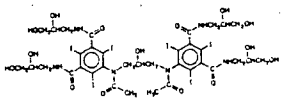
CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 020351/S01/S03

CHEMISTRY REVIEW(S)

JUN 23 1997

CHEMIST'S REVIEW	1. ORGANIZATION HFD-160	2. NDA Number(s) 20-351
3. Name and Address of Applicant (City & State): Nycomed Inc. 466 Devon Park Drive P.O. Box 6630 Wayne, PA 19087-8630		4. AF No. 5. Supplement(s) Number(s) Date(s) SEI-003 10-Oct-1996
6. Drug Name: Visipaque™ Injection	7. Nonproprietary Name: Iodixanol	8. Amendments & Other (reports, etc) - Dates BC - 04-Jun-1997
9. Supplement Provides For: Efficacy claims in pediatric patients.		
10. Pharmacological Category: Iodinated contrast media	11. How Dispensed: ☒ Rx ☐ OTC	12. Related IND(s)/ NDA(s)/DMF(s)
13. Dosage Form(s): Injectable solution	14. Potency(ies): 270mgI/mL 320mgI/mL	
15. Chemical Name and Structure: 1,3-Benzenedicarboxamide, 5,5'-[(2-hydroxy-1,3-propenediyl)bis(acetylimino)]bis[N,N'-bis(2,3-dihydroxypropyl)-2,4,6-triiodo. 		16. Records/Reports Current: ☐Yes ☐ No Reviewed: ☐Yes ☐No
17. Comments: This is a pediatric use supplement and there are no changes in the chemistry, manufacturing and controls section of the NDA. The sponsor has provided the draft labeling "highlighting the changes" made to the current approved package insert. No changes have been indicated in the description section, drug handling section, how supplied section, storage description and in the name and address of the manufacturer of the drug. In the amendment dated 6/4/97, the sponsor has requested categorical exclusion from submitting an environmental assessment for this supplement under 21 CFR 25.24(c)(2)(ii). This amendment provides justification for this request under the stated regulation. The provided justification is acceptable to allow categorical exclusion under the stated regulation.		
18. Conclusions and Recommendations: There are no chemistry concerns related to this pediatric use supplement. The supplement is recommended for "approval" from the chemistry's point of view. CC: Original NDA# 20-351 HFD-160/Division File NDA 20-351 HFD-160/Kasliwal HFD-160/CSO/Cusack R/D initialed by : Leutzinger		
19. REVIEWER		
Name Ravindra K. Kasliwal, Ph.D	Signature /S/	Date Completed 6/18/97

/S/ 6/23/97

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 020351/S01/S03

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

AUG 26 1996

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA 20-351 (SE1-003)	SUBMISSION DATE: 10/10/96
BRAND NAME: Visipaque®	ASSIGNED DATE: 12/19/96
GENERIC NAME: Iodixanol	REVIEW DATE: 8/21/97
SPONSOR: Nycomed Inc.	REVIEWER: Young-Moon Choi, Ph.D.
TYPE OF SUBMISSION: Supplemental NDA, 1S	

I. Synopsis

On 10/10/96, Nycomed Inc. submitted a supplement to NDA 20-351 for the approval of Visipaque® (Iodixanol) Injection for pediatric use.

Visipaque® (Iodixanol) Injection, 5,5'-[2-hydroxy-1,3-poropanediyl)bis(acetylimino)]bis[N,N'-bis(2,3-dihydroxypropyl)-2,4,6-triiodo-1,3-bezendicarboxamide], is a dimeric, nonionic, water-soluble, iodinated compound (Fig.1), which is developed to enhance the visualization of anatomic detail in organ and vascular systems in radiographic diagnosis procedures. This drug was approved on 3/22/96 in the United States for adults.

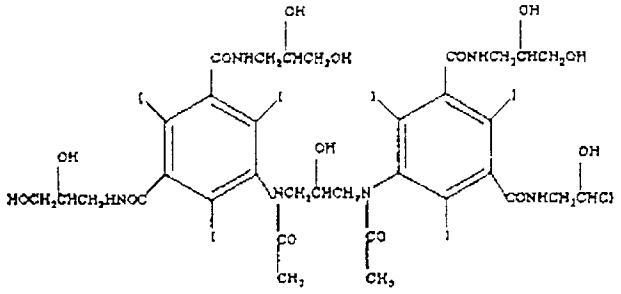


Figure 1. The structure of Visipaque® (Iodixanol) Injection

In the Agency's approval letter dated 3/22/96, the following Phase IV commitments were sent to the sponsor to remind them of the agreements that they had made in their correspondences of

(1) To complete the study addressing pediatric pharmacokinetics

In this submission (NDA 20-351, SE1-003) of 10/10/96, a response to the Phase IV commitment regarding the pediatric pharmacokinetic study is addressed

It should be noted that in addition to the pediatric pharmacokinetic study, the sponsor performed two clinical trials for each indication, i.e., total of eight clinical trials (Table II). Overall, efficacy and adverse events of Visipaque were evaluated in 459 pediatric patients; n = 26 for age 0-28 days; n = 148 for age 29 days to 2 years; n = 263 for age 2-12 years; n = 22 for age 12-18 years.

Table I. The applied for indications and concentrations of Vispaque in NDA 20-351 supplement SE1-003.

Indication	Concentration
Angiocardiography	320 mgI/ml
CT scanning of the head	270 mgI/ml and 320 mgI/ml
CT scanning of the body	270 mgI/ml and 320 mgI/ml
Excretory urography	270 mgI/ml and 320 mgI/ml

Table II. Summary of the submitted study reports in the present supplemental NDA.

No.	Report ID Number	Title	Protocol ID
(1)	Study report 2493	A phase I, open label, multi center, **pharmacokinetic** and safety study of Visipaque® (Iodixanol) Injection 320 mgI/ml in pediatric patients referred for a contrast-enhanced diagnostic procedure	39998-018
(2)	Study report 1310	Validation of a **high performance liquid chromatographic method** of the quantitation of Iodixanol in human plasma	NA
(3)	Study report 1968	A phase III, randomized, blinded comparison of Iodixanol (Visipaque® 320 mgI/ml) and Omnipaque® 350 (Iohexanol) in pediatric patients requiring **angiocardiography**	39998-013
(4)	Study report 2509	Visipaque® (Iodixanol) Injection in pediatric **angiography**: An open phase II trial with iodixanol 320 mgI/ml, and a double blind, parallel, randomized phase III trial with iodixanol 320 mgI/ml compared to iohexol (Omnipaque®) 350 mgI/ml	DXV 036
(5)	Study report 2510	Iodixanol (Visipaque®) in pediatric excretory **urography**: A multi center randomized, parallel group, double-blind phase III comparison between iodixanol(Visipaque®) 270 mgI/ml and 320 mgI/ml, and Iohexanol (Omnipaque®) 300 mgI/ml	DXV 037
(6)	Study report 2513	Iodixanol (Visipaque®) in pediatric excretory **urography**: An open phase II trial with iodixanol (Visipaque®) 320 mgI/ml, and a randomized, parallel, double blind phase III comparison between iodixanol (Visipaque®) 270 mgI/ml and 320 mgI/ml, and Iohexanol (Omnipaque®) 300 mgI/ml	DXV 041
(7)	Study report 1966	A phase III, randomized, double blind comparison of Iodixanol (Visipaque® 270 mgI/ml and 320 mgI/ml) and Iohexanol (Omnipaque® 300 mgI/ml) in pediatric patients requiring **computed tomography (CT) scanning of the head.**	39998-011
(8)	Study report 2512	Iodixanol (Visipaque®) in pediatric **computed tomography (CT) scanning of the head.** A randomized, parallel, double blind phase III comparison between iodixanol 270 mgI/ml and 320 mgI/ml, and Iohexol (Omnipaque®) 300 mgI/ml	DXV 039
(9)	Study report 1967	A phase III, randomized, double blind comparison of Iodixanol (Visipaque® 270 mgI/ml and 320 mgI/ml) and Iohexanol (Omnipaque® 300 mgI/ml) in pediatric patients requiring **computed tomography (CT) scanning of the body.**	39998-012
(10)	Study report 2512	Iodixanol (Visipaque®) in pediatric **computed tomography (CT) scanning of the body**: A randomized, parallel, double blind phase III comparison between iodixanol, 270 mgI/ml and 320 mgI/ml, and Iohexanol (Omnipaque®) 300 mgI/ml	DXV 038

NA: Not Applicable

The present review is concentrated on the pediatric pharmacokinetic study (Study report 2493) and a supportive assay validation report (Study report 1310) found under item 6 of the submitted supplemental NDA, the Human Pharmacokinetics and Bioavailability Section.

II. RECOMMENDATION

The Supplement SE1-003 that was filed under NDA 20-351 on October 10, 1996 has been reviewed by the Office of Clinical Pharmacology and Biopharmaceutics, Division of Pharmaceutical Evaluation II (OCPB/DPE II). The provided pharmacokinetic data/information indicate that the elimination rate constants for Visipaque in pediatric patients appear to be dependent on a patient's renal function. A similar elimination pattern has been shown in adults.

Regarding the proposed pediatric doses, from a pharmacokinetic perspective, they can not currently be accurately assessed as related to the adult doses based upon the limited pediatric pharmacokinetic data analysis information provided by the sponsor. That is, the sponsor's data analysis only determined elimination rate constants and not clearance and volume of distribution information for Visipaque in the studied pediatric patients. Therefore, additional pharmacokinetic data analyses need to be performed on the sponsor's provided plasma level data (i.e., using population pharmacokinetic type data analyses).

It should however be noted that in addition to the pharmacokinetic study in pediatric patients, the sponsor submitted results for eight additional clinical trials that evaluated the safety and efficacy of Visipaque in pediatric patients for the requested indications covering the proposed dosing ranges. The OCPB/DPE II is of the opinion that the supplement could be approved based upon the clinical safety and efficacy data if it is found to be acceptable for supporting the pediatric dosing ranges proposed in the package insert (i.e., under 21 CFR 320.24 (b) (4) of the bio-regulations). It is noted, however, that there are only 26 patients studied in the age range of 0-28 days.

Further pharmacokinetic data analyses are recommended to be performed and depending on those analyses future changes to the package insert may be recommended. Please forward the following comment to the sponsor.

> For Study Protocol #39998-018, it is felt that the obtained pediatric plasma level data may be able to be more thoroughly analyzed using a population pharmacokinetic approach. By applying such analyses future labeling changes may be needed.

Also, please forward to the sponsor Labeling Comment Nos. 1-3 that are found on Page 20 of this review if the reviewing medical staff concurs.

The Office of Clinical Pharmacology and Biopharmaceutics staff will contact the sponsor about the additional pharmacokinetic data analyses that are needed.

8/26/97

Young Moon Choi, Ph.D.
Office of Clinical Pharmacology and Biopharmaceutics
Division of Pharmaceutical Evaluation II

Concurrence

John Hunt, Deputy Director

8/26/17

CC:

HFD-160	NDA 20,351
HFD-160	DIV FILE
HFD-160	/CSO; (1X)
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HFD-850	/OCPB/SMHUANG (1X)
CDR	ATTN: BARBARA MURPHY

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III.Table of contents Page

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VI. Summary of Pharmacokinetic Study

A. Background

In the original NDA the pharmacokinetics (PK) of iodixanol were evaluated in a Phase I study in normal adult male volunteers. That study showed iodixanol was not bound in plasma proteins and it is not metabolized. Iodixanol was excreted via glomerular filtration with 97% of the injected dose excreted in the urine within 24 hours and less than 2 % excreted in the feces within 5 days after injection. The pharmacokinetics were also evaluated in adult patients with significantly impaired renal function (mean creatinine clearance of 13.61 ml/min/1.73m^2). In these patients, the plasma half life ($t_{1/2}$) increased to 23 hours (normal $t_{1/2}$ = 2 hours) and levels of iodixanol were detected 5 days after injection. Contrast enhance time in the kidneys increased from 6 hours to at least 24 hours.

In this supplement of NDA 20-351, SE1-003, Study Protocol No. 39998-018 (Report No. 2493) was conducted to characterize the pharmacokinetics and safety of iodixanol in pediatric patients, newborn to children ≤ 12 years of age. The sponsor hypothesized that the pharmacokinetics of iodixanol in children of at least three years of age are essentially same as the pharmacokinetics in adults. The basis for this is that in adults, iodixanol is passively excreted by the renal system, unmetabolized, so the rate of excretion depends primarily on the glomerular filtration rate (GFR). It was further hypothesized that GFR, not age *per se*, is the factor of importance in iodixanol elimination kinetics. As GFR increases with increasing age for children up to three years, age can be considered a surrogate for renal function. Therefore the pharmacokinetics in children less than three years old with age-normal GFR are anticipated to be characterized by an increased plasma $t_{1/2}$ and a decreased terminal elimination rate constant (k_{el}) due to decreased GFR.

> ***Reviewer's comment on the sponsor's assumption/hypothesis :***
> *It should be noted that the sponsor's provided iodixanol pediatric PK analysis (i.e., only elimination rate constants determined) does not give all the necessary information that is needed to support the hypothesis that iodixanol PK in children of at least three years of age is essentially the same as the PK in adults.(Note: Although k_{el} may be similar in two populations, one cannot conclude that the PK is actually similar because both volume of distribution (Vd) and clearance(CL) can affect k_{el} independently.)*
>
> *Additionally it is noted that the sponsor used serum creatinine values as an indicator of GFR. It is acceptable. The sponsor, however, also used age as a surrogate marker for renal function. This reviewer tested the appropriateness of age as a surrogate marker by correlating the GFR (as creatinine clearance) with age. The results indicate that there is a poor linear correlation between creatinine clearance and age (Figure 2) in the patients tested in Study Protocol No. 39998-018 (Study report No. 2493). Therefore, this reviewer is of the opinion that age may not be ideal as a surrogate marker. Two additional analyses were conducted that compared the k_{el} values of iodixanol in the pediatric patients tested in Study Protocol No. 39998-018 (Study report No. 2493) to age (Figure 3) or to creatinine clearance, which is estimated from the serum creatinine values provided by the sponsor (Figure 4). The data show that creatinine clearance, i.e., renal function, is a better predictor for k_{el} of iodixanol.*

Figure 2. Correlation of Age vs. CLcr

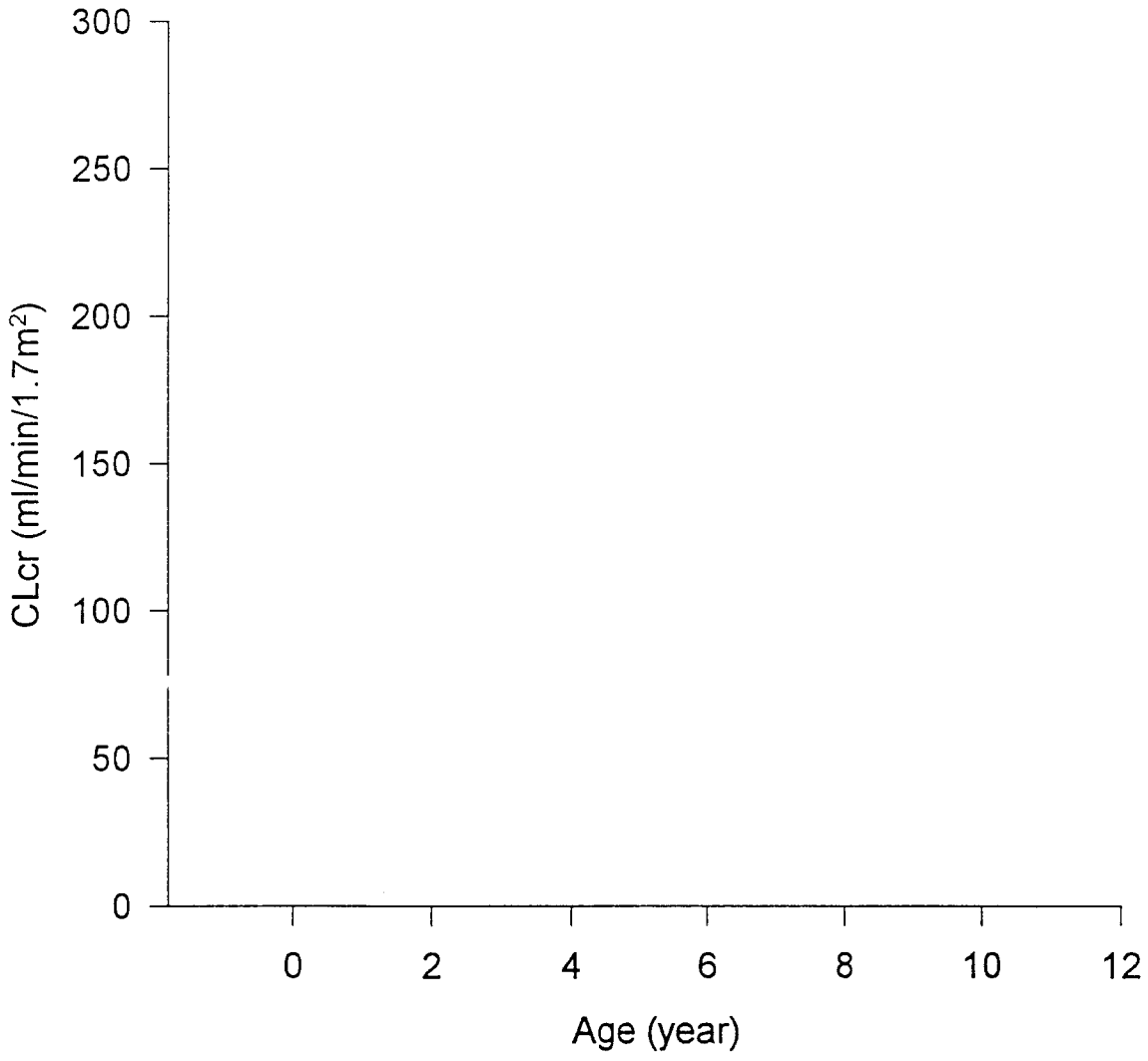


Figure 3. Correlation of k_{el} vs. Age

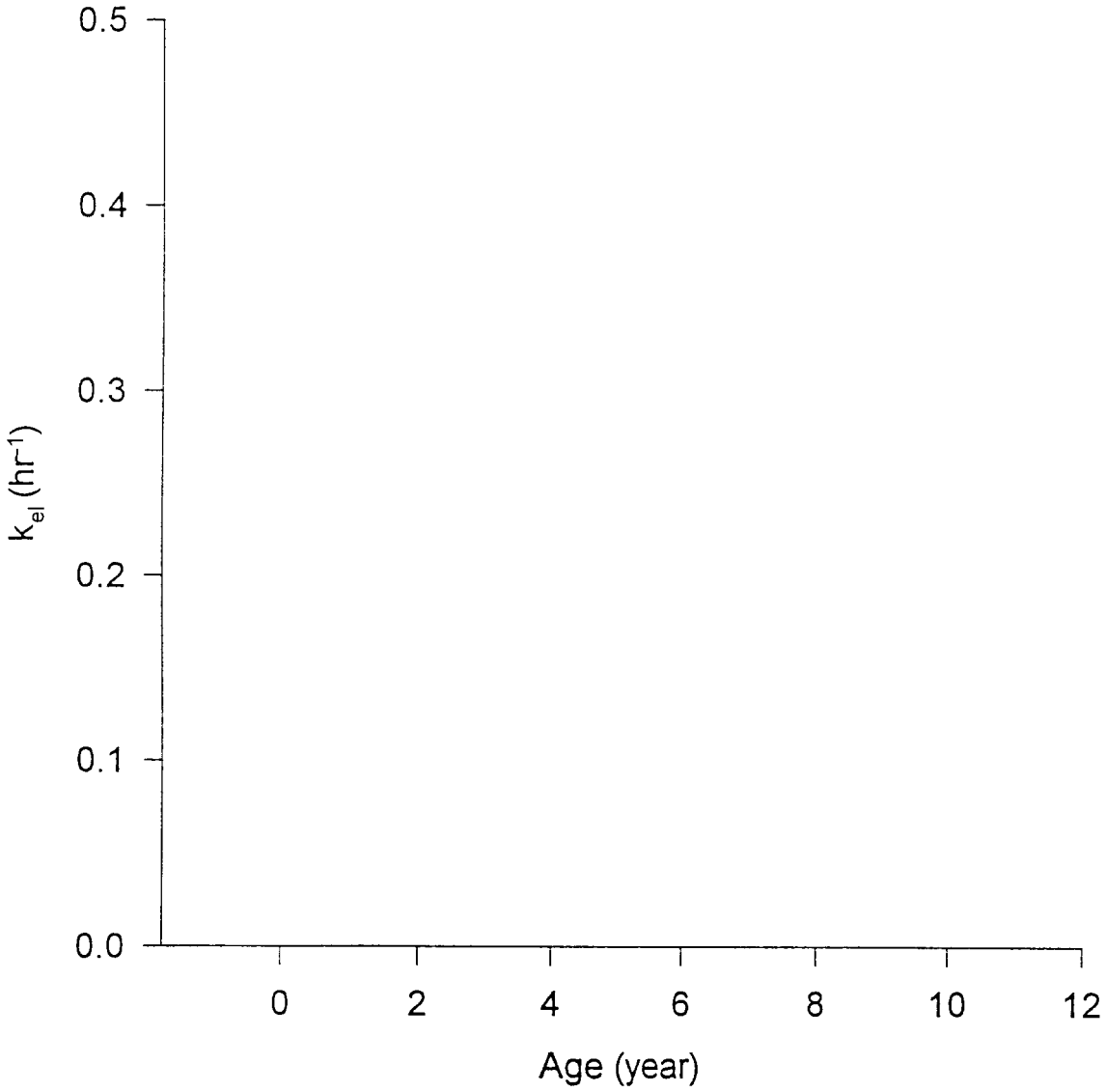
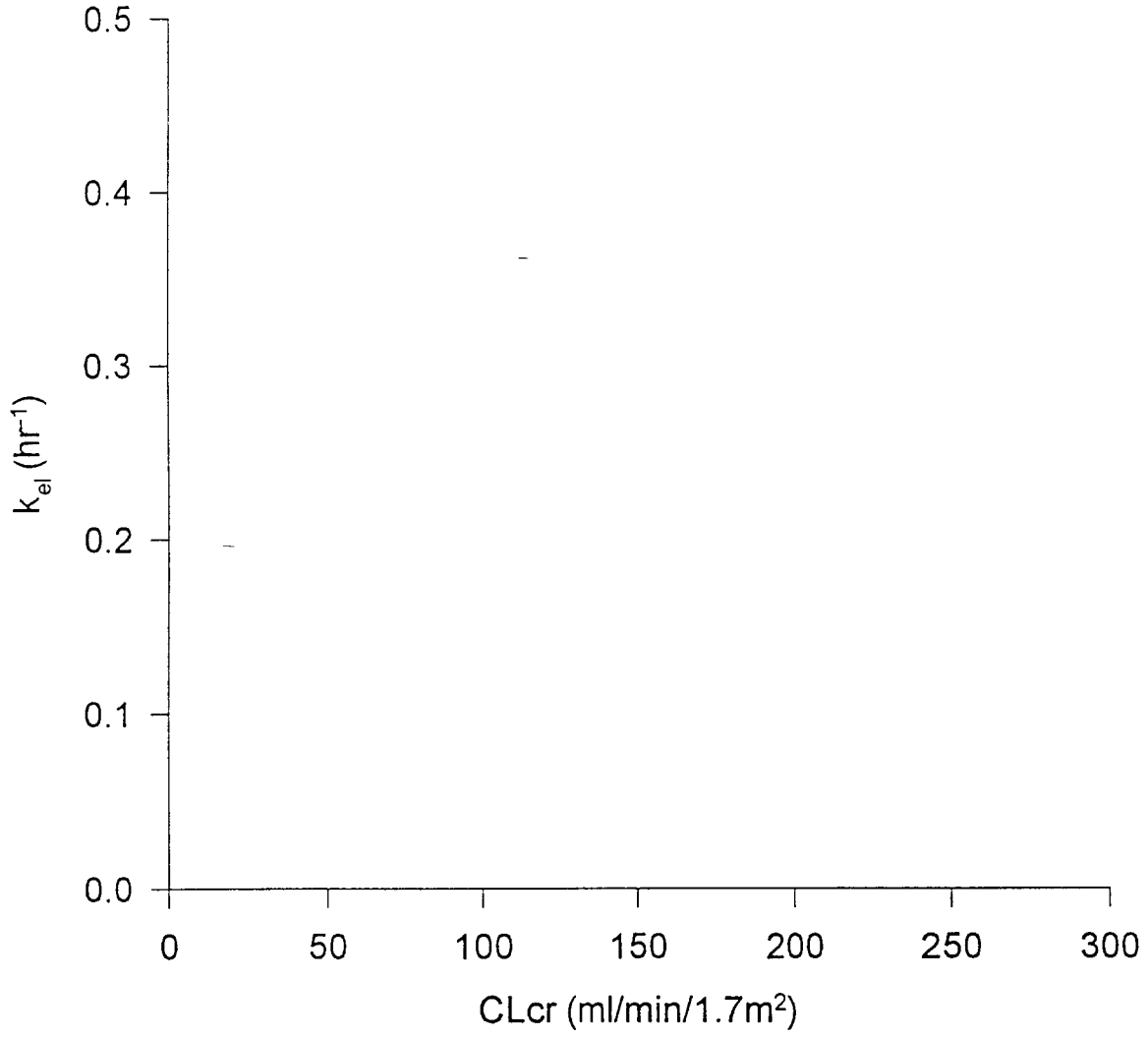


Figure 4. Correlation of k_{el} vs. CLcr



B. Study Design

This was a Phase 1, open-label, multicenter, PK and safety trial of iodixanol.

B-1. Patients

Patients were enrolled in one of five age groups (i.e., newborn to <2 months, 2 to <6 months, 6 to <12 months, I to <3 years, and 3 to ≤12 years). Eight to 10 patients were enrolled in each age group. (Table III)

Table III. Summary of the demographic characteristics by age group.

Demographic characteristics		Age Group					All age group (n=43)
		<2 mo. (N=8)	2-<6 mo. (n=9)	6-<12 mo. (N=10)	1-<3 yr. (N=8)	3-<12 yr (n=8)	
Age	mean ±SD	0.06±0.08	0.31±0.08	0.69±0.17	1.90±0.62	6.88±2.54	1.87±2.72
	min,max						
Weught (kg)	mean ±SD	3.7±0.8	4.9±1.1	7.6±1.9	10.7±2.2	22.0±9.8	0.06±0.08
	min,max						
Height (cm)	mean ±SD	52.0±3.7	59.1±5.0	70.5±6.2	81.9±7.9	119.0±18.2	75.8±24.9
	min,max						
Gender, N(%)	Male	4	5	7	5	6	27
	Female	4	4	3	3	2	16
Race, N(%)	Caucasian	6	6	4	4	6	26
	Black	2	3	5	3	2	15
	Oriental	0	0	0	1	0	1
	Other	0	0	1	0	0	1

All patients had been referred for radiographic diagnostic procedures. Thirty-seven patients (86%) had abnormal medical conditions relevant to the radiographic examination at enrollment in the trial, including congestive heart failure, ventricular septal defect, Down's syndrome, and heart murmur. Procedural and concomitantly administered medications are summarized in Tables IV and V, respectively.

Table IV. Summary of Procedural Medications, N (%) [a,b]

Medication Classification	N = 43
Any procedural medication	43 (100)
Alimentary tract and metabolism	11 (26)
Antiemetics and antinauseants	5 (12)
Gastrointestinal antispasmodics and anticholinergics	9 (21)
Blood and blood forming organs	26 (61)
Antithrombotic drugs	18 (42)
Plasma substitutes and perfusion solutions	12 (28)
Cardiovascular system	32 (74)
Cardiac therapy	32 (74)
Central nervous system	42 (98)
Anesthetics	26 (61)
Analgesics	20 (47)
Other CNS drugs, including parasympathomimetics	9 (21)
Psycholeptics	31 (72)
Dermatologicals	11 (26)
Antipuritics, including antihistamines, anesthetics, etc.	7 (16)
Musculoskeletal system	16 (37)
Muscle relaxants	16 (37)

[a] This table includes only those primary or secondary procedural medication classes that were taken by at least 10 % of the patients.
[b] A patient may have received more than one medication.

Table V. Summary of Concurrent Medications, N (%) [a, b]

Medication Classification	N=43
Any concurrent medication	36 (84)
Alimentary tract and metabolism	16 (37)
Antacids, antifulatulants, anti-peptic ulcer	5 (12)
Antidiarrials and gastrointestinal antiinfectives	5 (12)
Gastrointestinal antispasmodics and anticholinergics	5 (12)
Mineral supplements	8 (19)
Blood and blood forming organs	16 (37)
Antithrombotic drugs	12 (28)
Plasma substitutes and perfusion solutions	13 (30)
Cardiovascular system	27 (63)
Cardiac therapy	22 (51)
Diuretics	24 (56)
Hypotensives	6 (14)
Central nervous system	18 (42)
Anagesics	15 (35)
Psycholeptics	9 (21)
Dermatologicals	8 (19)
General antiinfectives, systemic	13 (30)
Systemic antibiotics	13 (30)
Musculoskeletal system	5 (12)
Various	6 (14)
All other nontherapeutic products	6 (14)

[a] This table includes only those primary or secondary procedural medication classes that were taken by at least 10 % of the patients.
[b] A patient may have received more than one medication.

Reviewer's comments on the potential effect of concomitantly administered drugs on the pharmacokinetics of iodixanol:
Some patients got sedatives. In those patients the cardiac output and hence GFR may have been reduced which might have affected the pharmacokinetics of iodixanol. Some other patients got diuretics which may change urine flow, and hence the renal clearance of iodixanol.

B-2. Visipaque (Iodixanol) Administration

Among the forty three patients in Study Protocol No. 39998-018 (Study report No. 2493), forty one patients underwent angiocardiography and received Visipaque intraarterially. Two patients underwent computed tomography of the head and neck and received Visipaque intravenously. The maximum injectable dose of Visipaque was up to 80 gI. Total doses of Visipaque ranged from (mean = 1.49 gI/kg), and the total volume of Visipaque ranged from (mean = 4.67 ml/kg). The duration of the radiographic procedures ranged from a few seconds to 102 minutes (mean = 30 minutes). Table V is a summary of the dosing information for all enrolled patients.

Table V. Summary of Dosing Data

Dosing Information		Age Group					All age group (n=43)
		<2 mo. (N=8)	2- <6 mo. (n=9)	6- <12 mo. (N=10)	1- <3 yr. (N=8)	3-≤12 yr (n=8)	
Dose (gI)	mean ±SD	6.1±2.9	8.6±4.3	11.1±4.4	16.6±8.07	17.9±7.6	12.0±7.0
	min,max						
Dose (gI/kg)	mean ±SD	1.73±0.87	1.73±0.58	1.50±0.62	1.67±0.97	0.81±0.29	1.49±0.75
	min,max				0.34, 2.96	0.32, 1.28	0.32, 3.2
Volume (ml)	mean ±SD	19.2±8.9	27.0±13.3	34.8±13.7	52.0±25.2	56.0±23.8	37.4±22.0
	min,max						
Volume (ml/kg)	mean ±SD	5.4±2.7	5.4±1.8	4.7±1.9	5.2±3.0	2.5±0.9	4.7±2.3
	min,max						
Numer of procedural injection	mean ±SD	2..8±1.3	3.0±1.0	2.7±0.9	3.1±2.1	1.6±0.5	2.7±1.3
	min,max						
Procedural duration (min)	mean ±SD	30±33	29±24	31±26	26±32	32±38	30±29
	min,max D						

Reviewer's comment on drug adminisration:

In this study various doses (range were administered. However, it is noted that for most patients the total administered dose was not given as a single bolus injection but was given instead as numerous spaced injections. Only 7 patients received their total dose as a single bolus injection. Additionally it is noted that iodixanol was injected at various sites (aorta, left or right ventricle, pulmonary arteries, veins and arteries). *The sponsor's mean pharmacokinetic parameters were pooled across injection sites and methods of injections (i.e., bolus vs. spaced injections)*

Reviewer's comment on the maximum allowable dose of iodixanol :

The maximum total pediatric iodixanol dose was 80 gI which is the same maximum dose for adults. Since pediatric body weights (or body surface area) are smaller than adults, the maximum dose of Visipaque should be standardized by body weight or body surface area.

B-3. Biological Sampling

Urine or fecal samples were not collected. Approximately 1-ml of blood samples were obtained from each patient at baseline (within 24 hours before the start of the first injection of Visipaque) and at 0.75 to 1.25 hours, 2 to 4 hours, 8 to 12 hours, and one day (16-32 hours) after the end of iodixanol administration. Exact sampling times within each sampling window were recorded for data analysis purposes. Each blood sample was collected in, or transferred to, a prelabeled vacutainer tube containing potassium oxalate and sodium fluoride. As soon as possible (within I hour), the sample was centrifuged, and immediately thereafter, the resulting supernatant (i.e., plasma) was transfer-red to a prelabeled test tube and frozen.

C. Assay

Plasma samples were analyzed for iodixanol by
This method was which is of all the samples. Assay validation data are summarized in Table VII.

Table VI. Summary of the Validation for the of iodixanol in human plasma.

Reviewer's Comment on the
The validation data for the determining iodixanol in human plasma (Study Report 1310) in the pediatric PK study (Study Report 2493; Protocol 39998-018) has been reviewed and found acceptable.

D. Pharmacokinetic Analysis and Results

For calculation of elimination PK parameters, preinjection sampling times were set to zero. Actual times were used for all postinjection samples. The terminal elimination rate constant (k_{el}) was computed by linear regression of the natural logarithm of the three or four sampled plasma concentrations as a function of time by assuming the one compartment model. The half-life ($t_{1/2}$) was calculated as $t_{1/2} = 0.693/k_{el}$. The sponsor states that the limited number of blood drawings per patient, the number of patients required to be studied, and the limited volume of each blood sample precluded assessment of additional pharmacokinetic parameters, e.g., total clearance, renal clearance, area under the curve, volume of distribution, etc. *(Note: These pharmacokinetic parameters may be able to be determined by population pharmacokinetic analyses).* All the sponsor's analyses were performed using SAS software.

Reviewer's comment on the possible overestimation of k_{el}:
The sponsor's reported k_{el} values using 4 sampling time points, including the 0.75-1.5 hr time point which may still be in the drug's distribution phase, may cause a possible overestimation of k_{el}. (Please refer to the individual data of plasma level vs. time curve in Appendix.)

Therefore this reviewer estimated the degree of potential overestimation using the previously submitted adult data. The mean k_{el} values obtained using the adult plasma concentrations at 1, 3, 9, and/or 24 hr after administration (i.e., the similar blood sampling time points in the pediatric pharmacokinetic study) were compared to the overall k_{el} value of 0.336 hr^{-1} that was obtained using all the blood sampling times in adults. The results are summarized in Table VIII.

Table VIII. The comparison of k_{el} values obtained using 1, 3, 9, and/or 24 hr plasma data and the mean values of k_{el} obtained using the full set of plasma data.

	Mean k_{el} using full data (hr^{-1})	*Mean k_{el} obtained using 4 sampling times (hr^{-1})*
Dose 0.3 gl/kg (N = 10)	*0.334*	*0.528*
Dose 0.6 gl/kg (N = 10)	*0.340*	*0.477*
Dose 0.9 gl/kg (N = 10)	*0.334*	*0.434*
Dose 1.2 gl/kg (N = 10)	*0.340*	*0.451*
Total Mean (N = 40)	*0.336*	*0.472*

The overall mean k_{el} value (0.472 hr^{-1}) estimated by using only 4 plasma samples that were obtained at 1, 3, 9, and/or 24 hr post administration appeared to be about 40 % larger than the overall mean k_{el} value (0.336 hr^{-1}) that was obtained by using 15 to 17 plasma samples from 3 min to 2 -3 days. Therefore, this reviewer is of the opinion that the sponsor's reported k_{el} values of iodixanol in the pediatric patients evaluated in Study Protocol No 39998-018 (Study Report No 2493) may also be similarly overestimated if the iodixanol pharmacokinetics in pediatrics are similar to that in adults. However, the issue of overestimation of k_{el} will be further addressed in the population based analyses.

This reviewer also performed the independent estimation of k_{el}, volume of distribution (Vd) as well as clearance (CL) using the plasma data of the 7 pediatric subjects received only one bolus injection. The one compartment model was assumed and the PK parameters were estimated by means of Data are summarized in Table IX.

Table IX. Pharmcokinetic parameters of iodixanol in pediatric patients obtained by assuming one compartment (or monoexponential) model.

Age (yr)	Subject I.D.	Body Weight(kg)	Dose (gl)	k_{el} [a] (hr-1)	Vd (ml/kg)	CL (ml/min/kg)
0.002	007-0004					
0.003	007-0003					
0.167	007-0008					
0.836	007-0005					
1.934	002-0001					
5.017	007-0001					
6.9	002-0006					
mean ± S.D.				*0.3004 ± 0.162*	*17.6 ± 10.4*	*4.2 ± 1.9*

The k_{el} in the seven pediatric patients (mean ± S.D. : 0.300 ± 0.162 hr^{-1}) appeared to be similar to the overall mean value of k_{el} in adults(0.336 hr^{-1}). However, the Vd (mean ± S.D. : 17.6 ± 10.4 ml/kg) and CL (mean ± S.D. : 4.2 ± 1.9 ml/min/kg) of iodixanol in pediatric patients estimated by assuming an one compartment model appeared several fold different from the values of Vd (mean of 260 ml/kg) and CL (mean of approximately 1.4 ml/min/kg) in adults. More appropriate analyses will be attempted using population pharmacokinetics.

Data from 40 patients out of 43 enrollments were used in the PK analysis.
Two of the 43 patients, Patient 003-0008 (6 months to <1 year age group) and Patient 006-0005 (2 to <6 months age group), had incomplete PK sampling. Both patients were replaced in the trial and were excluded from all PK calculations.

One more patient, Patient 002-0005 (27 months old), was excluded from the analysis of k_{el} because of the patient's apparently abnormal renal function before and during her participation in the trial.Patient 002-0005 had serum creatinine and blood urea nitrogen (BUN) values above the reference range (0.4 to 0.6 mg/dL and 5 to 20 mg/dL, respectively) at baseline, although they had been within the reference range during her hospital stay prior to the procedure. Her renal function decreased steadily thereafter, and her serum creatinine and BUN were respectively, by one day after the procedure. Approximately one and one-half days after the procedure, the patient experienced acute renal failure attributed to captopril. The patient's iodixanol plasma levels remained higher than any other patient in the trial. The patient's k_{el} was much lower than that of any other patient (range: 0.107 to 0.449 hr^{-1}). The patient eventually died and the sponsor claimed that the death is related to sepsis, not related to the iodixanol.

Table X is the data provided by the sponsor.

Table X. Summary of the terminal half lives ($t_{1/2}$) and elimination rate constants (k_{el}) in different age groups.

Age group	kel (hr^{-1})	$t_{1/2}$ (hr)
	mean ± sd	mean ± sd
0-2 month (n = 8)	0.185 ± 0.060	4.14 ± 1.41
2-6 month (n = 8)	0.256 ± 0.046	2.79 ± 0.55
6-12 month (n = 9)	0.299 ± 0.042	2.36 ± 0.37
1-3 yr (n = 7)	0.322 ± 0.058	2.23 ± 0.51
3-12 yr (n = 8)	0.307 ± 0.071	2.36 ± 0.52

Based upon the sponsor's analyses the mean k_{el} was statistically significantly lower in the newborn to < 2 months age group than in any of the three old age groups ($p < 0.0001$) for each comparison with no adjustment for multiple comparisons. The 2 to < 6 months age group mean k_{el} was intermediate between the newborn to < 2 months group and the groups with patients over 6 months of age.

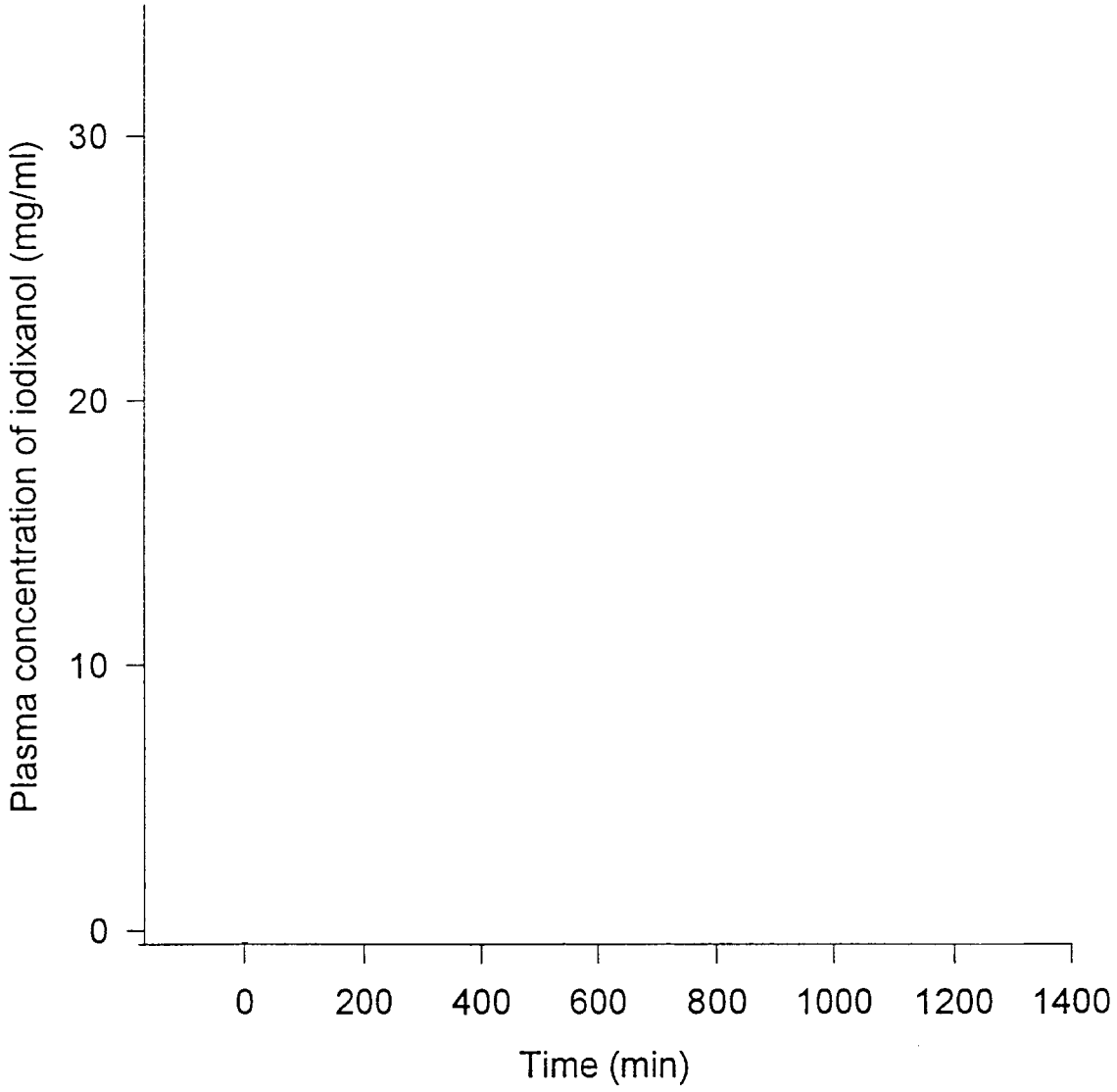
To further quantify the relationship between age and k_{el}, the sponsor did modeling with segmented linear regression which found increasing kel, from birth to approximately age 0.55 years (95% confidence interval: 0.36 to 0.75 years), then a plateau was reached after the age 0.55 years (Figure 3; Please note that Subject 002-0005 was excluded.).

It has been known that GFR is approximately 30% that of adults for newborns, 50% for children 2 months of age, 90% for 6 to 19-month-old children and 100% for 3- to 12-year-old children. The sponsor claimed that "since the renal elimination rate is directly proportional to GFR, and in adults, iodixanol is excreted unchanged in the urine, it is a reasonable assumption that the renal elimination rate in children will follow a pattern similar to that of GFR".

Comparison of iodixanol plasma levels in pediatric patients with adults

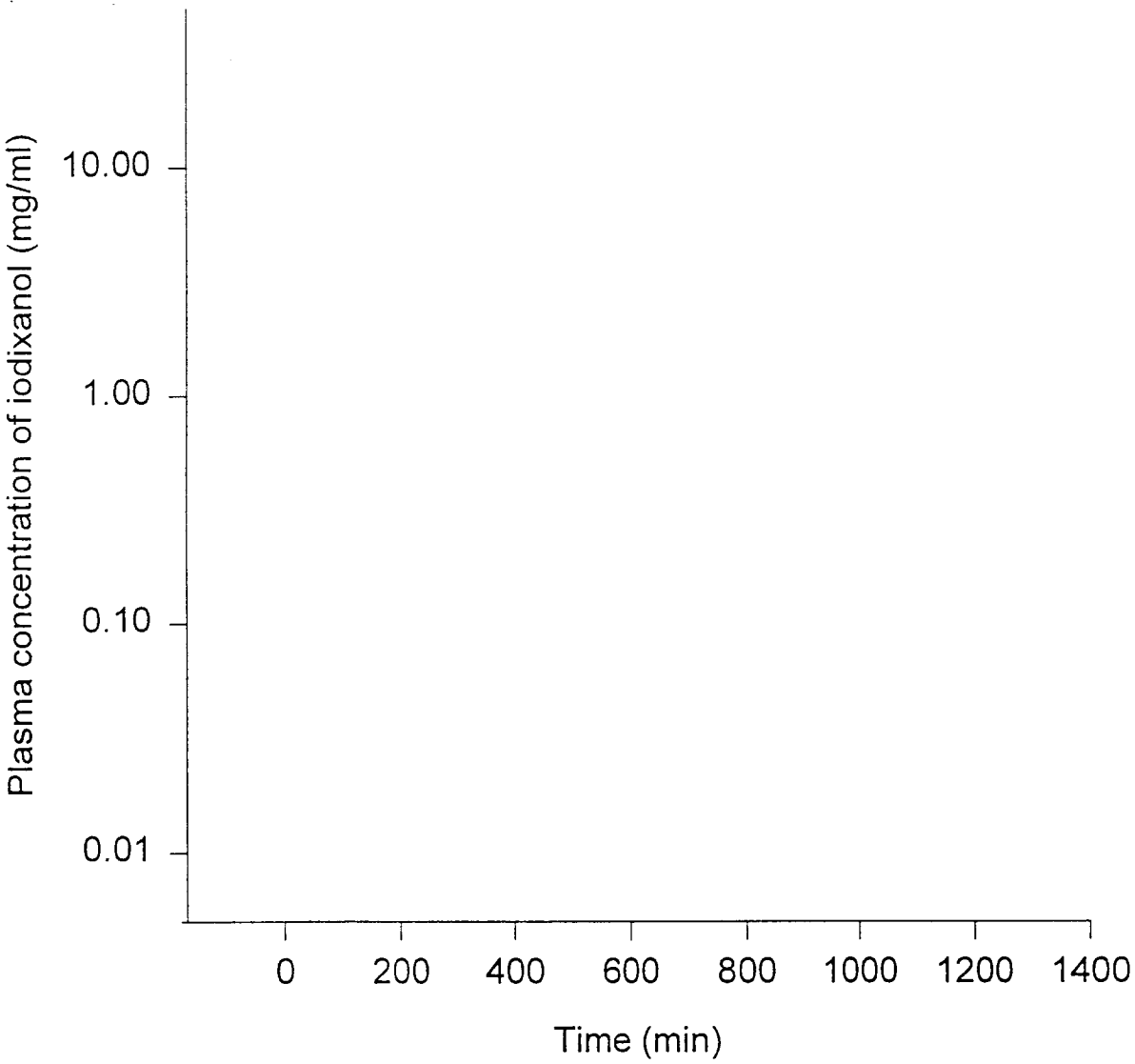
Figures 5 and 6 (semilog plot) attempt to compare iodixanol plasma concentrations for the 7 pediatric patients that recieved a single iv bolus dose (open symbols) to ten adults who also recieved a single iv bolus dose of iodixanol (0.3 mg/kg). For the blood level comparison, the plasma levels for the pediatric patients were normalized to the equivalent adult dose (0.3 mg/kg) by assuming linear pharmacokinetics, since the doses used in the 7 pediatric patients were 2-16 times smaller than the adults dose (Please refer to Table IX). Based upon the normalized pediatric plasma level data (that assumes linear PK characteristics), the iodixanol plasma levels are greater than those in adults. Further data analyses will be attempted to better address pediatric versus adult pharmacokinetics.

Figure 5. Comparison of Blood Levels of Iodixanol



Open symbols : Blood levels of Iodixanol in Pediatrics
Shaded symbols: Blood levels of Iodixanol in Adults

Figure 6. Comparison of Blood Levels of Iodixanol



Open symbols : Blood levels of Iodixanol in Pediatrics
Shaded symbols: Blood levels of Iodixanol in Adults

V. General Comment

Based upon the sponsor's limited data analysis, it is felt that additional pharmacokinetic analyses are needed using a population based approach.

VI. Labeling Comments

(1) Based upon concerns regarding the accuracy of determined elimination rate constants (and half-lives), it is recommended that the paragraph under the section titled "Special Populations" of the Clinical Pharmacology section of the package insert be deleted until further pharmaockinetic data analyses are performed. Also, the pediatric elimination half-lives should be deleted from the table under the section titled Drug-Drug Interactions.

(2) Under the Drug-Drug Interaction section, rather than saying "Not known", it may be appropriate to state that "drug-drug interaction studies have not been conducted in pediatric population".

(3) In the Dosage and Administration section, the applicant stated that "the combination of volume and concentration of Visipaque injection to be used should be individualized, accounting for factors such as age, body weight, size of the vessel, and rate of blood flow within the vessel". Furthermore, the applicant stated in the INTRAARTERIAL ADMINISTRATION that "injection rate should be approximately equal to the flow rate in the vessel being injected". The applicant should propose a dosing scheme which will administer VISIPAQUE effectively in pediatric patients, i.e., propose an optimal dosing scheme with combined age, body weight, size of blood vessel, etc. Also the maximum injection rate should be indicated.

Appendix I. Individual data

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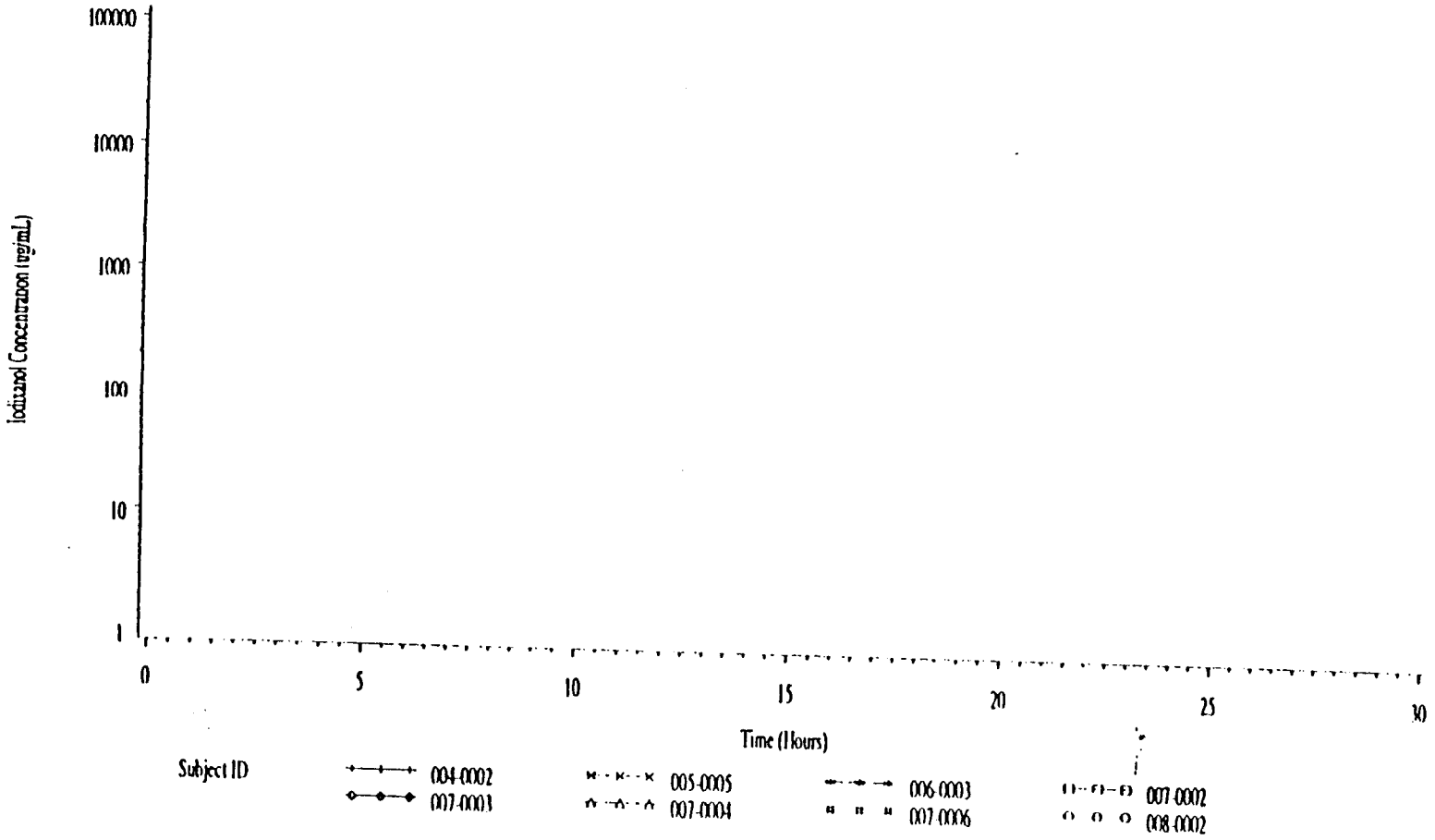
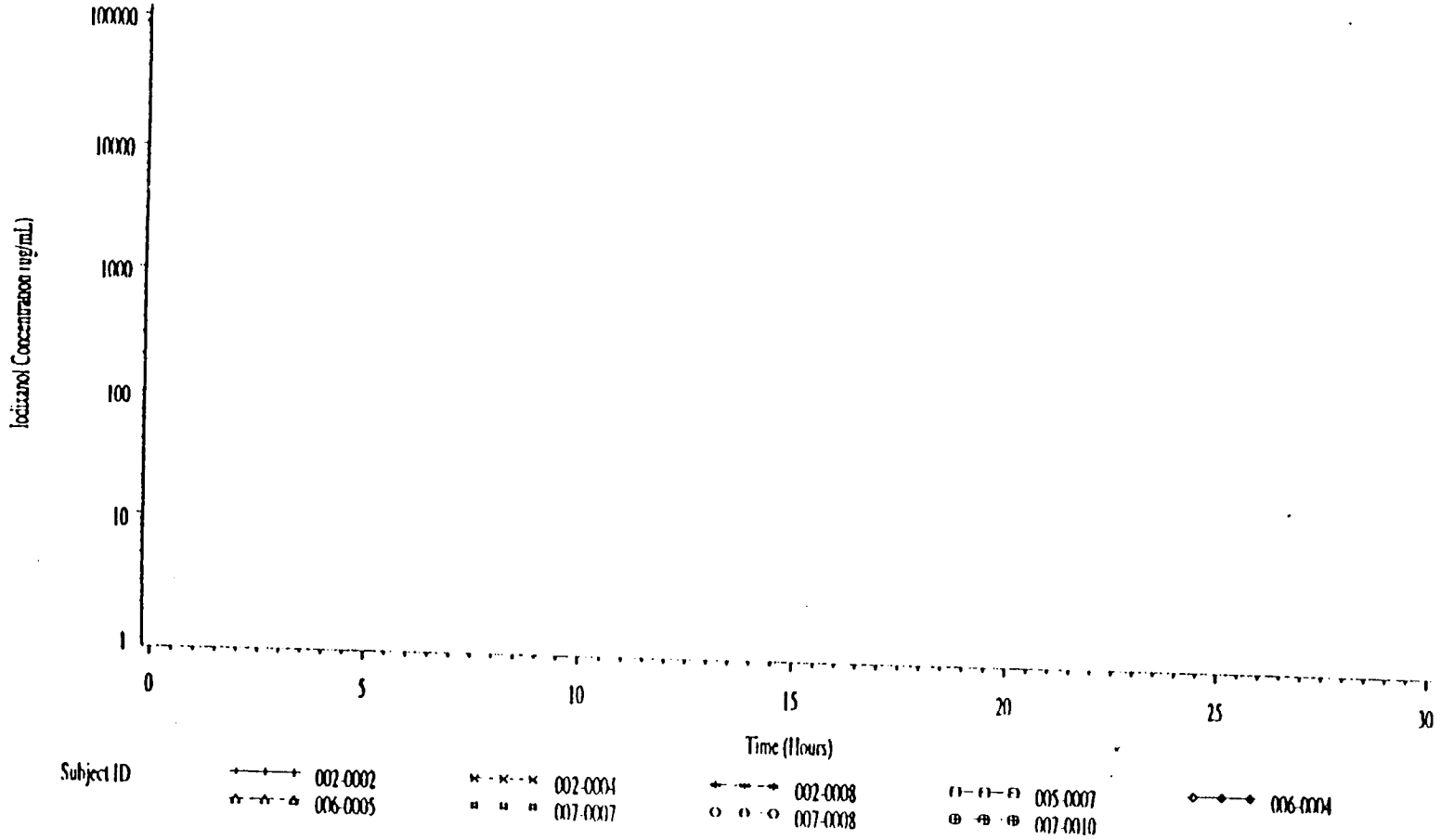
APPENDIX 5.2
PLOTS OF INDIVIDUAL PLASMA IODIXANOL CONCENTRATION PROFILES
AGE GROUP=< 2 MONTHS



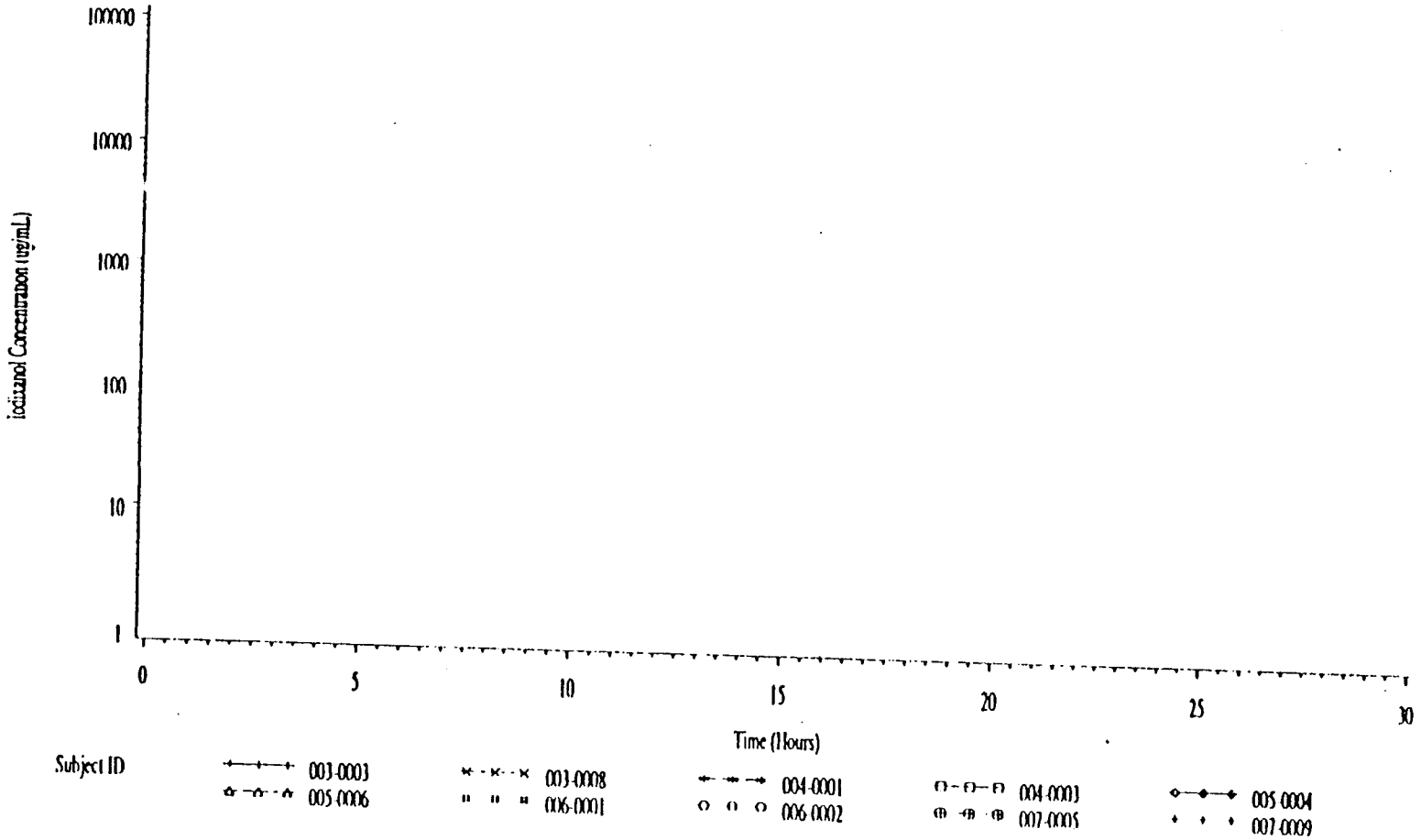
PROGRAM: USER_DISK1:[R10A116.IODIX.018]PPLOT.SAS OUTPUT: PPLOTA.GSF 03JUN96 16:39

APPENDIX 5.2
PLOTS OF INDIVIDUAL PLASMA IODIXANOL CONCENTRATION PROFILES
AGE GROUP=2 TO < 6 MONTHS



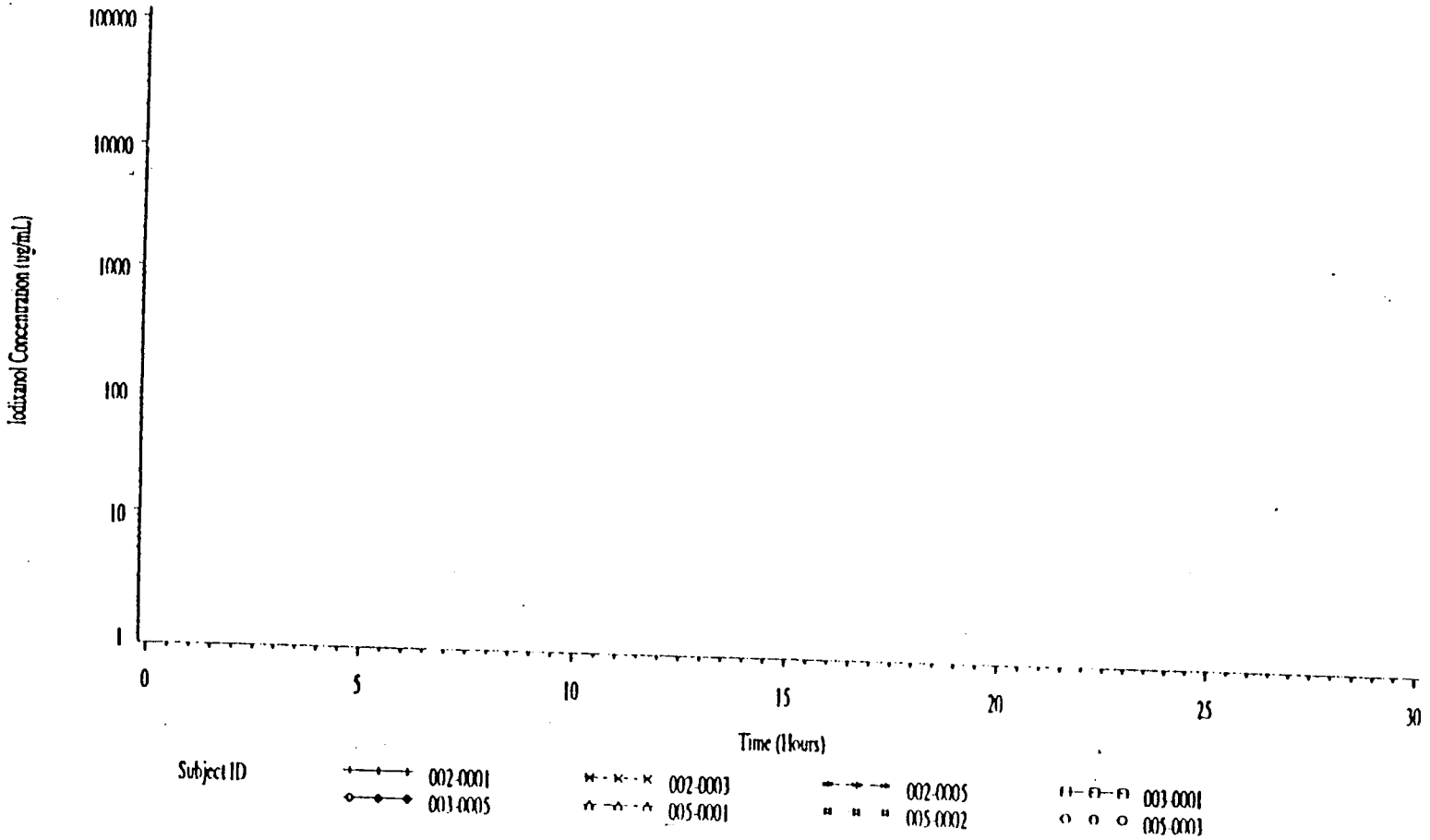
PROGRAM: USER_DISK1:[R10A116.IODIX018]PPLOT.SAS OUTPUT: PPLOTA.GSF 03JUN96 16:39

APPENDIX 5.2
PLOTS OF INDIVIDUAL PLASMA IODIXANOL CONCENTRATION PROFILES
AGE GROUP=6 TO < 12 MONTHS



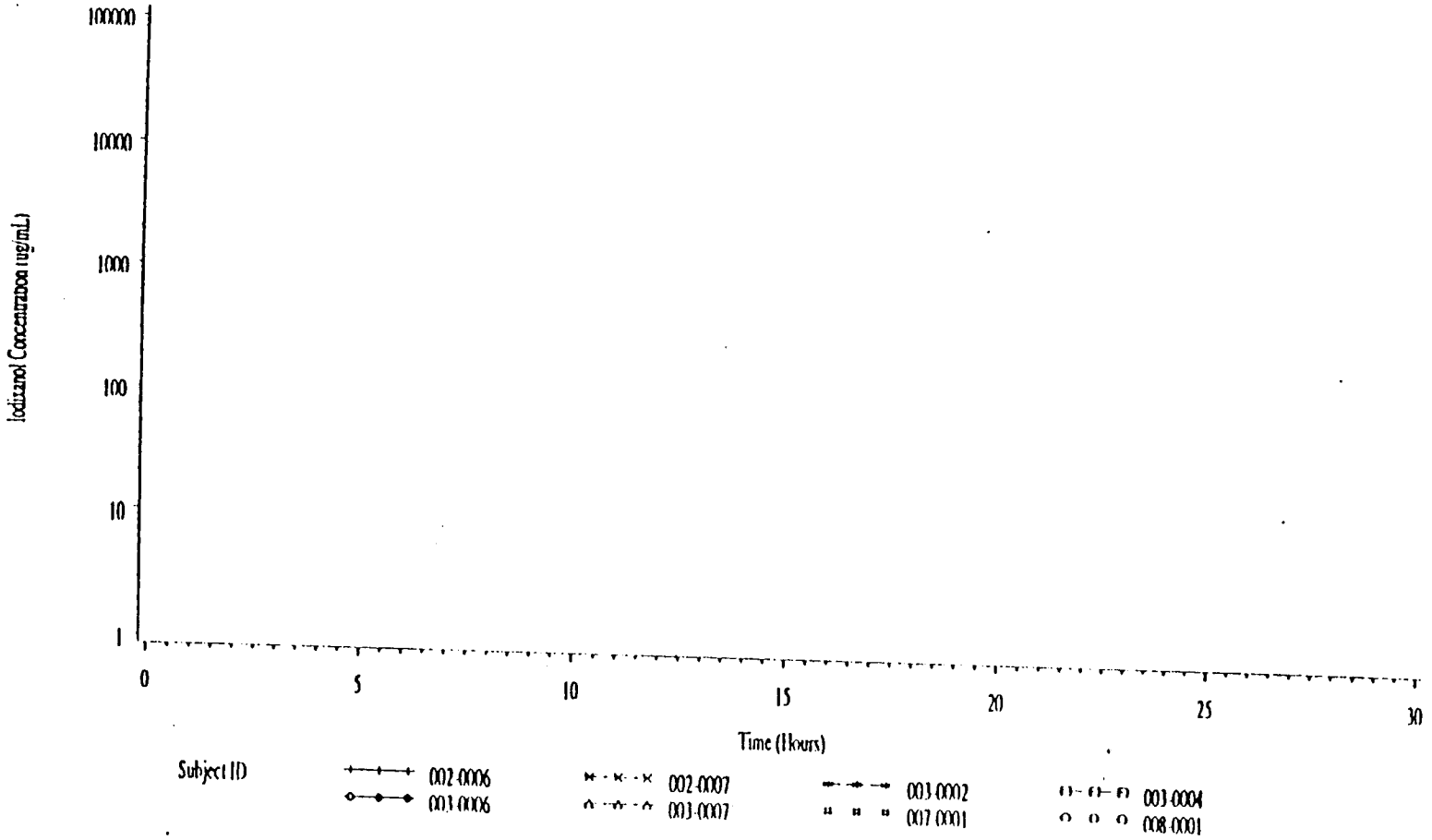
PROGRAM: USER_DISK1:[R10A116.IODIX.018]PPLOT.SAS OUTPUT: PPLOTA.GSF 03JUN96 16:39

APPENDIX 5.2
PLOTS OF INDIVIDUAL PLASMA IODIXANOL CONCENTRATION PROFILES
AGE GROUP=1 TO < 3 YEARS



PROGRAM: USER_DISK1:[R10A116.IODIX.018]PPLOT.SAS OUTPUT: PPLOTA.GSF 03JUN96 16:39

APPENDIX 5 2
PLOTS OF INDIVIDUAL PLASMA IODIXANOL CONCENTRATION PROFILES
AGE GROUP=3 TO < 12 YEARS



PROGRAM: USER_DISK1:[R10A116.IODIX.018]PPLOT.SAS OUTPUT: PPLOTA.GSF 03JUN96 16:39

APPENDIX 5.1
LISTING OF PLASMA IODIXANOL CONCENTRATION DATA

Subject ID	Age Group	Sample ID	Sample time (hr)	Iodixanol Concentration (ug/mL)	Comment
002-0001	1 TO < 3 YEARS		-0.40	M	
			1.23		
			3.15		
			11.50		
			21.72		
002-0002	2 TO < 6 MONTHS		-1.43		
			0.52		
			2.10		
			8.63		
			19.60		
002-0003	1 TO < 3 YEARS		-1.27		
			1.22		
			3.97		
			8.53		
			15.12		
002-0004	2 TO < 6 MONTHS		-0.60		
			1.20		
			3.50		
			8.47		
			22.65		
002-0005	1 TO < 3 YEARS		-1.67		
			0.77		
			2.53		
			11.58		
			20.07		
002-0006	3 TO <= 12 YEARS		-0.87		
			1.13		
			3.43		
			9.50		
			27.87		
002-0007	3 TO <= 12 YEARS		-1.95		
			0.90		
			3.32		

M = Less than the minimum quantifiable level of 1.5 ug/mL Iodixanol.
N = No sample obtained at clinical site

PROGRAM: USER_DISK1:[R10A116.IODIX.018]PLASMA1.SAS OUTPUT: PLASMA1A.LIS 03JUN96 16:39

APPENDIX 5.1
LISTING OF PLASMA IODIXANOL CONCENTRATION DATA

Subject ID	Age Group	Sample ID	Sample time (hr)	Iodixanol Concentration (ug/mL)	Comment
002-0007	3 TO <= 12 YEARS		8.02		
			21.27		
002-0008	2 TO < 6 MONTHS		-0.97		
			0.70		
			3.00		
			10.78		
			22.95		
003-0001	1 TO < 3 YEARS		-0.72		
			1.08		
			2.25		
			8.33		
			19.83		
003-0002	3 TO <= 12 YEARS		-0.75		
			1.08		
			3.58		
			11.58		
			16.83		
003-0003	6 TO < 12 MONTHS		-1.72		
			1.03		
			2.12		
			8.12		
			16.53		
003-0004	3 TO <= 12 YEARS		-2.03		
			0.87		
			2.03		
			8.03		
			21.78		
003-0005	1 TO < 3 YEARS		-1.62		
			0.80		
			2.05		
			7.88		
			17.38		
003-0006	3 TO <= 12 YEARS		-0.77		
			0.90		
			2.48		

M = Less than the minimum quantifiable level of 1.5 ug/mL Iodixanol
N = No sample obtained at clinical site

APPENDIX 5.1
LISTING OF PLASMA IODIXANOL CONCENTRATION DATA

Subject ID	Age Group	Sample ID	Sample time (hr)	Iodixanol Concentration (ug/mL)	Comment
003-0006	3 TO <= 12 YEARS		8.65		
			22.40		
003-0007	3 TO <= 12 YEARS		-0.75		
			0.78		
			2.92		
			10.25		
			23.08		
003-0008	6 TO < 12 MONTHS		-0.22		
			N		
			N		
			N		
			23.42		
004-0001	6 TO < 12 MONTHS		-1.13		
			0.93		
			2.28		
			10.32		
			20.45		
004-0002	< 2 MONTHS		-1.28		
			0.97		
			2.55		
			10.07		
			16.47		
004-0003	6 TO < 12 MONTHS		-0.37		
			0.75		
			2.22		
			10.22		
			22.97		
005-0001	1 TO < 3 YEARS		-0.40		
			1.03		
			2.45		
			8.37		
			21.37		

M = Less than the minimum quantifiable level of 1.5 ug/mL Iodixanol
N = No sample obtained at clinical site

PROGRAM: USER_DISK1:[R10A116.IODIX.018]PLASMA1.SAS OUTPUT: PLASMA1A.LIS 01JUN96 16:39

APPENDIX 5.1
LISTING OF PLASMA IODIXANOL CONCENTRATION DATA

Subject ID	Age Group	Sample ID	Sample time (hr)	Iodixanol Concentration (ug/mL)	Comment
005-0002	1 TO < 3 YEARS		-1.10	M	
			0.92		
			3.73		
			9.32		
			23.82		
005-0003	1 TO < 3 YEARS		-0.27		
			1.20		
			2.15		
			10.40		
			21.65		
005-0004	6 TO < 12 MONTHS		-0.37		
			1.55		
			3.55		
			8.38		
			29.13		
005-0005	< 2 MONTHS		-0.48		
			0.83		
			2.67		
			8.92		
			19.67		
005-0006	6 TO < 12 MONTHS		-0.47		
			1.22		
			2.22		
			8.47		
			23.30		
005-0007	2 TO < 6 MONTHS		-0.63		
			1.50		
			2.92		
			8.25		
			22.00		
006-0001	6 TO < 12 MONTHS		-20.75		
			1.42		
			3.58		
			9.12		
			21.42		

M = Less than the minimum quantifiable level of 1.5 ug/mL Iodixanol
N = No sample obtained at clinical site

PROGRAM: USER_DISK1:[R10A116.IODIX.018]PLASMA1.SAS OUTPUT: PLASMA1A.LIS 01JUN96 16:39

APPENDIX 5.1
LISTING OF PLASMA IODIXANOL CONCENTRATION DATA

Subject ID	Age Group	Sample ID	Sample time (hr)	Iodixanol Concentration (ug/mL)	Comment
006-0002	6 TO < 12 MONTHS		-1.20	M	
			0.92		
			2.88		
			10.20		
			24.88		
006-0003	< 2 MONTHS		-1.65		
			1.27		
			3.85		
			8.60		
			28.93		
006-0004	2 TO < 6 MONTHS		-0.68		
			0.83		
			3.82		
			8.90		
			21.90		
006-0005	2 TO < 6 MONTHS		-1.72		
			0.78		
			2.87		
			N		
			16.37		
007-0001	3 TO <= 12 YEARS		-0.45		
			0.75		
			2.57		
			8.60		
			18.33		
007-0002	< 2 MONTHS		-0.32		
			1.15		
			2.73		
			8.28		
			25.68		
007-0003	< 2 MONTHS		-2.22		
			1.12		
			2.93		
			9.05		
			16.17		

M = Less than the minimum quantifiable level of 1.5 ug/mL Iodixanol
N = No sample obtained at clinical site

APPENDIX 5.1
LISTING OF PLASMA IODIXANOL CONCENTRATION DATA

Subject ID	Age Group	Sample ID	Sample time (hr)	Iodixanol Concentration (ug/mL)	Comment
007-0004	< 2 MONTHS		-0.97	M	
			1.07		
			2.38		
			9.77		
			17.30		
007-0005	6 TO < 12 MONTHS		-0.72		
			0.82		
			3.75		
			8.40		
			18.23		
007-0006	< 2 MONTHS		-0.65		
			0.85		
			2.13		
			8.42		
			24.37		
007-0007	2 TO < 6 MONTHS		-0.27		
			0.95		
			2.07		
			11.03		
			24.17		
007-0008	2 TO < 6 MONTHS		-0.53		
			0.77		
			2.78		
			8.02		
			19.92		
007-0009	6 TO < 12 MONTHS		-0.35		
			0.98		
			4.00		
			8.05		
			22.32		
007-0010	2 TO < 6 MONTHS		-0.23		
			0.92		
			3.72		
			8.75		
			23.98		

M = Less than the minimum quantifiable level of 1.5 ug/mL Iodixanol.
N = No sample obtained at clinical site

APPENDIX 5.1
LISTING OF PLASMA IODIXANOL CONCENTRATION DATA

Subject ID	Age Group	Sample ID	Sample time (hr)	Iodixanol Concentration (ug/mL)	Comment
00A-0001	3 TO <= 12 YEARS		-0.87	M	
			1.42		SAMPLE DRAWN 1HR - 21MIN.
			2.52		
			8.87		
			23.28		
00A-0002	< 2 MONTHS		-0.77		
			0.90		
			2.20		
			8.28		
			25.88		

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M = Less than the minimum quantifiable level of 1.5 ug/mL Iodixanol
N = No sample obtained at clinical site

PROGRAM: USER_DISK1:[R10A116.IODIX.01A]PLASMA1.SAS OUTPUT: PLASMA1A.LIS 01JUN96 16:39

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APPENDIX 5.3
LISTING OF PLASMA IODIXANOL PHARMACOKINETIC DATA

Age Group	Subject ID	Age (yrs)	kel (1/hr)	Half-life (hrs)
< 2 MONTHS	007-0004	0.000		
	005-0005	0.000		
	007-0003	0.003		
	006-0003	0.005		
	007-0002	0.005		
	004-0002	0.129		
	007-0006	0.140		
	008-0002	0.162		
2 TO < 6 MONTHS	007-0008	0.167		
	005-0007	0.268		
	006-0004	0.271		
	002-0004	0.279		
	002-0002	0.288		
	007-0010	0.326		
	007-0007	0.370		
	002-0008	0.414		
6 TO < 12 MONTHS	005-0006	0.510		
	007-0009	0.518		
	005-0004	0.526		
	004-0001	0.529		
	004-0003	0.778		
	007-0005	0.836		
	006-0001	0.855		
	006-0002	0.874		
	003-0003	0.901		
1 TO < 3 YEARS	005-0001	1.060		
	003-0005	1.211		
	003-0001	1.666		
	005-0003	1.753		
	002-0001	1.934		
	005-0002	2.274		
	002-0005	2.304		
	002-0003	2.959		
3 TO < 12 YEARS	003-0002	3.164		
	007-0001	5.071		
	003-0006	5.386		
	003-0007	6.038		
	002-0006	6.888		
	002-0007	7.773		
	003-0004	10.337		
	008-0001	10.414		

PROGRAM: USER_DISK1:[R10A115.IODIX.018]PK1.SAS OUTPUT: PK1A.LIS

Appendix II.

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OCT - 9 1997

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

Labeling Review

NDA 20-351	REVIEWER: Young-Moon Choi, Ph.D.
Visipaque (Iodixanol injection)	ASSIGNED: 9/25/97
Sponsor: Nycomed	REVIEWED: 9/30/97

Comments

1. Under the pharmacokinetics section of "CLINICAL PHARMACOLOGY" (P.3 and P.4 of proposed package insert):

The follwing statement should be reworded from:
"Special Populations:
Pediatric: In 40 pediatric patients .....Therefore, in pediatric patients above 6 months of age, iodixanol is excreted at a rate similar to adults. (See Dosage and Administration of pediatric dosing).",

to:
"Special populations:
***Pediatrics:* In 40 pediatric patients (≤ 12 years old) receiving multiple intraarterial or intravenous administrations of VISIPAQUE Injection in doses of 0.32 to 3.2 gI/kg body weight, the mean terminal elimination rate constants were 0.185 hr^{-1} (newborn to < 2 months old, n=8), 0.256 hr^{-1} (2 to< 6 months old, n=8), 0.299 hr^{-1} (6 months to <1 year old, n=9), 0.322 hr^{-1} (1 to <3 years old, n=7), and 0.307 hr^{-1} (3 to <12 years old, n=8). In comparison, the adult value was 0.336 hr^{-1} (n=40). For the mean elimination half-life, see table below (Pharmacokinetic parameters). Dose optimization has not been systemically established.**

2. Page 4: The "PHARMACOKINETIC PARAMETERS" table should be located before the *Drug-Drug Interaction*. The Drug-Drug Interactions is not limited to the Special Populations. Therefore, *Drug-Drug Interactions* should be independently described with underline and the same font as "Special Populations".

3. **Page 4: For the Pediatric group, it is recommended to remove the N number of 40 in the "PHARMACOKINETIC PARAMETERS" table, and the table modified accordingly:**

PHARMACOKINETIC PARAMETERS			
		N	Elimination half-life (hr)
Adult		40	2.1 ± 0.1
Pediatric	Newborn to <2 months	8	4.1 ± 1.4
	2 to <6 months	8	2.8 ± 0.6
	6 months to < 1 year	9	2.4 ± 0.4
	1 to < 3 years	7	2.2 ± 0.5
	3 to ≤12 years	8	2.4 ± 0.5
Renal Insufficiency		16	23 ± 8

4. Page 9: Under **Indications and Usage section**, under Intraarterial, Intravenous subsection:

It is recommended that the sentence be changed from:
" .....in adults and pediatric patients (neonates, infants, children, and adolescents)"

to:
"**.....in adults and pediatric patients (e.g., ___ years old;** *the appropriate age range should be inserted based on the clinical data.*)".

5. Page 15: Under **Pediatric Use, Precautions** section:

It is recommended that the sentence be changed from:
"The safety and effectiveness in the pediatric population (neonates, infants, children, and adolescents) have been established....."

to:
"The safety and effectiveness in the pediatric population (e.g., ___ years old; *the appropriate age range should be inserted based on the clinical data.*) **have been established....."**

6. Pages 18 and 19: **Under Dosage and Administration** section, for Intraarterial administration (Page 18) and Intravenous administration, the following sentence should be deleted:

7. Page 19: The **"Pediatric -Usual Single Doses for Injection into Selected Arteries"** table:

Since the adolescence is classified as pediatrics, it is recommended to include "adolescence (12 to 16 years)" section in the table.

8. Page 20: The **"Pediatrics-Usual Visipaque Dosing for Intravenous Contrast Administration"**table:

Since the adolescence is classified as pediatrics, it is recommended to include the description of "adolescence (12 to 16 years) dosing information" in the footnote of the table, i.e., "Adolescents, >12 to 16 years".

/S/ 10/8/97

Young-Moon Choi, Ph.D.
Pharmacokineticist
Radiopharmaceuticals and Imaging Section
Division of Pharmaceutical Evaluation II
Office of Clinical Pharmacology and Biopharmaceutics

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Concurrence:

/S/ 10/9/97

David J. Lee, Ph.D.
Team Leader
Pharmacokineticist
Radiopharmaceuticals and Imaging Section
Division of Pharmaceutical Evaluation II
Office of Clinical Pharmacology and Biopharmaceutics

CC:	HFD-160	NDA 20-351
	HFD-160	DIV FILE
	HFD-160	/CSO/FERRE-HOCKENSMITH(1X)
	HFD-160	/OCPB/YMCHOI (1x)
	HFD-160	/OCPB/DLEE (1x)
	HFD-870	/OCPB/MLCHEN (1X)
	HFD-850	/OCPB/SHUANG
	CDR	Attn: Barbara Murphy

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