CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA: 19-813	Submission Date(s): 11/25/02
Submission Type; Code	Supplement SE1-036; Supplement to meet the terms of the Pediatric Written Request
Brand Name	Duragesic®
Generic Name	Fentanyl Transdermal System
Primary Reviewer	David Lee
Pharmacometrics Consultant	He Sun
Secondary Reviewer	Suresh Doddapaneni
OCPB Division	DPE 2
ORM division	Division of Anesthetic, Critical Care and Addiction Drug Products
Sponsor	ALZA Corporation
Relevant IND(s)	39,645 and 24,414
Formulation; Strength(s)	25, 50, 75, and 100 µg/hr (12.5 µg/hr used in pediatrics – Approval will be sought through a separate submission)
Proposed Indication	Management of chronic pain in patients who require continuous opioid analgesia for pain that cannot be managed by lesser means such as acetaminophen-opioid combinations, non-steroidal analgesics, or PRN dosing with short-acting opioids
Proposed Dosage Regimen	(b) (4)

1 Executive Summary

ALZA Corporation has submitted a Supplemental NDA in order to present the data for the completeness of dosing information in pediatric population and to fulfill the requirements of the Written Request for Pediatric Studies. The pediatric clinical program was developed to establish safety profile in opioid-tolerant children ages 2 and older, and, to address the need for effective and convenient management of chronic pain in pediatric patients who are opioid tolerant (currently using opioid analgesia) and are in need of opioid analgesia.

Three open-label Phase 3 studies in pediatric patients (FEN-USA-87, FEN-INT-24, and FEN-GBR-14) and a pharmacokinetic study comparing transdermal delivery of fentanyl in adults and children (FEN-FRA-4) were conducted. In addition to the results from these studies, published literature were provided in the submission. Additionally, an analysis of the population pharmacokinetics of Duragesic from studies FEN-USA-87 and FEN-INT-24 was conducted. The clinical trials essential to this NDA were conducted under INDs 39,645 and 24,414.

Fentanyl is an opioid analgesic with a pharmacological action similar to that of morphine. Fentanyl is approximately 75 to 100 times more potent than morphine. Duragesic patch is presumed to provide continuous systemic delivery of fentanyl throughout the recommended

dosing interval of 72 hours. According to the Applicant, Duragesic or Durogesic patch is approved in 64 countries worldwide, and marketed in 57 countries, and between 1991 and 2002, the estimated overall patient exposure for Duragesic systems was more than (b) (4) systems (approximately (b) (4) per year).

The studies utilized a clinical 12.5 μg/hr dose strength as a starting dose (titration doses used were 25, 50, 75, 100 μg/hr). The Applicant stated that they are not seeking an approval of this strength in this Supplement. Instead they will submit a separate Application for an approval in this strength. Thus, this Supplement does not contain information on Duragesic patch production, manufacturing, testing and controls or non-clinical development. The Applicant stated that all such information remains unchanged as previously provided in NDA 19-813 and supplements to this NDA.

Synopsis of pediatric safety profile from Duragesic patch usage

In the original application, the safety of Duragesic was evaluated in a total of 510 adult patients (n=357 postoperative and n=153 cancer patients). Patients, e.g., postoperative, with acute pain used the patch for 1 to 3 days. For cancer patients, 56% used the patch for more than 30 days, 28% continued treatment for more than 4 months, and 10% used the patch for more than 1 year. The adverse event (AE) profiles in adults included nausea, vomiting, constipation, somnolence, sweating, etc. Hypoventilation was the most serious AE observed (13 (4%) and 3 (2%) in the postoperative and cancer patients, respectively).

According to the current Supplement, the pediatric patients seemed to exhibit similar AEs (e.g., nausea, vomiting, etc.) to that of the adults (the reader should refer to the Medical Officer's Review for a comprehensive safety analysis).

Exposure-response (E-R) relationship

The correlation between occurrences of adverse events (nausea, fever, vomiting, anemia, and abdominal pain) and predicted fentanyl steady-state concentrations from the population PK model was evaluated by logistic regression in the submission. According to the data presented in the Supplement, no significant relationships between AEs and predicted fentanyl steady-state concentrations were observed.

Dose proportionality

Studies FEN-USA-87 and FEN-INT-24 used a dose-titration study design. A dose-normalized fentanyl concentration data (normalized to 12.5 μg/hr) indicated that concentrations from all strengths were similar across time intervals, possibly indicating that there was no accumulation after repeated patch applications. However, due to the variability from the sparse data set, it was not conclusive to observe clear dose proportionality from the studies.

Gender differences

According to a population PK analysis, no gender differences were observed.

Age differences

According to a population PK analysis, age differences were observed.

Body weight differences

According to a population PK analysis, body weight differences were observed for volume of distribution.

Observed steady state fentanyl concentrations (ng/mL) from pediatric patients after repeated application

The pediatric patients enrolled in these studies were between 2 to 16 years. The pediatric patients were arbitrarily grouped[#] as below; however, the first 2-5 year old group can be compared with Study FEN-FRA-4.

Study FEN-USA-87 (normalized to 12.5 μg/hr dose):

	AGE 2 – 5 YEARS[#]	AGE 6 – 10 YEARS[#]	AGE 11 – 16 YEARS[#]
Number of observations	134	250	523
Mean ± SD	**0.47 ± 0.53**	**0.41 ± 0.53**	**0.25 ± 0.37**

Study FEN-INT-24 (normalized to 12.5 μg/hr dose):

	AGE 2 – 5 YEARS[#]	AGE 6 – 10 YEARS[#]	AGE 11 – 16 YEARS[#]
Number of observations	113	81	37
Mean ± SD	**0.55 ± 0.80**	**0.38 ± 0.42**	**0.53 ± 0.68**

Both Studies FEN-USA-87 and FEN-INT-24 (normalized to 12.5 μg/hr dose):

	AGE 2 – 5 YEARS[#]	AGE 6 – 10 YEARS[#]	AGE 11 – 16 YEARS[#]	**ALL**
# of sample observations	247	331	560	1138
Mean ± SD	**0.51 ± 0.66**	**0.40 ± 0.50**	**0.27 ± 0.40**	**0.36 ± 0.51**

Pharmacokinetic parameters in pediatric patients 1.5 – 5 years old (Study FEN-FRA-4)

This study collected a complete fentanyl plasma profile from pediatric and adult patients dosed with a single 72 hour Duragesic patch. The Applicant reported the following PK parameters (n=16 total; n=8 each group):

	DOSE (μg/hr)	Cmax (ng/mL)	Tmax (h)	AUC_{0-144} (ng.h/mL)	**$T_{1/2}$ (h)**	Vd/f (L)	CL/f (L/hr)
Adults	50	**1.13 ± 0.51**	**33 ± 5.0**	**71 ± 29**	**20.6 ± 5.7**	-	-
Pediatrics	25	**1.70 ± 0.66**	**18 ± 11**	**87 ± 28**	**14.5 ± 6.2**	-	-

The adult controls were between 30 to 65 years.

The Cmax and AUC values for pediatric patients were approx. 50 and 23 % higher, respectively, than that of the adults, even with receiving one-half of the adult's doses. The Tmax value was shorter for the pediatrics.

Additional WinNonLin analysis was conducted for this population and the following PK parameters were generated from the analysis:

	DOSE (μg/hr)	Cmax (ng/mL)	Tmax (h)	AUC_{0-144} (ng.h/mL)	**$T_{1/2}$ (h)**	**Vd/f (L)**	**CL/f (L/hr)**	**CL/f/kg (L/hr)**
Adults	50	-	-	-	**13.6 ± 6.2**	**1080 ± 597**	**57 ± 21**	**0.76 ± 0.26**
Pediatrics	25	-	-	-	**13.3 ± 5.3**	**420 ± 255**	**21 ± 7.6**	**1.4 ± 0.22**

The estimated $t_{1/2}$ values were comparable between adults and pediatric patients. The values for apparent total CL and Vd for pediatric patients were 59 and 57% lower, respectively, than that of the adult values. When apparent CL was adjusted by body weight, pediatric patients had higher apparent total CL (84% greater) than that of the adults. Additionally, the WinNonLin analysis indicated that apparent Vd and CL are highly correlated (a positive slope), i.e., increase in apparent Vd will give increase in the apparent total CL.

Pediatric population PK analysis

The Applicant submitted estimated apparent total CL values from a population PK analysis using the sparse fentanyl concentration data from studies FEN-USA-87 and FEN-INT-24. The analysis was based on a linear model using the observed steady-state serum fentanly concentration (Css = (Dosing rate) / CL). The following covariates were included in the analysis: time from dosing, study, site, age, weight, height, body surface area (BSA), body mass index (BMI), lean body mass (LBM), gender, race, body temperature, system location, Tanner stage for sexual maturity, dosing gap, and concomitant administration of any medication, a cytochrome P450 3A4 (CYP3A4) inhibitor, or a CYP3A4 inducer. The final model included clinical site and body surface area (BSA): $CL = \exp(-\beta_0 - \beta_{2\_Site} - \beta_3 * BSA)$.

The estimated apparent total CL and body weight adjusted apparent total CL from this analysis were 28.1 ± 15.3 L/h and 0.92 ± 0.51 L/h/kg, respectively.

Structure model and parameter estimates from WinNonLin analysis (Study FEN-FRA-4) were used in Nonmem population PK analysis. The sparse data from studies FEN-USA-87 and FEN-INT-24 were analyzed with age, body weight, and BSA as covariates. The final model indicated that body weight was correlated with Vd and the degree of correlation due to age or BSA was similar on apparent CL. However, BSA as a covariate produced more robust curve fitting. Thus, if needed, the dosage adjustment based on BSA is preferred based on the analysis.

Based on Nonmem analysis' post hoc predictions, the following individual PK parameters were obtained (mean ± SD):

	AGE 2 – 5 YEARS[1]	AGE 6 – 10 YEARS[1]	AGE 11 – 16 YEARS[1]	ALL
Number of subjects	56	75	142	273
CL/f (L/h)	19.5 ± 2.4	23.8 ± 3.2	29.5 ± 4.9	25.9 ± 5.7
CL/f/kg (L/h/kg)	1.26 ± 0.20	0.92 ± 0.21	0.66 ± 0.17	0.85 ± 0.3
Vd/f (L)	200 ± 45	336 ± 119	547 ± 200	418 ± 213
Vd/f/kg (L/kg)	12.7 ± 0.5	12.0 ± 1.2	11.3 ± 0.75	11.8 ± 1.0

1: Arbitrary age grouping; however, the first 2-5 year old group can be compared with Study FEN-FRA-4.

Thus, overall comparison for the apparent CL is as follows:

	CL/f (L/hr)	**CL/f/kg (L/hr/kg)**
Applicant's adult data[1]	**-**	**0.77 ± 0.30**
Applicant's ped. pop. PK analysis (all subjects)	**28.1 ± 15.3**	**0.92 ± 0.51**
Study FEN-FRA-4 WinNonLin analysis[2]	**21 ± 7.6**	**1.4 ± 0.22**
Nonmem ped. pop. PK analysis (all subjects)	25.9 ± 5.7	0.85 ± 0.3

1: Population analysis from Studies FEN-GBR-3 and FEN-GBR-4; the adult clearance data were discussed in the Supplement; the actual adult data were not submitted.
2: Age group: 1.5 – 5 years old

The apparent CL values across all analysis were comparable. Looking at the numbers more closely, the Applicant's apparent total CL value was comparable to that of the pediatric 6 – 10 year old age group. It is noticeable that the apparent CL for the youngest group (2-5 year olds) is 64% larger than that of the adults. Furthermore, Nonmem analysis indicated that apparent CL for pediatric patients begins to differ than the adults at 9 years of age (based on 20% difference in mean adult apparent clearance using 0.77 ± 0.3 L/hr/kg as reference; range 0.62 – 0.92 L/h/kg). Therefore, if necessary, based on the fentanyl apparent clearance, pediatric patients less than 9 years old should be dose adjusted accordingly.

Additionally, the following steady state fentanyl concentrations were calculated using the mean apparent CL obtained from Nonmem analysis for each age group and compared with the

observed concentrations from Studies FEN-USA-87 and FEN-INT-24 (normalized to 12.5 μg/hr dose):

	AGE 2 – 5 YEARS[1]	AGE 6 – 10 YEARS[1]	AGE 11 – 16 YEARS[1]	ALL
Estimated steady state fentanyl conc. (ng/mL)[2]	0.64	0.53	0.42	0.48
Observed steady state fentanyl conc. (ng/mL)	**0.51** ± **0.66**	**0.40** ± **0.50**	**0.27** ± **0.40**	**0.36** ± **0.51**

1: Arbitrary age grouping; however, the first 2-5 year old group can be compared with Study FEN-FRA-4
2. Css = (Dosing rate) / CL/f ; dosing rate is 12.5 μg/hr.

1.1 Recommendation

The Office of Clinical Pharmacology and Biopharmaceutics / Division of Pharmaceutical Evaluation II (OCPB/DPE-II) has reviewed Supplement SE1-036 to NDA 19-813 submitted on November 25, 2002.

The information contained in the Supplemental NDA is acceptable. However, the proposed labeling should be communicated to the Applicant.

1.2 Comment to the Applicant

Proposed by the Applicant:

(b) (4)

2 Table of Contents

3 Summary of CPB Findings

FEN-USA-87 Study

This trial was a single-arm, multi-center, nonrandomized, open-label, dose titration, safety and population PK analysis trial in pediatric patients with malignant or nonmalignant diseases. The dose strengths used were 12.5 (starting dose), 25, 50, 75 and 100 μg/hr. The Duragesic patch was applied every 72 hours for 15 days. Serum fentanyl concentrations were also measured on Days 1, 2, 4, 7 and 16. Five blood samples per subject were drawn during the primary treatment period to determine fentanyl serum concentrations during the trial. The volume of blood to be collected with each sample was 2 mL. The limit of quantification (BLQ) concentration was 0.1 ng/mL. A total Number of pediatric subjects enrolled was 199:

	Age 2 – < 6	6 – <12	12 – <16
N	27	67	102

a) No PK parameters were computed from the study due to the fact that the data collection plan focused on concentrations toward the end of the dosing intervals. However, the following steady state fentanyl concentrations were reported *(normalized to 12.5 μg/hr dose):*

	AGE 2 – 5 YEARS[#]	AGE 6 – 10 YEARS[#]	AGE 11 – 16 YEARS[#]
Number of observations	134	250	523
Mean ± SD	0.47 ± 0.53	0.41 ± 0.53	0.25 ± 0.37

#: Arbitrary age grouping; however, the first 2-5 year old group can be compared with Study FEN-FRA-4

b) The profiles hinted that steady state was reached at approximately 24 hours post the first patch application. A large variability in concentration was observed within and between subjects and a substantial overlap in concentrations across all dose levels was observed.

c) After the normalization, the majority of individual subject fentanyl profiles were relatively flat (on average, normalized fentanyl concentrations from all strengths were similar across time intervals following application of the first patch, as well as subsequent patches), possibly indicating that there were no accumulation after repeated patch applications. Additionally, due to the variability from the sparse data set, it was not conclusive to observe clear dose proportionality in this study.
d) The Applicant stated that younger subjects were generally titrated to lower fentanyl doses than were older subjects, which is an expected finding in a population wherein weight is correlated with age. For example, all subjects >5 years of age were treated with doses ranging between 12.5 and 62.5 μg/hour, whereas older subjects received doses as high as 250 μg/hour. For similar reasons, subjects of smaller body size generally received lower fentanyl doses. Nausea, fever, and vomiting were the most common AEs.
e) A population PK analysis was performed on the pooled data from this study and the FEN-LNT-24 study; the results were reported in a separate stand-alone population PK report.

FEN-INT-24 Study

This was a single-arm, non-randomized, open-label, 15-day (patches were to be replaced every 72 hours) multi-center trial to determine the safety, clinical utility and PK of Duragesic patch in pediatric patients with continuous pain requiring opioid therapy for at least the duration of the trial. All subjects started treatment with a 12.5 μg/h patch. Trial medication was provided as 12.5, 25, 50, 75, and 100 μg/h patches. Five blood samples (serum fentanyl concentrations) were collected during the trial (Days 1, 2, 4,7 or 10, and 13 or 16; 2 mL each). The limit of quantification (BLQ) concentration was 0.1 ng/mL. A total number of pediatric subjects enrolled were 53:

	Age 2 – 6	Age 7 – 12
N	29	24

a) No PK parameters were computed from the study due to the fact that the data collection plan focused on concentrations toward the end of the dosing intervals. However, the , the following steady state fentanyl concentrations were reported (normalized to 12.5 μg/hr dose):

	AGE 2 – 5 YEARS[#]	AGE 6 – 10 YEARS[#]	AGE 11 – 16 YEARS[#]
Number of observations	113	81	37
Mean ± SD	0.55 ± 0.80	0.38 ± 0.42	0.53 ± 0.68

#: Arbitrary age grouping; however, the first 2-5 year old group can be compared with Study FEN-FRA-4

b) The profiles hinted that steady state was reached at approximately 24 hours post the first patch application. A large variability in concentration was observed within and between subjects and a substantial overlap in concentrations across all dose levels was observed.
c) After the normalization, the majority of individual subject fentanyl profiles were relatively flat (on average, normalized fentanyl concentrations from all strengths were similar across time intervals following application of the first patch, as well as subsequent patches), possibly indicating that there were no accumulation after repeated patch applications. Additionally, due to the variability from the sparse data set, it was not conclusive to observe clear dose proportionality in this study.
d) Nausea, fever, and vomiting were the most common AEs.
e) A population PK analysis was performed on the pooled data from this study and the Study FEN-USA-87; the results were reported in a separate stand-alone population PK report.

FEN-GBR-14 Study

This was an open label study comprising of 3 phases: a pre-dose, a Durogesic treatment and a follow-up phase. The treatment phase lasted for 15 days (every 72 hour patch application).

Duragesic was titrated in steps of 25 µg/hr to achieve adequate pain control. Plasma concentrations were to be reported. Twenty-six subjects completed the 15-day treatment phase, 23 entered the follow-up phase and 3 subjects completed as least 12 weeks of follow-up. The median age of subjects was 10.5 years (range 2.6 – 18.8 years). Of subjects participating, 30/41 (73%) was male and 11/41 (27%) was female. The median body weight was 32 kg (range 11.0-68.8 kg) and the median height was 139.15 cm (range 79.6 – 181.0 cm). Of participating subjects, 36/41 (88%) had pain caused by a malignancy; 5/31 (12%) subjects had pain due to other causes.

The Applicant stated that due to the limited number of PK samples obtained and the lack of post-treatment samples, PK analyses were not performed.

FEN-FRA-4 Study

This was an open-label, multi-center, single-arm, nonrandomized study in 8 pediatric (1.5 – 5 years old) and 8 adults (30 – 65 years old) patients. Subjects were hospitalized for abdominal surgery lasting at least 3 hours. Patch was applied 2 hours prior to anesthesia induction and left in place for 72 hours. Blood samples were taken during the 72 hours of patch use and 72 hours after patch removal. Patch strengths were 25 and 50 µg/hr for pediatric and adults, respectively.

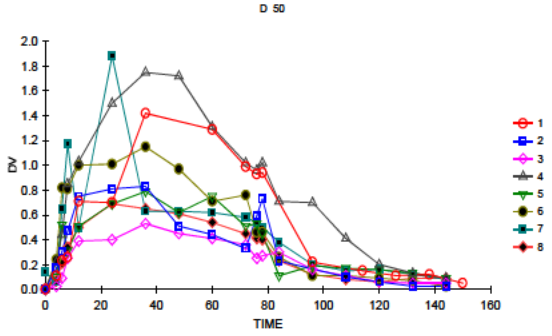
The Applicant reported that, in pediatric patients, Tmax was shorter (14.5 hours vs. 21 hours, pediatric vs. adults, respectively) and plasma concentrations were higher. No apparent plateau of plasma concentrations was observed in 6 of the 8 pediatric patients. After patch removal, the apparent t1/2 was shorter in pediatric patients than that of adults (14.5 ± 6.2 vs. 20.6 ± 5.7 hours), although the difference was not statistically significant:

	DOSE (µg/hr)	Cmax (ng/mL)	Tmax (h)	AUC_{0-144} (ng.h/mL)	**$T_{1/2}$ (h)**	Vd/f (L)	CL/f (L/hr)
Adults	50	**1.13 ± 0.51**	**33 ± 5.0**	**71 ± 29**	**20.6 ± 5.7**	-	-
Pediatrics	25	**1.70 ± 0.66**	**18 ± 11**	**87 ± 28**	**14.5 ± 6.2**	-	-

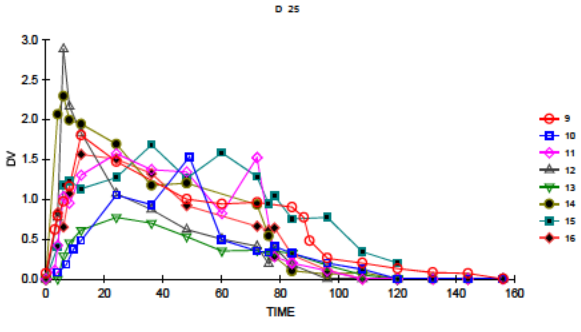
The adult controls were between 30 to 65 years.

Dr. He Sun (Pharmacometrics node) and this reviewer conducted further analysis (WinNonLin). The plasma concentration profiles (see below profiles) from all adult and pediatric patients were individually fitted by WinNonLin program (See appendix A). The model used was a percutaneous model with 3 compartments. The following profiles and table was generated from WinNonLin analysis.

Adult patients (Study 04; 50 µg/hr strength):



Pediatric patients (Study 04; 25 µg/hr strength)



WinNonlin individual subject parameters:

ID	Group	V1 (L)	V2 (L)	CL (L/h)	Q	DINF (μg)	TFST (h)	TINF (h)	THALF (h)	WT (kg)	CLwt (L/h/kg)
1	ADULT	924.3	296.97	36.44	0.55	1325.73	57.49	76.65	17.58	70	0.52
2	ADULT	705.58	114.69	68.02	1.66	2750.56	34.3	78.19	7.19	79	0.86
3	ADULT	1553.87	150.68	95.47	2.65	1991.61	53.37	89.96	11.28	85	1.12
4	ADULT	727.78	135.35	27.15	1.59	1419.59	41.87	81.71	18.58	84	0.32
5	ADULT	1140.73	72.5	64.82	0.85	2662.74	33.67	72.88	12.2	85	0.76
6	ADULT	321.76	398.78	47.32	4.96	2014.18	53.45	78.93	4.71	56	0.84
7	ADULT	1001.08	308.35	50.52	0.5	1699.46	22.59	76.81	13.73	75	0.67
8	ADULT	2263.31	464.44	66.52	0.2	349.22	41.21	166.7	23.58	66	1.01
9	CHILDREN	215.49	234.77	15.74	1.61	1293.36	16	83.41	9.49	14.5	1.09
10	CHILDREN	594.16	221.5	27.14	1.21	218.12	48.99	100.89	15.17	18	1.51
11	CHILDREN	168.1	201.77	18.21	0.38	1467.03	31.78	72.1	6.4	13	1.4
12	CHILDREN	509.98	166.13	23.24	0.23	504.64	6	67.18	15.21	13.5	1.72
13	CHILDREN	919.72	132.65	36.3	0.45	827.02	22.52	81.63	17.56	22	1.65
14	CHILDREN	197.49	212.82	15.72	0.09	1316.63	2.08	65.62	8.71	12	1.31
15	CHILDREN	436.01	236.9	13.44	0.05	1395.26	7.2	64.24	22.48	11	1.22
16	CHILDREN	317.89	193.7	19.16	0.13	1121.49	17.38	68.41	11.5	15	1.28

Mean values: Adults

	V1 (L)	V2 (L)	CL (L/hr)	Q	DINF	TFAST	TINF
Mean	1080	243	57	1.6	1776	42	90
Median	963	224	58	1.2	1845	42	79
SD	597	144	21	1.6	775	12	31

Mean values: Pediatrics

	V1 (L)	V2 (L)	CL (L/hr)	Q	DINF	TFAST	TINF
Mean	420	200	21	0.52	1018	19	75
Median	377	207	19	0.30	1207	17	70
SD	255	36	7.6	0.58	457	15	13

V1: Apparent central Vd
V2: Apparent peripheral Vd
CL: Apparent CL
Q : Inter-compartment clearance (K21*V2/K12/V1)
Dinf: Predicted 'slow infusion dose
Tfast: Predicted 'fast' infusion time – set as time to reach steady-state plasma concentration
Tinf: Predicted 'slow' infusion time – set as total patch application duration (72 hours)

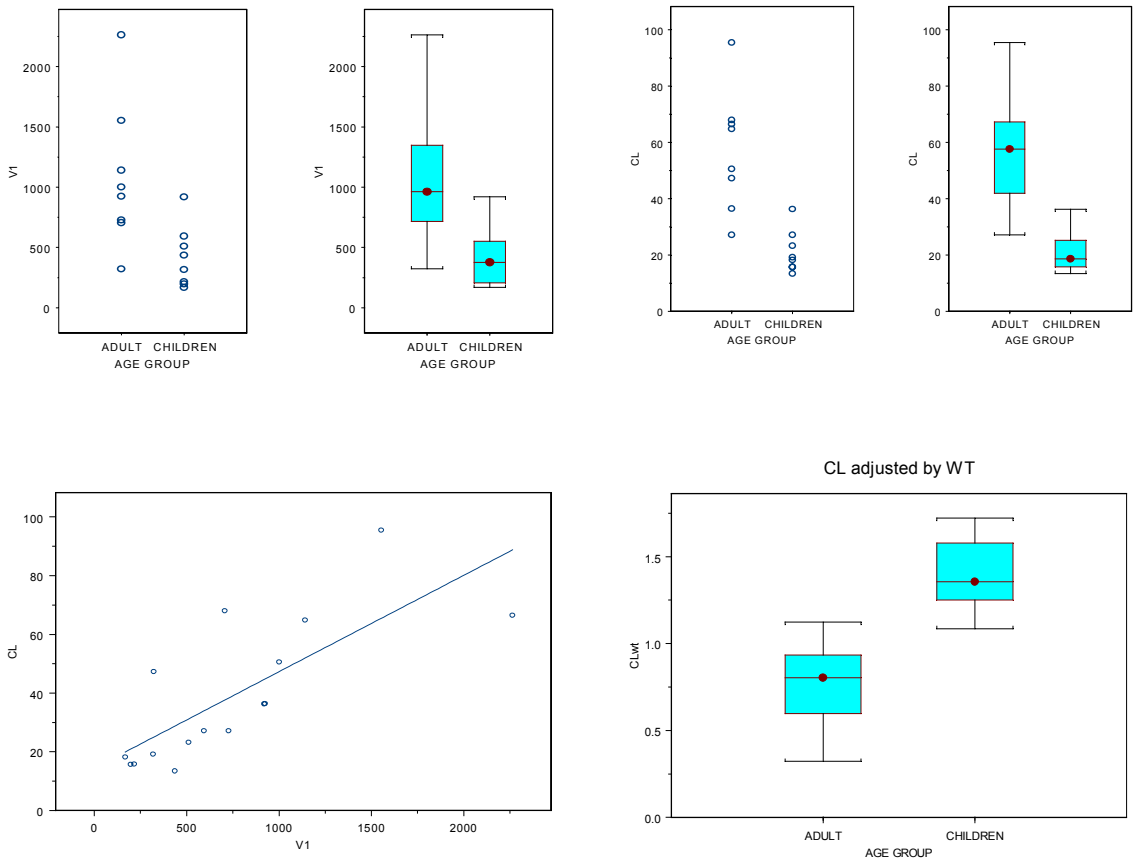
$T_{1/2}$ (hr) comparison:

	Adult	Pediatrics
Mean ± SD	13.6 ± 6.2	13.3 ± 5.3

Weight adjusted CL : CLwt (L/hr) comparison:

	Adult	Pediatrics
Mean± SD	0.76 ± 0.26	1.40 ± 0.22

Relationships between various parameters plotted as box diagrams:



This study indicated that there was a correlation between apparent CL and Vd. When apparent CL was adjusted by body weight, pediatric patients had higher values than that of the adults.

In conclusion the following PK parameters were compiled from the analysis:

	DOSE (µg/hr)	Cmax (ng/mL)	Tmax (h)	AUC_{0-144} (ng.h/mL)	**$T_{1/2}$ (h)**	**Vd/f (L)**	**CL/f (L/hr)**	**CL/f/kg (L/hr)**
Adults	50	-	-	-	**13.6 ± 6.2**	**1080 ± 597**	**57 ± 21**	**0.76 ± 0.26**
Pediatrics	25	-	-	-	**13.3 ± 5.3**	**420 ± 255**	**21 ± 7.6**	**1.4 ± 0.22**

The estimated $t_{1/2}$ values were comparable between adults and pediatric patients. The values for apparent total CL and Vd for pediatric patients were 59 and 57% lower, respectively, than that of the adult values. When apparent CL was adjusted by body weight, pediatric patients had higher apparent total CL (84% greater) than that of the adults. Additionally, the WinNonLin analysis indicated that apparent Vd and CL are highly correlated (a positive slope), i.e., increase in apparent Vd will give increase in the apparent total CL.

Nonmem analysis

The model initial specifications were further utilized in Nonmem analysis to obtain the population parameters (e.g., CL/f, Vd/f, etc.) from the sparse data set from studies FEN-INT-24 and FEN-USA-87. The sparse data from studies FEN-USA-87 and FEN-INT-24 were analyzed with age, wt, and BSA as covariates. The final model indicated that body weight was correlated with Vd.

Structure model and parameter estimates from WinNonLin analysis (Study FEN-FRA-4) were used in Nonmem population PK analysis. The sparse data from studies FEN-USA-87 and FEN-INT-24 were analyzed with age, body weight, and BSA as covariates. The final model indicated that body weight was correlated with Vd and the degree of correlation due to age or BSA was similar on apparent CL. However, BSA as a covariate produced more robust curve fitting. Thus, if needed, the dosage adjustment based on BSA is preferred based on the analysis.

The following relationships were obtained from the analysis:

$$Vd/f = 36.2 + 10.4*wt$$
$$CL/f = 10.8 + 13.5*BSA$$

Based on Nonmem analysis' post hoc predictions, the following individual PK parameters were obtained (mean ± SD):

	AGE 2 – 5 YEARS[1]	AGE 6 – 10 YEARS[1]	AGE 11 – 16 YEARS[1]	ALL
Number of subjects	56	75	142	273
CL/f (L/h)	19.5 ± 2.4	23.8 ± 3.2	29.5 ± 4.9	25.9 ± 5.7
CL/f/kg (L/h/kg)	1.26 ± 0.20	0.92 ± 0.21	0.66 ± 0.17	0.85 ± 0.3
Vd/f (L)	200 ± 45	336 ± 119	547 ± 200	418 ± 213
Vd/f/kg (L/kg)	12.7 ± 0.5	12.0 ± 1.2	11.3 ± 0.75	11.8 ± 1.0

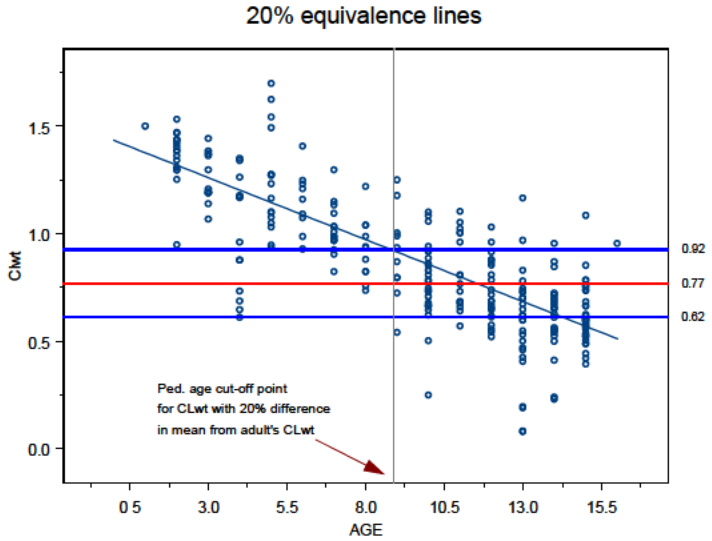
1: Arbitrary age grouping; however, the first 2-5 year old group can be compared with Study FEN-FRA-4.

Thus, overall comparison for the apparent CL is as follows:

	CL/f (L/hr)	**CL/f/kg (L/hr/kg)**
Applicant's adult data[1]	**-**	**0.77 ± 0.30**
Applicant's pop. PK analysis	**28.1 ± 15.3**	**0.92 ± 0.51**
FEN-FRA-4 WinNonLin analysis	**21 ± 7.6**	**1.4 ± 0.22**
Nonmem pop. PK analysis (all subjects)	25.9 ± 5.7	0.85 ± 0.3

1: Population analysis from Studies FEN-GBR-3 and FEN-GBR-4; the adult clearance data were discussed in the Supplement; the actual adult data were not submitted.

The apparent CL values across all analysis were comparable. However, the Applicant's apparent total CL value was comparable to that of the pediatric 6 – 10 year old age group. It is noticeable that the apparent CL for the youngest group (2-5 year olds) is 64% larger than that of the adults. Furthermore, Nonmem analysis indicated that apparent CL for pediatric patients begins to differ than the adults at 9 years of age (based on 20% difference in mean adult apparent clearance using 0.77 ± 0.3 L/hr/kg as reference; range 0.62 – 0.92 L/h/kg). Therefore, if necessary, based on the fentanyl apparent clearance, pediatric patients less than 9 years old should be dose adjusted accordingly.



Finally, the following steady state fentanyl concentrations were calculated using the mean apparent CL obtained from Nonmem analysis for each age group and compared with the observed concentrations from Studies FEN-USA-87 and FEN-INT-24 (normalized to 12.5 µg/hr dose):

	AGE 2 – 5 YEARS[1]	AGE 6 – 10 YEARS[1]	AGE 11 – 16 YEARS[1]	ALL
Estimated steady state fentanyl conc. (ng/mL)[2]	0.64	0.53	0.42	0.48
Observed steady state fentanyl conc. (ng/mL)	**0.51 ± 0.66**	**0.40 ± 0.50**	**0.27 ± 0.40**	**0.36 ± 0.51**

1: Arbitrary age grouping; however, the first 2-5 year old group can be compared with Study FEN-FRA-4

2. Css = (Dosing rate) / CL/f ; dosing rate is 12.5 µg/hr.

Applicant's Pop PK analysis of Studies FEN-INT-24 and FEN-USA-87

Data characterizing the population PK of fentanyl after transdermal administration (Duragesic) in pediatric subjects were derived from two studies, FEN-INT-24 and FEN-USA-87 using linear mixed-effects modeling (Proc Mixed in SAS for Windows, Version 8.1). The 242 subjects provided 886 evaluable serum concentrations, including 188 concentrations from 50 subjects in FEN-INT-24 and 698 concentrations from 192 subjects in FEN-USA-87. The following covariates were included in the analysis: time from dosing, study, site, age, weight, height, body surface area (BSA), body mass index (BMI), lean body mass (LBM), gender, race, body temperature, system location, Tanner stage for sexual maturity, dosing gap, and concomitant administration of any medication, a cytochrome P450 3A4 (CYP3A4) inhibitor, or a CYP3A4 inducer.

The following definitions were used for BSA, LBM, and BMI.

- Body surface area (BSA) using the method of Haycock :

$$BSA(m^2) = 0.024265 * Weight(kg)^{0.5378} * Height(cm)^{0.3964}$$

- **Lean body mass (LBM) using the method of James :**

$$LBM\,(kg) = 1.10 * Weight(kg) - 128 * \left(\frac{Weight(kg)}{Height(cm)}\right)^2 \text{ for males}$$

$$LBM\,(kg) = 1.07 * Weight(kg) - 148 * \left(\frac{Weight(kg)}{Height(cm)}\right)^2 \text{ for females}$$

- **Body mass index (BMI) using the method of Stevens**

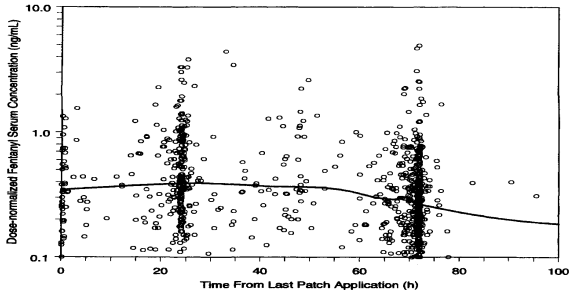
$$BMI = \frac{Weight(kg)}{[Height(cm)]^2}$$

The basic model (equation below) was based on the steady-state serum fentanly concentration, where CL is the apparent clearance. This is a linear model with no intercept and slope equal to CL^{-1} :

$$C_{ss} = \left(\frac{Dosing}{Rate}\right) * \frac{1}{CL}$$

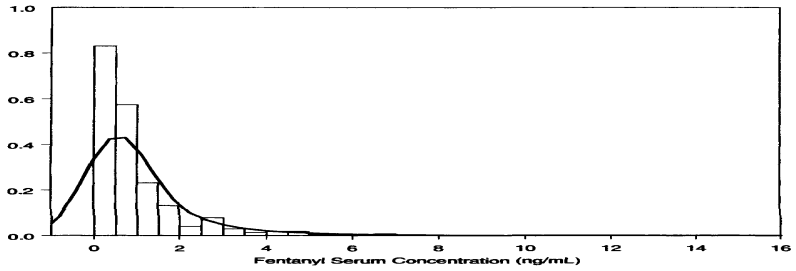
In this model, the distribution of serum fentanyl concentrations was assumed to be log-normal:

Dose-Normalized Serum Fentanyl Concentration-Time Profile



Note: The solid line is a locally weighted smoother with 0.5 span, equal weights, and linear model.

Distribution of Serum Fentanyl Concentrations



The final model for fentanyl at steady state included clinical site and body surface area (BSA):

$$Ln(C_{ij}) = \beta_0 + \beta_1 * Ln\left(\frac{Dosing}{Rate}\right) + \beta_{2\_Site} + \beta_3 * BSA + e_{ij}$$

Finally, empirical Bayes estimates of fentanyl apparent clearance and steady-state concentration were calculated from the following equations:

$$CL = \exp\left(-\beta_0 - \beta_{2\_Site} - \beta_3 * BSA\right)$$

and

$$C_{ss} = \left(\frac{Dosing}{Rate}\right) * \frac{1}{CL}$$

The following results were reported from the Applicant's population PK analysis:

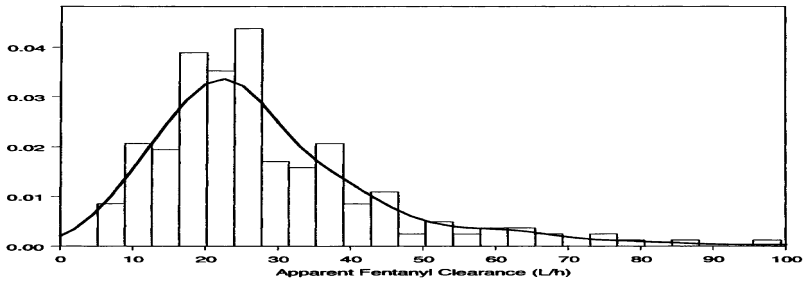
a) Calculated and distribution of apparent CL (L/h)

Distribution of CL (L/h) Across BSA Quartiles

BSA quartile	n	Statistics Mean ± SD	CV%	Median	Range
1st Quartile (<0.8 m^2)	50	20.09 ± 8.59	42.8	18.57	5.09 – 43.71
2nd Quartile (0.8-1.1 m^2)	56	25.49 ± 11.43	44.9	24.40	5.29 – 52.65
3rd Quartile (1.1-1.4 m^2)	56	29.25 ± 13.86	47.4	25.84	7.03 – 73.01
4th Quartile (>1.4 m^2)	56	36.72 ± 19.88	54.1	29.49	9.76 – 99.33
All Quartiles	218	28.10 ± 15.32	54.5	24.48	5.09 – 99.33

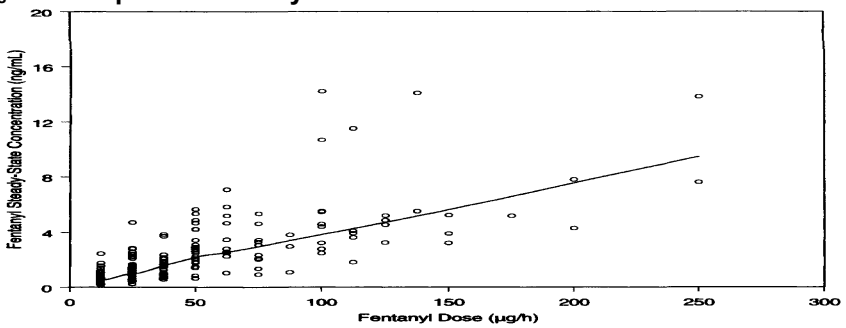
(Cross-Reference: Section 8, Attachment 4.1)

Distribution of Apparent Fentanyl Clearance Estimated from the Final Model



b) Steady-state concentrations and apparent clearance (CL) were dependent upon BSA and study site. The effect of BSA was the most pronounced of all body size—related covariates. An increase in BSA of 0.1 in^2 is predicted to result in a 4.8% increase in CL and a 4.6% decrease in steady-state concentration.

Estimated C_{ss} with respect to fentanyl dose



Note: The solid line is a locally weighted smoother with 0.5 span, equal weights and linear model.
(Cross-Reference: Section 8, Attachment 4.4)

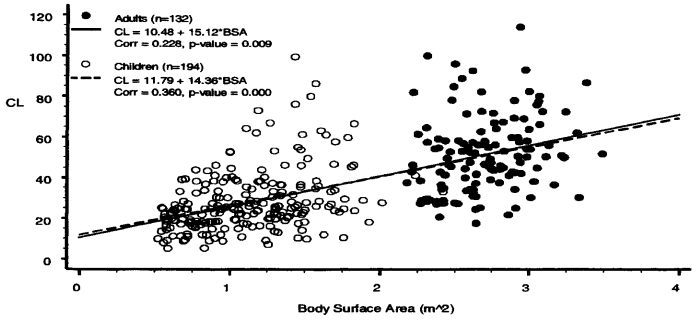
c) Adult subject values were derived from population analysis of data from studies FEN-GBR-3 and FEN-GBR-4 in adult subjects. The reported body weight adjusted total clearance for adults is 0.77±0.30 L/h/kg. The Applicant did not specify whether this value is an apparent clearance.

d) When clearance values were adjusted for body weight, the clearance values were 20% higher in the pediatric group (0.92±0.51 L/h/kg in pediatric subjects vs. 0.77±0.30 L/h/kg in adults).

e) Since BSA had the most pronounced effect on fentanyl clearance, the correlation between these two parameters was examined for the pediatric and adult data together (Figure 11). As seen in this figure, the regression line for the two populations overlaps, indicating BSA to be

the most relevant parameter for comparing fentanyl pharmacokinetics in adult and pediatric subjects. Fentanyl clearance values adjusted to BSA appear to be similar in adults and pediatric subjects: 19.0 ± 7.0 and 26.0 ± 13 L/h/m2, respectively.

Relationship between Clearance (L/h) and Body Surface Area (m^2)



4 QBR

4.1 General Attributes

What is the pharmacological class for fentanyl?

Fentanyl is an opioid analgesic with a pharmacologic action similar to that of morphine but with 75 to 100 times greater potency.

4.2 General Clinical Pharmacology

Is there any exposure-response relationship information for combination tablet?

The correlation between occurrences of AEs such as nausea, fever, vomiting, anemia, and abdominal pain and predicted fentanyl steady-state concentrations from the population PK model was evaluated by logistic regression in the submission. According to the data presented, no significant relationships between AEs and predicted fentanly steady-state concentrations were observed.

Does the patch show accumulation after multiple dosing?

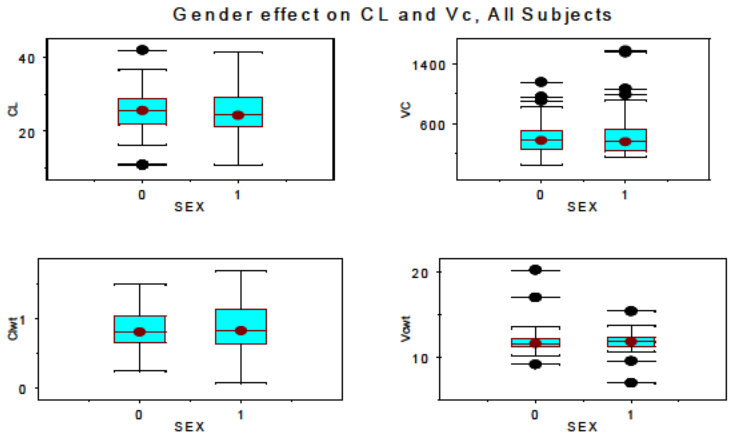
Studies FEN-USA-87 and FEN-INT-24 used a dose-titration study design. A dose-normalized fentanyl concentration data (normalized to 12.5 μg/hr) indicated that concentrations from all strengths were similar across time intervals, possibly indicating that there was no accumulation after repeated patch applications. However, due to the variability from the sparse data set, it was not conclusive to observe clear dose proportionality from the studies.

Note that the Applicant is not seeking approval of the 12.5 μg/hr dose strength at this time.

4.3 Intrinsic Factors

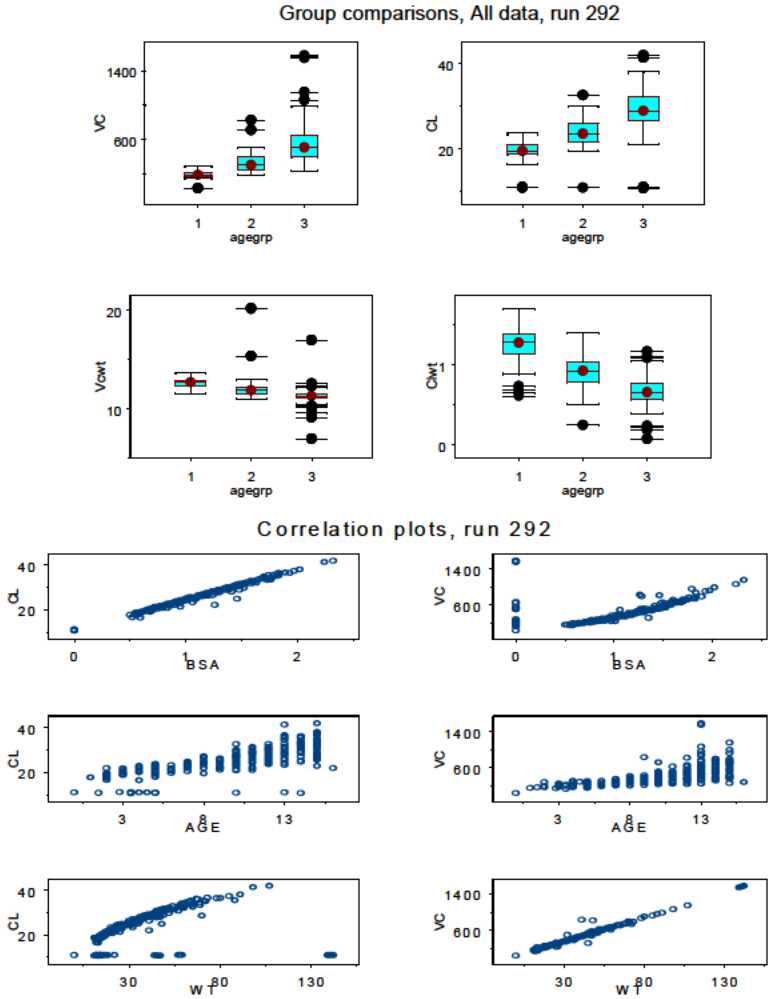
Are there any gender differences observed?

No significant differences between pediatric males and females were observed (WinNonLin and NonMem print out).



Are there any age or weight differences observed?

Effects of age on the pharmacokinetics, CL/f and Vd/f, of fentanyl were observed (Nonmem). The following box diagram showed that both CL/f and Vd/f decreased with decrease in age.



The covariates, BSA, age and wt, were correlated with Vd/f or CL/f. (Nonmem output).

4.4 General Biopharmaceutics

Is an approval of 12.5 μg/hr patch pursued in the Supplement?

No, an approval of 12.5 μg/hr patch is not requested in the Supplement. The Applicant will be submitting a separate submission to pursue the 12.5 μg/hr patch.

4.5 Analytical

Were the analytical procedures used to determine drug concentrations in this NDA acceptable?

Yes, fentanyl was analyzed by the validated radioimmunoassay method. The limit of quantitation was 0.1 ng/mL.

5 Labeling

The Applicant's proposed labeling contain a modest revision under the Clinical Pharmacology section (e.g., clearance). A review of the proposed labeling is as follows:
Proposed by the Applicant:

(b) (4)

39 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page

---

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

/s/

David Lee
5/14/03 11:11:38 AM
BIOPHARMACEUTICS
Review includes Agency's WinNonlin (FEN-FRA-04) and Nonmem (FEN-USA-87 and FEN-INT-24) analyses.

He Sun
5/14/03 11:50:40 AM
PHARMACOLOGIST

Suresh Doddapaneni
5/14/03 11:54:18 AM
BIOPHARMACEUTICS