22
explore 160:25
explored 160:21
exposed 23:6 92:15
92:25 93:3 96:10 107:9
107:10 128:5 202:4
222:6 242:4
exposure 34:24 34:24
92:22 92:25 93:16 98:23
102:15 102:17 102:17
102:17 102:19 204:9
205:4 207:6 208:3
208:8 208:9 208:21
237:18 237:20
expression 121:20
extemporaneous
154:7 154:12 157:16
163:11 165:15
extemporaneously
20:21 163:23 170:20
extended 84:4 172:12
extensive 17:25 155:23
162:10 207:14 229:3
extensively 65:5 154:5
237:5
extenuating 188:23
extra 120:16
extracellular 123:13
123:16 123:19
extrapolate 114:14
extremely 21:9 61:3
68:16 109:12 170:13
197:8
extubated 69:14 226:2
extubation 71:16 71:19
eye 208:15

- F -

face 182:7
faced 153:18
facilitate 154:18
facilitates 155:6
factor 52:3 73:3 93:17
111:9 149:10 183:3
223:8
factors 29:7 44:3 51:11
65:24 72:6 97:6 97:7
124:16 182:24 182:25
215:17 232:5
fall 142:3
failed 25:13 30:17
84:18 99:22 231:23
failure 33:3 35:16
35:17 46:18 48:18 66:3
91:2 123:25 166:7
failures 36:21

fair 113:24 182:6
189:18
fairly 41:7 54:14 55:6
145:10 165:16
fairness 13:17 113:7
faith 61:18
falls 182:10
false 177:5
familiar 77:24 243:18
familiarization 42:25
farther 126:9 131:14
131:19
fashion 72:7 172:16
201:13
faster 26:10
fatal 170:25
favor 35:21 35:25 36:10
36:25 37:2 37:6 37:17
37:20 89:8 99:24 194:8
199:24 200:6 200:10
200:18 201:10 218:5
218:13 220:8 220:14
220:15
favorable 180:17
181:24
favorite 123:6
FDA'S 12:13 82:6
147:16 193:8
feasibility 171:20
171:24 183:2 183:3
183:6
feasible 116:5 116:8
feature 135:25
features 16:19 109:10
February 15:7
feed 134:5
feedback 78:3
feeding 18:16 39:25
47:13 133:16
feelings 221:12
fellows 230:15
ferret 210:20
fever 125:23
fewer 16:24 51:21
fibroplasia 122:12
fifth 30:25
fill 121:10
finalized 10:25 42:22
254:16
financial 13:12 13:18
214:4
finding 207:18 252:3
findings 98:22 100:23
100:25 106:10 156:20
156:21 156:23 222:8
236:8
finer 191:7
firm 235:19
firmly 185:22
firms 13:7 13:11 13:18
first 10:10 10:15 10:18
10:25 11:9 21:13 21:17
22:7 25:21 28:25 35:5
39:2 45:3 45:23 47:22
52:14 55:7 56:2 58:8
59:17 60:22 68:4 71:22

74:13 90:2 92:24 97:14
112:24 117:20 121:8
126:18 129:8 136:24
165:18 166:10 175:20
178:16 186:15 187:21
222:4 224:22 232:13
233:23 249:11 252:4
252:17
Firstly 92:13
Fisher's 38:22 237:22
238:7
fixed-dose 54:3 74:23
fixed 50:5 54:25 75:2
flavors 250:14
flaw 142:14
flawed 143:20
flaws 185:6
flexibility 181:22
182:19 183:10 186:12
234:7
flicking 127:13
flora 105:5 105:18
Florida 9:22
flow 24:4 24:7 24:11
24:12 73:9 73:9 73:12
73:14 76:4 76:7 76:15
77:5 77:6 77:8 77:9
77:11 77:13 77:16 77:19
78:11 104:25 155:20
fluctuations 16:21
fluid 16:23 123:13
123:16 123:19
fluorescence 164:23
flush 206:12
focus 82:23 89:18 92:10
96:24 105:20 106:2
167:3 175:4 180:18
191:9
focused 154:25 167:7
178:18 255:6
focusing 141:10 167:2
FOI 253:21 253:22
folder 12:11
folders 42:21
folks 191:18
follow-up 94:15 116:5
131:3 131:23 235:8
247:10 248:12 251:11
follow 107:22 108:22
113:14 114:16 118:18
164:16 174:11
follows 97:13
Food 182:11
foot 127:14
forget 147:22 161:3
166:10
formal 12:17
formality 12:18
format 153:15
formerly 9:15 19:23
formula 78:21
formulas 97:9
formulated 17:16
formulation 154:7
154:13 163:11
formulations 20:22

164:2
forth 112:2 134:5
166:20 178:3
forthright 80:18
forum 253:20
fourth 24:23
fraction 35:9
frame 254:19
framework 182:12
frankly 185:20
fraught 154:8
free 12:12 14:4 17:21
17:21 134:20 184:12
freedom 138:7 138:8
254:10 254:18
frequency 18:23 19:8
21:14 22:8 25:13 76:19
92:16 101:19 125:10
160:24 217:11
frequent 23:8 96:20
frequently 19:3 23:12
29:24 44:10
Friday 136:21
friendly 156:10
friends 169:13
fulfill 71:11 162:19
fulfilled 172:10
full-blown 79:7
full-fledged 12:19
future 151:13 160:25
162:8 171:17 171:18
188:25

- G -

gain 205:2
garbage 237:18
gastric 24:20
gastroesophageal
24:16
gastrointestinal 23:10
24:13 24:17 26:12
105:5 105:19
gavage 47:13
Gaye 125:18
Gebert 82:16 110:9
110:9 238:6 238:7
generalized 28:16
137:21 191:18
generated 58:22 82:22
gentlemen 8:2 80:23
Georgia 8:17
germane 14:3
gestalt 219:10
gestation 41:16 44:6
44:9 44:10 68:20 226:3
gestational 21:3 31:23
41:21 44:3 51:14 51:17
59:21 60:3 60:6 65:14
67:13 83:9 90:22 125:19
168:21 226:14
gets 119:4 133:14
133:17 148:15 164:16
170:2 172:16 196:15

208:23 247:19
GFR 123:21 124:2
GI 39:25 40:25 78:7
97:18 98:11 98:14
207:20 213:11
giving 117:19 133:3
205:14 216:21 231:18
244:2 244:5
glean 101:24 104:5
gleaned 22:6
glucocorticoid 206:16
goal 192:7
goals 99:2
goes 59:2 110:21
116:17 121:20 124:24
126:9 188:17 210:8
gold 221:17
Goldsmith's 186:14
gotten 240:8
grams 28:23 48:3 60:9
60:18 125:7 125:8
152:18 152:21 160:14
173:8 206:6
granted 12:21 15:2
237:18
graphic 88:12 89:13
grasp 221:10
gray 182:10
Grosfeld 97:20
groups 25:14 32:3
32:19 35:2 46:12 72:5
84:19 85:24 86:8 91:9
91:12 91:16 92:13 93:8
93:24 97:4 101:21
102:2 111:17 112:7
112:20 120:6 120:9
135:19 137:7 145:18
149:3 149:12 149:16
175:4 190:6 211:7
212:7 248:15
grow 67:2 68:19
growth 25:19 157:3
guarantee 47:20
guaranteed 229:6
guardian 28:14
guess 43:11 61:13
63:5 66:20 102:11
102:14 104:3 114:21
119:11 148:4 148:25
172:8 172:15 183:8
187:6 189:13 190:16
194:25 197:12 197:16
197:20 204:16 204:23
205:4 206:25 208:15
214:11 215:5 215:18
215:22 220:8 221:7
221:16 221:20 222:6
223:8 232:14 244:9
guesstimation 61:11
guidance 154:16 154:18
159:23 181:7 183:18
guideline 177:16
196:24
guidelines 75:20 152:4
161:3 161:6 162:20
188:7 214:6 214:8

214:9 215:11 234:16
Gunn 174:17 174:18
174:18 175:4
gut 73:12

- H -

H2 29:7 105:4 105:4
105:7 105:17 105:17
105:17 203:25 206:14
217:21
Haack 14:25 26:25
52:11 53:2 53:2 53:22
60:22 61:5 61:21 62:4
62:19 63:3 63:19
half-life 16:22 54:14
55:10 155:5 246:11
half-lives 124:6
hampered 211:11
241:23
hand 14:4 24:11 133:23
177:8 194:16 199:24
200:19 218:5 220:9
240:20
handed 196:15
handle 247:17 248:18
handles 226:24
handout 167:8
hands 157:19 199:25
200:3 200:20 200:21
200:23 218:6 218:10
220:10 220:13
happen 53:5 121:20
137:12 176:17 234:3
happening 140:25
happens 108:15 122:17
123:5 124:5 140:2
148:12 245:11 249:22
hard-pressed 158:11
harder 211:15
harmful 205:2
hate 50:21 162:6
hazard 138:11 138:13
hazards 138:6 149:7
Health 9:12 9:19 80:12
239:17 239:19
healthy 99:7 207:7
heart 18:12 46:18 66:3
85:3 91:11 127:17
heat 180:6
heavier 51:24 91:8
helped 144:7 183:20
helpful 81:2 147:5
150:6 160:16 161:12
162:5 183:23 197:6
helps 185:15 229:5
hematocrit 127:24
129:16
hematologist 16:2
hemic 38:18
hemorrhage 122:13
131:9
henceforth 31:5
HENDELES 9:21 9:21

11:14 48:16 58:4 75:7
75:13 106:7 106:17
107:7 140:13 140:14
141:5 164:21 169:17
170:15 171:11 175:11
177:8 192:13 196:23
197:9 209:8 209:14
210:2 213:12 218:21
223:12 226:17 230:5
230:6 230:18 231:8
231:12 231:17 234:15
234:20 235:11 236:3
236:16 236:19 239:5
240:22 246:7
Henry 125:17
Hershey 9:4
hierarchy 240:13
highest 97:3
highlights 154:13
highly 37:6 37:16 37:19
HIMMEL 9:24 9:24
hindsight 192:14
Hines 9:15 166:13
Hispanic 160:22
histamine 105:24
106:2 204:2
historical 20:24 22:12
22:25 59:7 104:3 191:12
193:14 193:16 212:13
248:17 249:23
historically 179:24
212:21
history 14:21 15:21
16:5 19:13 39:5 45:3
45:11 56:7 56:13 67:6
67:8 144:13
hit 120:8 126:18 127:17
127:17 127:18 128:18
hoc 62:23 87:15 88:6
111:25 113:20 143:17
143:21 143:23 144:2
185:10
Holding 15:10 158:15
homemade 165:5
hone 115:11
honestly 195:20
hook 116:14
hoped 110:23
hopefully 180:20
181:11
Hospital 9:7 9:17 17:7
32:25 33:15 41:18 47:8
80:9 80:10 80:11 80:11
88:5 146:3 167:12
167:25 169:13 250:18
hospitalizations 203:7
hospitalized 168:2
hospitals 164:14 168:22
250:10
host 51:4
housekeeping 42:19
HPLC 169:19
huge 177:11 237:9
244:7
human 235:3
hypercarbia 126:8

hyperosmolar 78:20
78:22
hypersensitive 238:23
hyperventilation 24:4
hypo-osmolar 78:21
Hyponatremia 40:12
48:4 48:12
hypotheses 142:7
hypothesis 78:3 78:14
hypothesized 24:3
hypoventilation 125:24
hypoxemia 18:25 47:14
47:16 47:18 126:15
hypoxia 125:16 126:7
126:15 126:20 127:2
127:8 127:10 153:2
hypoxic 126:25 127:7

- I -

ICU'S 223:7 224:3
ICU 109:3 205:13
247:20
idea 113:22 169:5
188:14 188:20 234:25
ideal 103:23 116:10
166:16
Ideally 224:24
ideas 209:20 228:11
248:13
identified 18:9 20:4
20:14 20:15 21:17 22:22
25:9 26:7 31:19 72:7
73:6 143:25 144:2
151:19
identify 21:10 47:21
57:18 143:25 249:10
identifying 86:24
ignorant 198:4
ignore 158:5
II 10:6 222:11
ileal 42:4
illness 107:2 107:11
107:25 111:13 204:11
imagine 50:11 173:9
173:22
immature 68:17
immaturity 41:5
immediate 59:9 118:24
immunoassay 164:24
impact 146:16 146:18
151:13 238:15
impacting 168:4 168:6
impacts 125:14 238:16
implicated 97:10
implication 162:15
implicitly 233:21
implies 235:5
importance 229:22
important 21:7 23:7
24:22 27:12 32:7 71:18
82:12 103:8 105:7
118:19 149:10 152:11
169:9 179:15 198:19

201:8 217:19 221:18
234:14 234:22 244:11
impressed 111:19
impression 152:9
152:15 152:24
impressions 177:22
184:14
improve 94:19 100:5
154:22
improved 94:17 102:8
improvement 22:10
35:23 95:11 155:2
215:8
impurity 17:22
imputation 139:20
in-house 163:24
inadequate 182:8
inappropriately 231:7
Inc 15:2
Incidence 24:25 25:12
41:4 41:5 41:8 45:5
47:12 59:19 59:20 60:5
60:11 81:22 92:21 92:24
93:7 96:13 97:2 97:3
97:10 98:5 98:15 98:20
98:25 100:17 105:16
105:25 122:9 125:5
125:7 127:25 134:17
152:16 158:7 201:22
211:6 212:14 235:18
237:9 246:15 248:18
249:22 249:25 250:17
incidences 250:3
incidents 46:11 98:17
102:12
inclined 117:20
included 20:3 20:5
20:18 22:19 22:23 23:13
28:15 31:5 38:17 96:9
181:7 192:20 198:13
includes 15:9 93:4
160:18 207:5
inclusion 25:25 28:5
28:6 71:2 202:23 234:10
incomplete 142:13
142:15 143:14
incorporate 196:20
228:12
incorporating 111:12
incorrectly 170:9
increases 127:24
208:21
increasing 54:4 74:11
126:2 127:22 129:15
134:9 166:12
incremental 212:3
incubator 109:13
IND 15:6 15:8 103:20
independent 133:19
182:16
independently 190:24
index 16:20 21:22
95:3 95:3 95:11 95:19
95:21 96:5 101:21
indicate 42:8 137:17
159:9 161:17 192:5

indicated 16:12 16:18
19:14 20:12 22:14 46:23
141:14 143:23 155:15
156:24 227:11 231:8
239:21
indicates 157:6
indicating 157:17
227:9 239:13
indication 11:17 12:2
12:4 17:3 17:5 162:9
171:7 180:4 188:14
188:19 193:2 196:3
197:6 198:15 220:3
227:4 227:5 227:13
241:19 242:24 255:6
indications 19:20
142:25 143:3 143:4
192:22 207:13 222:2
244:13
indirectly 53:20
individualize 232:7
individually 17:7
individuals 51:2 119:12
indomethacin 243:25
244:3 245:2
induced 223:4
industry 181:9 181:25
214:3 215:3 215:10
infant's 127:14
infant 18:22 23:17
24:17 24:25 28:11 33:15
38:3 40:23 41:16 41:21
41:24 43:18 44:6 45:15
46:17 46:24 47:10 47:11
48:5 48:8 53:7 53:12
66:2 68:17 68:17 68:22
97:10 106:20 108:5
122:14 122:25 123:2
125:25 126:6 133:14
134:19 176:11 194:23
201:24 226:2 235:9
infection 203:5 206:15
infiltration 40:9
inflammation 40:7
40:10 78:12
inflation 134:4
influenced 125:11
informed 28:13
informs 235:4
infrequent 217:16
ingenious 252:3
inhaled 125:20 136:11
initial 47:15 47:18
63:25 64:2 231:23
initially 126:19 126:23
159:13 161:10
initiate 79:7 225:19
initiated 17:16 44:15
69:7 69:8 69:13 70:16
203:10
initiation 43:9
initiative 162:19
initiatives 156:6 162:20
injection 17:16 40:7
82:12 135:2
injured 78:12 213:11

injuries 131:4
injury 77:23 78:7 78:9
78:16 78:23 78:25
104:24 130:8 131:7
131:8 207:20
insert 75:8 176:10
177:9 177:20 177:22
192:21 194:19 196:22
228:4 233:11 233:17
234:8 234:17 238:18
246:24
inspired 127:22
instance 102:18 117:8
136:4 139:16
instituted 127:16
institution 60:13
126:24 145:25 164:7
212:23
institutions 29:18
145:22 163:17 164:7
164:11
insults 97:23
integral 15:24
intended 226:9
intensive 17:8 18:9
28:10 130:9 130:17
130:20 167:11 167:20
169:2 173:22 174:25
intent 231:22
intention 162:19
interaction 62:7 103:5
104:21 105:3 105:9
106:14 106:21 203:24
204:3 204:4 206:17
interactions 62:3 96:15
99:5 99:9 101:2 106:8
106:12 106:18 176:5
176:15 176:23 176:25
242:16
interest 12:7 12:24
13:2 13:9 13:12 13:17
245:22
interested 43:10 65:8
65:13 107:23 209:20
220:24 247:21 248:13
interesting 10:14 11:17
23:19 139:24 160:25
186:18 207:4 213:24
interestingly 214:13
interests 13:7
interference 133:16
interleukin-1 186:5
internally 179:16
187:6
international 20:6
interpret 94:2 141:16
182:19 203:3 203:15
interpretation 100:14
141:21 219:11
interpreted 182:14
interval 138:19 138:21
intervals 229:20
intervene 133:22
intervened 128:24
intervention 43:15
133:13

interventions 108:17
128:3 128:20 128:24
133:23 134:15 144:13
intolerance 98:11
intravenously 30:2
30:7 30:14 30:19
intraventricular 122:13
131:9
introduce 8:7 8:11
14:16 19:22 26:20
124:24
introduced 213:21
introduction 243:16
250:6 250:7
introductory 10:9
intubated 96:5
invasion 105:2
invasive 134:2 134:3
134:15
inversely 41:4
investigated 242:18
investigator's 46:18
investigator 33:13
38:25 39:8 39:13 40:19
46:23 85:22 118:6
135:9 135:13 135:17
138:3
investigators 27:6
39:10 53:16 94:16
117:18 118:2 190:8
252:14
invitation 221:4
invite 42:14 82:5
invited 12:20
involve 13:10
involvement 13:14
103:9
involvements 13:18
involving 106:8 171:21
Iowa 16:6 18:4
IRB'S 172:7
IRB 158:10 211:14
244:17
irritability 23:13 156:23
Irvine 80:13
ischemia 97:21 104:24
ischemic 97:23
Island 80:11
isoflurane 122:18
Isolettes 130:3
issued 181:8
issues 10:21 82:23
83:3 92:11 96:12 97:12
121:13 128:16 132:5
168:5 173:13 173:14
179:24 184:15 214:23
221:10 234:22 248:12
251:5
item 199:17 210:3
218:15 231:20
items 229:15 230:2
iterations 113:11
IV 40:9 148:15 209:17
209:25 210:15 210:24
230:15 243:8 243:9
IVH 250:4

IVIG 216:11

- J -

Jack 155:13
Jacob 151:25
James 8:3
January 15:17
Jay's 227:18
Jay 8:13
JENKINS 10:3 10:3
10:7 10:10 151:6 179:4
179:15 179:21 182:14
209:8 209:12 209:16
210:8 210:15 211:9
211:16 219:12 219:14
219:19 228:8 228:24
237:25 238:2 238:10
239:7 240:7 243:5
246:7 248:8 248:9
253:4 253:6 254:8
254:24 255:8
JENNE 9:14 9:14 54:13
73:16 73:17 74:17 75:4
160:7 166:6 177:21
190:22 199:7 208:2
208:18 208:20 233:23
241:4 251:18 251:22
251:25 252:7 252:13
Jewish 9:2
Jim 10:5 82:15 110:9
243:5
jitteriness 23:14 156:23
JOBE 9:16 9:16 11:10
43:5 43:6 43:19 43:22
44:7 68:15 69:8 71:15
128:15 128:16 133:8
133:9 159:21 163:14
164:4 191:11 194:10
195:7 195:12 196:8
196:12 199:7 206:2
213:15 214:11 214:22
215:2 215:13 216:10
216:19 225:16 227:12
243:25 250:11 251:3
253:11
John 9:14 10:3 12:6
166:5 208:20 210:5
228:7 228:23 239:21
240:4 252:10
join 11:8 11:13
joined 253:10
joining 10:23 11:4
11:11
jotted 229:15
Journal 73:24
journals 254:5
judged 145:8
judgment 143:14
144:4 182:10 182:21
183:11 183:24 241:15
junction 123:2

- K -

Kansas 18:5 80:8
Kaplan-meier 112:21
137:5 137:14 138:15
Keeping 88:6 190:9
217:12
keeps 209:2
KELLY 9:18 9:18 11:3
12:16 58:5 58:6 59:5
74:3 112:16 112:17
113:4 137:6 148:20
148:21 149:13 176:13
192:2 208:20 233:2
235:14 240:25 245:24
246:17 252:18 252:20
Kern 18:6
ketoconazole 99:16
key 108:15 156:16
178:23 185:17 247:5
kicked 75:4
kicking 130:2
kid 132:8
kidney 124:12 176:14
kids 123:9 127:25
128:2 130:3 131:13
131:15 131:24 168:12
187:17 244:24
kilogram 29:25 30:5
30:6 30:13 30:15
kilograms 21:4
kinds 50:6 111:16
128:21 146:7 173:16
203:12 215:3 215:11
217:18 244:2 251:5
kinetic 58:20
kinetics 132:20 132:22
168:21
Kirk 14:20 15:20 18:7
kit 164:20 164:24
169:18
knowing 245:23
knowledge 11:18
156:11 202:12 246:25
knowledgeable 161:6
known 10:16 24:8
99:18 128:24 132:2
240:9
knows 105:10 239:13
Kristen 14:22 19:22
26:24

- L -

Lp 15:9
lab 169:15
label 27:14 43:11 74:12
117:22 117:24 146:2
206:23 228:25
labeled 108:3
labeling 53:14 75:8
75:15 196:23 198:15
198:25 207:6 207:14
220:18 220:21 225:12
226:12 227:10 229:3
229:6 229:17 230:7

230:13 232:16 234:13
238:22 240:3 240:15
labels 208:4
Laboratories 14:9
15:6 15:11 15:13 15:23
17:17 19:24 26:22
174:19
laboratory 19:14 38:2
38:9
Labs 53:3
lacks 106:20
ladies 8:2 80:23
laid 240:12
landmark 151:6 151:8
162:18
largely 151:9
largest 73:2
Larsen 98:16
lasted 226:13
laugh 142:11
Laughter 61:19 121:22
121:25 142:8 144:6
147:25 150:22 179:5
179:20 184:5 184:19
187:9 187:11 187:13
194:20 200:25 201:3
205:15 207:2 218:24
219:18 224:15 229:9
230:17 233:18 248:21
leading 47:14
lean 241:17
Leander 9:9 218:7
learn 211:25
leaves 183:25
leaving 198:9 241:18
Lee 73:25
legal 177:24 181:12
legislation 151:14
162:7
legislative 182:19
length 30:9
Les 11:13 11:15 48:15
75:6 75:12 153:25
164:18 177:7 210:11
218:20 232:10 234:12
240:20
Leslie 9:21
lessons 162:25
Let's 80:20 85:17 85:20
110:11 120:15 124:19
145:24 146:7 167:3
173:10 187:17 199:16
218:15 220:7 234:21
242:23 243:2 250:17
letting 230:8
leukomalacia 131:4
level 39:3 39:8 39:13
45:15 45:23 48:18 58:21
73:19 123:3 149:2
149:8 165:20 165:22
168:13 168:23 171:3
175:8 175:14 175:21
181:22 183:19 229:25
231:19 233:9 233:10
233:12 234:6 236:10
238:14 240:11 240:16

240:22 242:21 243:14
250:24
levels 26:4 39:9 39:20
48:10 48:19 48:20 50:3
54:18 54:18 54:20 55:8
55:9 58:7 74:20 90:24
106:15 140:22 148:25
149:12 161:3 163:19
164:11 164:12 164:22
165:2 165:24 175:6
175:8 175:19 176:19
177:18 178:2 229:19
230:12 230:13 231:5
231:6 231:9 231:15
231:24 232:2 232:3
232:6 232:15 233:21
233:24 234:10
liberal 211:24 219:9
liberty 121:5
licensed 70:6
life-threatening 70:10
239:10
life 9:8 28:25 54:16
69:19 70:22 121:24
124:8 126:2 131:10
239:22
lifesaving 223:18
ligation 41:19
light 85:23 204:17
liked 190:12
likelihood 207:9
Likewise 190:3
limb 132:18
limit 29:3 39:15 169:24
248:16
limitation 159:22
198:12
limitations 72:21
limited 50:4 99:12
108:9 160:5 161:23
170:14 192:22 227:9
243:2
limiting 181:3
Lindsay 82:19
lines 67:4 67:11 67:12
107:25 110:14 115:15
119:12 138:18 251:23
link 76:12
listed 38:5 38:10 49:2
152:2
liter 26:5 165:21 165:25
literature-based 180:14
liver 177:2
load 233:5
loading 29:21 29:25
30:12 48:19 55:5 58:8
58:15 58:19 58:21 74:8
74:12 74:19 84:12 85:7
99:24 119:23 141:7
231:18 231:23 245:13
logged 15:18
logic 205:13
logical 209:11
logistic 52:6
logrank 137:21
logs 66:11

long-term 25:15 26:2
131:3 132:4 157:2
161:17 161:25 186:20
186:22 190:21 194:14
197:14
longer-term 186:17
looks 101:20 205:4
237:21 242:20
loose 161:5
lowest 85:3 85:3 91:10
91:15 97:3
Loyola 9:15
luck 157:22
Ludden 49:17 49:19
50:16 54:3 54:22 54:23
58:17 58:17 59:12 74:18
74:20
lump 122:6
lunch 120:15 179:17
lunchtime 179:4
lung 28:16 40:14
133:18
lymphatic 38:19

- M -

machine 169:18
MADOO 9:9 9:9 12:6
12:8 13:22 13:24 42:16
50:12 200:4 200:9
200:13 200:21 200:24
201:12 218:8 218:13
220:11 220:14 236:14
242:20 242:22 253:21
mail 150:12
main 92:11 92:19
189:22 247:14
mainly 99:6 109:18
136:2
maintain 88:8 88:16
90:8 202:25 233:11
maintained 88:11
88:16 88:24 90:11
119:20
maintenance 29:22
30:4 30:8 30:14 48:21
54:4 55:5 245:14 246:12
major 18:24 31:19
44:17 66:5 96:25 117:24
134:16 134:21 135:25
150:10 175:5 176:13
177:17 184:15 250:9
majority 43:13 44:2
management 153:11
153:18 154:24 162:4
163:9 204:19 214:7
214:8 214:10
Manager 19:23 82:19
99:17 174:19
manuals 214:16
manufactured 17:20
manufacturer 196:24
manufacturing 174:15
March 71:25

margin 26:3
marked 85:23
markedly 122:24
market 148:15 153:25
170:23 187:22 189:6
marketed 251:20
Marketing 15:23 174:18
182:5 218:19
marketplace 190:18
marriage 215:9
Marty 9:24
marvelous 215:25
match 55:6 72:20
matching 124:16
223:6
materials 11:12 17:22
130:7
maternal 45:3 45:10
matters 236:6
maturation 133:2
mature 225:23
max 145:22
maximum 84:3 159:7
159:7
Mayo 8:8
meaningful 114:8
115:12
measure 63:16 89:11
177:18 224:3
measurement 233:21
measures 167:19
measuring 164:22
meat 121:10
mechanical 70:12
71:2 83:19 153:7 248:24
mechanically 29:4
mechanism 116:15
186:16
medazolam 192:24
median 136:25 137:2
145:17
medical-legal 197:4
197:23
Medical 8:21 9:2 9:4
9:6 15:22 18:5 18:6
26:21 26:21 50:18 80:9
80:13 80:14 82:6 82:9
97:6 107:11 128:2
150:10 152:22 154:24
155:3 175:9 254:15
254:23 254:24 255:2
medication 29:9 154:7
154:22 155:12 155:15
156:18 158:21 162:20
164:5 198:9 217:19
217:20
medications 78:21
156:7 156:9 162:23
medicine 9:15 129:20
151:7 151:15 222:7
Medline 20:5
medullary 19:10
meeting 10:13 11:16
12:22 13:2 13:4 13:9
13:23 14:2 14:15 15:19
50:15 118:9 118:10

121:4 150:14 255:10
meetings 63:25 121:20
memory 104:4 116:13
116:17 116:23
mention 55:18 61:24
76:6 160:20 166:6
167:10 184:3 228:17
234:13
mentioned 50:24 54:3
55:19 63:22 64:7 65:23
71:15 74:3 105:24
119:16 125:11 130:7
140:20 145:17 149:5
151:24 153:3 155:19
160:6 161:10 165:10
166:8 178:5 182:14
193:13 213:7 216:19
224:2 236:11 241:5
mentioning 56:11
mentions 228:20
merit 161:25 238:20
239:24
merits 236:20
message 239:16
meta-analyses 147:3
meta-analysis 147:4
147:7 147:10
meta 147:16
metabolic 28:17 38:19
176:17
metabolizing 177:2
methylxanthine 52:5
79:7 98:2 173:11 173:18
174:20 211:7
methylxanthines 19:7
24:3 25:3 27:17 29:5
29:17 61:13 65:5 68:24
69:3 69:20 70:2 72:7
72:15 72:17 72:24 73:8
73:13 96:13 96:23 98:23
100:20 105:4 105:17
128:23 129:23 132:16
134:2 134:8 158:8
163:9 167:17 168:6
169:3 176:16 195:20
204:3 206:10 213:16
216:15 216:21 225:20
240:10
Mexico 9:19 11:4
micro-beings 123:15
microgram 45:16
micrograms 39:20
48:22 74:2
mike 14:4
mild 25:22 40:3 40:14
153:6
milder 239:18
milligram 170:17
170:18 171:12
milligrams 17:18 26:5
28:24 29:25 30:5 30:13
30:15 165:21 165:24
171:11
milliliter 17:18 48:22
74:2
milliliters 30:6

mind 54:10 66:16 76:16
88:6 183:20 211:9
221:14
mine 247:16
mined 206:8 217:14
minimal 58:13
minimum 244:23
minor 169:22
minuscule 142:5
minute 18:13 80:20
91:14 126:11 205:12
218:23
Miriam 82:8
mirrors 123:19
Misoon 82:17
missed 46:4
missing 139:20 207:24
249:13
mixed 18:20
mixing 124:16
ml 39:20
modalities 19:17
129:5 129:24
modality 129:25
mode 12:23
model 62:7 97:21
213:5
modeling 111:11
models 207:19 207:19
moderate 25:23 39:25
40:7
modern 130:9 130:17
modified 228:9 229:4
250:24
Molly's 113:14
Molly 9:11 77:21
132:11 175:24 186:9
197:11 198:21 249:6
mom 45:19
Monday 150:15
monitor 48:9 95:8
116:6 116:11 136:6
136:12 249:20
monitored 148:14
148:17 162:22
monitoring 116:23
119:16 130:13 153:13
154:21 161:3 162:4
164:12 168:16 168:23
171:22 195:16 224:6
232:24 233:4 244:22
monitors 70:3 116:13
116:16 116:25 195:16
monoclonal 186:3
month 167:21 172:10
months 10:22 21:5
66:20 67:21 72:2 168:18
172:18 176:19 185:2
197:7 197:7 197:22
221:9 244:23
Montreal 151:25
morbidity 96:21
morning's 14:20
morphine 124:6
mortality 40:22 93:25
96:21 97:5 153:3 153:23

239:23
Mosdell 14:22 19:23
19:25 40:17 41:8 59:19
67:25 72:9 72:11 76:14
77:4 77:19 105:13
105:20 165:14
mothers 45:4
motility 97:18
Mount 126:17
MS 8:15 163:6 164:2
185:9 241:25
mucosa 213:11
mucosal 77:22 78:7
78:9 78:16 78:23 78:25
104:23 207:20
multi-center 83:6
146:12 179:9
multi-dose 74:25
multi-variate 72:7
multi 61:21
multiple 113:20 114:18
114:24 128:2 128:3
129:24 139:11 175:8
182:25 217:15 217:20
Murat 94:22 95:10
101:17 103:11 115:16
115:20 115:25 144:22
145:7 148:21 149:17
149:22 149:25
mustard 131:22

- N -

NAIAD 15:10
name 8:3 14:15 50:13
53:2 166:10 174:18
names 151:24
narrow 153:21 173:17
174:11
natural 136:16 140:3
144:13
naturally 137:15 140:24
141:4 164:16
naturetics 48:6
NDA 15:16 15:17
201:15 217:25 254:10
near-miss 69:19
Nebraska 50:18
nebulous 232:25
necessarily 74:16
167:5 193:18 194:22
239:2 252:15
necessity 64:15
necrotic 178:4
necrotizing 24:23 24:24
25:2 25:6 25:8 25:12
33:10 40:16 60:11 77:23
77:25 78:13 78:20 79:2
79:5 79:8 93:12 96:14
96:24 98:17 100:18
104:23 147:23 158:2
203:20 204:13 206:22
211:6 217:10 222:21
234:23 242:14

negative 113:16 115:21
203:14 222:7 224:12
neglected 151:10
Neofax 214:18
neonatal 17:7 18:9
28:9 40:20 54:6 70:5
77:17 129:5 129:19
130:9 130:20 158:4
171:7 171:8 173:21
174:25 206:4 207:19
214:12 214:17 224:2
244:12
neonate 126:18 151:20
168:7 168:18 170:18
176:6 176:11
neonates 99:14 123:13
123:14 136:5 148:12
150:25 151:10 170:13
176:3 243:21 243:23
neonatologist 8:14 9:8
9:16 152:7 195:22
neonatologists 64:12
65:3 108:2 116:9 116:21
163:7 172:22 198:2
201:5 211:5 222:16
224:5 243:18 245:24
253:13 255:5
Neonatology 18:3
167:14 168:6 169:2
196:19 206:18 214:5
214:20 250:4 253:9
nervous 23:9 23:11
23:12 23:21 26:12 27:19
38:19 156:19
net 75:2
network 206:5 206:7
214:5 214:12 214:25
215:2 215:10 246:13
250:2 250:12
networks 206:5 214:2
neurologic 171:2
neurological 25:18
26:6 154:3 157:3
neuromuscular 123:2
newborn 123:24 125:16
125:22 125:23 127:5
196:9 212:17 214:7
newborns 16:9 64:18
122:20 123:9 123:22
124:7 126:14 160:12
169:14 212:24
newly 254:25
nice-to-know 245:18
nice 110:17 111:24
112:20 155:24 232:11
243:9 243:12 246:21
nicely 110:21
NICHD 206:5 214:12
216:13 249:9 250:12
250:22
NICU'S 116:16
NIH 174:2 214:2 216:10
nilly 198:10
nine 61:22 71:23 79:24
79:25 145:22 172:9
172:18 172:23 174:6

221:9
nitrogen 28:23
nobody 103:16
nodding 234:20 251:13
252:18
non-approved 197:5
non-issue 214:20
non-rem 127:9
non-theophylline
102:13
non-university 250:13
nonapproval 205:11
none 14:8 34:2 36:18
56:4 69:15 105:23
131:23 202:6 222:14
237:3
Nonetheless 76:23
nonpharmacologic
129:5
nonresponder 119:3
nonresponders 74:25
75:3 119:7 119:8 159:12
242:13
nonresponse 46:13
47:2
norm 203:6
normalization 19:9
22:3
normally 125:21
nosocomial 203:5
not-exposed 208:16
242:9
notation 12:12
noted 13:14 18:22
22:10 35:23 46:12 47:9
47:25 53:4 93:7 93:23
94:12 201:12
notes 242:5
noteworthy 20:11
42:3
notice 35:22 123:22
137:7 181:6
noticed 147:22
nowadays 129:7
numerical 93:11 100:17
138:22 140:7
Numerically 138:16
numerous 11:24 21:7
232:5
nurse-to-patient
130:15
nurse 8:16 47:16 91:20
91:21 115:23 134:18
nurseries 43:8 43:13
46:4 216:20
nursery 43:19 155:17
216:24
nurses 46:4 116:7
nutrient 38:19

- O -

O.p.r 14:12 15:8 15:12
15:14

Oakwood 80:11
Obay 166:18
objective 27:24 116:3
156:20 156:22
objectively 224:3
obligated 247:8
observation 28:19
46:7 64:6 76:3 76:10
117:7 119:9 191:25
215:20 247:6
observational 204:20
observations 116:7
142:13 201:5
observed 23:25 24:2
26:5 26:16 28:9 83:13
85:15 115:22
obstruction 28:21
obstructive 18:20 18:21
28:18 109:11 109:12
obtain 28:3 161:5
obtained 95:5 95:13
97:12 164:25 202:13
232:2
obtaining 157:24
161:7
obvious 49:23 132:12
147:4
occasion 43:16
occasions 167:15
occur 19:3 78:9 157:4
176:25 249:12 254:19
occurred 25:25 56:20
76:10 76:21 78:23 93:15
93:21
occurrence 18:23
occurring 177:6 237:13
occurs 52:25 125:10
152:17 152:20 239:10
Ochsner 8:14
offer 238:11
offered 244:25
offers 203:17
Office 10:5
officer 254:15
official 10:24
offset 159:8
older 67:2 123:9 124:24
162:12 164:12 191:23
Omaha 50:18
once-daily 16:20
155:6 157:12
oncologist 16:3
one-sided 204:9 208:14
onset 118:24 119:22
120:10 157:9 159:6
204:13
opens 155:2
operate 182:12
operating 122:19
opinion 46:18 99:3
101:5 152:3 155:13
178:25 184:7 188:2
188:16 198:22 198:25
205:21 217:4 219:12
223:19 230:12 230:23
232:14 236:12 252:10

opinions 151:23 201:6
222:15 222:16
opportunity 79:23
80:25 132:4
opposed 67:13 170:20
198:9 200:2 200:4
200:10 200:11 200:22
200:24 201:10 218:14
220:11 220:23 220:24
246:16 251:24
opposing 228:7
OPR-001 26:23 27:3
41:11 83:4 83:5 92:10
95:2 96:18 99:19 100:7
100:12 115:24 178:20
199:21 200:15
opt-out 244:17
option 27:7 53:18 54:4
54:6 220:3 231:13
optional 251:24
oral 78:24
orally 30:8 30:19
Oread 15:6 15:10
Oregon 9:12
organ 122:4 128:3
organism 105:2
original 47:7 74:24
84:3 84:9 85:5 103:17
104:10 237:2
Orleans 8:14
orphan 15:2 17:14
156:12 183:5 188:24
244:12
Osborne's 199:15
OSBORNE 9:11 9:11
50:20 50:21 52:6 77:22
79:10 104:22 110:13
110:14 112:12 113:5
113:6 132:12 133:4
147:2 147:23 175:25
183:16 183:17 190:14
198:22 205:12 205:16
205:20 217:3 217:4
236:24 241:6 249:7
254:21 254:22
Otherwise 45:10 75:24
126:16
ought 44:8 114:22
195:10 246:13
ours 63:11 68:8
ourselves 181:3 248:17
outbreak 60:14
outcome 200:9
outliers 146:3
outline 199:18
outpatient 164:5
output 28:25
outstanding 183:19
186:11 253:7
over-estimating 144:18
Overall 21:11 22:21
38:11 92:4 98:22 146:11
146:22 156:15 181:2
218:16 219:2 221:10
224:17 224:20 224:23
overcome 92:20 93:17

overdose 23:15 26:4
153:23 154:12 157:4
165:20 165:23 166:3
overdoses 165:14
169:22
overgrowth 97:18
overhead 129:3 137:24
overheads 124:20
overrated 187:25
overview 14:23 81:19
ownership 15:5 15:7
Oxford 174:2 206:7
250:2 250:13
oxygen 21:25 46:5
85:3 91:15 126:20
127:3 127:22 128:21
129:15 134:10 205:14

- P -

p.m 120:20 121:2
255:11
P450 106:20 176:3
pacemakers 131:25
package 75:8 150:12
176:10 177:8 177:20
177:21 181:6 192:21
196:21 228:4 228:25
232:16 233:10 233:16
234:8 234:17 238:18
246:24
packaged 171:7
packaging 170:4 170:5
170:11
PADAC 15:19
page 80:6 110:19
paint 159:10
pair-wise 112:13
panel 10:16 70:4
101:5 108:3 171:19
185:13 193:24 194:3
220:25 229:14 240:11
panelists 8:6 172:2
240:5 255:7
paper 41:6 41:7 54:14
55:13 74:3 74:4 99:9
106:11 106:12 106:13
234:3
papers 41:9 73:20
98:7 106:18 217:10
paperwork 10:25
parallel 83:7 212:2
parameters 21:17
22:15 23:2 25:19 32:3
38:2 38:4 38:9 58:20
93:10 114:8 122:17
124:17 224:3
parent 28:13
Parents 81:14
partially 254:11
participant 13:12
participants 13:6 13:12
13:16
participate 71:18 79:23

174:7
participated 79:22
participation 135:16
particle 17:21
particulars 188:22
partnership 15:9
patent 46:11 47:2 47:9
66:2 122:11
pathogenesis 40:24
73:10
patient's 229:22 233:9
233:9
patient 27:19 32:20
32:20 32:24 33:2 33:3
39:24 39:25 40:2 40:3
40:8 42:6 81:16 83:23
84:2 88:4 90:11 90:12
90:13 90:14 99:8 108:20
118:2 118:5 135:4
135:10 154:4 158:6
158:7 162:13 162:15
163:13 168:8 170:24
174:20 174:23 175:12
176:23 177:10 198:6
207:9 219:21 231:17
233:6
patterns 19:9
pause 83:11 198:6
pauses 18:10 18:14
pco2 21:25 166:19
PDA 39:5 41:19 46:12
46:16 46:22 47:3 81:22
243:25
peak 125:10 140:23
pediatric 8:16 9:7 9:19
9:22 15:9 99:8 144:25
250:10 250:18
pediatrician 150:19
195:21 196:15 197:20
197:21 199:4
pediatricians 66:24
196:20
Pediatrics 18:4 151:4
152:7
penetration 16:22
Penn 9:4
people's 243:19
percentage 43:21 44:19
44:20 57:7 63:5 63:20
69:25 89:3 135:22
139:23 163:10
percentages 148:7
237:10
perform 16:6
performed 42:4 86:13
95:8 114:18 176:8
176:8 198:17 222:12
229:19
performing 221:11
perfusion 19:2 41:2
periodic 18:19
periods 35:7 89:3
periventricular 131:4
permanently 11:2
32:19 33:5 33:12 33:17
86:6 135:15

persistent 39:6 39:7
88:2
personally 50:9 198:23
personnel 83:13 134:20
perspective 213:15
persuasive 16:14
pertains 12:11 66:17
Peter 9:5 129:3 131:11
144:9 195:13 199:12
226:10 253:17
ph 105:18
Pharmaceutical 20:7
50:17
Pharmaceuticals 15:2
15:10
pharmacies 17:7
pharmacist 9:22 171:10
pharmaco-economic
153:15
pharmacodynamic
50:7 162:15 232:18
245:12
pharmacodynamics
118:21 118:23 159:6
pharmacokinetic 49:21
234:2
pharmacokinetics
122:16 162:16 246:25
pharmacologic 19:20
43:15 58:14 73:25
pharmacological 97:8
pharmacologist 150:19

pharmacology-toxicology
82:17
pharmacology 76:2
76:13 150:10 157:14
169:12 245:8
pharmacy 41:24 154:9
164:4 165:19
phase 13:23 27:8 30:17
32:13 32:14 83:7 83:21
88:8 103:20 112:6
135:6 135:15 148:15
209:17 209:23 209:25
210:15 210:24 222:10
230:15 243:8 243:9
phenobarbital 99:11
99:17 106:14
phenomenon 59:10
148:24
phrase 185:17 226:19
physical 19:13 153:13
physician's 197:2
physician 196:25
238:18
physicians 27:18 69:20
128:22 153:17 158:24
195:3 195:5 197:4
244:17
physiologic 18:24
physiology 127:5
140:19 226:5
pick 85:15 93:9
picked 65:16
picture 68:15 79:8

121:12 159:11
pilot 225:5
Pina's 12:13 81:3
231:8
Pina 82:5 82:7 82:8
82:8 101:10 101:12
102:3 102:9 102:20
103:15 103:21 104:10
105:11 106:7 106:11
107:5 107:14 108:18
109:15 109:18 109:22
110:8 110:15 112:4
112:15 112:22 113:13
113:25 114:11 114:25
115:20 116:9 116:24
117:2 118:12 119:18
120:12 149:23 149:24
202:2 202:4 213:6
213:7 238:2 238:5
255:8
pivotal 222:12
placebo-controlled
17:24 27:4 29:16 83:6
94:12 99:20 142:24
147:13 180:8 188:4
193:9 193:12 210:6
210:16 211:10 211:18
placebo-treated 85:9
100:16
placebos 118:11 118:12
places 249:21
planned 17:24 58:3
139:3
plasma 16:21 26:14
26:15 28:3 55:8 90:24
163:19 212:4
plate 158:17
play 217:22
please 105:14 119:25
200:19 218:5
pleased 42:17
plots 137:5
plus 88:24 93:2 153:25
pneumocardiogram
69:22
pneumocardiograms
22:4 69:24
pneumograms 109:23
pointed 160:12 191:13
236:25
pointing 219:15
polarization 164:23
poorly 151:10
pops 228:21
popular 166:13
popularized 213:19
populations 109:3
160:22 162:6 162:13
219:21
portion 37:21 56:17
174:24
Portland 9:13
posed 76:8
positions 10:17
positive 19:18 107:19
108:19 127:20 144:16

202:24 212:24 213:20
positively 177:25
possibility 58:24 93:19
111:9 189:7
possibly 39:22 40:2
45:18 60:2 128:4 204:4
242:9
post-approval 209:23
post-conception 27:22
Post-conceptual 28:10
31:23 51:18 195:14
195:19 196:5 196:17
post-discharge 196:15
post-marketing 161:16
210:5 242:25 251:9
251:19 252:6
postponed 75:9 153:6
postulated 97:17
potent 16:23
potential 13:9 78:8
78:18 78:24 79:6 104:22
104:24 108:13 154:14
157:13 162:21 174:20
177:6 207:15 207:18
207:20 213:25 239:4
241:2 242:17
potentially 149:18
161:13 170:25 180:15
204:24 239:22
potentials 228:22
powerful 64:13
powering 185:24
practical 116:8 225:17
226:5
practicality 70:6
practice 68:16 68:21
69:16 133:25 163:16
189:21 197:2 225:18
225:19 249:3
practices 216:21
practicing 195:21
195:22 196:14 212:17
practitioners 191:6
pray 129:21
pre-caffeine 212:15
pre-submitted 15:16
pre-term 201:24
precaution 192:21
235:2 236:15 236:18
239:5 239:11 240:14
240:22 240:25 241:6
241:9 241:10 241:11
241:17 241:19 241:22
241:25 242:12 242:21
precautions 160:3
192:19 239:19
precedent 179:11
181:23
precisely 233:24
precision 137:25
138:3 138:17
preclinical 213:3
preclude 13:3
precursor 147:6
predict 51:3 64:19
predicted 85:12

predicting 51:11 52:3
prediction 52:24
predictive 52:16 148:24
prednisone 136:13
predominantly 76:24
preempted 205:6
preexisting 56:13
preferably 72:6
preliminary 103:16
premature 28:4 59:22
78:6 83:8 94:25 96:10
97:16 106:8 106:12
106:19 107:10 109:12
126:18 160:11
prematurely 32:23
178:13
premise 130:6 132:10
preparation 57:12
57:16 57:22 152:10
154:15 154:17 155:16
156:22 157:15 161:19
162:3 163:18 170:20
223:16 248:24
preparations 17:6
155:5 157:16 160:9
165:5
prepare 121:6 170:20
prepared 11:24 17:6
154:9 186:10
preparing 166:24
Presbyterian 9:6
prescribe 207:8
prescribed 99:14
164:5
prescribing 240:18
prescription 70:9
presence 10:17 28:20
presentation 12:11
12:13 12:13 14:9 14:10
14:13 42:11 42:13 62:11
64:7 80:21 81:3 82:6
82:20 83:3 113:15
121:10 121:15
presentations 12:10
103:4 121:8
presented 33:7 66:18
83:14 90:7 91:24 92:9
96:12 117:5 117:15
135:11 141:17 141:19
148:3 150:9 179:25
182:9 188:17 225:4
253:19
presently 206:16
presents 225:21
President 15:22
prespecified 180:23
181:3
presser 78:10
presumably 134:12
presume 64:11
preterm 18:16 18:22
19:4 24:25 27:21 40:18
40:23 99:14 133:11
133:14 152:17
pretty 114:5 114:8
155:25 156:4 156:19

169:3 185:22 216:23
247:19 255:6
prevalence 152:23
158:9 237:9
prevent 158:24
preview 121:9
previous 9:8 13:18
29:5 29:6 41:9 55:11
74:24 144:15 215:17
229:15
previously 26:2 35:4
36:15 40:16 41:8 100:21
115:9 119:16 148:23
216:4
primarily 30:21 58:6
68:13 176:14 227:6
251:10
primary 21:10 27:24
28:16 43:15 47:17 62:14
62:15 63:23 73:3 84:8
84:12 84:15 84:21 85:5
86:11 86:13 86:14 89:11
95:2 99:23 103:6 103:10
103:14 104:11 105:20
106:20 113:16 113:19
116:2 116:3 138:25
139:3 141:10 141:14
150:17 157:21 179:10
180:19 181:3 181:17
190:13 192:6 192:7
principles 154:16
162:23
printout 116:15
printouts 46:5
prior 14:2 29:6 43:15
47:4 71:14 71:16 79:7
117:22 157:4
priori 45:17
probability 187:7
probable 128:19
problematic 221:7
procedure 131:22
136:6
procedures 42:20
164:17
proceed 12:24 14:8
178:15
processes 108:13
125:2
proctor 115:19
produce 123:8 205:9
produces 58:21
product 11:22 15:6
15:23 17:17 17:20
151:11 154:19 154:20
158:17 158:25 159:4
161:4 161:12 161:14
161:23 162:2 163:12
170:5 170:23 238:17
productive 253:14
professor 15:25 50:17
profile 156:18 157:9
157:11
profiles 17:22
programmed 160:10
project 82:18

prolonged 48:2 48:9
130:14 196:8 197:25
203:6
prominently 207:25
promising 222:11
promote 196:25 238:17
prompted 230:6
promptly 120:17
properly 70:5
proportion 114:5
114:9
proportional 41:4
138:6 149:7
proportions 148:19
proposal 230:12
propose 235:25
proposed 19:7 78:19
156:6 228:3 229:2
proprietary 254:12
prospective 94:25
215:21
protect 254:12
protocol-specified
86:10 86:14 100:2
104:10
protocol 27:9 31:20
32:22 33:25 34:8 46:9
53:16 74:7 84:9 84:15
103:8 103:17 103:22
104:9 173:5 173:17
174:11 180:21
prove 116:14
proved 222:12 247:25
proven 108:6 108:7
109:20 130:9 236:2
236:10 247:18
providers 239:17
239:19
provides 182:11
providing 238:18
provision 84:6 211:21
proviso 186:14
provocative 215:6
prudent 147:15
publication 254:2
254:20 255:4
publications 165:8
publicly 82:14
published 16:7 17:12
22:17 23:7 23:23 25:15
25:22 55:13 72:13 96:8
97:15 98:20 115:17
119:10 150:20 166:10
178:21 185:4 199:22
200:15 201:16 214:6
216:12 250:3
pull 101:16
pulling 50:11
Pulmonary 8:3 8:20
9:11 9:14 9:19 9:23 9:25
10:2 10:4 14:14 82:9
82:10 151:7
pulmonologist-intensivist
8:24
pulse 37:25

pure 129:25
pursue 146:23 147:15
purview 210:7
putting 112:3 131:2
136:5 227:13
puzzles 114:13
PVL 131:5
pyrogen 17:21

- Q -

qualifier 194:2
qualify 31:18
quality 17:19 154:10
154:19 155:10 167:19
quantify 145:14
quarter 123:21
query 215:18
questionable 208:7
questioned 100:21
210:21
quick 79:19 113:6
quicker 74:14
quickly 28:5 136:20
254:14
quota 172:10
quote 207:21
quoted 41:6 125:9

- R -

R&d 15:24
race 31:23
radius 163:23
rag 130:6
raise 194:3 199:24
200:19 218:5 220:9
raised 81:6 96:22
122:9 123:20 198:19
224:20 235:23
ramifications 177:24
179:7 179:12 197:24
198:3
random 129:10 207:17
208:13
randomization 92:23
93:15 112:7 237:3
237:20
randomize 211:22
randomized 27:3 59:3
69:15 83:6 99:20 135:6
135:10 135:15 135:19
135:21 143:7 147:11
185:19 185:21 193:9
193:12 193:19 205:5
209:4 216:11 222:9
223:2
randomly 27:5 31:10
32:11 39:6
ranged 21:3 21:4 66:19
ranges 50:6 97:2
237:9

ranging 145:22 246:2
246:6 252:8
Rapid 157:9 211:20
rapidly 128:4
rated 69:24
rates 26:10 35:21 50:25
63:23 85:11 85:16 87:5
91:3
ratio 138:11
rationale 175:14 187:22
189:10 207:18 207:22
ratios 130:16 130:19
RDS 122:11
re-admitted 41:18
reach 88:18 142:3
reactions 167:14
readdressing 221:19
READE 14:12 14:15
realistic 159:22 171:20
realize 56:19 148:2
191:16 225:16
reasonable 55:3 75:12
78:2 78:14 104:8 116:3
156:19 172:5 178:14
reasonably 139:21
reasons 33:5 65:11
81:11 87:25 140:18
147:4 170:22 224:23
225:17
recall 11:20 57:13
76:5 106:9
recapture 120:16
receive 27:5 71:15
83:18 108:20 254:25
received 30:7 30:12
31:12 31:13 31:14 32:21
41:16 41:22 42:2 44:20
45:18 83:22 148:5
150:12 183:18 202:21
247:7
receiving 27:20 29:8
43:24 57:2 57:4 72:15
81:13 85:18 175:2
219:21 219:22 248:16
receptor 186:5 192:25
Recess 80:22
recessed 120:20
recipes 214:17
recognized 70:17 71:3
79:3 130:15 154:3
165:24
recognizing 117:10
212:13
recommend 132:13
139:23 152:2 161:20
189:5 198:12 214:9
218:18 220:21 224:21
225:12 226:20 226:21
227:7 229:19 230:20
231:21 232:18 232:19
234:23 242:25 243:15
252:11
recommendation 29:23
142:20 148:13 180:7
184:3 196:2 197:17
205:22 227:16 251:11

252:5
recommendations
253:16
recommended 29:24
156:14 156:14 159:2
161:5 231:15 243:12
251:9
recommending 189:2
220:25 227:13
recommends 179:8
reconvene 120:17
120:20 121:3
recorded 83:13 91:19
95:5
recording 91:22 115:22
115:25 116:11 247:25
recordings 95:7
recover 65:13
recruit 172:9
recruitment 172:12
recur 95:16
recurrence 33:11
135:16 194:12
recurs 68:25
redacted 254:11
reduce 169:6 170:24
194:23
reduced 138:15 177:16
reduces 155:6
reducing 21:14 22:8
99:25 141:23
reduction 30:22 35:5
36:4 36:6 37:14 49:6
49:9 49:10 62:12 62:21
63:6 63:10 63:21 63:24
84:10 84:21 85:6 85:23
86:24 87:4 87:8 87:21
88:10 88:17 90:25 91:3
104:11 104:16 110:23
110:25 118:10 119:20
141:11 141:12
reevaluated 199:2
reevaluation 199:4
refer 80:4
reference 60:8 60:17
63:14 165:8 254:4
referred 60:9 73:20
88:4
referring 33:15 41:18
47:7 64:2 170:16 232:9
refers 182:12
refine 215:11
refinement 213:25
reflected 30:20
reflux 18:25 24:16
refused 71:17 81:14
regaining 202:25
regard 13:2 55:14 66:21
107:4 135:19 166:7
169:20 178:4
Regarding 16:5 25:21
82:25 89:23 96:8 96:22
99:3 100:12 100:24
101:2 102:10 105:16
120:10 206:22 212:11
252:8

regardless 93:16
regards 71:22 72:4
105:8 238:17
regimens 210:21
212:3 217:20
registered 206:6
registry 217:13
regression 52:7 138:6
140:19 149:7
regularly 163:10
regulate 197:2
regulated 13:7
regulates 196:24
regulation 24:9
regulations 193:13
Regulatory 14:16 82:25
182:3 183:9 239:7
reiterate 12:15
rejected 63:15
relate 49:12
related 39:3 41:20
97:18 145:24 176:15
213:4
relates 75:14 204:10
relating 101:13
relationship 48:17
49:22 106:19 106:22
132:20 148:11 148:24
152:19 159:6 222:20
231:20 246:10 246:18
246:19
relative 138:11 138:16
138:19 138:20 158:9
relatively 139:18
178:2 198:4 217:2
released 216:13
religion 129:21
reload 233:6
reluctance 117:11
relying 144:22
REM 19:4 125:13
127:8
remain 83:25 89:19
120:14 203:24
remainder 10:20
remained 33:2 35:13
35:17 89:16 89:21 89:23
89:24 90:4
remains 40:24 223:11
reminder 110:22
remotely 40:6 40:10
removal 46:24
remove 146:20 146:21
194:10
removed 53:5 53:9
renal 75:16 123:20
123:25 124:3 133:2
133:2 175:13 177:10
177:13 177:16 229:22
234:12 234:18 246:11
repeat 64:9 105:14
107:5
repeated 199:8
rephrase 200:14
replaces 189:16
reporting 59:18 69:12

201:17 218:2
reports 11:24 22:13
25:6 26:5 72:23 81:23
97:24 154:11 157:7
250:8
represent 122:23
183:24
representative 8:18
11:2
representatives 45:8
represents 114:7
reproduced 135:17
reputable 252:14
request 171:21 253:22
requested 13:25 180:4
206:12
require 12:12 44:23
130:20 209:9 209:25
210:6 210:24 236:9
requirement 81:12
81:13 251:14 251:22
254:3
requires 19:13 228:19
rescue 83:7 135:5
135:23 136:3 136:8
136:13 136:17 136:25
137:2 145:19 211:17
211:21 211:24
rescued 83:23 137:11
242:6
resection 41:19 42:4
208:5
reserved 238:14 239:3
residents 192:4
resistance 24:9
resolution 226:15
resolve 194:22 226:7
resolved 175:6
resolves 191:22
respectively 32:18
respiration 186:20
respirators 160:8
respiratory 16:23 18:10
18:14 19:9 19:10 22:3
26:10 28:20 37:24 38:20
57:14 83:11 126:16
126:20 127:9 127:10
127:21 150:20 150:24
166:7 212:22 249:3
respond 52:20 52:22
53:8 58:18 119:13
130:21 131:7 149:15
159:13 161:11 207:3
231:18 231:23 231:25
233:6
responded 53:21 53:23
68:8 74:14 119:12
119:13 119:18 119:19
149:14 233:7
responder 119:2
responders 119:6
119:7 159:9 159:11
159:11 190:16
responding 34:19
118:9 175:12 242:10
responses 125:15

125:18 127:6 128:4
responsiveness 49:25
restarted 191:24
restate 67:17
restlessness 23:14
156:23
restrict 193:2 194:9
226:25
restricted 132:14
220:22 225:13 226:19
226:20
restriction 54:10
196:21 227:3 227:10
228:3 229:14
restrictions 232:4
resulted 35:24 48:19
165:15
resulting 24:4 24:5
retrieval 167:24
retrolental 122:12
retrospective 72:13
72:21 98:3 102:21
returning 47:11
reverse 47:23 72:4
192:23
review 11:12 15:18
16:7 16:10 20:4 20:19
22:20 28:5 48:12 60:17
66:18 67:19 72:14 72:21
76:14 82:15 94:12
101:14 147:8 167:12
169:21 178:6 182:9
185:3 185:9 191:12
229:3 231:8 254:15
254:25
reviewed 25:23 40:17
56:4 67:24 72:12 94:11
156:12 167:20 170:4
186:24 212:12 219:3
229:4
reviewer's 85:13 92:3
reviewer 82:6 82:9
82:16 82:17 86:13
150:17
Reviewing 25:5 190:4
253:8
reviews 22:17 24:13
235:2 254:9 254:12
254:17
revise 229:8
revised 84:13 229:7
revisit 230:3 234:25
reworking 147:20
rhinitis 220:2
Rhode 80:11
rhythm 131:24
Richmond 8:22
rid 177:17 192:10
Rigatto 125:18
right-hand 38:15
rigorous 222:22
rigorously 167:20
rise 250:25
risk-benefit 219:20
220:4
risk 24:16 59:22 72:6

72:8 84:2 100:20 115:13
135:11 136:5 138:11
138:12 138:13 138:15
138:16 138:19 138:21
152:24 152:25 153:9
158:2 158:7 158:20
170:19 189:2 203:21
209:15 213:10 215:17
219:20 240:6
risks 170:24 218:17
246:20
Robert 152:5
Robinson 97:13
room 107:24 122:19
127:23 215:8 221:12
Rothstein's 89:22
routinely 109:3
row 90:16
Roxane's 12:11 180:11
Roxane 14:9 15:11
15:13 15:23 15:25 17:17
19:24 26:22 50:14 50:16
53:3 79:15 103:4 151:16
173:3 173:16 174:19
176:8
Roxitrate 15:10
rule-out 19:12
rule 56:10 56:12 57:6
57:9 202:17
rules 185:18 186:7

- S -

safe 42:8 178:2 187:21
192:18 210:18 210:25
217:5 219:8 219:16
219:24
safely 159:19
safer 187:2 187:20
205:11
sample 60:23 60:25
61:6 62:20 63:4 85:4
85:24 93:9 110:22
111:8 111:16 115:2
115:4 139:4 139:6
146:11 146:22 147:3
148:9 237:5
samples 252:22
sampling 49:21 54:25
satisfied 54:17
satisfy 236:13
saturation 46:6 85:3
91:15 127:17
scale 35:6 138:9 222:9
246:12
scaled 35:8 35:10
scaling 86:15
Scandinavian 160:16
Scanlon's 74:14
Scanlon 74:4 120:2
scarce 160:13
scenario 189:11 211:23
scenarios 135:7
schedule 14:11 120:14

159:25
Science 80:12 196:21
204:20
Sciences 9:12 9:19
50:17
scientific 46:6 181:12
201:4
scope 196:6
score 109:3 111:14
screen 29:12 38:15
screened 44:19 65:9
81:9 81:20
se 80:2 104:16
Sean 14:15 16:4
search 16:7 20:5 20:13
94:9 96:9 105:21 106:2
176:18
Secondary 84:20 91:10
91:19 143:25 144:2
153:2
Secondly 45:6 46:3
92:16 121:11 177:18
seconds 18:11 28:8
83:11 124:25 130:18
sections 239:8 240:15
sector 216:13 216:16
sedation 192:24
seeing 58:11 143:9
200:21 200:24 237:10
seek 198:7
sees 127:2
Seizures 23:14 157:3
157:6
selected 16:8 16:9
selection 133:12
self-limiting 18:16
send 43:18
sending 163:13
sends 229:8
Senior 15:22
senses 38:21
sensitive 146:10 202:15
sensitivity 19:10 146:7
146:15
sentences 235:3
separate 32:23 220:19
separation 112:20
septic 247:23 248:5
sequelae 26:3 26:6
seriously 208:13
serum 28:23 45:15
45:23 48:24 49:4 49:8
155:7 161:7 233:7
serve 10:19 180:15
service 11:6
session 14:17 253:15
SESSLER 8:19 8:19
71:20 71:21 72:3 106:24
107:22 108:22 108:25
147:19 172:14 172:15
174:5 185:16 201:4
204:8 205:18 206:25
207:4 208:14 213:3
215:14 215:15 221:6
221:25 223:8 223:13
236:5 236:13 237:16

238:9 241:22 242:3
247:4 248:3 251:16
setting 162:5 188:22
217:22 249:24 250:17
severe 39:23 40:12
69:4 74:5 133:11 149:18
166:18 235:17 239:4
241:23
severely 211:24
severity 25:23 107:2
107:12 107:25 111:13
111:17 148:25 204:11
238:16 241:20
sex 31:22
Shah 82:16
share 188:6
Shepard 14:20 15:20
15:22 16:3 16:4
shock 41:2
shocking 150:17
short-term 184:23
184:24 186:15 188:20
190:20 194:2 194:7
194:13 195:4 196:4
197:15 197:17 198:5
198:14 199:8 199:10
201:18 217:6 218:3
shortly 12:16 12:18
84:17 126:24 213:21
showing 143:8 155:25
192:9
shows 29:21 36:2 36:12
36:15 89:3 89:13 90:18
118:13 157:8
sick 208:24
sicker 65:12 111:10
112:5 208:22 235:17
250:16
sided 205:4
sides 133:19
SIDS 69:19
sign 75:19 173:2
signal 199:4
signed 12:17 28:13
significance 114:20
114:23 140:10 142:4
145:11 169:23 179:10
significantly 24:20
36:13 48:3 91:13 123:17
137:16 149:18
signs 37:24 38:7 40:25
79:5 98:12 107:19
simplest 162:9
simulations 19:20
simultaneously 94:20
208:5
sinus 131:24
sit 128:23 169:21
site 40:7 47:7 47:10
106:20 138:3 138:8
146:8 146:8 164:8
171:9
sites 71:17 79:20 79:21
79:22 79:24 79:25 80:3
172:7
sitting 50:22

situations 160:7 181:15
six-fold 124:7
sizable 145:10
sizes 147:3
skin 38:20
skip 124:19 220:17
sleep 19:4 19:5 21:20
125:12 127:7
slide 12:10 12:13 21:6
24:13 24:23 34:14 36:2
51:7 51:13 55:24 101:16
102:11
slides 62:12 121:17
121:21 122:15
slight 78:9
slightly 39:16 51:21
91:8 129:4 135:23
137:13 143:17 171:14
194:4
slope 168:14
slow 127:14
smaller 16:21 145:3
146:22 191:8 246:20
254:7
sodium 48:9 153:24
212:22
soft 228:18
solicited 152:3
solution 17:17 30:2
30:6 170:17
solved 191:8
Somehow 184:3 235:21
someone 78:6 127:13
129:9 163:10 237:16
243:10
sometime 226:23
227:15
somewhere 44:5 60:24
64:14 76:5 172:18
174:9 236:9 241:6
sophisticated 138:5
217:17
Sorry 48:23 107:5
215:15 223:14
sorted 190:17
sorts 113:20 134:10
sounded 172:3 172:4
172:6 202:11
sounds 113:7 172:12
197:9
soup 250:4
source 182:17
Sources 22:23 111:5
space 123:13 123:16
123:19
spare 151:3
sparse 49:21 252:21
speaker 15:20
speakers 14:11 14:19
speaks 64:15
specialist 8:20
specialty 8:12
specifically 46:21 59:13
68:7 106:4 172:21
183:17 198:25 199:18
203:25 227:21 243:23

specified 180:19
specify 233:24
spectra 243:13
spectrum 240:2
speculate 255:2
spell 181:9
spells 109:6
spend 19:4 121:23
128:8 131:15
spent 21:19 89:14
192:3
spinal 16:23
Spoken 187:10
sponsor's 14:8 14:10
42:10 45:8 103:15
147:16 230:7
sponsor 10:12 11:24
12:11 43:4 50:19 70:20
80:17 80:23 82:22 83:5
85:6 85:12 86:12 86:23
89:11 91:24 92:5 92:8
94:8 96:11 96:25 102:20
103:25 105:10 107:23
109:14 113:8 115:2
117:5 135:12 135:18
138:10 139:12 141:13
141:18 147:7 156:4
176:8 179:25 180:19
192:15 206:12 229:2
229:8 238:17 241:13
255:9
sponsored 216:11
sponsors 42:12 42:15
110:20 128:20 174:5
215:18 215:22
spontaneous 52:4
201:17
spontaneously 69:9
SPR'S 244:5
spread 54:15 54:19
54:25 55:3
stability 154:9 154:19
155:10 164:9
stable 154:10
stages 250:24
Stan 8:25 75:25 79:13
114:22 118:17 165:4
172:2 199:12 202:7
210:4 253:24
standardized 17:17
163:12 223:16
standing 127:13 221:21
standpoint 145:16
183:9
starting 184:16 195:18
208:10 249:4
startles 18:15
starts 124:22 132:6
stated 19:2 25:10 25:20
26:2 76:17 81:18 175:9
177:25 199:9-233:21
251:16
statement 12:7 12:25
102:15 130:11 200:12
200:18 205:6 218:14
232:23 234:10 235:2

states 125:13 127:7
130:20 172:20
stating 98:21 240:9
statistical 61:25 76:18
82:16 85:13 86:13 92:3
114:19 114:23 139:5
140:10 142:3 142:10
145:10 145:16 179:9
237:4 237:20
statistically 84:18
86:22 87:7 87:12 88:25
89:8 89:10 91:13 95:11
95:23 96:7 99:22 99:25
102:2 102:4 102:8
113:17 137:16 137:18
138:24 148:8
statistician 144:5
187:10
statisticians 142:12
208:18
statistics 55:21 136:25
137:17 139:25 147:20
184:3 208:12 237:17
status 12:22
staying 77:22
steady 123:18
steep 168:18
sterility 17:20
steroids 136:11
stimulant 57:14 126:16
127:10 127:21 186:16
186:20 212:23
stimulating 134:3
stimulation 19:19
23:13 127:16 129:15
129:22 130:21 133:15
134:9 153:13
stimulus 126:3 127:3
stomach 134:4
stopping 159:25
stops 132:6 134:19
194:14
straightforward 136:23
strict 29:12 31:6 37:12
51:16
strikes 110:16
striking 207:24 208:3
209:5 210:13
strikingly 208:14
stringent 36:21 114:23
stronger 52:22 239:20
247:23
strongly 177:23 184:12
253:16
struck 50:23 107:7
188:8 204:8
students 192:4
studied 21:2 57:18
93:14 94:14 94:25 97:20
98:8 99:21 100:6 120:3
159:2 196:6 205:25
226:22 226:22 228:4
studying 214:14 251:23
stuff 252:22
style 55:12
styles 163:16

subjective 57:18 57:19
 143:14 156:21
 subjects 23:5 59:14
 77:18 117:15 145:21
 146:13 146:14 146:19
 submit 86:12
 submits 229:2
 submitted 13:5 15:17
 16:11 20:17 41:15 92:5
 94:11 99:8 106:11
 223:2 229:2
 submitters 43:6
 subpopulations 210:22
 Subsequent 17:13
 47:22 47:24 119:13
 222:11
 subsequently 42:5
 49:2
 subset 91:6 98:25
 160:20
 subsets 162:15
 substantial 95:14
 182:12 182:22 183:12
 183:25 184:2 184:9
 184:21
 substantially 229:7
 229:7
 substantiate 78:19
 185:15
 substantiation 182:16
 substantive 255:3
 succeeding 35:14
 Success 30:20 32:25
 33:25 34:17 35:3 35:12
 35:14 37:13 50:25 51:3
 51:8 61:2 61:8 62:10
 62:11 62:22 63:9 63:16
 63:20 63:24 64:2 74:15
 84:9 85:11 85:15
 successes 34:9 34:9
 successful 192:9
 successive 69:24
 sudden 23:17 24:17
 210:14
 suffering 242:8
 sufficient 101:7 178:21
 178:23 184:9 185:17
 185:21 187:5 188:8
 188:11 190:14 192:11
 192:11 192:13 194:6
 199:22 200:16 201:7
 246:22
 sufficiently 208:11
 suggest 23:21 76:21
 97:14 189:24 190:11
 193:25 200:5 209:24
 228:9 249:12
 suggested 97:22
 suggesting 77:15
 171:5 231:5 248:12
 suggestion 199:16
 234:19 236:17
 suggestions 209:21
 245:17
 suggestive 190:3
 190:4

suggests 225:8
 sum 127:11
 summarization 92:4
 summarize 77:3
 summarizes 21:6
 summary 16:7 22:5
 83:3 99:19 183:8 196:16
 251:8 254:7
 superior 166:11
 Supinski 166:9
 support 20:9 26:18
 100:9 113:22 155:22
 156:8 156:16 180:3
 186:25 188:14 188:20
 215:10 223:22 224:22
 227:2 233:20 236:22
 246:17
 supported 17:25 214:2
 supporting 223:23
 supportive 140:8
 156:13 203:11
 supports 94:24
 suppose 178:23
 surfactant 243:22
 244:6 250:7
 surprise 201:22 201:23
 201:25
 surprised 64:22
 surveillance 161:16
 161:21 205:9 206:23
 209:10 209:13
 surveyed 43:22 44:9
 survival 97:11 112:19
 112:21 137:5 137:10
 137:10 137:14
 survive 137:11 212:24
 surviving 137:11
 suspect 65:11 108:4
 108:8 132:19 132:25
 168:20 169:2
 suspected 135:10
 202:13 202:16 202:17
 202:20 247:18
 suspicion 202:10
 swallowing 18:15
 switched 148:6 242:8
 switching 175:18
 symptom 169:25
 symptomatic 108:12
 symptomatology
 108:5
 symptoms 79:5 98:14
 syndrome 23:17 24:17
 247:17
 synopsis 227:8
 system 23:9 23:9 23:10
 23:11 23:13 23:21 26:12
 38:18 38:18 38:19 38:20
 38:20 100:16 105:5
 156:19 162:5 176:3
 201:17 218:2
 systematic 72:23
 systemic 40:25
 systems 38:13 38:17
 38:21 116:23 161:21
 Szefer's 168:15

- T -

T-test 36:11 37:7
 tables 135:18
 tachycardia 23:25
 40:2
 tackle 242:23
 tactile 19:19
 tainted 222:6
 takes 131:6
 talked 64:11 111:5
 163:8 185:12 191:20
 202:8 237:5
 talking 57:21 70:4
 81:23 118:23 159:10
 177:21 197:18 199:8
 209:13 217:8 223:3
 tantalizing 121:9
 tapering 159:25
 target 83:8 159:4
 targeted 212:4
 task 180:11
 TDX 164:21 169:18
 teaching 192:4
 team 82:15
 tease 165:10 205:12
 technology 116:18
 224:2 224:25
 tells 118:6
 temperature 28:18
 37:24 202:25
 tendency 185:4
 tending 178:12
 tends 94:19 226:7
 tenfold 165:18
 tension 24:5
 tested 68:24 69:6
 227:14
 testing 69:21 69:22
 tests 19:14 114:3
 Texas 80:12
 textbooks 19:16 214:19
 Thank 8:5 10:7 10:10
 10:18 13:20 13:22 16:4
 18:7 26:23 26:24 42:10
 42:12 43:3 48:14 55:15
 79:10 80:17 81:5 82:3
 82:4 82:10 82:19 101:9
 101:10 128:6 128:7
 134:22 140:11 144:8
 150:5 150:11 163:2
 166:4 166:22 183:14
 193:20 225:10 228:15
 238:9 240:24 242:22
 253:2 253:6 253:9
 255:8
 thanking 10:11
 Thanks 11:15 12:5
 12:6 193:4 255:7 255:8
 theophylline-treated
 24:19 25:9 25:11 26:11
 102:13
 theoretical 189:4

247:24
 theoretically 189:9
 therapeutic 16:20
 39:14 58:16 73:18
 108:17 153:22 157:13
 177:23 212:5 229:25
 229:25 233:4 233:9
 233:10 233:12 233:22
 Therapeutics 73:25
 therapies 129:11
 133:12 254:25
 therapy 32:21 32:25
 33:6 34:19 44:15 54:8
 79:7 85:18 95:9 174:21
 192:7 219:25 221:14
 225:22 231:18 232:8
 thereafter 213:21
 they'd 169:3
 They'll 232:21 255:4
 thick 150:13
 thinks 133:25
 thirdly 28:3
 Thompson 55:13
 thorough 147:8
 though 43:16 46:22
 55:4 61:16 111:20
 116:2 118:8 142:22
 156:16 247:7 247:17
 thoughtful 163:3
 166:23
 thoughts 107:23 121:6
 181:22 184:7 184:14
 199:12 247:11
 thousand 146:14
 245:2
 threatening 69:19
 239:23
 throw 187:16 233:3
 throwing 223:7
 thrown 65:17 66:10
 tie 76:9 153:10
 ties 76:2
 tightly 17:22
 till 176:19 195:14
 233:3
 tireless 82:18
 titrate 232:22
 titration 212:2
 today's 8:3 10:13 11:7
 11:16 12:10 13:23
 tolerance 23:22 156:25
 161:9 186:17
 tolerated 205:24
 toll 213:2
 Tom 58:17
 topic 11:7 121:19
 171:15
 touch 234:24
 touched 151:20 155:5
 164:10
 towards 171:6 183:21
 203:18 241:17
 toxic 163:25 168:11
 223:3
 toxicities 39:19
 toxicity 153:22 154:11

170:25
Toxline 20:6
tract 78:7 105:19
tradition 71:15
transcripts 253:18
transfer 27:13 33:4
33:22 34:7 34:9 42:4
54:7 54:9
transferred 15:6 15:8
30:11 32:9 32:15 32:24
33:3 33:15 33:20 34:4
34:15 35:13 35:16 36:16
39:7 41:17 42:3 47:7
47:8 53:21 81:17 81:25
85:21 86:5 87:17 87:22
88:21 93:3 93:5 93:18
112:8 112:10 118:5
118:8 135:5
transferring 27:7 33:24
53:19
translocation 207:21
transposition 131:21
treat 16:8 16:13 16:18
53:12 127:12 132:8
174:22 226:2
treated 28:4 44:11
44:17 45:5 46:14 66:25
67:7 67:22 67:23 68:8
83:18 95:12 96:4 98:4
98:6 98:18 102:23
102:24 108:9 194:13
194:24 195:13 195:15
244:24
treating 16:17 55:25
129:5 130:22 130:23
treatments 127:11
153:19
tremendous 54:15
122:2 122:4 132:4
168:16 168:20 169:23
188:3 244:15 245:3
tremendously 124:13
124:17 125:3 125:15
168:7
trend 35:22 36:12 36:25
37:8 52:21 111:24
112:2 112:12
trends 113:21 113:22
trials 20:23 22:13 59:5
59:7 68:7 69:16 73:4
94:11 96:9 100:3 105:24
129:10 132:5 146:12
180:5 180:22 181:2
181:13 181:17 182:13
185:19 188:10 188:25
191:12 209:18 210:16
210:17 210:20 211:10
222:7 222:9 222:12
244:8
tries 181:8
trimester 122:4
true 129:14 144:17
187:10 189:8 215:13
truly 203:11 242:6
tubes 47:13
turns 133:13 142:13

189:11 189:20 206:3
Twelve 201:10
Typically 109:2 146:12

- U -

U.s 15:14
Uauy 41:6
UCLA 163:15 163:20
168:22
ultimately 133:17
umbilical 97:7
unable 81:14
unacceptable 84:2
unapproved 153:20
unaware 42:20
unblinded 180:21
180:24 209:6
uncertain 241:4
uncertainties 221:14
uncertainty 241:21
unchanged 176:14
unclear 25:4 65:7
176:22 177:3 247:16
uncomfortable 203:16
uncontrolled 22:13
22:25 94:11 142:23
under-powered 110:5
140:6 141:24 142:14
145:8
undergo 229:3
underlying 39:4 78:16
81:15 83:15
undertake 221:13
unethical 29:18 64:8
180:7
Unfortunately 69:17
79:2 158:8 236:7 241:24
unhappy 201:4
uniform 123:8
uniformity 35:10
unique 11:9 11:20
188:24 191:17
unit 18:10 28:10 54:6
70:5 125:22 131:13
167:14 168:6 170:8
170:12 224:5 227:24
249:21
units 17:8 127:21
129:22 129:23 129:25
130:10 130:17 130:20
167:12 167:20 167:22
169:2 173:22 174:25
175:2 212:17 248:22
249:21
University 8:22 8:23
9:10 9:12 9:18 9:21
11:3 16:6 18:4 18:5
50:18 80:8 80:12 80:12
152:7 250:9 250:12
250:16
unknown 25:2 215:23
237:18
unless 156:21 193:2

202:14 210:12
unlikely 176:25 226:3
unprecedented 136:9
unpublished 206:16
unreasonable 174:16
unrelated 71:21
unreliable 91:23
unsettled 222:19
untreated 20:24 22:11
22:24 46:17 95:19 98:15
153:4
unusual 39:2 136:14
upgrading 116:22
upper 29:3 234:6
urea 28:22
urinary 75:21
urine 28:25 164:22
urogenital 38:21
useful 16:17 161:8
161:22 162:14 209:21
221:5 221:22 240:4
240:7 240:11 240:16
243:6 253:15
uses 88:14 197:5
usual 137:21 188:9
193:8 193:18
Utah 152:8
utilized 248:6

- V -

VA 9:15
valve 232:3
variability 26:14 55:6
119:21 124:5 155:7
168:17 168:20 168:20
variable 21:10 23:24
62:14 62:23 62:25
103:10 103:14 136:16
157:21 172:6 179:11
variables 51:4 51:24
51:25 73:5 103:7 113:16
113:19 114:2 138:25
144:3 156:16 190:13
217:18
variation 55:25 123:5
123:8 204:18
varies 97:5
vary 124:13 170:7
216:22
varying 18:10 73:5
75:18 162:16 177:12
vascular 24:9
vasoconstriction 24:6
ventilated 69:10 71:13
166:14 166:17 248:24
ventilation 29:4 70:12
71:2 81:14 83:19 126:11
126:19 126:23 126:24
153:7 248:25 249:2
ventilator 44:15 69:10
133:17 225:22 227:25
ventilators 44:14 69:13
227:22

ventilatory 127:6
Vermont 174:2 206:7
250:2 250:12
Vern 9:3 115:9 147:19
157:22
Vernon 140:11 141:15
150:5 247:11
version 84:14
versions 74:24
versus 26:8 26:11 47:14
54:17 59:13 86:8 90:11
93:12 93:13 93:13 95:19
95:20 95:22 95:25
119:10 120:3 126:2
126:11 126:11 133:2
148:23 173:13 175:8
207:11 208:9 211:22
219:22 237:21 243:9
243:12 245:2 245:9
250:3
vessels 131:21
vested 245:22
vials 171:13
Vibhakar 82:16
Vice 15:22
view 73:18 82:25 92:8
94:10 103:16 105:11
129:17 142:10 150:8
182:7 183:12 189:13
189:19 222:6 228:7
viewed 182:8 239:9
viewpoint 197:12
views 134:24
violation 31:20
Virginia 8:21 8:21
80:9
virtually 195:16
visible 131:9
visual 28:19
vital 37:23 38:7
vitamin 97:9
VLBW 203:5
voice 184:13 188:2
235:15
voiced 188:7
volume 17:8 58:20
83:22 123:18 160:23
170:8 170:12 171:8
171:9
volumes 124:14
volunteers 99:7
vote 179:2 184:10
184:13 184:13 187:8
199:20 200:5 200:9
200:11 217:25 218:22
219:4 219:7 220:7
221:21 223:9 224:9
228:11 228:13 229:13
234:9
voted 223:22 224:11
224:12 224:19
voting 12:21 12:23
224:23

- W -

waffles 187:12
wanting 168:15
wants 173:24 193:23
Ward 152:5 159:10
warned 179:4
warning 75:19 79:11
179:17 179:18 198:17
199:4 199:19 206:23
234:23 235:4 236:11
236:14 236:21 236:22
237:14 238:11 238:11
238:13 238:14 238:16
238:21 238:22 239:2
239:2 239:6 239:24
240:14 240:14 240:15
241:7 241:20
warnings 238:12 238:25
239:8 239:21 239:25
240:14
warrant 239:20
warranted 232:24
watch 128:23 162:10
weak 222:5
weaknesses 182:2
wealth 230:15
wean 69:11
weaned 44:14
weaning 227:22
Web 254:14
Wednesday 136:20
week 161:7 175:9
226:2
weeker 245:10
weeks 21:3 27:22 28:11
28:11 41:16 41:21 44:9
44:10 60:4 68:20 68:23
69:5 69:5 69:21 70:5
83:9 126:11 126:11
131:6 131:14 194:24
195:14 195:19 196:5
196:17 226:3 226:3
226:7 226:16 226:23
227:15
weighed 222:16
weight 21:4 31:24
38:7 41:5 49:23 51:22
90:23 91:6 97:3 152:18
152:21 173:8 249:16
250:4
welcome 8:4 14:12
121:3
well-constructed
132:4
well-controlled 11:23
100:4 180:5 180:15
181:13 181:17 182:13
188:9 193:10
well-established 215:16
weren't 32:22 59:11
202:15 242:10
wet 130:5
whenever 126:6 202:12
Whereas 34:20 76:7
77:8 155:21 171:2
178:10 239:10
Whereupon 120:19

255:11
wherever-130:18
who's 42:16 151:25
152:5 194:19 198:2
220:15
widely 98:2 144:11
144:12 157:16 187:18
204:22 205:8 255:5
widespread 11:25
Wilcoxon 137:21
willing 174:11 193:3
willingness 11:12
willy 198:9
wind 244:2
window 225:25
withdrawn 191:23
194:11
within-day 155:7
Women 80:10
wonder 145:5 145:12
207:5 242:6
wondered 73:18
wondering 48:16 54:16
61:7 117:17 176:9
209:8 250:15
Woodcock 12:21
worded 195:7 198:23
wording 198:18 199:3
work 82:15 134:8
156:16 172:21 176:5
185:20 241:13
worked 156:4
working 10:20 11:5
64:18 122:5 131:15
243:18
works 114:4 139:18
139:21 150:24 205:17
245:25
worldwide 40:18
worried 136:4 206:3
worrisome 236:8
worse 225:9
worst 189:11
worth 55:9 223:16
233:25
worthless 69:23 208:12
write-up 72:12
write 228:13 232:2
232:10 233:10
wrong 143:13 204:23
249:19
Wynne 14:24 26:21
26:24 45:12 48:11 48:23
50:21 51:6 52:9 52:16
53:15 54:2 54:21 55:22
56:11 57:9 57:21 57:25
59:24 60:7 60:8 61:9
62:17 63:7 63:17 64:21
65:19 67:15 71:25 72:9
80:3 80:4 80:24 81:3
81:5 82:4 83:14 84:6
105:12 216:2 216:3

- X -

xanthine 97:14
xanthines 97:19 100:25

- Y -

Yale 9:9
yellow 36:5
You'd 67:15 116:14
171:13 175:12 240:17
240:20 247:2
you'll 30:23 31:22
32:8 42:24 48:24 51:17
51:20 51:22 181:6
you've 143:22 150:19
193:24 226:2 226:11
253:7
younger 122:10 122:14
122:25 125:25 160:19

- Z -

zero 36:9 51:14 89:2
zeroes 208:16

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

Director, Office of Drug Evaluation II,
HFD-102

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



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

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 can 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

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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		

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