F_0 in-life:

Mortality: Five F_0 females in the 10 mg/kg/day group and 1 female in the 25 mg/kg/day group were found dead. One 10 mg/kg/day female was found dead on lactation day 0, all other deaths were between lactation day 13 and 19.

Maternal Survival and Pregnancy Status F_0 Females	Dose (mg/kg)				
	0	1	5	10	25
Females in study	25	25	25	25	25
Females that died early	0	0	0	5	1
Females that were euthanized	0	0	0	0	0
Females Allowed to deliver	25	25	25	25	25
Gravid	24	24	25	24	25
Females with total litter loss	0	1	2	0	13
Females with viable pups	25	24	23	24	12
NonGravid	0	0	0	1	0

Clinical Signs: Clinical signs included exophthalmia and Straub tail in the females that died early prior to death. The female in the 25 mg/kg/day group that died early displayed hypoactivity and exhibited whole-body tetany and salivation on gestation day 7. This animal also rocked, lurched and/or swayed while walking on four occasions, the first of which was gestation day 10. Rales and wet material around the nose and mouth were observed in one 10 mg/kg/day female on day 19.

Clinical signs in the animals that survived until scheduled sacrifice that appeared to be related to drug treatment are summarized in the table below:

Clinical Signs (Daily Examinations) F_0 Females	Dose (mg/kg)				
	0	1	5	10	25
Cardio-Pulmonary					
Rales	0/0	0/0	0/0	1/1	4/1
Eyes/Ears/Nose					
Dried red material around eyes	0/0	0/0	0/0	0/0	2/1
Dried red material around nose	0/0	0/0	1/1	0/0	3/1
Excreta					
Decreased defecation	0/0	1/1	1/1	1/1	4/2
Soft stool	0/0	0/0	0/0	0/0	1/1

N/N = Total occurrence / Number of animals

Clinical signs noted 1 hour post-dosing were generally consistent with opioid-mediated effects.

Clinical Signs (1-hour post-dose) F_0 Females	Dose (mg/kg)				
	0	1	5	10	25

Behavioral/CNS					
Straub tail	1/1	44/18	127/25	171/25	239/25
Whole body tetany	0/0	0/0	0/0	1/1	4/4
Hypoactive	0/0	0/0	0/0	1/1	10/8
Hyperactive	0/0	0/0	2/1	1/1	1/1
Rocks/lurches, and sways as it walks	0/0	0/0	2/2	15/12	61/21
Piloerection	0/0	0/0	1/1	1/1	8/5
Cardiopulmonary					
Rales	0/0	0/0	0/0	2/1	0/0
Shallow respiration	0/0	0/0	0/0	0/0	1/1
Eyes/Ears/Nose					
Exophthalmus right eye	2/2	306/25	330/25	351/25	426/25
Exophthalmus left eye	2/2	309/25	334/25	357/25	435/25
Dried red material around nose	0/0	0/0	0/0	0/0	1/1
Lacrimation	0/0	0/0	0/0	0/0	1/1
Oral/Dental					
Salivation	0/0	0/0	0/0	2/1	7/6

N/N = Total occurrence / Number of animals

Mean body weight losses were observed in the 25 mg/kg/day group from gestation day 6-9 and 9-12. Mean body weight gain in this group was similar to the control group from gestation day 12-20, however, body weights in these animals remained significantly below control animals throughout gestation. Mean body weights in animals treated with the 10 mg/kg/day dose of oxymorphone were significantly lower than the control animals beginning on gestation day 9. Body weights in the 1 and 5 mg/kg/day groups were significantly reduced compared to controls beginning on study day 12. The sponsor's table 6 (reproduced below) represents the mean body weights of the F_0 generation.

TABLE 6 (F0)
PROJECT NO. [redacted]411009 STUDY OF OXYMORPHONE HYDROCHLORIDE ON PRE/POSTNATAL DEV. IN RATS
SPONSOR:ENDO PHARM., INC. MEAN BODY WEIGHTS (GRAMS) DURING GESTATION

GROUP :		1	2	3	4	5
DAY 0	MEAN	256.	254.	255.	254.	254.
	S.D./N	16.3/25	15.7/25	16.1/25	14.5/24	11.6/25
DAY 6	MEAN	293.	281.	290.	287.	288.
	S.D./N	20.1/25	24.1/25	15.8/25	16.9/24	14.1/25
DAY 9	MEAN	304.	293.	292.	286.**	287.**
	S.D./N	20.5/25	19.7/25	16.2/25	17.0/24	16.8/25
DAY 12	MEAN	320.	306.*	302.**	290.**	282.**
	S.D./N	23.2/25	21.8/25	16.4/25	16.6/24	15.4/25
DAY 15	MEAN	335.	318.*	314.**	304.**	298.**
	S.D./N	21.4/25	23.6/25	18.1/25	17.0/24	18.2/25
DAY 18	MEAN	375.	351.**	349.**	342.**	331.**
	S.D./N	28.2/25	30.5/25	25.7/25	21.8/24	24.9/25
DAY 20	MEAN	407.	380.**	377.**	371.**	364.**
	S.D./N	31.3/25	35.0/25	30.5/25	23.0/24	31.0/25

1- 0 MG/KG/DAY 2- 1 MG/KG/DAY 3- 5 MG/KG/DAY 4- 10 MG/KG/DAY 5- 25 MG/KG/DAY

* = Significantly different from the control group at 0.05 using Dunnett's test
** = Significantly different from the control group at 0.01 using Dunnett's test
NONGRAVID WEIGHT(S) NOT INCLUDED IN CALCULATION OF MEAN

Body weight changes during lactation were also still evident in oxymorphone treated animals, as indicated the sponsor's table 8 reproduced below:

TABLE 8 (F0)
PROJECT NO. [redacted]-411009 STUDY OF OXYMORPHONE HYDROCHLORIDE ON PRE/POSTNATAL DEV. IN RATS
SPONSOR:ENDO PHARM., INC. MEAN BODY WEIGHTS (GRAMS) DURING LACTATION

	GROUP :	1	2	3	4	5
DAY 1	MEAN	302.	290.	280.**	275.**	264.**
	S.D./N	24.6/25	24.9/25	17.4/24	16.4/23	28.7/23
DAY 4	MEAN	318.	303.	290.**	281.**	265.**
	S.D./N	26.4/25	26.9/24	18.3/23	17.5/23	17.5/14
DAY 7	MEAN	323.	305.**	298.**	291.**	290.**
	S.D./N	14.8/25	17.3/24	22.9/23	14.9/23	16.6/13
DAY 10	MEAN	338.	324.	314.**	307.**	308.**
	S.D./N	22.2/25	24.7/24	18.4/23	18.7/23	14.4/12
DAY 14	MEAN	356.	337.*	323.**	315.**	314.**
	S.D./N	23.3/25	25.6/24	18.4/23	21.8/21	19.9/12
DAY 17	MEAN	359.	343.*	332.**	322.**	319.**
	S.D./N	22.1/25	25.6/24	16.4/23	19.1/21	16.5/12
DAY 21	MEAN	337.	323.	320.*	302.**	305.**
	S.D./N	23.1/25	24.9/24	21.1/23	16.8/19	17.3/11

1- 0 MG/KG/DAY 2- 1 MG/KG/DAY 3- 5 MG/KG/DAY 4- 10 MG/KG/DAY 5- 25 MG/KG/DAY

* = Significantly different from the control group at 0.05 using Dunnett's test
** = Significantly different from the control group at 0.01 using Dunnett's test

Appears This Way
On Original

Food consumption in the F_0 animals was reduced by oxymorphone treatment in a dose-dependent manner, consistent with the changes in body weight. The Sponsor's table 10 below demonstrates that as early as day 6, food consumption was statistically lower than controls in animals treated with 5 mg/kg/day and above. Animals treated with 1 mg/kg/day consumed statistically lower mass of food on gestation days 12-15. Over the course of the gestational period (day 6-20), all doses of oxycodone produced significantly lower food consumption compared to controls.

TABLE 10 (F0)
PROJECT NO.: [redacted]-411009 STUDY OF OXYMORPHONE HYDROCHLORIDE ON PRE/POSTNATAL DEV. IN RATS
SPONSOR:ENDO PHARM., INC. MEAN FOOD CONSUMPTION DURING GESTATION (GRAMS/ANIMAL/DAY)

GROUP :	1	2	3	4	5
DAY 0- 6 MEAN	22.	20.*	22.	21.	21.
S.D./N	2.0/25	2.4/25	1.6/25	1.7/24	1.9/25
DAY 6- 9 MEAN	23.	21.	19.**	17.**	14.**
S.D./N	2.3/25	2.0/25	1.8/25	2.9/24	3.3/25
DAY 9- 12 MEAN	24.	22.	21.**	19.**	19.**
S.D./N	2.3/24	2.4/25	1.8/25	2.1/24	3.9/25
DAY 12- 15 MEAN	25.	23.**	22.**	21.**	20.**
S.D./N	2.6/24	2.6/25	2.0/25	2.1/24	2.4/25
DAY 15- 18 MEAN	26.	25.	24.	23.**	21.**
S.D./N	3.2/25	3.2/25	2.5/25	1.8/24	3.6/25
DAY 18- 20 MEAN	26.	24.	23.*	23.*	23.*
S.D./N	3.2/25	3.5/25	3.9/25	4.2/24	4.4/25
DAY 6- 20 MEAN	25.	23.**	22.**	21.**	19.**
S.D./N	2.1/25	2.3/25	1.8/25	2.0/24	2.7/25
DAY 0- 20 MEAN	24.	22.**	22.**	21.**	20.**
S.D./N	2.1/25	2.1/25	1.4/25	1.6/24	2.2/25

1- 0 MG/KG/DAY 2- 1 MG/KG/DAY 3- 5 MG/KG/DAY 4- 10 MG/KG/DAY 5- 25 MG/KG/DAY

* = Significantly different from the control group at 0.05 using Dunnett's test
** = Significantly different from the control group at 0.01 using Dunnett's test
NONGRAVID WEIGHT(S) NOT INCLUDED IN CALCULATION OF MEAN

Mean Food Consumption was also reduced by oxymorphone treatment during lactation, as indicated in the sponsor's table 12 below:

TABLE 12 (F0)
PROJECT NO. [redacted] 411009 STUDY OF OXYMORPHONE HYDROCHLORIDE ON PRE/POSTNATAL DEV. IN RATS
SPONSOR:ENDO PHARM., INC. MEAN FOOD CONSUMPTION DURING LACTATION (GRAMS/ANIMAL/DAY)

GROUP :	1	2	3	4	5
DAY 1- 4 MEAN	37.	36.	35.	34.	26.**
S.D./N	5.3/25	5.4/24	8.9/23	5.2/23	4.8/14
DAY 4- 7 MEAN	42.	42.	39.	41.	37.
S.D./N	7.3/25	7.2/24	7.4/23	3.6/23	4.6/12
DAY 7- 10 MEAN	52.	55.	47.	49.	44.**
S.D./N	6.2/25	5.9/24	10.6/23	5.6/23	5.7/12
DAY 10- 14 MEAN	62.	63.	56.*	59.	53.**
S.D./N	6.2/25	7.3/24	13.9/23	6.5/21	7.5/12
DAY 14- 17 MEAN	68.	68.	61.	64.	57.**
S.D./N	5.4/25	5.8/24	16.5/23	5.9/21	10.2/12
DAY 17- 21 MEAN	68.	68.	61.	73.	72.
S.D./N	5.8/24	7.3/24	17.0/23	9.4/19	8.9/11
DAY 1- 21 MEAN	56.	56.	51.*	55.	49.*
S.D./N	3.3/24	4.6/24	11.6/23	2.9/19	5.1/11

1- 0 MG/KG/DAY 2- 1 MG/KG/DAY 3- 5 MG/KG/DAY 4- 10 MG/KG/DAY 5- 25 MG/KG/DAY

* = Significantly different from the control group at 0.05 using Dunnett's test
** = Significantly different from the control group at 0.01 using Dunnett's test

The effects of oxymorphone on food consumption during lactation was significant primarily in the animals dosed with 25 mg/kg/day.

Gestation length. Oxymorphone treatment produced a slight (maximum of 2.3% or less than one day) but statistically significant increase in the mean gestation length. The gestational lengths noted in oxymorphone treated rats were, however, within the historical control data for the laboratory (21.6 to 22.3 days). Therefore, the clinical significance of this observation appears to be minimal.

F_0 necropsy: The female animal in the 25 mg/kg/day treatment group that was found dead on lactation day 18 had enlarged adrenal glands and a dark red pituitary. The female in the 10 mg/kg/day group that died early had a distended stomach and intestine at necropsy. The pathology report indicated that these findings were not considered to be test article related.

One, two and 13 females in the 1, 5 and 25 mg/kg/day group had total litter loss. One animal in the high dose group had a mass in the renal cortex and medulla. There were no other observations noted upon necropsy in these animals.

Female animals that survived to the scheduled sacrifice on lactation day 21 did not show any treatment-related findings on necropsy. There were no differences between the number of pups born and the number of implantation sites between groups.

F_1 physical development: There were no significant differences in the mean number of pups born, % males at birth or the mean litter size between groups. Mean litter size in the high dose oxymorphone treatment group (12.4) was 18% lower than the mean litter size in control animals (15.2). Although this effect was not statistically significant, the reduction is likely attributed to the administration of the test article.

Post-natal survival was reduced in the 25 mg/kg/day treatment group throughout the pre-weaning period (PND 0, 0-1, 1-4, birth-PND 4 and PND 4-21). This is consistent with 13 of 25 animals in the high dose group demonstrating total litter loss. In addition, there was significantly lower survival in the 5 and 10 mg/kg/day groups from PND 0-1. Although these effects were not dose-related, they are likely related to the treatment administration. In the 1 mg/kg/day group, post-natal survival

	Summary of Postnatal Survival (F_1) % per litter				
Parameter (mean) Dose (mg/kg) →	**0**	**1**	**5**	**10**	**25**
PND 0	97.4	96.9	92.1	97.5	79.9*
PND 0-1	99.8	94.8	86.2*	92.9*	45.6*
PND 1-4	99.0	99.7	96.7	99.1	79.6
PND 4-7	99.5	100	98.4	100	84.5
PND 7-14	100	99.5	97.4	100	100
PND 14-21	100	100	100	100	98.9
Birth to PND 4	96.2	91.6	80.7	87.5	35*
PND 4 to PND 21	99.5	99.5	96.7	100	82.4*

* $p < 0.05$ compared to control group

The general physical condition of the surviving pups in the oxymorphone treated groups were overall similar to the control group during the pre-weening period.

Offspring mean body weights during the pre-weaning period were significantly reduced in the 25 mg/kg/day treatment group compared to controls on PND 1, 4 (pre-selection), 7, 10, 14, 17 and 21. In general, pups in the 1 mg/kg/day treatment group demonstrated higher mean offspring weights compared to control animals.

PROJECT NO. [redacted]411009
SPONSOR:ENDO PHARM., INC.

TABLE 23 (F1 - PRE-WEANING)
STUDY OF OXYMORPHONE HYDROCHLORIDE ON PRE/POSTNATAL DEV. IN RATS
SUMMARY OF MEAN OFFSPRING WEIGHTS (GRAMS)

(LITTER AS EXPERIMENTAL UNIT)

DOSE GROUP:		0 MG/KG/DAY	1 MG/KG/DAY	5 MG/KG/DAY	10 MG/KG/DAY	25 MG/KG/DAY
PND 1						
MALES	MEAN	7.0	7.4	7.0	6.8	5.8**
	S.D.	0.69	0.49	0.84	0.47	0.37
	N	25	24	23	23	15
FEMALES	MEAN	6.6	7.0	6.7	6.5	5.4**
	S.D.	0.61	0.49	0.62	0.47	0.56
	N	25	24	21	23	16
PND 4 (BEFORE SELECTION)						
MALES	MEAN	9.7	10.6*	9.5	9.4	7.9**
	S.D.	1.09	1.04	1.19	0.75	1.57
	N	25	24	23	23	14
FEMALES	MEAN	9.1	10.1**	9.2	8.9	7.8**
	S.D.	0.93	0.99	1.01	0.65	1.61
	N	25	24	21	23	13
PND 7						
MALES	MEAN	15.4	16.9*	14.5	14.9	11.3**
	S.D.	2.15	1.86	2.66	1.30	1.71
	N	25	24	23	23	12
FEMALES	MEAN	14.4	16.3**	14.1	13.9	11.3**
	S.D.	1.66	1.57	2.06	1.28	2.07
	N	25	24	21	23	12
PND 10						
MALES	MEAN	22.2	24.5*	20.8	21.2	16.6**
	S.D.	3.02	2.34	4.41	2.02	2.31
	N	25	24	23	23	12
FEMALES	MEAN	21.0	23.6**	20.7	20.2	16.4**
	S.D.	2.51	2.10	2.98	1.62	2.84
	N	25	24	21	23	12
PND 14						
MALES	MEAN	32.4	34.7	29.5	30.7	24.9**
	S.D.	4.19	3.07	6.83	2.73	2.63
	N	24	24	23	22	12
FEMALES	MEAN	30.9	33.7*	29.7	29.2	24.2**
	S.D.	3.28	2.78	3.81	2.46	3.36
	N	24	24	21	22	12
PND 17						
MALES	MEAN	39.7	41.5	35.1*	37.4	30.8**
	S.D.	4.64	3.55	8.62	3.00	2.95
	N	25	24	23	21	12
FEMALES	MEAN	37.9	40.3	35.7	35.4	29.3**
	S.D.	3.66	3.30	4.88	3.02	4.69
	N	25	24	21	21	12
PND 21						
MALES	MEAN	50.0	53.1	44.9*	49.2	39.6**
	S.D.	5.81	4.42	10.98	3.89	3.12
	N	25	24	23	19	11
FEMALES	MEAN	47.2	51.4*	45.8	46.9	38.0**
	S.D.	4.54	4.41	6.23	3.74	4.78
	N	25	24	21	19	11

PND - POSTNATAL DAY
* - Significantly different from the control group at 0.05 using Dunnett's test
** - Significantly different from the control group at 0.01 using Dunnett's test

Necropsies were completed on pups that were found dead and on pups that were not selected for further study. There were no remarkable findings in the pups that were found dead that could be attributed to maternal treatment with the test article. One pup in

the 25 mg/kg/day treatment group had an absent right kidney and ureter. At scheduled necropsy (PND 21) for pups not selective for further, there were no internal findings that could be attributed to maternal care.

Developmental landmarks in the F_1 pups were examined. Balanopreputial separation in males in the 25 mg/kg/day group was delayed compared to the control group. As this delay was also longer than the historical control mean, this finding may be attributable to the drug treatment. This delay is likely due to the reduction in body weight. Pups in the 1 mg/kg/day treatment group reached balanopreputial separation earlier than controls.

Developmental Landmarks	**Day of acquisition and body weights (F_1)**				
Parameter (mean) Dose (mg/kg) →	**0**	**1**	**5**	**10**	**25**
Balanopreputial Separation (males)					
Day (PND)	44.4	42.8*	44.3	44.2	46.1*
Body Weight (grams)	231.8	229.1	222.0	223.0	211.0*

* $p < 0.05$ compared to control group

There was no difference in the mean day of acquisition of vaginal patency in females between treatment groups.

F_1 behavioral evaluation: Behavioral evaluations included the acoustic startle test (PND 20 and 60), locomotor activity (PND 21 and 61), or the Biel Maze Swimming Trials (PND 22 and 62). There were no treatment-related findings in the oxymorphone treated animals that were significantly different from control values.

There were no treatment-related effects of oxymorphone on either clinical observations or survival of the F_1 generation males or females.

F_1 reproduction: Reproductive performance in the F_1 generation was not altered by F_0 maternal treatment. There were no differences in female or male mating indices or fertility indices. Likewise, there were no differences in the pre-coital interval or estrous cycle duration.

Body weights in the F_1 generation during the post-weaning period were significantly reduced in the 25 mg/kg/day groups on PND 28, 35, 42, 49, 56, 62 and 70. Mean body weights in the 10 mg/kg/day group were significantly reduced compared to controls on PND 49, 56, 63 and 70. Mean body weights in males in the 5 mg/kg/day group were also significantly reduced compared to controls on PND 63.

TABLE 39 (F1 - POST-WEANING)
PROJECT NO.: [redacted]411009 STUDY OF OXYMORPHONE HYDROCHLORIDE ON PRE/POSTNATAL DEV. IN RATS
SPONSOR:ENDO PHARM., INC. SUMMARY OF MEAN OFFSPRING WEIGHTS (GRAMS)

(LITTER AS EXPERIMENTAL UNIT)

DOSE GROUP:		0 MG/KG/DAY	1 MG/KG/DAY	5 MG/KG/DAY	10 MG/KG/DAY	25 MG/KG/DAY
PND 28						
MALES	MEAN	87.8	94.8	83.3	85.5	71.5**
	S.D.	11.40	9.19	13.15	6.81	6.50
	N	25	24	22	19	11
FEMALES	MEAN	82.1	85.9	79.8	79.4	67.3**
	S.D.	8.22	5.25	7.84	6.55	10.52
	N	25	24	21	19	11
PND 35						
MALES	MEAN	148.9	157.6	140.4	143.1	123.6**
	S.D.	17.91	17.11	20.61	7.68	9.32
	N	25	24	22	19	11
FEMALES	MEAN	136.8	134.9	127.3	125.4	109.9**
	S.D.	11.19	9.27	9.25	9.49	15.14
	N	25	24	21	19	11
PND 42						
MALES	MEAN	212.1	221.5	201.6	204.7	180.6**
	S.D.	22.34	23.61	25.67	12.67	12.78
	N	25	24	22	19	11
FEMALES	MEAN	166.7	167.4	161.6	157.9	144.3**
	S.D.	11.97	11.06	10.63	11.25	14.61
	N	25	24	21	19	11
PND 49						
MALES	MEAN	272.7	282.7	258.2	258.2	225.6**
	S.D.	27.15	29.81	30.54	14.96	17.16
	N	25	24	22	19	11
FEMALES	MEAN	195.0	191.3	186.8	183.6*	168.9**
	S.D.	15.00	15.23	13.43	12.29	15.52
	N	25	24	21	19	11
PND 56						
MALES	MEAN	335.8	344.8	317.0	315.3	284.9**
	S.D.	30.44	34.82	33.01	15.55	21.52
	N	25	24	22	19	11
FEMALES	MEAN	220.4	212.2	211.4	204.8*	188.8**
	S.D.	18.32	19.22	16.24	17.11	19.20
	N	25	24	21	19	11
PND 63						
MALES	MEAN	392.3	385.5	357.2*	352.6*	326.1**
	S.D.	40.59	36.92	37.18	19.80	24.27
	N	25	24	22	19	11
FEMALES	MEAN	236.1	229.4	225.6	220.7*	206.3**
	S.D.	20.47	18.36	18.04	19.51	18.66
	N	25	24	21	19	11
PND 70						
MALES	MEAN	410.8	422.3	392.0	385.5	368.1**
	S.D.	38.55	40.25	43.00	27.39	24.68
	N	25	24	22	19	11
FEMALES	MEAN	254.7	246.3	241.6	238.3*	223.4**
	S.D.	20.01	21.26	17.93	20.99	14.36
	N	25	24	21	19	11

PND - POSTNATAL DAY
* - Significantly different from the control group at 0.05 using Dunnett's test
** - Significantly different from the control group at 0.01 using Dunnett's test

The table below summarizes the overall differences in mean body weight of the offspring during the post-weaning period.

Interval	Dose (mg/kg) →	Summary of Mean Offspring Weight (F_1) Changes (F_1) % Δ of Control				
		0	**1**	**5**	**10**	**25**
PND 21 to 70						
Males			+2	-4	-7	-9*
Females			-6	-5	-7*	-11*

* $p < 0.05$ compared to control group

Mean material body weights were reduced for the females in the 25 mg/kg/day treatment group throughout gestation. These changes were statistically significant days 0-16 and on day 20. Mean maternal body weight gains in the group were not affected by F_0 test article administration. Mean gravid uterine weights and net body weight gains in the 1, 5, 10 and 25 mg/kg/day groups were similar to controls.

	Summary of Mean Gravid Uterine Weights and Net Body Weight Changes (F_1) % Δ of Control				
Parameter (mean) Dose (mg/kg) →	**0**	**1**	**5**	**10**	**25**
Initial body weight		-1	-4	-6	-12*
Terminal body weight		0	-0.5	-2	-7*
Gravid uterine weights		+3	+4	+3	+2
Net body weights		+0	-1	-3	-8*
Net body weight changes		+4	+9	+7	+8

* $p < 0.05$ compared to control group

Necropsy of the dams and F_1 males failed to detect any treatment-related findings that could be attributed to treatment of the F_0 generation.

F_2 findings: Intrauterine growth and survival of the F_2 fetuses were not altered by F_0 maternal treatment at any dose level tested. Parameters evaluated included postimplantation loss, viable fetuses, fetal body weights and fetal sex ratios. The numbers of corpora lutea and implantation sites were similar among all groups, including the control group. Morphologically, there were no external malformations or developmental variations in the fetuses in this study.

3.4.7 Local tolerance

There were no local tolerance studies submitted with these NDA applications.

3.4.8 Special toxicology studies

Study title: Dermal Sensitization Study in Guinea Pigs/Maximization Procedure Using Oxymorphone

Key study findings: The ability for oxymorphone to induce skin sensitization was tested in the guinea pig maximization test in rabbits with the following results:

1. Oxymorphone and the positive control DNCB induced clear erythema and edema in the rabbit and should be considered to be dermal irritants.
2. The guinea pig maximization test is currently accepted by CDER to identify the sensitization potential of drugs intended for topical use.
3. The study suggests that oxymorphone may have the potential to produce a hypersensitivity reaction when applied topically.

Study no.: 410-1964
Volume #, and page #: Electronic Document Room
Conducting laboratory and location: [redacted]

Date of study initiation: Unspecified, report dated April 3, 1986.
GLP compliance: Yes
QA reports: yes (X) no ( )
Drug, lot #, and % purity: Oxymorphone base, Lot R84-188, purity unspecified.
Formulation/vehicle: The vehicle control was propylene glycol (lot 417620) from [redacted]. The sensitization control was DNCB (1-chloro-2,4-dinitrobenzene). The adjuvant used was [redacted] Complete H37 RA from [redacted]

Methods
Young adult male and female Hartley guinea pigs were used to test the dermal sensitization potential of oxymorphone. The back of each animal was clipped free of hair 24 hours prior to the initiation of treatment. The induction phase consisted of an intradermal injection into the right flank

Doses: Induction with 5% oxymorphone and challenged with 30% oxymorphone.

Study design: The basic study design is depicted below:

		Treatment		
		Induction Phase		Challenge Phase
Group	Number of Animals	Intradermal Injection Sites 1,2,3	Topical Application	Topical Application
Vehicle Control	10M/10F	1 FCA 2 Vehicle 3 FCA/Vehicle	Vehicle	Vehicle
Irritation Control	10M/10F	1 FCA 2 FCA 3 FCA	None	Test article
Positive Control	10M/10F	1 FCA 2 PC Article 3 FCA/PC Article	PC Article	PC Article
Test Article	10M/10F	1 FCA 2 Test Article 3 FCA/Test Article	Test Article	Test Article

FCA denotes 50% FCA/50% deionized water emulsion
Vehicle denotes the test article carrier (propylene glycol)
PC Article denotes DNCB
FCA denotes Freund's Adjuvant, complete

The following groups were employed for the Induction Phase (Day 1):

Group (n=10/sex/group)	Paired Injection Sites[1]	Article Administered
Vehicle Control	1 2 3	Adjuvant emulsion Propylene glycol (vehicle) 5% propylene glycol in adjuvant emulsion
Irritation Control	1, 2 and 3	Adjuvant emulsion
Sensitization Control	1 2 3	Sensitization control adjuvant emulsion 0.1% DNCB suspension 0.1% DNCB in sensitization control adjuvant emulsion
Test	1 2 3	Adjuvant emulsion Oxymorphone in propylene glycol (5%) Oxymorphone in adjuvant emulsion (5%)

[1] There were six intradermal injection sites on each animal within a 2 x 4 cm area. Paired injection sites 1 and 2 were closest to the head and injection sites 3 were posterior to 1 and 2.

Two 0.1 ml of each of the article listed above were administered intradermally to each animal of the appropriate group. Seven days after the intradermal injections, the topical induction applications (see table below) were applied to 2 x 4 cm [redacted] patches attached to [redacted] tape to the induction area. The entire trunk was wrapped with an impervious binder consisting of a plastic wrap, adhesive tape and masking tape.

Group (n=10/sex/group)	Article Applied	Volume or weight/animal
Vehicle Control	Propylene glycol	0.2 ml
Irritation Control	None	--
Sensitization Control	0.1% DNCB suspension	0.2 ml
Test	Oxymorphone	200 mg (moistened)

After 48 hours of topical induction exposure the impervious binders and patches were removed and the application sites were gently cleaned with gauze moistened with propylene glycol for vehicle control or reagent grade water for sensitization control animals.
Fourteen days after the topical induction, surviving animals were challenged as follows:

Group (n=10/sex/group)	Article Applied	Volume or weight/animal
Vehicle Control	Propylene glycol	0.1 ml
Irritation Control	30% (w/w) oxymorphone	100 mg
Sensitization Control	30% (w/w) oxymorphone	100 mg
Test	0.1% DNCB suspension	0.1 ml

The articles above were applied to a 2 x 2 cm [redacted] patch attached to [redacted] tape and applied to the right flank of the appropriate animal (clipped free of hair). The trunk was wrapped with an impervious binder as previously described. After 24 hours of topical challenge exposure, the wrapping was removed, the sites were gently cleaned and

the challenge sites were evaluated for erythema and edema according to the method of Draize (see below) at 24 and 48 hours after the removal of the challenge articles.

The Draize Grading Scale for Evaluation of Dermal Reactions	
Erythema and Eschar Formation	
No erythema	0
Very slight erythema (barely perceptible)	1
Well defined erythema	2
Moderate to severe erythema	3
Severe erythema (beet redness) to slight eschar formation (injuries in depth)	4
Total Possible Erythema Score	**4**
Edema Formation	
No edema	0
Very slight edema (barely perceptible)	1
Slight edema (edges of area well defined by definite raising)	2
Moderate edema (raised approximately 1 mm)	3
Severe edema (raised more than 1 mm and extending beyond area of exposure)	4
Total Possible Edema Score	**4**

Sensitizers were graded and classified using the following allergenicity rating (Magnusson and Kligman, 1969).

Allergenicity Rating		
Sensitization Rate (%)	**Grade**	**Classification**
0 to 8	I	Weak
9 to 28	II	Mild
29 to 64	III	Moderate
65 to 80	IV	Strong
81 to 100	V	Extreme

Results:

Mortality: One male in the oxymorphone test group was found in a moribund condition and was sacrificed in extremis on day 10. Two other animals in the oxymorphone test group were found dead during the study (one male and one female, both on day 11). Abnormalities noted in these animals were as follows:

Animal Number	Sex	Area or Organ	Abnormality
AG6826	M	External Surface Intestine Liver Urinary Bladder	Multiple ulcerative dermatitis Hyperemia, Gaseous distension Mottled, white Distended by red fluid
AG6827	M	Treated Skin Urinary Bladder	Ulceration, multiple, focal, red tan Distended with amber fluid
AG6873	F	External Surface Liver Intestine	2 cm^2 area of deep dermal necrosis Mottle, white Hyperemia

Clinical signs: Clinical signs in the oxymorphone treated group included cowering and rigid/strained body, lacrimation, muscle tremors, squinting, slow respiration, lethargy and ataxia. No clinical signs were noted in other groups.

Skin reaction: A summary of the incidences of erythema and edema observed for the test and sensitization control groups is reproduced below:

		Incidence of Challenge Dermal Reactions (number affected/number evaluated)							
		Test Group[1]				**Sensitization Control Group[2]**			
		Males		**Females**		**Males**		**Females**	
	Grade	**24 hr**	**48 hr**	**24 hr**	**48 hr**	**24 hr**	**48 hr**	**24 hr**	**48 hr**
Erythema	1	5/8	3/8	1/9	--	3/10	1/10	--	--
	2	3/8	4/8	5/9	2/9	6/10	2/10	1/10	1/10
	3	--	--	1/9	1/9	--	3/10	2/10	2/10
	4	--	1/8	2/9	6/9	1/10	4/10	7/10	7/10
Edema	1	2/8	1/8	--	--	3/10	1/10	--	--
	2	6/8	5/8	4/9	--	5/10	--	5/10	--
	3	--	2/8	5/9	5/9	2/10	7/10	5/10	7/10
	4	--	--	--	4/9	--	2/10	--	3/10

[1] Test group was induced with oxymorphone and challenged with oxymorphone.
[2] Sensitization group was induced with DNCB and challenged with DNCB.

Based upon the results presented above, both oxymorphone and DNCB were characterized as extreme sensitizers (Grade 5) based upon the allergenicity rating of Magnusson and Kligman.

Histological examination of sections of treated and untreated skin indicates that the test article produced changes such as acanthosis, hyperkeratosis, lymphocytic infiltrate and superficial epidermitis. The incidence of these findings and severity were generally higher in female guinea pigs than males. A summary of these changes were provided by the pathology report reproduced below:

MALE GUINEA PIGS

GROUP:	POSITIVE CONTROL	VEHICLE CONTROL	IRRITATION CONTROL	TEST ARTICLE
UNTREATED SKIN				
Number Examined	(10)	(10)	(10)	(8)
Acanthosis	8	2	3	6
Acantholysis	0	0	0	1
Acute Dermatitis	1	0	0	0
Hyperkeratosis	1	2	2	6
Lymphocytic Infiltrate	3	0	0	3
Panniculitis	1	3	0	1
Superficial Epidermitis	1	1	0	1
TREATED SKIN				
Number Examined	(10)	(10)	(10)	(8)
Acanthosis	10	3	0	8
Acantholysis	0	0	0	3
Acute Dermatitis	2	0	0	0
Hyperkeratosis	6	2	0	7
Lymphocytic Infiltrate	4	0	0	2
Panniculitis	3	0	1	0
Superficial Epidermitis	5	0	0	3

FEMALE GUINEA PIGS

GROUP:	POSITIVE CONTROL	VEHICLE CONTROL	IRRITATION CONTROL	TEST ARTICLE
UNTREATED SKIN				
Number Examined	(10)	(10)	(10)	(9)
Acanthosis	10	6	3	7
Acantholysis	1	1	0	1
Acute Dermatitis	0	0	0	0
Hyperkeratosis	9	4	1	4
Lymphocytic Infiltrate	6	5	3	6
Panniculitis	1	3	2	3
Superficial Epidermitis	1	2	0	1
TREATED SKIN				
Number Examined	(10)	(10)	(10)	(9)
Acanthosis	10	6	6	9
Acantholysis	0	1	0	1
Acute Dermatitis	6	0	0	0
Hyperkeratosis	9	4	1	7
Lymphocytic Infiltrate	4	5	4	9
Panniculitis	5	4	3	4
Superficial Epidermitis	8	1	0	7

3.6 OVERALL CONCLUSIONS AND RECOMMENDATIONS

Conclusions: The sponsor has provided repeat-dose toxicology studies in the rodent and non-rodent, a full battery of genetic toxicology studies and reproductive and developmental toxicology studies in support of the NDAs for oxymorphone ER (21-610) and IR (21-611). The non-clinical data is the same for both drug products and therefore the NDAs were reviewed together. Overall, oxymorphone produced characteristic opioid toxicities. There does not appear to be any unique toxicity noted with oxymorphone compared to other opioids of the phenanthracene class.

Oxymorphone tested positive in the *in vivo* mouse and rat micronucleus assay. Kinetochore analysis indicated that in the mouse, the DNA damage is due to chromosomal breakage rather than loss of the entire chromosome. These findings should be further explored via mechanistic studies to determine the mechanism of oxymorphone-induced micronuclei and evaluate the potential clinical relevance of these findings as part of the development of these drug products.

The sponsor has proposed that the positive *in vivo* genotoxicity data in the rat and mouse are not biologically relevant. They provide the following arguments for this position:

1. The "apparent clastogenic activity of oxymorphone seen in the mouse and rat micronucleus studies is a class-related phenomenon that is of no demonstrated clinical significance and does not pose a health threat to human." This statement is based upon the following:

   A. The effect is indirect and mediated through glucocorticoids and/or opioid receptor binding.
   B. The effect resolves rapidly following repeated daily dosing.
   C. There are no corroborative findings in the chronic toxicology or reproductive/developmental studies suggesting evidence for pre-neoplastic changes or mutagenic activity.
   D. Codeine, a structurally related compound, did not increase incidence of tumors in rats or mice (NTP).

2. Humans have been exposed to oxymorphone directly and indirectly (oxymorphone is a major metabolite of oxycodone).

FDA Response to Point 1.

a. The Sponsor concludes that the response is due to a class-effect and is indirect based upon previously published results with morphine sulfate (Swain et al., 1980;Das and Swain, 1982;Sawant and Couch, 1995;Couch and Sawant, 1995;Sawant et al., 2001). These reports suggest that the *in vivo* effects of morphine sulfate are mediated by opioid receptors and adrenal-dependent-factors. Although these results suggest that opioid-induced alterations in *in vivo* mutagenicity testing is due to activation of the HPA axis, the authors note several observations that suggest that the effect of morphine is more complex. Specifically, N-methylmorphine, a quaternary opioid agonist that does not readily cross the blood brain barrier, also produces an increase in the frequency of micronucleated cells. Second, metyrapone, an inhibitor of glucocorticoid biosynthesis, did not alter morphine-induced clastogenicity. Third, the concentrations of dexamethasone that induce micronuclei *in vitro* are approximately 5-fold higher than the concentrations of corticosterone obtained at clastogenic doses of morphine sulfate. Fourth, intravenous β-endorphin, which should not readily cross the blood brain barrier, also produces a clastogenic response *in vivo*. Fifth, 5 consecutive treatments with codeine, which is structurally similar to morphine and oxymorphone, did not produce alterations in the mouse *in vivo* micronucleus test (Bruce and Heddle, 1979). Overall, the evidence suggests that opioids may make cells more susceptible to genetic damage via depressed DNA repair capacity (Madden et al., 1979), however, the exact mechanism of morphine-induced alterations in the frequency of micronuclei is not known.

   The Sponsor's data from the *in vitro* mutagenicity studies were negative, while the data in the *in vivo* studies were positive. As such, this reviewer agrees that the mechanism of oxymorphone-induced mutagenicity appears to be indirect.

However, this alone does not support the conclusion that the findings have no relevance to humans. The positive result *in vivo* could be mediated by an opioid-receptor/adrenal-dependent mechanism, like morphine, or it could be due to a mutagenic metabolite of oxymorphone. The sponsor has provided no data to support either assumption for oxymorphone.

b. The Sponsor claims that the effect is transient and resolves following repeated administration. This conclusion is based upon a literature reference for morphine (Swain et al., 1980), but has not been demonstrated for oxymorphone. Therefore, the sponsor has not provided evidence that this is true for their product.

c. The Sponsor claims that there are no corroborative findings in either the 13-week repeat-dose toxicity studies or the reproductive/developmental studies to suggest mutagenic or pre-neoplastic changes following oxymorphone treatment. Although this appears to be a true statement, the studies did not administer oxymorphone for a sufficient duration to be of use for accurate assessment of carcinogenic potential. It is also not likely that pre-neoplastic changes will be detected in studies of these durations.

d. The Sponsor claims that codeine, a structurally similar compound has been evaluated for carcinogenic potential by the NTP and found negative. This is true. However, in contrast to oxymorphone, codeine was negative in the *in vivo* micronucleus test, questioning the claim for a class-effect in this test. In addition, the results of the carcinogenicity assessment for codeine can not be extrapolated to oxymorphone.

FDA Response to Point 2.

Although humans have been exposed to oxymorphone, there are no epidemiological studies available that can demonstrate any assessment of increases or decreases in tumor incidence in patients which receive oxymorphone. As a result, there is no human data to support the claim made by the sponsor.

The positive result for oxymorphone in the *in vivo* micronucleus test indicates that oxymorphone has the potential to cause DNA damage when administered to both rats and mice. The mechanism mediating this effect is not clear. The scientific rationale provided by the Sponsor does not adequately demonstrate the lack of risk for carcinogenic potential. The sponsor is currently conducting carcinogenicity assessment of oxymorphone via a standard rat and mouse 2-year bioassay.

Aside for the requirement to characterize the — degradation products in the drug products ( ) the primary pharmacology toxicology issues complicating these NDAs is the positive *in vivo* micronucleus assays with oxymorphone and the positive in vitro genetic toxicology result with the impurity . These NDAs are also complicated by the discovery of —

[redacted] which has not been characterized to date and contains the same structural alert for mutagenicity as [redacted].

There are no formal FDA guidance documents that describe the Agency's position on acceptable levels of genotoxicity impurities in drug products. The European Agency for the Evaluation of Medicinal Products (EMEA) published a draft position paper on the limits of genotoxic impurities in December 2002. This document proposes that there are two classes of genotoxic impurities: 1) genotoxic compounds with sufficient evidence for a threshold-related mechanism, and 2) genotoxic compounds without sufficient evidence for a threshold-related mechanism. The EMEA document maintains that in some circumstances, there may be a threshold for genotoxicity with some compounds. EMEA notes that this is particularly true for potential mutagens that are rapidly detoxified, and as such, a NOEL level can be established for risk assessment. The position paper also recommends that if there is no clear evidence for a threshold mechanism, there sponsor should evaluate their manufacturing process to determine if the impurity can be eliminated by changing the synthetic pathway or in the formulation. If you can not eliminate the impurity, the EMEA document recommends that the sponsor explore alternative synthetic schemes or formulations to eliminate the genotoxic impurity or justify why the impurity is unavoidable. If the impurity is unavoidable, technical efforts to reduce the content of the impurity to levels as low as technically feasible should be undertaken. They refer to this approach as the pharmaceutical (quality) assessment. Should the presence of the impurity be sufficiently justified, a critical assessment of the toxicological acceptability should be provided. This could be a quantitative risk assessment based on mathematical models or a determination of a no effect level of carcinogen response modified by uncertainly factors in order to establish an acceptable safety margin.

The Genetic Toxicology Subcommittee of PTCC at FDA has commented upon the draft guidance proposed by EMEA. The Genetic Toxicology Subcommittee acknowledges that position that a threshold mechanism for some genotoxic effects exist has begun to gain acceptability. They note that current practice is to assume that there is no threshold for the genotoxic effect. Further, they conclude that at this time, methods to demonstrate that a threshold-related mechanism for a genotoxic response is not well established. Although the approach is commendable, it is not feasible at this time due to the difficulties in extrapolating a NOEL in the currently accepted genetic toxicology tests to a human dose. A NOEL can not be extrapolated from an in vitro study. The existing in vivo test in the standard batter (in vivo micronucleus test) detects clastogenic events, but not mutagenic ones. Further this test only monitors one target tissue and does not take into account the potential accumulation of the impurity into specific tissues. This reviewer concurs with CDER's Genetic Toxicology Subcommittee. Further the sponsor has provided no data demonstrating that a threshold for the oxymorphone or [redacted] effects exists.

The determination of an acceptable specification for this impurity has been discussed extensively in the division. The specification of NMT [redacted], for the [redacted] in the drug products is based, in part, upon the acceptable levels of

benzene (known human carcinogen) in drinking water, as defined by the EPA (maximum contaminant level for drinking water is 5 ppb). EPA's qualitative risk estimate of carcinogenic risk from oral exposure to benzene is 1 in 1,000,000 with a concentration in drinking water of 1-10 μg/L (assuming 2 L/day = 20 μg/day). For a person taking a daily dose of 1000 mg/day of oxymorphone, a maximum of 20 μg/day would require the [redacted] to be at a level of [redacted]. A specification of NMT [redacted] for [redacted] corresponds to a maximum daily dose of 10 μg/day.

Unresolved toxicology issues (if any):

1. The sponsor has initiated carcinogenicity assessment of oxymorphone and the Division agreed to the submission of these results as a Phase 4 commitment. The sponsor should make every effort to finalize the study reports to be submitted with the NDA resubmission.
2. The impurities [redacted] have been identified and contain a structural alert for mutagenicity. A minimal genetic toxicology screen for [redacted] has been completed and the results indicate that this impurity tests positive in the *in vitro* chromosome aberrations assay. The sponsor has initiated genetic toxicology studies on [redacted] however, there are no data at this time. If this compound also tests positive, the sponsor should either reduce the levels of each impurity to NMT [redacted] or further qualify each impurity via carcinogenicity assessment in a single species.
3. There are [redacted] additional impurities which exceed ICH Q3B thresholds for qualification [redacted] which should be either reduced from NMT [redacted] respectively, to NMT [redacted] Alternately, the sponsor should adequately qualify each impurity via a minimal genetic toxicology screen (one *in vitro* gene mutation and one *in vitro* chromosomal aberrations assay) and a 14-day repeat dose toxicology study in a single species.
4. Oxymorphone has tested positive in the *in vivo* micronucleus assay in both the rat and the mouse. Although the sponsor has hypothesized that oxymorphone produces this result in a manner similar to that reported for morphine in the literature, this hypothesis has not been tested for oxymorphone. The sponsor should determine the mechanism of oxymorphone-induced *in vivo* clastogenicity and define the relevance of these findings to humans.

Recommendations: From a pharmacology/toxicology perspective, based upon review of the non-clinical data, NDA 21-611 (oxymorphone ER) and NDA 21-610 (oxymorphone IR) are approvable.

Suggested labeling: The non-clinical sections of the labeling for both products should read as follows:

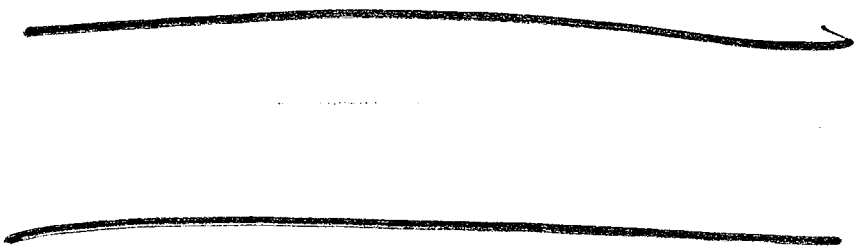
1 Page(s) Withheld

_____ Trade Secret / Confidential

9 Draft Labeling

_____ Deliberative Process

Withheld Track Number: Pharm/Tox-_____



Signatures (optional):

Reviewer Signature _____

Supervisor Signature_____ Concurrence Yes ___ No ___

3.7. APPENDIX/ATTACHMENTS

Reference List

Bruce WR and Heddle JA (1979) The mutagenic activity of 61 agents as determined by the micronucleus, Salmonella, and sperm abnormality assays. *Can.J.Genet.Cytol.* **21**:319-334.

Cone EJ, Darwin WD, Buchwald WF, and Gorodetzky CW (1983) Oxymorphone metabolism and urinary excretion in human, rat, guinea pig, rabbit, and dog. *Drug Metab Dispos.* **11**:446-450.

Copland VS, Haskins SC, and Patz J (1989) Naloxone reversal of oxymorphone effects in dogs. *Am.J.Vet.Res.* **50**:1854-1858.

Copland VS, Haskins SC, and Patz JD (1987) Oxymorphone: cardiovascular, pulmonary, and behavioral effects in dogs. *Am.J.Vet.Res.* **48**:1626-1630.

Copland VS, Haskins SC, and Patz JD (1992) Cardiovascular and pulmonary effects of atropine reversal of oxymorphone-induced bradycardia in dogs. *Vet.Surg.* **21**:414-417.

Couch DB and Sawant SG (1995) The clastogenicity of morphine sulfate in vivo. *Adv Exp Med Biol* **373**:123-129.

Das RK and Swain N (1982) Mutagenic evaluation of morphine sulphate and pethidine hydrochloride in mice by the micronucleus test. *Indian J Med Res* **75**:112-117.

Fujinaga M and Mazze RI (1988) Teratogenic and postnatal developmental studies of morphine in Sprague- Dawley rats. *Teratology* **38**:401-410.

Fujinaga M, Stevenson JB, and Mazze RI (1986) Reproductive and teratogenic effects of fentanyl in Sprague-Dawley rats. *Teratology* **34**:51-57.

Gutstein HB and Akil H (2002) Opioid Analgesics, in *Goodman & Gilman's The Pharmacological Basis of Therapeutics* (Hardman JG, Limbird LE, and Gilman AG eds) pp 569-619, McGraw-Hill, New York.

Hermens JM, Ebertz JM, Hanifin JM, and Hirshman CA (1985) Comparison of histamine release in human skin mast cells induced by morphine, fentanyl, and oxymorphone. *Anesthesiology* **62**:124-129.

Lessard A and Bachelard H (2002) Tonic inhibitory control exerted by opioid peptides in the paraventricular nuclei of the hypothalamus on regional hemodynamic activity in rats. *Br.J.Pharmacol.* **136**:753-763.

Lewis JW, Shavit Y, Terman GW, Gale RP, and Liebeskind JC (1983) Stress and morphine affect survival of rats challenged with a mammary ascites tumor (MAT 13762B). *Nat.Immun.Cell Growth Regul.* **3**:43-50.

Madden JJ, Falek A, Shafer DA, and Glick JH (1979) Effects of opiates and demographic factors on DNA repair synthesis in human leukocytes. *Proc.Natl.Acad.Sci.U.S.A* **76**:5769-5773.

Magnusson B and Kligman AM (1969) The identification of contact allergens by animal assay. The guinea pig maximization test. *J.Invest Dermatol.* **52**:268-276.

Mellon RD and Bayer BM (1998) Evidence for central opioid receptors in the immunomodulatory effects of morphine: Review of potential mechanism(s) of action. *J.Neuroimmunol.* **83**:19-28.

Metzger TG, Paterlini MG, Ferguson DM, and Portoghese PS (2001) Investigation of the selectivity of oxymorphone- and naltrexone-derived ligands via site-directed mutagenesis of opioid receptors: exploring the "address" recognition locus. *J.Med.Chem.* **44**:857-862.

O'Brien CP (2001) Drug addiction and drug abuse, in *Goodman & Gilman's The Pharmacological Basis of Therapeutics* (Hardman JG, Limbird LE, and Gilman AG eds) pp 621-642, McGraw-Hill, New York.

Robinson EP, Faggella AM, Henry DP, and Russell WL (1988) Comparison of histamine release induced by morphine and oxymorphone administration in dogs. *Am.J.Vet.Res.* **49**:1699-1701.

Sawant SG and Couch DB (1995) Induction of micronuclei in murine lymphocytes by morphine. *Environ Mol Mutagen.* **25**:279-283.

Sawant SG, Kozlowski RS, and Couch DB (2001) The role of adrenal corticosteroids in induction of micronuclei by morphine. *Mutat.Res* **498**:129-133.

Shavit Y, Terman GW, Martin FC, Lewis JW, Liebeskind JC, and Gale RP (1985) Stress, opioid peptides, the immune system, and cancer. *J.Immunol.* **135**:834s-837s.

Smith LJ, Yu JK, Bjorling DE, and Waller K (2001) Effects of hydromorphone or oxymorphone, with or without acepromazine, on preanesthetic sedation, physiologic values, and histamine release in dogs. *J.Am.Vet.Med.Assoc.* **218**:1101-1105.

Swain N, Das RK, and Paul M (1980) Cytogenetic assay of potential mutagenicity in vivo of two narcotic analgesics. *Mutat.Res* **78**:97-100.

Weber RJ and Pert A (1989) The periaqueductal gray matter mediates opiate-induced immunosuppression. *Science* **245**:188-190.

Wybran J, Appelboom T, Famaey JP, and Govaerts A (1979) Suggestive evidence for receptors for morphine and methionine- enkephalin on normal human blood T lymphocytes. *J Immunol.* **123**:1068-1070.

Yeager MP, Procopio MA, DeLeo JA, Arruda JL, Hildebrandt L, and Howell AL (2002) Intravenous fentanyl increases natural killer cell cytotoxicity and circulating CD16(+) lymphocytes in humans. *Anesth Analg.* **94**:94-9, table.

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

/s/

R. Daniel Mellon
10/15/03 06:03:25 PM
PHARMACOLOGIST

NDA 21-611 (Oxymorphone HCl, IR)
45 DAY MEETING CHECKLIST
(Answer Yes or No to the questions below)

FILEABILITY:

On initial overview of the NDA application: **NDA appears to be fileable.**

PHARMACOLOGY AND TOXICOLOGY:

(1) On its face, is the pharmacology section of the NDA organized in a manner to allow substantive review to begin?

YES

(2) Is the pharmacology section of the NDA indexed and paginated in a manner to allow substantive review to begin?

The NDA was filed to the electronic document room. Review can begin.

(3) On its face, is the pharmacology section of the NDA legible so that substantive review can being?

YES

(4) Are all required (*) and requested IND studies completed and submitted in this NDA (carcinogenicity, mutagenicity, teratogenicity*, effects on fertility*, juvenile studies, acute adult studies*, chronic adult studies*, maximum tolerated dosage determination, dermal irritancy, ocular irritancy, photocarcinogenicity, animal pharmacokinetics studies, etc)?

The Sponsor has provided acute dose tox, repeat dose tox (13-weeks in dogs, rats and mice), reproductive tox studies (segment 1 in rats, segment 2 in rats and rabbits, segment 3 in rats), genetic toxicology studies (full battery), special toxicology studies (dermal sensitization, dermal irritancy, [redacted]). Carcinogenicity has been deferred to phase 4 and are underway.

(5) If the formulation to be marketed is different from the formulation used in the toxicology studies, has the sponsor made an appropriate effort to either repeat the studies using the marketed product or to explain why such repetition should be required?

Formulation is different from that used in the tox studies. However, the excipients in the final drug product are GRAS/certified and have been used in FDA-approved products and thus have been adequately qualified.

(6) Are the proposed labeling sections relative to pharmacology appropriate (including human dose multiples expressed in either mg/m^2 or comparative serum/plasma levels) and in accordance with 201.57?

Described based on AUC...acceptable.

(7) Has the sponsor submitted all special studies/data requested by the Division during Pre-submission discussions with the sponsor?

Yes, we only requested 13-week studies and reproductive toxicology studies in March of 2000. We have granted them Phase 4 for the CA studies, which are underway.

(8) On its face, does the route of administration used in the animal studies appear to be the same as the intended human exposure route? If not, has the sponsor submitted rationale to justify the alternative route?

Route was oral, acceptable.

(9) Has the sponsor submitted a statement(s) that all the pivotal Pharm/Tox studies have been performed in accordance with the GLP regulations (21 CFR 58) or an explanation for any significant deviations?

No, but, pivitol Pharm/Tox studies are GLP.

(10)Has the sponsor submitted a statement(s) that the Pharm/Tox studies have been performed using acceptable, state-of-the-art protocols which also reflect agency animal welfare concerns?

More recent studies were conducted in accordance with current regulatory guidance and GLP. Acceptable.

(11) From a pharmacology perspective, is this NDA fileable? If "no", please state below why it is not.

YES

Reviewing Pharmacology Officer Date

Supervisory Pharmacology Officer Date

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

/s/

R. Daniel Mellon
2/19/03 08:55:28 AM
PHARMACOLOGIST

Timothy McGovern
2/19/03 11:15:11 AM
PHARMACOLOGIST
I concur.