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APPROVAL PACKAGE FOR:

APPLICATION NUMBER

NDA 21-044

Clinical Pharmacology and Biopharmaceutics Review

DEC 2 2 1999

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA 21-044
Submission Date: December 29, 1998; August 26, 1999; September 15 and 30, 1999; October 19, 1999
Drug Name, Dose and Formulation: Palladone — ™ (hydromorphone hydrochloride) Controlled-Release Capsules 12, 16, 24 and 32 mg
Sponsor: Purdue Pharma L.P., 100 Connecticut Ave, Norwalk, CT 06850-3590
Type of Submission: NDA related Response **Reviewer:** Shinja R. Kim, Ph.D.

The topics discussed at a teleconference with the sponsor on October 14, 1999 regarding the dissolution specifications are summarized here.

The sponsor was informed by the agency the recommended dissolution specifications as:

Time (hours)	Lower	Upper
2		
8		

The sponsor was also asked to clarify whether their proposed last time point for dissolution specification was — hours (since both of these were mentioned in different sections of their NDA).

The sponsor agreed with the agency on the dissolution specification at 8 hours. However, they wanted the final dissolution specification of NLT — in 22 hours.

The current sponsor requested dissolution specifications to be as shown in the table below:

Time (hours)	Lower	Upper
2		
8		
22		

Comment: Based on IVIVC analysis, predicted C_{max} will exceed the dissolution specification criteria (i.e., PE would be — compared to the to-be marketed formulation 4L) using the dissolution specifications shown in the table above (same as the 'proposed' lower limit dissolution specification in IVIVC report). However, based on study HD96-1206 the slowest dissolution batch CB25-34B, which meets the sponsor requested dissolution specifications (and is — % dissolution in — hours), was shown to be bioequivalent to the to be marketed and clinical batch 5L. Based on this data, the following dissolution specifications are acceptable:

Time (hours)	Lower	Upper
2		
8		
22		

RECOMMENDATION:

The Office of Clinical Pharmacology and Biopharmaceutics reviewed the submission (October 19, 1999). Please forward above comment to the sponsor.

Shinja R. Kim, Ph.D.
Division of Pharmaceutical Evaluation II

RD/FT 12/3/99 Ramana Uppoor, Ph.D.

cc: NDA (21,044), HFD-170 (Divisional File; FongD, Scheinbaum), HFD-870 (ChenME, Uppoor, Kim), CDR (Barbara Murphy)

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Drug Name, Dose and Formulation: Palladone – (hydromorphone hydrochloride) Controlled-Release Capsules 12, 16, 24 and 32 mg
Sponsor: Purdue Pharma L.P., 100 Connecticut Ave, Norwalk, CT 06850-3590
Type of Submission: New Drug application **Reviewer:** Shinja R. Kim, Ph.D.

SYNOPSIS:

Palladone — capsule contains hydromorphone HCl indicated for the management of moderate to severe pain. The sponsor proposes to market four capsule strengths, 12 mg, 16 mg, 24 mg, and 32 mg, as a controlled release oral formulation for once-daily administration. This is the first controlled release product of hydromorphone that has been proposed for marketing (hydromorphone HCl immediate release tablets are on the market).

To support the development of this product, pharmacokinetics of controlled-release hydromorphone hydrochloride (HHCR) were studied in 17 clinical studies involving approximately 700 volunteers and patients. Clinical trials to demonstrate safety and efficacy compared to immediate release hydromorphone were also conducted. Among these studies, four initial clinical studies were with prototype formulations, which were not chosen for further development and three pilot pharmacokinetic and safety studies using MEMs based formulation, were used to support continued product development. Therefore these seven studies were not reviewed at this time. Subsequent ten clinical studies (seven Phase I, one Phase II and two Phase III studies), which provide the necessary PK information, were conducted using the to-be-marketed formulation, and these are reviewed. In addition, an in vitro-in vivo correlation (IVIVC) study was reviewed.

Since this NDA submission is for change in formulation, from currently marketed Immediate Release to Controlled Release formulation, and consequently administration of dose from 'Q4-6 hr to QD' regimen, the primary focus of the present review was to determine if all of the following conditions are met from a bioavailability perspective.

(1) The drug product meets the controlled release claims made for it.
(2) The bioavailability profile established for the drug product rules out the occurrence of any dose dumping.
(3) Dose proportionality.
(4) The drug product's steady-state performance is equivalent to a currently marketed non-controlled release product.
(5) PK parameters in 'Special Populations' (for labeling purpose).
(6) Establishment of In Vitro-In Vivo Correlation (not a requirement, but an important issue)

The pharmacokinetic studies conducted by the sponsor meet the criteria listed above satisfactorily, therefore this submission supports the approval of the product.

COMMENTS TO THE MEDICAL OFFICER:

- The controlled release hydromorphone (HHCR) capsule has been compared to the immediate release (HHIR) tablet (which is bioequivalent to Dilaudid). HHCR has similar AUC to that of HHIR both after single dose and at steady state. The steady state C_{max} is lower with HHCR than that of HHIR, but C_{min} is higher with HHCR than that of HHIR, and these factors resulted in a lower fluctuation index with HHCR than that of HHIR.

- Food had no effect on the extent of absorption based on AUC, however, food caused a 16.9% increase in C_{max}, shifting t_{max} from 21.06 hour to 8.54 hour. Opening HHCR capsule and sprinkling the contents over apple sauce for oral ingestion, had no effect on the rate or extent of hydromorphone absorption.
- All 4 capsule strengths have the same pellets differing only in the number of pellets per capsule. They have been either shown to be bioequivalent to each other or are considered to be equivalent based on dissolution profiles.

COMMENTS TO THE SPONSOR:

Dissolution method proposed by the sponsor is acceptable. The agency recommends the following dissolution specifications for all four strengths of Palladone — [illegible] capsules:

2 hours: —
8 hours: —
— Not less than —

RECOMMENDATION:

The NDA 21-044 is acceptable from the Clinical Pharmacology and Biopharmaceutics perspective provided the sponsor accepts the above dissolution specifications. Please forward above comment to the sponsor.

Shinja R. Kim, Ph.D.
Division of Pharmaceutical Evaluation II

RD/FT 10/15/99 Ramana Uppoor, Ph.D.

cc: NDA (21,044), HFD-170 (Divisional File; ~~Chamberlin~~ FONG D, Scheinbaum), HFD-850 (Lesko), HFD-870 (ChenME, Uppoor, Kim), CDR (Barbara Murphy)

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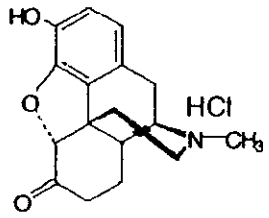
BACKGROUND

Palladone — capsule contains hydromorphone HCl, and the sponsor proposes to market four capsule strengths (12 mg, 16 mg, 24 mg, and 32 mg) as a controlled release oral formulation for once-daily administration. The capsules are indicated in patients requiring a minimum total daily opioid dose equivalent to 12 mg of oral hydromorphone, and the 24 mg and 32 mg capsules are for use only in opioid tolerant patients requiring daily hydromorphone equivalent of 24 mg or greater. The structural formula, molecular description, and molecular weight are shown below:



$C_{17}H_{19}NO_3 \bullet HCl$, MW 321.81
The chemical name is 4,5α-epoxy-3-hydroxy-17 methylmorphinan-6-one hydrochloride

Question 1: What are the characteristics of the to-be-marketed Hydromorphone HCl Controlled Release formulation?

The formulation selected for clinical development was based on the Controlled-Release "Melt Extrusion technology. The — material is Thus, the different strengths supported in this application are Qualitative and quantitative composition of four strengths of hydromorphone HCl controlled release capsules (HHCR) are shown below:

INGREDIENT	FUNCTION	UNIT DOSAGE STRENGTH (MG / CAPSULE)			
Pellets		12 MG	16 MG	24 MG	32 MG
Hydromorphone HCl, USP	Active Ingredient	12.0	16.0	24.0	32.0

Question 2: Does this drug product meet the controlled release claims made for it?

Studies of **HD95-0701, HD95-0702, HD95-0805, HD96-1101. HD96-1206, HD97-0502, HD98-0505** and **HD96-0505** provide the information for this question.

Definition of a controlled/extended release dosage: one that allows at least a twofold reduction in dosing frequency as compared to that drug presented as a conventional dosage form (e.g., immediate release drug product in this case).

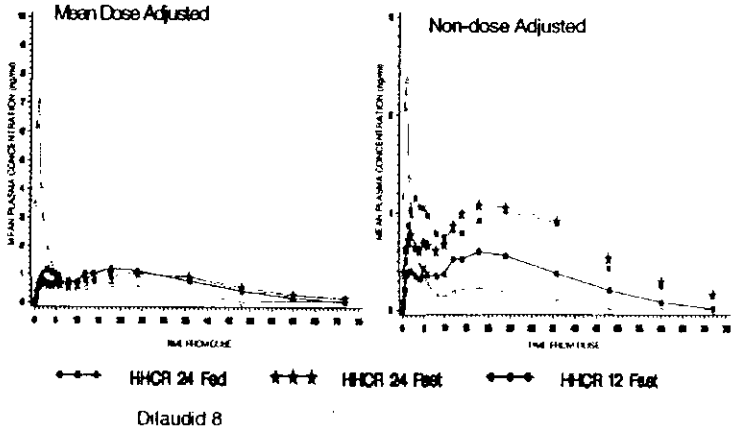
HHCR administration typically resulted in plasma hydromorphone concentrations which attained an initial peak within 2 to 4 hours after dosing, followed by a broad secondary peak which helped to maintain relatively constant values for at least 24 hours after dosing (Figure 1). This sustained peak for the controlled release product is in contrast to the sharper peak observed in the studies with the immediate release product hydromorphone. The mean ± SD values of PK parameters from single dosing studies are shown in Table 1.

Table 1: Summary of PK parameters following a single-dose (dose normalized to 24 mg)

Parameter	HHCR 24 mg
AUC_{0-72} (ng/mL•h)	53.7 ± 5.93
C_{max} (ng/mL)	1.43 ± 0.09
T_{max} (h)	16.95 ± 3.5
$t_{1/2}$ (h)	18.8 ± 3.0
MRT (h)	28.5 ± 2.0

Note: (any) Comparisons made based on AUCs are from time-zero (beginning) to the last sample point, whose time is 72 or 96 hours post dose (*i.e.*, AUC_{0-t}, not $AUC_{0-\infty}$). The reason AUC_{0-t} was used instead of $AUC_{0-\infty}$, per the sponsor is due to the difficulty of obtaining $t_{1/2}$ in most of the subjects and/or concentrations at the last time point were so low, which consequently had clinically insignificant meaning.

Figure 1: Mean plasma hydromorphone concentrations over time following single administration of HHCR 24 mg (fasted or fed), 12 mg fasted or 8 mg Dilaudid (HD95-701)



Characteristics of HHCR can also be described from the steady-state data, study **HD95-702**. The results of this study are shown in Table 2 and Figure 2; (1) Consistent with controlled-release characteristics, HHCR capsules produced a lower $C_{ss,max}$, a longer $t_{ss,max}$, and less % fluctuation. (2)

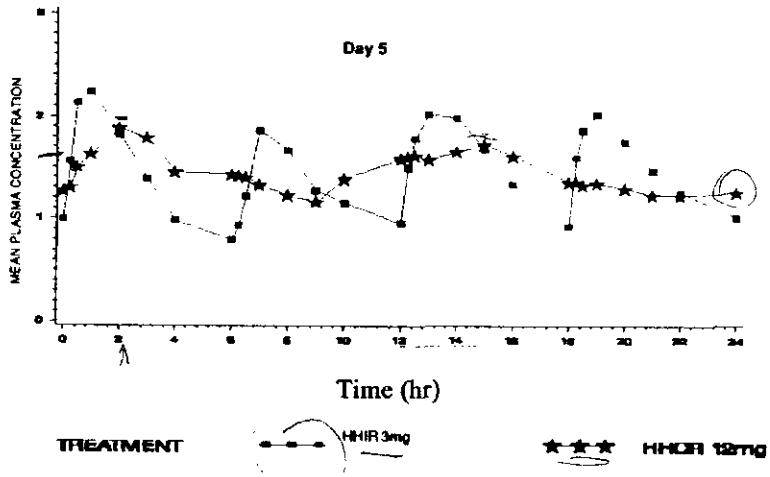
Steady state was achieved within 3 to 4 days for most subjects. (3) Accumulation factor for HHCR was < 2 (based on simulation $C_{t,min}$ using Table 1 PK parameter values and $C_{ss,min}$, Table 2).

Table 2: Mean plasma hydromorphone PK following administration of 12 mg HHCR qd or 3 mg HHIR q6h for 5 Days (HD95-0702).

Metric	Arithmetic mean (SD) HHCR 12 mg Q24h	HHIR 3 mg Q6h	LSM Ratio (%)[a]	90% CI[b]
AUC_{ss}(0-24) (ng/mL•h)	34.86 (10.15)	34.40(8.93)	101.36	96.31-106.40
$C_{ss,max}$ (ng/mL)	2.12 (0.64)	2.89 (0.96)	73.33	64.31-82.34
$C_{ss,min}$ (ng/mL)	0.99 (0.35)	0.70 (0.21)	142.24	130.8-153.68
$C_{t,min}$ (ng/mL)	1.26 (0.41)	0.99 (0.23)		
$t_{ss,max}$ (h)	8.44 (6.34)	0.86 (0.52)		
% Fluctuation	125.8(62.04)	327.9 (124.3)	38.36	26.14-50.58
T_{ss} (d)	3	3		

SD = Standard deviation
[a]Ratio (%) (test/reference) of LSM (ANOVA) derived from Logarithmic-transformed data.
[b]90% confidence interval (CI) around LSM ratio.

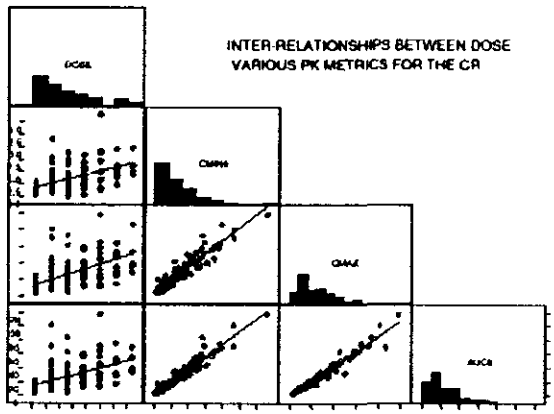
Figure 2: Plasma hydromorphone concentrations following administration of 12 mg HHCR qd or 3 mg HHIR q6h for 5 Days (HD95-0702).



HHCR steady-state pharmacokinetics were also assessed at daily doses ranging from 12 to 84 mg, in the pooled Phase III patient population (HD95-0801 and HD95-0802). In these studies, all patients were first titrated to an effective level of pain control, then randomized to receive equal daily doses of the HHIR or HHCR products. Five blood samples were scheduled to be collected from all subjects while at steady state for up to 6 hours, with an optional sampling at 24 hours. Comparisons between doses were made based on AUC_{0-6}, C_{min6} and C_{max}. A good correlation between these pharmacokinetic parameters, AUC_{0-6}, C_{min6} and C_{max}, with dose was established (Figure 3).

***Note**: Evaluation based on AUC_{0-24} is preferred (more accurate), however, AUC_{0-6} is considered valuable since most volunteers completed the 6 hour portion of the sampling scheme (i.e., most subjects did not have 24 hour blood draws) and C_{max} may not be captured in the first 6 hours (therefore this metric is incomplete). Additionally, steady state plasma concentrations are relatively flat for HHCR, therefore AUC_{0-6} and C_{min6} can serve as indicators for comparison between subgroups.*

Figure 3: Combined Studies H95-0801 and HD95-0802 Relationships Between C_{max}, C_{min6}, AUC_{0-6} and Dose.



Characteristics of HHCR can also be found by evaluating 'bioequivalence (BE)' between formulations and products. The following are **BE** comparisons in particular studies: (1) The single dose 8 mg Dilaudid® product compared to a single dose of the 12 and 24 mg HHCR formulations **(HD95-0701)**; the dose adjusted C_{max} values for the Dilaudid® were 5-6 times higher than that observed for the controlled release product. However, the 12 and 24 mg HHCR formulations also appeared to be 25-34% more bioavailable than the Dilaudid®, based on AUC comparisons (Table 3). (2) A steady-state administration (5 day study) of the 3 mg HHIR product every 6 hours was compared to 12 mg of HHCR administered once daily **(HD95-0702)**; HHCR C_{max} and C_{min} were 73% and 141% of the immediate release product respectively, resulting in lower daily fluctuation for the HHCR generated plasma concentrations. HHCR and HHIR were bioequivalent based on AUC_{ss} (Table 2 and Figure 2). (3) Single dose comparisons of Phase III clinical study Lots CB25-34A and CB25-34B with reference Lot 5L **(HD96-1206)**; clinical study batches were bioequivalent to the reference with AUC and C_{max} differences of less than 5 and 10%, respectively. (4) Assessment of the bioequivalence of internally produced, immediate release hydromorphone hydrochloride (HHIR) to the marketed reference (Dilaudid®) was made to support the HHIR comparisons made in the clinical program **(HD98-0505)**; HHIR produced by Purdue Pharma was bioequivalent to Dilaudid®, with difference in AUC and C_{max} of < 3% between the two products. (5) Although not specifically designed for bioequivalence assessment due to a limited number of subjects, comparisons of C_{max} and AUC could be made for 24 mg HHCR batches with different dissolution profiles studied in the IV/IVC protocol **(HD97-0502)**; bioequivalence was demonstrated for both the faster (CB26-15) and slower (4L-B) dissolving HHCR batches (compared to 4L, reference lot), based on 90% confidence intervals on AUC and C_{max} falling between 80-125%. Slight differences in C_{max} were noted for the very slow dissolving formulation (CB26-16).

Question 3: Does the bioavailability profile established for the drug product rule out the occurrence of any dose dumping?

Impact of food on the performance of the HHCR was assessed in two studies. **HD95-0701** was a standard fed-fast study in subjects administered 24 mg of HHCR with a high-fat breakfast compared to fasted subjects. The results are shown in Table 3 (and Figure 1). Food had no effect on the extent of absorption with a 4% decrease in AUC during the fed period of the study. However, there was a 16.9% increase in C_{max}, about 59% shorter t_{max} (from 21 hour to 8.5 hour), and shifting C_{max} from the secondary peak for the fed group compared to those in fasted group. The second study, **HD96-1101**,

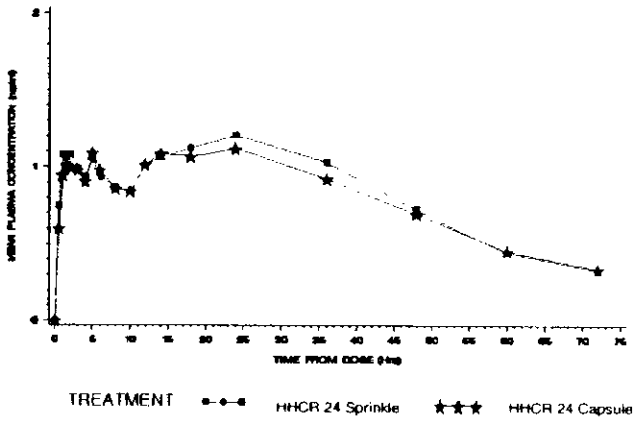
was designed to evaluate the potential for dose dumping of hydromorphone when HHCR was removed from the capsules and sprinkled over soft-food (apple sauce). This study was designed to offer different intake options to the patient population whose physical conditions could make intake of an intact capsule difficult. Opening HHCR capsule and sprinkling the contents over apple sauce for oral ingestion, had no effect on the rate or extent of hydromorphone absorption (Figure 4). AUC and C_{max} values differed by less than 3% between the capsule contents sprinkled on apple sauce and intact capsules.

Table 3: Summary of Pharmacokinetic Data with Statistical Analysis (HD95-701)

Metric	Arithmetic Mean (Standard Deviation)			
	HHCR 24 mg Fed	HHCR 24 mg Fasted	HHCR 12 mg[c] Fasted	Dilaudid® 8 mg[c] Fasted
AUCt (ng/mL•h)	46.38 (12.60)	48.66 (13.95)	43.14 (14.07)	32.26 (12.23)
Cmax (ng/mL)	1.48 (0.49)	1.27 (0.37)	1.50 (0.50)	8.36 (3.68)
Tmax (h)	8.54 (9.95)	21.06 (9.72)	16.06 (9.82)	0.79 (0.29)
1½ (h)	16.82 (7.65)[a]	15.44 (5.19)[a]	16.74 (4.84)[a]	—[b]
MRT (h)	27.20 (3.51)	28.91 (2.98)	24.05 (4.42)	10.82 (4.87)
	LSM Ratio[d] (90% Confidence Interval)[e]			
Test/Reference	Cmax	AUC		
Fed/Fasted 24 mg HHCR	116.9 (106-128)	96.3 (87-106)		
12 mg vs 24 mg HHCR Fasted	119.0 (108-131)	89.5 (81-99)		
HHCR 24 mg vs Dilaudid® Fasted	15.5 (14-17)	155.3 (141-171)		
HHCR12 mg vs Dilauded® Fasted	18.4 (17-20)	139.1 (126-153)		

[a] Evaluable 1½ of HHCR 24 mg fed, HHCR 24 mg fasted, and HHCR 12 mg fasted were 21, 22, and 19, respectively.
[b] Due to limited sample size for this treatment group (N=7), the calculated mean 1½ did not provide clinically meaningful results.
[c] Values for AUCt and Cmax were normalized to a dose of 24 mg.
[d] Ratio(%) (Test mean/Reference mean) of L.S. means (ANOVA) from logarithmic-transformed values of AUCt and Cmax.
[e] 90% confidence interval (CI) of the ratio.

Figure 4: Mean plasma hydromorphone concentrations following administration of intact capsules and capsule contents sprinkled on applesauce (HD96-1101).



Question 4: Is dose proportionality demonstrated?

Dose proportionality was assessed in three different types of studies. The dosage strength bioequivalence of the 12 and 24 mg dosages was assessed in standard single dose crossover study in 24 normal healthy subjects where bioequivalence for the two HHCR capsules strengths was demonstrated based on acceptable 90% confidence intervals for dose adjusted AUC but not for C_{max} (**HD95-0701**;Table 3 and Figure 1). A second study also primarily evaluated dosage form

proportionality (**HD95-0805**). This single dose crossover study, showed that dose adjusted values for 3 x 12 mg HHCR capsules were bioequivalent to a single 32 mg HHCR capsule with dose adjusted mean values for AUC and C_{max} (90% CI were 96.2-106 and 90.6-104, respectively) for the 2 dosage strengths. Dose proportionality for HHCR at steady-state was also assessed in the combined pharmacokinetic results from the Phase III studies (**HD95-0801** and **HD95-0802**). The results, with respect to C_{min} and AUC_{0-6}, are shown in Table 4;

Table 4: Dose Proportionality of HHCR in Phase III Studies HD95-0801 and HD95- 0802 at Steady-State: Pooled Phase III Data (Mean ± SD)

Metric	12 mg	24 mg	36 mg	48 mg	60 mg	72 mg	84 mg
Number of subjects	42	31	20	16	12	9	5
Cmin (ng/mL)	1.33 (0.59)	3.63 (2.67)	3.61 (2.38)	4.09 (2.05)	5.99 (4.26)	5.18 (1.98)	6.40 (2.09)
AUC0-6 (ng*hr/mL)	10.20 (4.26)	26.57 (19.51)	29.20 (19.56)	32.35 (13.54)	46.63 (30.31)	38.34 (17.51)	46.96 (15.09)

A linear relationship was established for AUC_{0-6}, C_{max}, and C_{min} with dose (Figure 3): the linear fit for C_{min} and AUC_{0-6} are 1.07 + 0.07 x dose and 8.14 + 0.529 x dose, respectively with $p < 0.0001$ for both. Strictly speaking, C_{min} or AUC_{0-6} increase less than dose proportionally as dose increased (slopes of these parameters are < 1) in Phase III studies. However, considering the nature of the study conditions (*i.e.*, multi-center, non-controlled Phase III studies), it is difficult to determine the linearity accurately from these Phase III studies. Based on the data from single dose PK studies, it can be concluded that the PK of hydromorphone is dose proportional.

Question 5: Is the drug product's steady-state performance equivalent to a currently marketed noncontrolled release product?

A steady-state administration (5 day study) of the 3 mg HHIR product every 6 hours was compared to 12 mg of HHCR administered once daily (**HD95-0702**); HHCR C_{max} and C_{min} were 73% and 141% of the immediate release product respectively, resulting in lower daily fluctuation for the HHCR generated plasma concentrations. HHCR and HHIR were bioequivalent based on AUC_{ss} (Table 2 and Figure 2).

Study **HD96-0505** was conducted to evaluate the efficacy (and safety) of **single dose** of HHCR (2 x 12 mg) comparing it to HHIR (2 x 3 mg) or placebo in surgical patients with moderate to severe pain. After surgery, patients used PCA fentanyl to titrate pain to a comfortable intensity (with tolerable adverse events). PCA was then discontinued, and when pain became moderate to severe, a single dose of HHCR, HHIR, or placebo was given. PCA fentanyl was used as rescue medication to maintain pain at a comfortable intensity. Analgesic efficacy, plasma hydromorphone concentration, and safety were assessed over a 24-hour post-dose period in this declining pain model. The results of this study are summarized as; (1) The mean total amount of rescue fentanyl used for over 24 hours was 1004.0, 985.8, and 1186.9 μg in the HHCR, HHIR, and placebo groups, respectively. There is no significant difference between treatment groups per statistician in the Agency (sponsor stated that Least-squares-mean comparisons of these values for HHCR and HHIR were each significantly different from placebo but no difference between the HHCR and HHIR groups). (2) The overall pain intensity (0 to 10 scale) was 2.48, 2.76, and 2.69 for the HHCR, HHIR, and placebo treatment groups, respectively and no clinically meaningful differences were observed between treatment groups. (3) No sensible relationships were shown between the plasma hydromorphone concentrations and mean amount of fentanyl (μg) administered (to the patients) or mean current pain intensity. This suggests

that plasma concentrations do not directly represent 'pharmacological responses'. In addition, rescue medication renders demonstration of a PK-PD relationship very complicated. (4) This study failed to show (any) advantages of taking HHCR over HHIR except convenience of dosing. (5) It appears that the effects of hydromorphone (with respect to pain) are minimized by the potent fentanyl administration.

From Phase III studies, **HD95-0801** and **HD95-0802**, the efficacy of HHCR at steady state can be obtained. The results with respect to efficacy are summarized as follows; (1) The mean (least squares mean) of average pain intensity (0-10 scale) over the last 2 days prior to the PK/PD day was 2.54 for the HHCR group and 2.50 for the HHIR group. (2) The mean daily dose of rescue medication ranged from 6.51-9.86 mg and 5.43-11.89 mg for the HHCR and HHIR groups, respectively. The number and % of patients who used rescue medication during the combined double blind periods were 69 of 91 patients (76%) on HHCR and 66 of 91 patients (73%) on HHIR for the efficacy population. The corresponding results for the intent-to-treat population were 78% for HHCR and 74% for HHIR. (3) The number of rescue doses used was similar between the HHCR and HHIR groups (1.38 ± 0.17 and 1.36 ± 0.17, respectively).

Overall, the performance of HHCR appears to be similar to HHIR.

Question 5: What are the PK characteristics of the HHCR in Special populations?

Subsets of patients from the Phase III studies (HD95-0801 and HD95-0802) have provided pharmacokinetic information for several 'special populations'. Since these studies were identical in design, data was pooled across both studies to provide for sufficient numbers of patients in each of the subset populations. The primary pharmacokinetic metrics assessed were C_{min} and AUC_{0-6}. (the reasons for using AUC_{0-6} instead of $AUC_{0-\infty}$, are explained on page 6, 'Note').

Age:

Table 5 and Figure 5 demonstrate pharmacokinetic comparisons at steady state in different age groups. Mean dose normalized pharmacokinetic values show increase in AUC_{0-6}, C_{min} and C_{max} with increasing age. The linear fit of Figure 5, was significant ($p = 0.0014$), and the linear line can be expressed as $AUC_{0-6} = 0.155 + 0.012 \times Age$. The slope, 0.012, is shallow which suggests that difference in age may not be critical. However, the slope might have been steeper if AUC_{0-24} was used instead of AUC_{0-6}.

Figure 5: Age versus Dose-Adjusted AUC (HD95-0801 and HD95-0802).

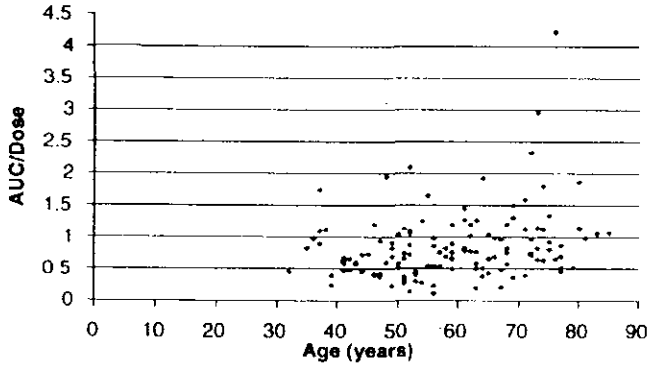


Table 5: Age comparisons at steady state (mean ± SD) in HD95-0801 and HD95-0802

Age	N	AUC0-6/Dose (ng*hr/mL)	Cmin (ng/mL)
20-64 years	89	0.75 (0.40)	0.098 (0.06)
65-74 years	31	0.98 (0.58)	0.12 (0.09)
>75 years	15	1.14 (0.92)	0.16 (0.11)

Gender:

There was no significant gender effect noted when the phase III trial PK data was evaluated based on $AUC_{0\text{-}6}$ and C_{min6} (Table 6). While this conclusion is not confirmatory (since PK assessment metrics were not based on 0-24 hours), absence of gender effect was confirmed from the traditional, single dose studies.

Table 6: HHCR Pharmacokinetics: Gender Comparisons at Steady-State (Mean ± SD)

Gender	N	AUC0-6 (ng*hr/mL)	Cmin (ng/mL)
Male	64	0.76 (0.40)	0.10 (0.06)
Female	71	0.92 (0.64)	0.12 (0.08)

Race:

Significant differences in dose normalized PK parameters were not observed in this patient population (Table 7). However, the numbers of patients in other ethnic groups (*i.e.*, Black, Hispanic and other races) were limited, and therefore comparisons regarding PK parameters between different ethnic groups could not be made conclusively from this study.

Table 7: HHCR Pharmacokinetics in Phase III by Race

Race	N	AUC0-6 (ng*hr/mL)	Cmin (ng/mL)
White	120	0.94 (0.63)	0.11 (0.08)
Black	11	0.78 (0.36)	0.10 (0.05)
Hispanic	3	0.73 (0.28)	0.09 (0.04)
Other	1		

Hepatic Impairment:

The results of regression analysis with respect to hepatic function indices with $AUC_{0\text{-}6}$ are presented in Table 9.

Table 9: Regression analysis: Hepatic function

Parameter	Mean	Max	N	F value	P value	R^2
GGT	107		123	6.05	0.015	0.048
AST	23		132	8.21	0.005	0.059
ALT	25		126	0.38	0.540	0.003
Albumin	3.9		130	4.01	0.047	0.030
Bilirubin	0.06		134	4.08	0.045	0.030

Several of these regressions resulted in statistically significant F values. However, the sponsor concluded that these associations are not clinically meaningful due to low coefficients of determination (e.g., highest value 0.059 for AST). However, whether clinically meaningful or not could not be predicted solely by R^2 values. The sponsor needs to classify these subjects as mild, moderate and severe hepatic impairment and then evaluate if hepatic impairment affects the PK of hydromorphone. Based on the sponsor's response, it is clear that all the patients with hepatic impairment (n=10) had only mild elevations in any two measures of liver disease. No patients with moderate and severe disease were included.

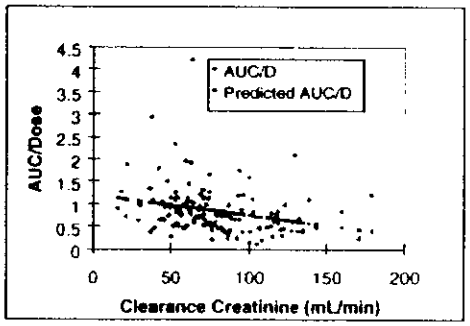
Renal Impairment:

Renal function was classified by the calculated creatinine clearance (using Cockcroft and Gault method). Mean increases of approximately 50% in C_{min} and AUC_{0-6} values were observed from the normal to the moderate groups (Table 8). The relationship between calculated creatinine clearance and AUC_{0-6} is shown graphically in Figure 6. A clear trend of increased AUC with decreased creatinine clearance was observed in the regression analysis; predicted AUC_{0-6} = 1.19 - 0.004 x Clcr, $p = 0.0026$. However, the slope is shallow suggesting that the relationship between renal function and clearance, as expected for this highly metabolized drug, may not be critical for hydromorphone clearance. However, the magnitude of effect of renal impairment found in this study may not be accurate since only AUC_{0-6} was evaluated.

Table 8: Effect of Renal Function on Hydromorphone Pharmacokinetics (mean ± SD) of dose-adjusted metrics)

Creatinine Clearance (mL/min)	N	AUC_{0-6} (ng•hr/mL/mg)	C_{min6} (ng/mL/mg)
Normal (> 80)	54	0.66 (0.40)	0.09 (0.06)
Mild (50-80)	61	0.93 (0.59)	0.12 (0.07)
Moderate (30-49)	15	1.07 (0.65)	0.14 (0.11)
Severe (< 30)	5	1.08 (0.50)	0.16 (0.10)

Figure 6: Dose adjusted AUC and calculated creatinine clearance (Clcr)

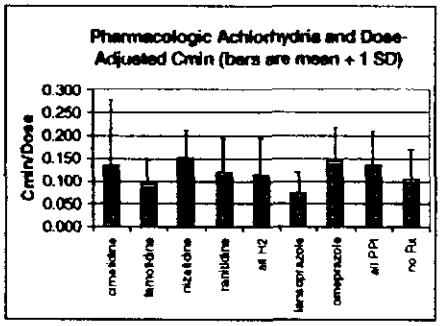


Drug Interactions:

Since hydromorphone is cleared through multiple metabolic pathways (Phase I oxidations and Phase II conjugations), it reduces the likelihood for metabolic based drug interactions with classical cytochrome P450 inhibitors and therefore metabolism-based drug interaction studies have not been

conducted with the HHCR. Instead, the HHCR has been studied (in Phase III trials) for potential interactions with gastrointestinal tract modifying agents, which could potentially modify release rates and drug absorption (e.g., proton pump inhibitors or H_2 blockers). The results with respect to C_{min} are shown in Figure 7; no alterations in the steady-state pharmacokinetic parameters were observed with the multiple agents studied (note: nizatidine and lansoprazole only had 2 subjects for evaluation while cimetidine had 8 subjects, all other co-medications had >15 subjects for evaluation). Similar results were found with AUC_{0-6} (not shown). Additionally, release of hydromorphone from HHCR is pH-independent, and is not influenced by change in motility (as indicated by lack of food effect).

Figure 7: Pooled data from HD95-0801 and HD95-0802



METABOLISM

Since the metabolism of hydromorphone and most opioids is generally understood (6-ketoreduction and conjugation), hydromorphone and its metabolites in human plasma, urine and human hepatocyte incubations from HHCR formulation was compared to HHIR formulation using [ ] technology and where available, reference standards and NMR support. Results indicate that the metabolites identified from both controlled-release and immediate release formulations are the same. Therefore, it can be concluded that the hydromorphone metabolite profile from the HHCR formulation is not different from that generated by the HHIR formulation. Proposed hydromorphone metabolism pathways are shown on page 68.

DISSOLUTION

Release of hydromorphone from HHCR is pH-independent, however depends on chloride content in the dissolution medium. Dissolution is carried out by using USP Apparatus I Basket method at a rotation speed of 100 rpm. The dissolution medium is 900 mL of simulated intestinal fluid without enzymes (SIF) plus — NaCl at 37 ^{0}C. The samples are drawn at 1, 2, 4, 8, 12, 18 and 24 hours, and analyzed by HPLC. The following dissolution specifications are proposed for HHCR products by the sponsor based on IVIVC & BE to a fast release product (details are presented on page 61); — — (2 hours); — (8 hours); — (22 hours). However, the agency recommends the dissolution specifications as — (at 2 hours); — (at 8 hours); not less than (NLT) — (at — hours), based on IVIVC and the dissolution data.

IN VITRO-IN VIVO CORRELATION (IVIVC)

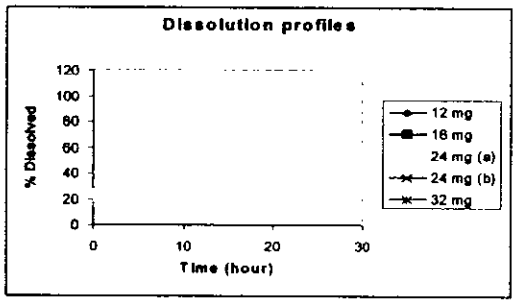
Modeling of the dissolution (Hixson-Crowell model) and pooled plasma concentration data (one-compartment model with no lag time) was used to develop the overall IVIVC model using 3 release rate formulations. The sponsor's internal and external predictability testing of the IVIVC model was

acceptable with prediction errors of — It appears that a Level A correlation was established. Since the fastest release rate used in IVIVC development is the to-be marketed product, in future, if a major change is made to the HHCR product that requires a biostudy, IVIVC can be used to grant biowaiver only when the release rates are lower than the to-be marketed product. However, since bioequivalence has been shown between CB26-15 and —, it is possible to grant waivers within the dissolution range of CB26-15 and IVIVC (at 2 hrs: — at 8 hrs: — . and at — hrs NLT —).

WAIVER OF 16 MG STRENGTH

Bioequivalence was established on HHCR product for, 2 x 12 mg *vs.* 24 mg and 3 x 12 mg *vs.* 32 mg capsules. Sixteen-mg capsule form was not evaluated in *in vivo* studies, however, the only difference in capsule contents among the four strengths is incremental weights of common pellets. Thus, as expected, dissolution profile for 16-mg strength was similar to other strengths (Figure 9). In addition, f_2 factor between 16 mg and 24 mg (Lot tested on 7/14/97) is calculated to be 72.2, therefore, it can be said that dissolution profiles of these two are similar (and two strengths are considered bioequivalent). Therefore a biowaiver for the 16-mg strength can be granted. Note: Dissolution of HHCR is pH independent, therefore, comparison of this profile in one dissolution medium is sufficient.

Figure 9: Dissolution profiles for 4 different strengths



ANALYTICAL METHODOLOGY

Determination of hydromorphone in plasma samples from the pharmacokinetic studies was carried out by [ ] With the — assay, the intra-batch coefficient of variation (%CV) and accuracy (%RE) ranged from [ ] and [ ] The inter-batch CV and RE ranged from [ ] Absolute recoveries of hydromorphone ranged from [ ] At the lower limit of quantitation (LLOQ) of — ng/mL, accuracy was — with precision of — For the [ ] method, inter and intra-batch precision and accuracy was within — of nominal values. At the LOQ of — ng/mL, intra-batch and inter-batch accuracy and precision was within — of normal values. Cross-validation of this assay with the — assay at — was also demonstrated.

CONCLUSIONS

- Following HHCR administration, the plasma hydromorphone concentrations attained an initial peak within 2 to 4 hours after dosing, followed by a broad secondary peak and maintained

relatively constant values for at least 24 hours after dosing.

- Following single dose normalized to 24 mg HHCR dose, AUC_{0-72}, C_{max}, T_{max}, $t_{1/2}$ and MRT were 53.7 ± 6 ng/ml•h, 1.43 ± 0.08 ng/ml, 16.95 ± 3.5, 18.8 ± 3.0, 28.5 ± 2.0 hours, respectively.
- Food had no effect on the extent of absorption based on AUC (4% lower during the fed period); however, food caused a 16.9% increase in C_{max}, shifting t_{max} from 21.06 hour to 8.54 hour. Opening HHCR capsule and sprinkling the contents over apple sauce for oral ingestion, had no effect on the rate or extent of hydromorphone absorption (AUC and C_{max} values differed by less than 3% between the capsule contents sprinkled on apple sauce and intact capsules).
- HHIR produced by Purdue Pharma was bioequivalent to Dilaudid®.
- Following multiple dose HHCR capsules produced a lower $C_{ss,max}$, a longer $t_{ss,max}$, and less % fluctuation compared to HHIR. Steady state was achieved within three days for most subjects. Accumulation factor for HHCR was low (< 2). HHCR was bioequivalent to HHIR at steady state, based on AUC_{0-24}. $C_{ss,min}$ for HHCR product was about 40% higher than HHIR (at steady state) when administered as same total daily hydromorphone dose.
- 12 and 24 mg HHCR formulations after a single dose were dose proportional with respect to AUC and C_{max}. Similarly, dose adjusted values for 3 x 12 mg HHCR capsules were bioequivalent to a single 32 mg HHCR capsule with dose adjusted mean values for AUC and C_{max}. However, based on Phase III studies, dose proportionality data for HHCR at steady-state show that C_{min} and AUC_{0-6} increased less than proportionally as dose increased.
- Increase in AUC_{0-6}, C_{min} and C_{max} with increasing age were observed based on mean dose normalized pharmacokinetic values. There were no significant PK differences in different gender. From the Phase III studies, there appears to be an increase in AUC_{0-6} as hepatic or renal function decreased.
- Drug interaction study with gastrointestinal tract modifying agents (e.g., proton pump inhibitors or H_2 blockers) showed no alterations in the steady-state pharmacokinetic parameters (i.e., C_{min} and AUC_{0-6}).
- A biowaiver for the 16-mg strength formulation can be granted based on comparative dissolution data.
- Level A IVIVC has been established by the sponsor.

PROPOSED PACKAGE INSERT

Note: Strikeouts and underlined text indicate this reviewer's suggested deletions and additions respectively.

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5 Page(s) Withheld

_____ § 552(b)(4) Trade Secret / Confidential

_____ § 552(b)(5) Deliberative Process

✓ § 552(b)(5) Draft Labeling

APPENDIX

HD95-0701: A Single-Dose, Four-Way, Randomized, Crossover, Analytically Blinded Pharmacokinetic/Pharmacodynamic Comparison Study of Hydromorphone Hydrochloride Controlled-Release Capsules (HHCR); One 24 mg Capsule (Fed/Fasted), Two 12 mg Capsules (Fasted), and One Dilaudid 8 mg Tablet (Fasted) in Normal Volunteers.

Reference: Volume 22 – 23
Investigators: [ ]
Study Location: [ ] (Clinical)
Purdue Research Center Laboratory, Yonkers, NY 10701 (Analytical)

Formulation: batch size was — ʒ (this yields — capsules)

Dosage Form	Strength	Lot #
HHCR Capsule	24 mg	CB25-34
HHCR Capsule	12 mg	CB25-33
Dilaudid® Tablet	8 mg	11200054

Objective: To assess the effect of food on the pharmacokinetic/pharmacodynamic profile of HHCR 24 mg; to evaluate the dose-proportionality of HHCR 12 mg and HHCR 24 mg; and to evaluate the bioavailability of HHCR 12 mg and 24 mg relative to Dilaudid 8 mg.

Study Design: This was an open-label, analytically blinded, single-dose, four-treatment, randomized and crossover study in 24 normal, healthy, male volunteers (mean age = 29.4 years; range 21-43), with a washout period of 7 days. Four treatment sequences include HHCR 24 mg capsules in fed and fasted subjects, HHCR 12 mg capsules and Dilaudid 8 mg tablets in fasted subjects. Subjects to be fed received the high fat meal just prior (within 30 minutes) to dosing. This meal consisted of: 2 eggs fried in butter, 2 slices of buttered toast, 4 ounces of hash brown potatoes fried in butter, 2 strips of bacon and 8 ounces of whole milk.

Criteria for Evaluation:
Pharmacokinetics: Area under the curve to the last quantifiable plasma concentration [AUC_t], maximum plasma concentration [C_{max}], time to maximum plasma concentration [t_{max}], apparent terminal half-life [$t_{½}$], and mean residence time [MRT].
Pharmacodynamics: Subject "drug effect".
Safety: Clinical laboratory tests, vital signs monitoring, physical examinations, electrocardiograms, and reports of adverse events.

Analytical Methodology:
Plasma Sampling Times: pre-dose (0 hour), 0.25, 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 10, 12, 14, 18, 24, 36, 48, 60, and 72 hours after dosing.
Assay Method: —
Assay Sensitivity: The limit of quantitation was — ng/mL with linear range of — to — ng/mL.
Assay Precision/Accuracy: The inter-day values %CV (& %RE) of hydromorphone QC samples for low (— ng/mL), mid (— ng/mL) and high (— ng/mL) were [ ] and [ ] respectively.

Statistical methods: Bioequivalence, food-effect, and dose-proportionality were assessed by comparison of C_{max} and AUC_t (test *vs* reference or fed *vs* fasted) using analysis of variance (ANOVA)

with the appropriate model. Confidence intervals (90%) were estimated around ratios (test/reference) (fed/fasted) of least squares means derived from logarithmic-transformed values of AUC_t and C_{max}.

Results:

The mean plasma concentration-time profiles (dose-adjusted to 24 mg) and the mean "drug effect" over time after each treatment dosing are shown in Figures 1-2, respectively. Summary of PK metrics with statistical analysis is presented in Table 1.

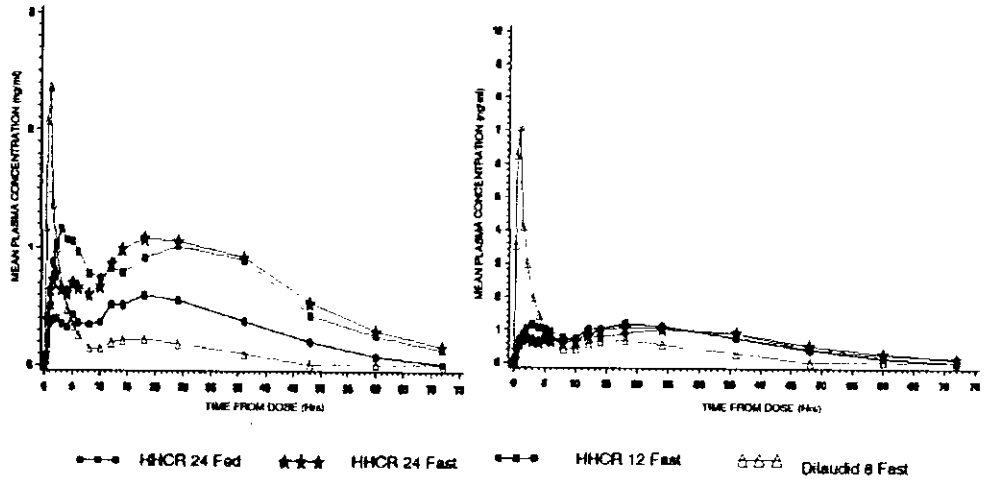


Figure 1: Mean hydromorphone plasma concentrations over time (left panel) and mean dose adjusted hydromorphone plasma concentrations over time (right panel) following single administration of HHCR 24 mg (fasted or fed), 12 mg fasted or 8 mg Dilaudid (N = 24)

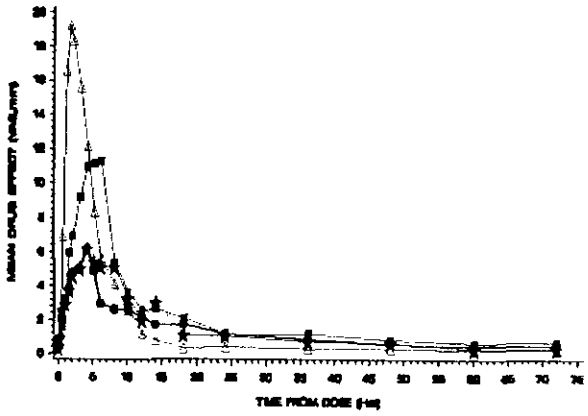


Figure 2: Mean "drug effect" over time, determined by subject response to "Do You Feel any Effect of The Drug?' on a 100 mm Visual Analog Scale from 0=Not At All to 100=An Awful Lot (N = 24). Symbols are the same as Figure 1.

Table 1: Summary of Pharmacokinetic Data with Statistical Analysis

Parameter	A HH 24 mg Fed	B HH 24 mg Fasted	C HH 12 mg Fasted[c]	D Dilaudid 8 mg Fasted[c]		LSM Ratio (%)[d]	90% CI[e]
AUC_t (ng/mL•h)	46.4±12.6	48.66±14	43.1±14.1	32.26±12.23	A *vs* B	96.29	87.38-106.12
					B *vs* C	89.53	81.24-98.67
					B *vs* D	155.31	140.9-171.15
					C *vs* D	139.05	126.2-153.24
C_{max} (ng/mL)	1.48±0.49	1.27±0.37	1.5 ± 0.5	8.36 ± 3.68	A *vs* B	116.91	106.4-128.5
					B *vs* C	119.02	108.3-130.8
					B *vs* D	15.47	14.08-17.01
					C *vs* D	18.42	16.76-20.24
T_{max} (h)	8.54±9.95	21.1±9.72	16.06±9.8	0.79 ± 0.29		NA	NA
$t_{1/2}$ (h)[a]	16.8±7.7[a]	15.4±5.2[a]	16.74±4.8[a]	-[b]		NA	NA
MRT (h)	27.2±3.5	28.9±2.98	24.05±4.4	10.82 ± 4.87		NA	NA

[a]Evaluable subjects for t½ of HHCR 24 mg fed, HHCR 24 mg fasted, and HHCR 12 mg fasted were 21, 22, and 19, respectively.
[b]Due to limited sample size for this treatment group (N=7), the calculated mean t½ did not provide clinically meaningful results.
[c]Values for AUC_t and C_{max} were normalized to a dose of 24 mg.
[d]Ratio(%) (Test mean/Reference mean) of least square means (ANOVA) derived from logarithmic-transformed ·lues of AUC_t and C_{max}.
[e] % confidence interval (CI) of the ratio

Conclusions:

- Plasma concentration-time profiles show relatively rapid increases to initial early peak followed by a second broader peak with plateau concentrations being maintained beyond 24 hours.
- No food effect is shown with respect to AUC_t for the HHCR 24 mg capsule formulation. However, food caused 16.9% increase in C_{max} and a substantially shorter t_{max} than that observed under fasted conditions.
- HHCR 12 and 24 mg capsule dosage forms were equivalent with respect to AUC_t, but not equivalent with respect to C_{max} (based on 90% confidence intervals).
- Under fasted conditions, AUC_t values for HHCR 24 and 12 mg capsules were greater than the AUC_t for Dilaudid 8 mg (55% and 39% for HHCR 24 and 12 mg, respectively).
- Under fasted conditions, the dose adjusted mean C_{max} values of the HHCR 24 mg (1.27 ng/mL) and 12 mg capsules (1.50 ng/mL) were lower than the C_{max} of Dilaudid 8 mg tablets (8.36 ng/mL).
- Under fasted conditions, mean t_{max} values of the HHCR 24 (21.1 hours) and 12 mg capsule (16.1 hours) were considerably longer than the t_{max} of the Dilaudid 8 mg tablet (0.8 hours).
- MRT values do not appear to be statistically different between HHCR 24 and 12 mg (fasted or fed) capsule formulations.
- The sponsor stated that the majority of the subjects had either no response or too small a response (to permit statistical analysis).

HD96-1101: A Single Dose, Randomized, Crossover, Relative Bioavailability Study of one Hydromorphone Hydrochloride Controlled-Release 24 mg Capsule Administered in the Fasted State Compared to one Hydromorphone Hydrochloride Controlled-Release 24 mg Capsule Contents Administered with Soft Palatable Food in Normal, Healthy Adult Volunteers.

Reference: Volume 26
Investigators: [ ]
Study Location: [ ]
Purdue Research Center Laboratory, Yonkers, NY 10701 (Analytical)

Formulation:

Dosage Form	Dose	Lot #
HHCR Capsule (sprinkle)	24 mg	5L
HHCR Capsule (intact)	24 mg	5L

Objective:

To compare the bioavailability of an unopened hydromorphone hydrochloride controlled-release (HHCR) 24 mg capsule administered intact without food with that of the contents of an HHCR 24 mg capsule sprinkled on soft, palatable food.

Study Design:

This was a single-dose, randomized, two-way crossover, analytically blinded study, conducted in 26 healthy subjects (15 males and 11 females). Treatments were unopened hydromorphone hydrochloride controlled-release (HHCR) 24 mg capsule administered whole without food and contents of an opened HHCR 24 mg capsule sprinkled on soft, palatable food.

Criteria for Pharmacokinetic Evaluation:

Area under the curve to the last quantifiable maximum plasma concentration (AUC_t), maximum plasma concentration (C_{max}), time to maximum plasma concentration (t_{max}), apparent terminal half-life ($t_{½}$), and mean residence time (MRT).

Analytical Methodology:
Plasma Sampling Times: pre-dose (0 hour), 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 10, 12, 14, 18, 24, 36, 48, 60, and 72 hours post dosing.
Assay Method: [ ]
Assay Sensitivity: The limit of quantitation was [ ] ng/mL with linear range of [ ] ng/mL.
Assay Precision/Accuracy: The quality control sample precision and accuracy ranged from [ ] to [ ] respectively.

Statistical methods:

Bioequivalence was assessed by comparison of C_{max} and AUC_t values between test treatment to the reference treatment by analysis of variance (ANOVA) using the appropriate model for this study design. Confidence intervals, 90%, were estimated around ratios (test/reference) of least squares

means derived from logarithmic-transformed values of C_{max} and AUC_t using two one-sided tests. Other metrics were reported as mean and standard deviation.

Results:

The mean hydromorphone concentration-time profile following each treatment is shown in Figure 1. Summary of PK metrics with statistical analysis is presented in Tables 1-2.

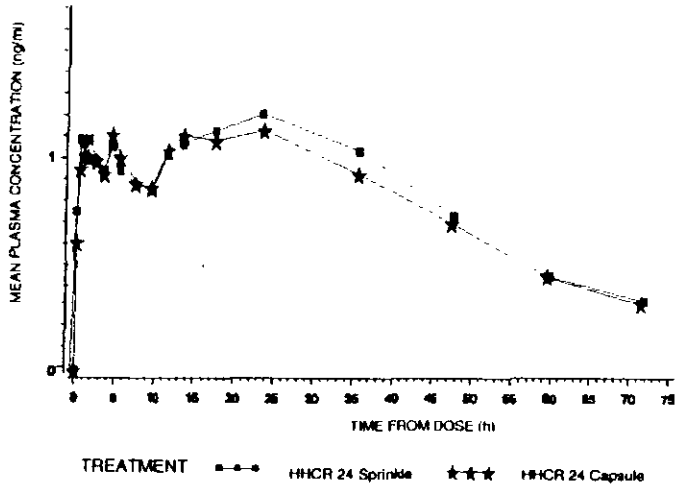


Figure 1: MEAN hydromorphone Concentrations over 72 hours Following Administration of 24 mg HHCR sprinkle and HHCR capsule.

Table 1: Summary of Pharmacokinetic Metrics (Arithmetic Means and Standard Deviations)

	Arithmetic Mean (SD)			90% CI[b]	
Metric	HHCR 24 mg Sprinkle	HHCR 24 mg Capsule	LSM Ratio (%)[a]	Lower	Upper
AUCt (ng/mL h)					
Males(N=14)	56.21(16.15)	51.90 (14.58)	108.30	103.27	112.02
Females (N=10)	65.90 (12.15)	65.52 (12.28)	100.58	96.45	106.38
Cmax (ng/mL)					
Males(N=14)	1.39 (0.37)	1.32 (0.36)	105.18	93.42	114.90
Females (N=10)	1.53 (0.35)	1.52 (0.37)	100.79	96.78	116.45
tmax (h)					
Males(N=14)	13.25 (9.01)	13.57 (12.05)			
Females (N=10)	12.80 (15.25)	13.50 (12.65)			
t1/2 (h)					
Males(N=12)	19.71(5.62)	23.41 (6.33)			
Females (N=9)	22.47(6.35)	25.23 (11.57)			
MRT (h)					
Males(N=14)	29.36 (1.61)	29.10 (2.61)			
Females (N=10)	30.60 (2.12)	31.15 (2.00)			

[a] Ratio (%) (test/reference) of least squares means (ANOVA) derived from logarithmic-transformed values f AUC_t and C_{max}.
[b] 90% confidence interval (CI) around the least squares mean ratio.

Table 2: Summary of AUC_t and C_{max} Means and Confidence Intervals (N=24)

	Arithmetic Mean (SD)				
				90% CI[c]	
Metric	HHCR 24 mg Sprinkle	HHCR 24 mg Capsule	LSM Ratio (%)[a]	Lower	Upper
AUCt (ng/mL·h)	60.25 (15.13)	57.58 (15.04)	104.64	102.21	106.13
Cmax (ng/mL)	1.45 (0.36)	1.41 (0.37)	103.20	97.39	110.67

(Cross-reference: Table 14.4.33 and Appendix 16.1.9 and 16.2.5.1)
SD = Standard deviation.
[a]: Ratio (%) (test/reference) of least squares means (ANOVA) derived from logarithmic-transformed values of AUCt and Cmax.
[c]: 90% confidence interval (CI) around the least squares mean ratio.

Conclusions:

- Comparisons of AUC_t and C_{max} indicated that HHCR administered as a sprinkle and as a capsule were bioequivalent.
- The mean t_{max} and MRT for HHCR administered as a sprinkle and capsule were 13.06 and 13.54 hours and 20.89 and 24.19 hours, respectively (providing further evidence of bioequivalence).
- No gender differences in AUC_t or C_{max} were detected between HHCR sprinkle and capsule. Additionally, the results indicated bioequivalence of the two formulations in both genders with respect to AUC_t and C_{max}.

HD95-0805: A Single Dose, Randomized, Two-Period, Crossover Bioequivalency Study Comparing One Hydromorphone Hydrochloride Controlled-Release Capsule 32 mg and Three Hydromorphone Hydrochloride Controlled-Release Capsules 12 mg, Each Given with Naltrexone under Fasting Conditions in Normal, Healthy Volunteers.

Reference: Volume 24 – 25
Investigators: [redacted]
Study Location: [redacted] (Clinical)
Purdue Research Center Laboratory, Yonkers, NY 10701 (Analytical)

Formulation:

Dosage Form	Dose	Lot #
HHCR Capsule	32 mg	8L
HHCR Capsule	3 x 12 mg	9K
Revia™ Tablet	2 x 50 mg	KCO78A
Narcan® injection vial	0.8 mg	MH0676A2

Objective:

To assess the bioequivalence of hydromorphone hydrochloride (HHCR) 1 x 32 mg and HHCR 3 x 12 mg under fasting conditions in normal, healthy volunteers.

Study Design:

Single-dose, randomized, two-way crossover, open-label, analytically blinded study in normal volunteers (22 male and 4 female). There was a 7-day washout period between treatments. To minimize adverse effects, naltrexone (100 mg) was given 24 hours before, at the time of, and 24, 48, and 72 hours after administration of HHCR. Naloxone (0.8 mg) was administered intravenously to each subject to test for signs or symptoms of opioid withdrawal before the naltrexone dose.

Criteria for Evaluation:
Pharmacokinetic: Area under the curve to the last quantifiable concentration (AUC_t), maximum plasma concentration (C_{max}), time to maximum plasma concentration (t_{max}), apparent terminal half-life ($t_{½}$), and mean residence time (MRT).
Safety: Clinical laboratory tests, vital signs monitoring, physical examinations, electrocardiograms, and reports of adverse events.

Analytical Methodology:
Plasma Sampling Times: pre-dose (0 hour), 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 10, 12, 14, 18, 24, 36, 48, 60, 72 and 96 hours after dosing.
Assay Method: [redacted]
Assay Sensitivity: The limit of quantitation was [redacted] ng/ml with linear range of [redacted] ng/ml.
Assay Precision/Accuracy: The quality control sample precision and accuracy ranged from [redacted] and [redacted] respectively.

Statistical methods:

Bioequivalence was assessed by comparison of C_{max} and AUC_t values from test treatment to the reference treatment by analysis of variance (ANOVA) using the appropriate model (including sequence, subject within sequence, period and treatment as factors). 90% confidence intervals were estimated around ratios (test/reference) of least squares means derived from logarithmic-transformed values of C_{max} and AUC_t. Other metrics were reported as mean and standard deviation.

Results:

The mean hydromorphone plasma concentration-time profile following each treatment (dose adjusted to 32 mg) is presented in Figure 1. Summary of PK metrics with statistical analysis is listed in Table 1.

Figure 1

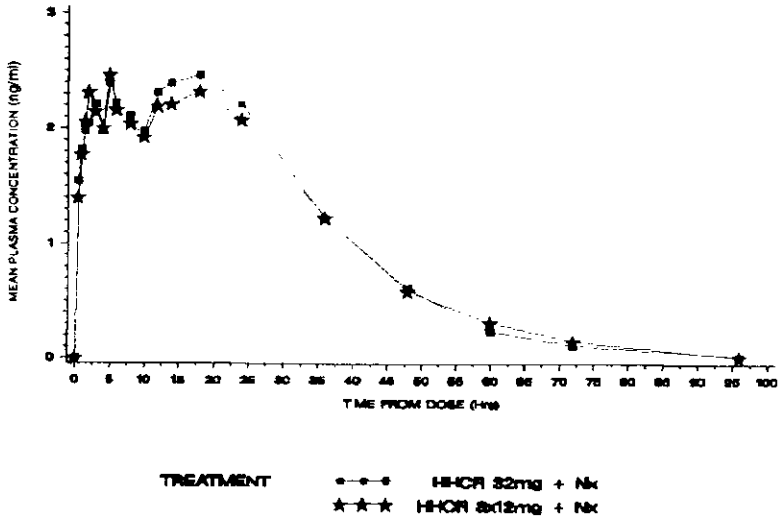


Table 1: Summary of Pharmacokinetic Metrics (Arithmetic Means and Standard Deviations)

Parameter	HHCR 32 mg + Nx[a]	HHCR 3 x 12 mg + Nx[a]	LSM Ratio(%)[b]	90% CI[c]
AUC_t (ng/mL•h)	91.65 ± 29.35	90.51 ± 31.45	101.26	96.19-105.98
C_{max} (ng/mL)	3.05 ± 0.88	3.13 ± 1.12	97.57	90.61-103.93
T_{max} (h)	11.56 ± 7.11	10.5 ± 7.83		
$t_{1/2}$ (h)[d]	11.71 ± 4.95	12.44 ± 5.34		
MRT (h)	21.86 ± 5.11	22.57 ± 4.86		

NOTE: Concentrations were dose adjusted to 32 mg (only AUC and Cmax are affected).
[a]Nx = naltrexone.
[b]Ratio (%) (test/reference) of least squares means (ANOVA) derived from logarithmic-transformed values of AUCt and Cmax.
[c]90% confidence interval (CI) around the least squares mean ratio.
[d]Evaluable subjects for $t_{1/2}$ of HHCR 32 mg & Nx and 3 x 12 mg & Nx were 23 and 25 respectively.

Conclusions:

- Plasma concentration-time curves show relatively rapid increase to initial peak concentrations, each followed by a second broader peak (C_{max}). Plateau concentrations were maintained beyond 24 hours (Figure 1).
- Comparisons of HHCR 32-mg and HHCR 3 x 12-mg capsules data indicated that the two formulations were bioequivalent with respect to mean AUC_t (CI, 96-106%) and C_{max} (CI, 91-104%).
- The mean apparent terminal half-life of HHCR 32-mg capsules was 11.71 hours compared with 12.44 hours for HHCR 3 x 12-mg capsules.
- Controlled-release characteristics extended the plasma concentration-time course profiles and produced relatively long MRT values for each treatment. Similarities of MRT values from test and reference treatments (21.86 and 22.57 hours, respectively) provided further evidence of bioequivalence.
- The effect of concomitant administration of naltrexone with hydromorphone in terms of hydromorphone concentration is not discussed. However, this should not affect the assessment of bioequivalence between the two products (*i.e.*, 32 mg versus 3 x 12 mg).

HD96-1206: A Single Dose, Three-Way, Randomized, Crossover, Analytically Blinded Pharmacokinetic Study to Compare Hydromorphone HCl Controlled-Release 24 mg Capsule used in Phase III study to the commercial scale product in Fasted Normal Volunteers.

Reference: Volume 27
Investigators: [redacted]
Study Center: [redacted]
Purdue Research Center Laboratory, Yonkers, NY 10701 (Analytical)

Formulation:

Dosage Form	Dose	Lot #
HHCR Capsule	24 mg	CB25-34A
HHCR Capsule	24 mg	CB25-34B
HHCR Capsule	24 mg	5L

Objective:

To assess the bioequivalence of HHCR 24 mg Phase III clinical study Lots CB25-34A and CB25-34B using HHCR 24 mg Lot 5L, a primary stability batch manufactured at full commercial scale, as the reference treatment.

Study Design:

This was a single-dose, randomized, 3-way crossover, analytically blinded study with a 7-day washout period between each dosing. This study was conducted in 23 healthy male subjects.

Criteria for Evaluation:
Pharmacokinetic: Area under the curve to the last quantifiable maximum plasma concentration (AUC_t), maximum plasma concentration (C_{max}), time to maximum plasma concentration (t_{max}), apparent terminal half-life ($t_{½}$), and mean residence time (MRT).
Safety: Clinical laboratory tests, vital signs monitoring, physical examinations, electrocardiograms, and reports of adverse events.

Analytical Methodology:
Plasma Sampling Times: pre-dose (0 hour), 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 10, 12, 14, 18, 24, 36, 48, 60, and 72 hours after dosing.
Assay Method: [redacted]
Assay Sensitivity: The limit of quantitation was [redacted] ng/mL with linear range of [redacted] ng/mL.
Assay Precision/Accuracy: Quality control sample precision and accuracy ranged from [redacted] and [redacted] respectively.

Statistical methods:

Bioequivalence was assessed by comparison of C_{max} and AUC_t values from test treatment to the reference treatment by analysis of variance (ANOVA) using the appropriate model. Confidence intervals, 90%, were estimated around ratios (test/reference) of least squares means derived from

logarithmic-transformed values of C_{max} and AUC_t. Other metrics were reported as mean and standard deviation.

Results: The mean hydromorphone concentration-time profiles following each treatment is shown in Figure 1. Summary of PK metrics with statistical analysis is presented in Table 1.

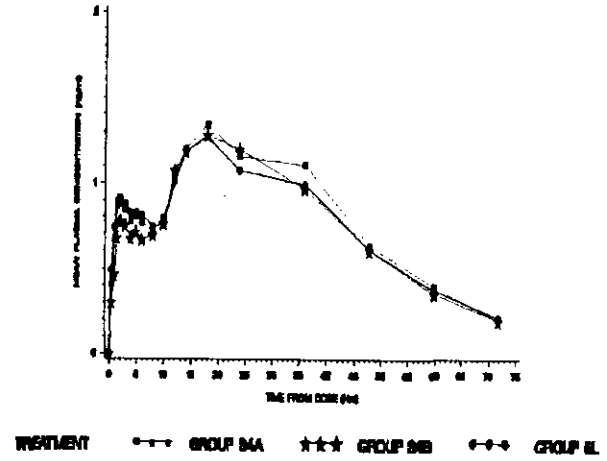


Figure 1: Mean hydromorphone concentrations following each treatment.

Table 1: Summary of Pharmacokinetic Metrics (Arithmetic Means and Standard Deviations)

Metric	CB25-34A	5L	LSM Ratio(%)[a]	90% CI[b]
AUC_t (ng/mL•h)	57.44 ± 15.07	54.84 ± 12.79	103.52	94.28-113.67
C_{max} (ng/mL)	1.54 ± 0.43	1.40 ± 0.32	107.89	97.24-119.72
T_{max} (h)	21.39 ± 8.6	15.41 ± 5.41		
$t_{1/2}$ (h)	17.59 ± 10.9	19.42 ± 9.79		
MRT	28.98 3.06	28.94 ± 2.6		
	CB25-34B	5L		
AUC_t (ng/mL•h)	54.06 ± 14.21	54.84 ± 12.79	97.0	88.34-106.51
C_{max} (ng/mL)	1.45 ± 0.39	1.40 ± 0.32	101.93	91.86-113.10
T_{max} (h)	19.35 ± 7.57	15.41 ± 5.41		
$t_{1/2}$ (h)	17.68 ± 6.78	19.42 ± 9.79		
MRT	28.90 ± 3.39	28.94 ± 2.6		

[a]Ratio (%) (test/reference) of least squares means (ANOVA) derived from logarithmic-transformed values of AUCt and Cmax. [b]90% confidence interval (CI) around the least squares mean ratio.

Conclusions:

- Plasma hydromorphone concentration-time profiles from three product Lots were similar.
- Comparisons of primary metrics indicated that test Lots 34A and 34B were bioequivalent to reference Lot 5L based on AUC_t and C_{max}.
- Lots 34A and 34B had longer mean t_{max} values (21.39 and 19.35 hours, respectively) than Lot 5L (15.41 hours).
- Apparent terminal half-lives of 34A, 34B and 5L were 17.59, 17.68, and 19.42 hours, respectively.

HD98-0505: A Phase I, Single Dose, Crossover Study to Evaluate the Comparative Bioavailability of Immediate-Release Hydromorphone and Dilaudid®.

Reference: Volume 31
Investigators: [ ]
Study Location: [
] (Clinical)
Purdue Research Center Laboratory, Yonkers, NY 10701 (Analytical)

Formulation:

Dosage Form	Dose	Lot #
HHIR Tablet	3 x 2 mg	CB25-38
Dilaudid® Tablet	3 x 2 mg	11100028

Objective:

To assess the relative bioavailability of immediate-release hydromorphone (HHIR) 3 x 2 mg tablets, manufactured by Purdue Pharma L.P., and commercially available hydromorphone (Dilaudid®) 3 x 2 mg tablets, when each is given orally as a single dose.

Study Design:

Single-dose, randomized, two-way crossover, analytically blinded study in 36 healthy male volunteers. There was a 7-day washout period between periods.

Criteria for Evaluation:
Pharmacokinetic: Area under the plasma concentration-time curve to the last quantifiable value (AUC_t); area under the plasma concentration-time profile from time = 0 (dosing) to infinity (AUC_{inf}); maximum plasma concentration (C_{max}), time to maximum plasma concentration (t_{max}), apparent terminal half-life ($t_{½}$), and mean residence time (MRT).
Safety: Clinical laboratory tests, vital signs monitoring, physical examinations, electrocardiograms, and reports of adverse events.

Analytical Methodology:
Plasma Sampling Times: pre-dose (0 hour), 0.25, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8, 10, 12, 18, and 24 hours after dosing.
Assay Method: [ ]
Assay Sensitivity: The limit of detection was — ng/ml with linear range of — ng/ml.
Assay Precision/Accuracy: The quality control sample precision and accuracy ranged from [ ] and [ ], respectively.

Statistical methods:

Bioequivalence was assessed by comparison of C_{max} and AUC_t values from test treatment to the reference treatment by analysis of variance (ANOVA) using the appropriate model. 90% confidence intervals were estimated around ratios (test/reference) of least squares means derived from logarithmic-transformed values of C_{max} and AUC_t. Other metrics were reported as mean and standard deviation.

Results: Mean hydromorphone plasma concentration-time profiles following each treatment are presented in Figure 1. Summary of PK metrics with statistical analysis is listed in Table 1.

Figure 1

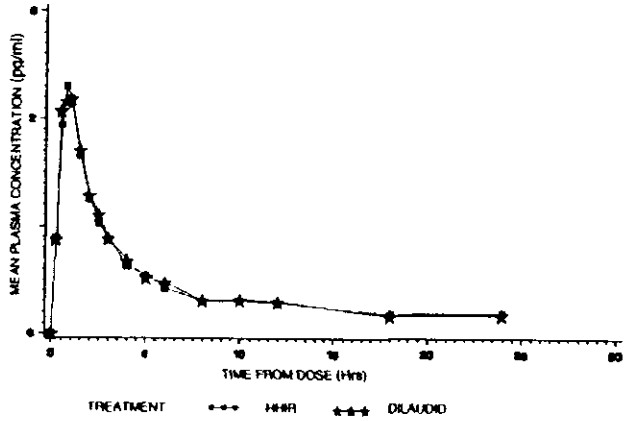


Table 1: Summary of Pharmacokinetic Metrics (Arithmetic Means and Standard Deviations)

Parameter	HHIR (3 x 2 mg)	Dilaudid® (3 x 2 mg)	LSM Ratio(%)[a]	90% CI[b]
AUC_t (ng/mL•h)	10.6 ± 3.35	10.61 ± 3.31	100.14	94.95-105.61
C_{max} (ng/mL)	2.55 ± 1.15	2.64 ± 1.18	97.03	89.20-105.55
T_{max} (h)	0.95 ± 0.83	0.85 ± 0.46		
$t_{1/2}$ (h)[c]	13.13 ± 6.1	13.46 ± 4.74		
MRT (h)	7.05 ± 1.29	6.78 ± 1.31		

[a]Ratio (%) (test/reference) of least squares means (ANOVA) derived from logarithmic-transformed values of AUCt and Cmax.
[b]90% confidence intervals were constructed around the least squares mean ratio.
[c]Only 23/72 subjects for $t_{1/2}$ were estimable: 14/36 and 9/36 in HHIR and Dilaudid® treatment group, respectively.

Conclusions:

- Following a single dose, comparison of mean C_{max} and AUC_t values indicated that HHIR 3 x 2 mg tablets and Dilaudid® 3 x 2 mg tablets are bioequivalent in terms of maximum and total exposure, respectively.
- HHIR 3 x 2 mg and Dilaudid® 3 x 2 mg tablets were rapidly absorbed, attaining peak plasma concentrations in 0.95 hours and 0.85 hours, respectively, followed by a relatively rapid decline, with apparent terminal half-lives of 13.1 and 13.5 hours.
- The sponsor indicated that treatment comparisons were not made based on t½ and, accordingly, AUC_{inf}, due to limited subjects where $t_{1/2}$ could be estimated; 14/36 in the HHIR treatment group and 9/36 in the Dilaudid® treatment group.
- Even though $t_{1/2}$ is around 13 hrs, the assessment of bioequivalency based on AUC_{0-24} seems reasonable, because the effect of the terminal exponent appears to be negligible.
- Similar MRT and t_{max} values provided additional evidence of bioequivalence.
- Formulation composition of HHIR 2 and 3 mg are not provided, therefore, BE between these are unknown.

HD96-0505: A Randomized, Double-Blind, Single Dose, Parallel Group Study to Determine Analgesic Efficacy of Hydromorphone Hydrochloride Controlled-Release Capsules, Hydromorphone Hydrochloride Immediate-Release Tablets and Placebo in Patients With Post-Operative Orthopedic Surgery Pain.

Reference: Volume 35 - 36
Investigators: [ ]
Study Location: [ ]
Purdue Research Center Laboratory, Yonkers, NY 10701 (Analytical)

Formulation:

Dosage Form	Dose	Lot #
Treatment		
HHCR Capsule	2 x 12 mg	3B25-33
Reference		
HHIR Tablet	2 x 3 mg	3B25-37
HHIR Placebo	0 mg	3B25-36
HHIR Placebo	0 mg	3B25-31

Objective:

(1) To determine the efficacy and safety of single doses of HHCR capsules (2 x 12 mg), HHIR tablets (2 x 3 mg) and placebo in patients with moderate to severe pain following surgery. (2) To characterize (i) the plasma hydromorphone time-concentration profile, (ii) the time-effect (use of rescue, pain intensity) profiles, and (iii) the concentration-effect relationships.

Study Design:

This was a randomized, double-blind, placebo-controlled, single-dose, parallel-group study in patients with moderate to severe postsurgical pain to compare HHCR, HHIR, and placebo. After orthopedic surgery, patients used PCA fentanyl to titrate pain to a comfortable intensity (with tolerable adverse events). PCA was then discontinued, and when pain became moderate to severe, a single dose of HHCR, HHIR, or placebo was given. PCA fentanyl was used as rescue medication to maintain pain at a comfortable intensity. Analgesic efficacy, plasma hydromorphone concentration, and safety were assessed over a 24-hour post-dose period in this declining pain model. Number of patients that participated in this study was 132 for intent-to-treat (ITT) analysis, 122 for rescue medication analysis, 122 for pharmacokinetics and 132 for safety analysis.

Criteria for Evaluation:
Pharmacokinetic: Plasma hydromorphone concentration at periodic sampling times with C_{max}, t_{max}, and AUC estimates.
Efficacy: Amount of rescue medication (by time intervals) during the 24-hour evaluation period and patients' ratings of current pain intensity (0 = "no pain," 10 = "pain as bad as you can imagine") at pre-specified assessment times.
Safety: Vital signs monitoring, oxygen saturation, respiration rate, and spontaneous reports of adverse events.

Analytical Methodology:
Plasma Sampling Times: pre-dose (0 hour), 1, 3, 6, 12, and 24 hours after dosing.
Pharmacodynamics — at baseline (0 hour) and at 0.5, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 14, 16, 20, and 24 hours post-dose. If the patient discontinued, current pain intensity at discontinuation was to be reported.
Assay Method: —
Assay Sensitivity: The limit of quantitation was — ng/mL with linear range of — ng/mL.
Assay Precision/Accuracy: The quality control sample precision and accuracy ranged from [ ] to [ ] respectively.

Statistical methods:
Pharmacokinetics: Plasma hydromorphone concentrations were plotted over time and C_{max}, t_{max}, and AUC values were presented in tabular form.
Efficacy: To test for statistically significant treatment differences in the primary efficacy endpoint, amount of rescue medication use (PCA fentanyl), a repeated measures ANOVA was performed on the total amount over the 24-hour interval (treatment, baseline pain level as factors) with time of rescue as the repeated factor. The number of fentanyl injections was also tabulated over the study period. Clustering of rescue medication use by time intervals were summarized. For the evaluation of current pain intensity, the design of this study assumed that pain intensity would remain at about the same level at all pain assessment times in all three treatment groups. Concentration-effect (rescue use and pain intensity) was graphed over time. The relationship between plasma hydromorphone concentration and rescue use was further evaluated by calculating the % change of the active formulations from placebo [(placebo - active)/placebo x 100%] over time. The peak effect and time to peak effect were evaluated with further assessment of the diurnal variation. Pain intensity and plasma hydromorphone concentrations were tabulated and graphed.

Results:

The mean hydromorphone concentration-time profile and summary of PK parameters following each treatment are presented in Figure 1 and in Table 1, respectively. Mean amount of fentanyl (μg) over time and mean current pain intensity by Treatments are shown in Figure 2. Total amount of fentanyl rescue medication over 24 hours and mean number of rescue injections by time interval and current pain intensity over time by treatment are presented in Tables 2 and 3, respectively. Plasma hydromorphone concentrations versus mean amount of fentanyl or current pain intensity is presented in Figure 3.

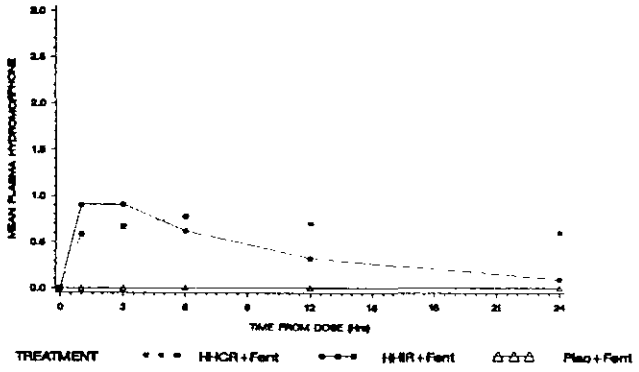


Figure 1: Mean plasma hydromorphone concentrations over time.

Table 1: Summary of Pharmacokinetic Metrics; Arithmetic Mean and Standard Deviations (n = 44)

Parameter	HHCR (2 x 12mg)	HHIR (2 x 3 mg)
$AUC_{0\text{-}24}$ (ng/mL•h)	16.07 ± 7.875	9.92 ± 5.84
C_{max} (ng/mL)	1.09 ± 0.53	1.47 ± 0.86
T_{max} (h)	9.36 ± 7.96	3.86 ± 3.85

Figure 2: Mean Amount of Fentanyl (mg) over time (left panel) and Mean current Pain intensity over time by Treatments (right panel).

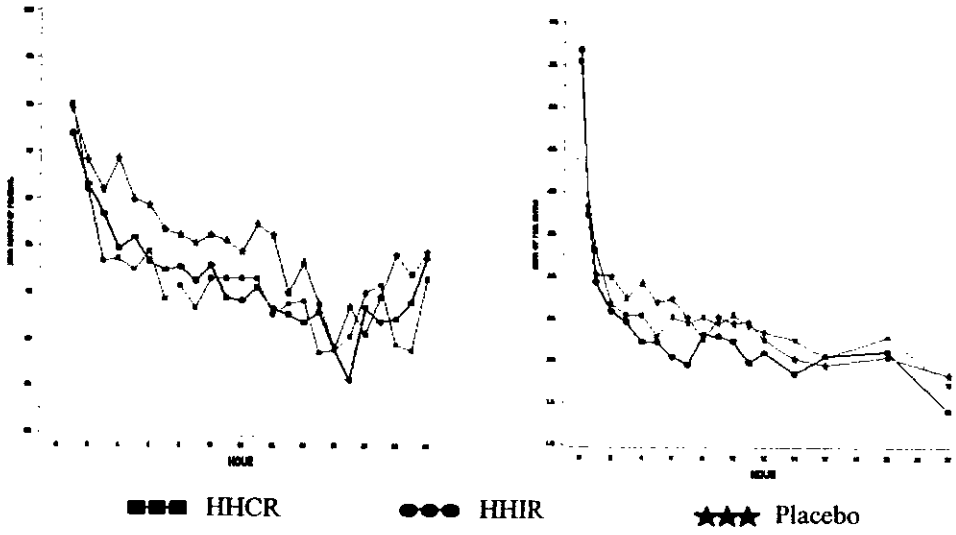


Table 2: Total amount of fentanyl rescue medication over 24 hours mean number of rescue injections by time interval.

	ITT Population		
	HHCR (N = 44)	HHIR (N = 44)	Placebo (N = 44)
Total Amount of Fentanyl Rescue Medication (µg) Over 24 Hours			
Mean*	1004.0	985.8	1186.9
Range	125 – 2225	50 – 2625	175 – 3600
Mean Number of Rescue Injections by Time Interval (Hours)			
0 – 3	7.75	7.55	8.36
3 – 6	5.91	5.64	7.49
6 – 12	10.14	9.73	12.35
12 – 24	16.74	16.91	20.19
0 – 6	13.66	13.18	15.68
6 – 12	10.14	9.73	12.35
12 – 18	8.44	8.40	10.40
18 – 24	8.50	8.51	9.79

* HHCR was significantly different from placebo ($p = 0.0086$), and HHIR was significantly different from placebo ($p = 0.0029$). There was no significant difference between the HHCR and HHIR treatment groups ($p = 0.7126$).

Table 3: Current pain intensity over time by treatment.

Time of Pain Intensity Postdose	Current Pain Intensity	ITT Population HHCR* (N = 44)	HHIR* (N = 44)	Placebo* (N = 44)
0 (Baseline)†	Mean	5.68	5.55	5.55
	Range	5 – 9	5 – 8	4 – 8
24 Hours	Mean	1.40	1.72	1.83
	Range	0 – 5	0 – 5	0 – 5
Overall‡	Mean	2.48	2.76	2.69
	Range	0.56 – 4.72	1.00 – 4.91	1.03 – 5.09

*All patients received PCA fentanyl as rescue medication.
†Pain intensity after the PCA was discontinued and the patient first reported "moderate" (5-6) to "severe" (7-10) pain on the NRS.

Figure 3: Plasma hydromorphone concentrations versus Mean Amount of Fentanyl (μg) (left panel) or Mean current Pain intensity (right panel).

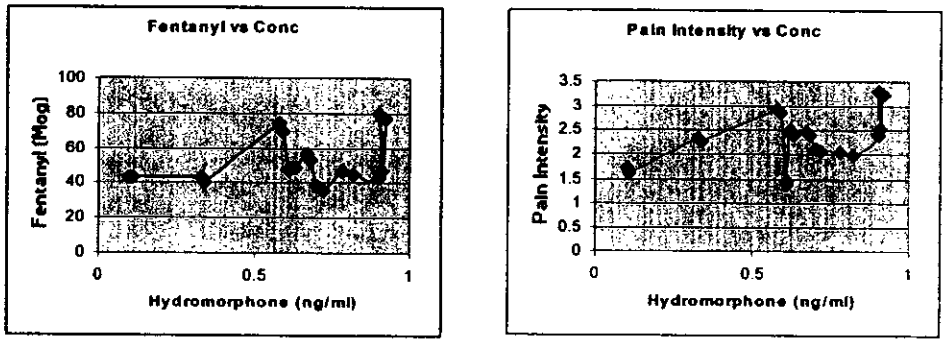
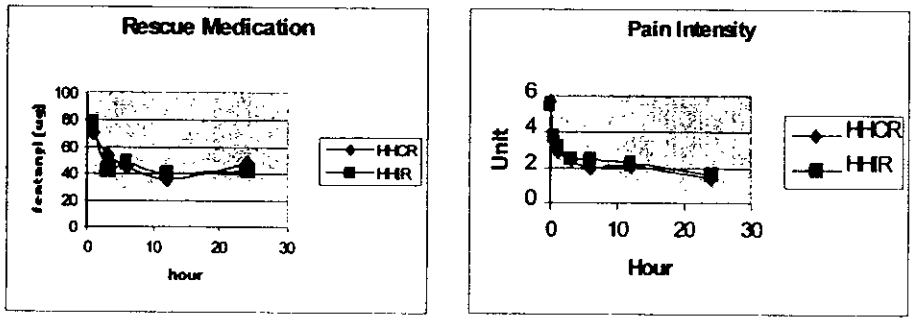


Figure 4: Mean Amount (μg) of Fentanyl or Mean Pain intensity *vs.* time.



Conclusions:

- The mean C_{max} for the HHCR, HHIR, and placebo groups were 1.09, 1.47, and 0.01 ng/mL, respectively. The mean t_{max} for the HHCR, HHIR, and placebo groups were 9.36, 3.86, and 0.82 hours, respectively. The mean AUC over 24 hours for the HHCR, HHIR, and placebo groups were 16.07, 9.92, and 0.13 ng/mL• hours, respectively.
- The mean total amount of rescue fentanyl over 24 hours was 1004.0, 985.8, and 1186.9 μg in the HHCR, HHIR, and placebo groups, respectively. The sponsor reported that Least-squares-mean comparisons of these values for HHCR and HHIR were each significantly different from placebo ($p = 0.0086$ and $p = 0.0029$, respectively), and that there was no significant difference between the HHCR and HHIR treatment groups.
- The overall pain intensity (on a 0 to 10 scale) was 2.48, 2.76, and 2.69 for the HHCR, HHIR, and placebo treatment groups, respectively; no clinically meaningful differences were observed between treatment groups.
- No sensible relationships were shown between the plasma hydromorphone concentrations and mean amount of fentanyl (μg) administered (to the patients) or mean current pain intensity. This suggests that plasma concentrations do not directly represent 'pharmacological responses'. In addition, rescue medication renders demonstration of a PK-PD relationship more complicated.
- It appears that the effect of hydromorphone (with respect to pain) is minimized by potent fentanyl (approximately 10 times potent compared to that of hydromorphone) administered as rescue medication.
- This study failed to show (any) advantages of taking HHCR over HHIR, other than convenience of dosing.

HD95-0702: A Multiple-Dose, Two-Treatment, Randomized, Cross-Over, Analytically Blinded Pharmacokinetic/Pharmacodynamic Comparison Study of Hydromorphone Hydrochloride Controlled-Release Capsule 12mg Once Daily and Hydromorphone Hydrochloride Immediate-Release 3 mg Tablet q6hr.

Reference: Volume 32 – 33
Investigators: [redacted]
Study Location: [redacted] (Clinical)
Purdue Research Center Laboratory, Yonkers, NY 10701 (Analytical)

Formulation:

Dosage Form	Strength	Lot #
HHCR Capsule	12 mg	CB25-33
HHIR Tablet	3 mg	CB25-37

Objective:

To assess relative bioavailabilities (including gender effects) and to compare the pharmacokinetic / pharmacodynamic (PK/PD) profiles of HHCR 12 mg capsules q24h and HHIR 3 mg tablets q 6 h under apparent steady-state (multiple-dose) conditions in normal young adult male and female volunteers.

Study Design:

This was an open-label, analytically-blinded, 5-day, repeated-dose (steady-state), two-treatment, randomized, crossover study in normal, healthy, young male and female volunteers (15 males and 11 females). HHIR was dosed q6h (2-8-14-20h) and HHCR was dosed daily at 8AM, on days from 1-5 with a 7-day washout period between treatment. Each dose was given on empty stomach.

Criteria for Evaluation:
Pharmacokinetic: Area under the plasma concentration time curve from dosing to 24h at steady-state [$AUC_{ss,(0-24)}$], maximum plasma concentration at steady-state [$C_{ss,max}$], minimum plasma concentration at steady-state [$C_{ss,min}$], minimum plasma concentration prior to steady-state [$C_{t,min}$], time to maximum plasma concentration at steady-state [$t_{ss,max}$], % fluctuation at steady-state, and time from initiation of therapy to steady-state [T_{ss}].
Pharmacodynamics: Subject "drug effect".
Safety: Clinical laboratory tests, vital signs monitoring, physical examinations, electrocardiograms, and reports of adverse events.

Analytical Methodology:
Plasma Sampling Times: pre-dose (0 hour), 0.25, 0.5, 1, 2, 3, 4, 5, 6, 6.25, 6.5, 8, 9, 10, 12, 12.25, 12.5, 13, 14, 15, 16, 18, 18.25, 18.5, 19, 20, 21, 22, and 24 hours after dosing on days from 2-5 of each study period. Measurements of "drug effect" (measures by VAS, scale 0-100) were made just prior to blood sampling at baseline (within 30 minutes prior to dosing) and within 5 minutes prior to all scheduled blood sampling times.
Assay Method: [redacted]
Assay Sensitivity: The limit of quantitation was [redacted] ng/mL with linear range of [redacted] ng/mL.

Assay Precision/Accuracy: The quality control sample precision ranged from [redacted]
Accuracy was [redacted] regardless of concentration level.

Statistical methods:

Bioequivalence was assessed by comparison of $C_{ss,max}$ and $AUC_{ss,(0-24)}$ values from test treatment to the reference treatment by analysis of variance (ANOVA) using the appropriate model for this study design. 90% Confidence intervals were estimated around ratios (test/reference) of least squares means derived from logarithmic-transformed values of $C_{ss,max}$ and $AUC_{ss,(0-24)}$. A 90% confidence interval analysis compared the same metrics between males and females. The PK/PD analysis involved a graphic assessment of the relationship between plasma drug concentrations and the subject "drug effect".

Results: The results are shown in Figures 1-5 and in Table 1.

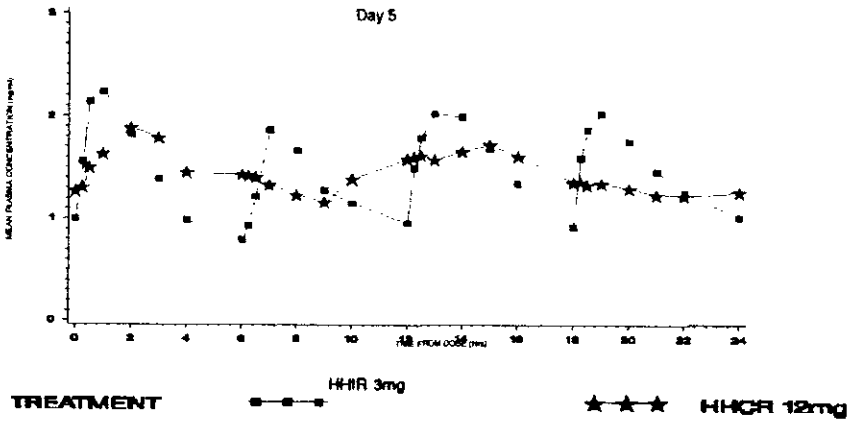


Figure 1: Plasma Hydromorphone Concentrations Following Administration of 12 mg Hydromorphone as 12 mg HHCR or 3 mg HHIR q6h for 5 Days (Mean Data N=26).

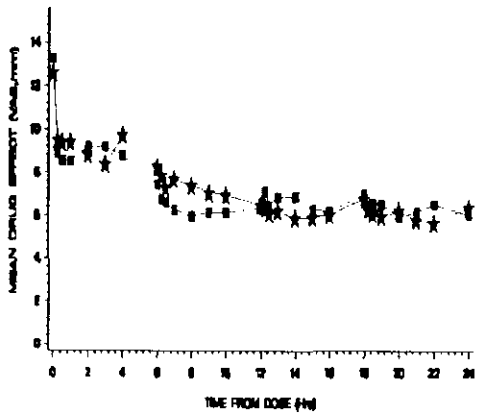


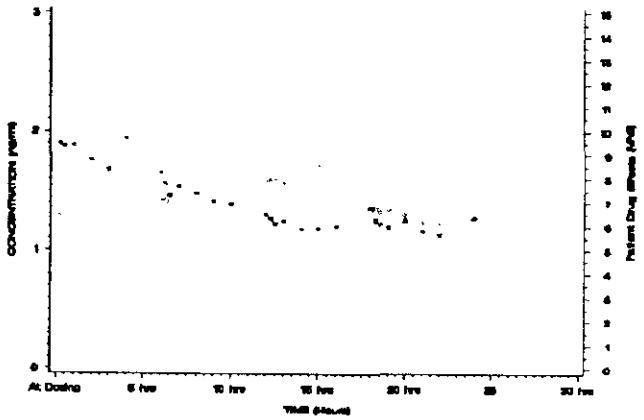
Figure 2: Mean "Drug Effect" over Time as Determined by Subject Response to "Do You Feel any Effect of the Drug?" on a 100 mm Visual Analog Scale from 0= Not at All to 100= An Awful Lot (N= 26). Symbols are the same as Figure 1.

Table 1: Summary of Pharmacokinetic Data with Statistical Analysis after each treatment (male = 15; female = 11)

Parameter	HHCR 12 mg Q24h	HHIR 3 mg Q6h	LSM Ratio(%)[a]	90% CI[b]
AUC_{ss} (0-24)(ng/mL•h)				
Male	34.86±11.49	32.83±10.3	106.17	101.2-111.22
Female	34.87±8.54	36.53±6.45	95.46	85.5-105.33
All subjects	34.86±10.15	34.4±8.93	101.36	96.31-106.4
$C_{ss,\ max}$ (ng/mL)				
Male	2.04±0.65	2.55±1.0	80.05	68.65-91.94
Female	2.23±0.64	3.36±0.69	66.36	52.72-80.47
All subjects	2.12±0.64	2.89±0.96	73.33	64.31-82.34
$C_{ss,\ min}$ (ng/mL)				
Male	1.03±0.38	0.69±0.23	148.96	135.2-160.96
Female	0.94±0.3	0.71±0.2	133.29	110.9-154.2
All subjects	0.99±0.35	0.70±0.21	142.24	130.8-153.68
$T_{ss,\ max}$ (h)				
Male	7.18±6.95	0.92±0.54	783.64	410.2-1140.7
Female	10.16±5.22	0.77±0.51	1314.71	1075.6-1670.8
All subjects	8.44±6.34	0.86±0.52	986.52	733-1240.0
% fluctuation				
Male	106.97±44.63	276.92±95.53	38.63	23.81-54.78
Female	151.47±74.7	397.47±129	38.11	19.17-57.43
All subjects	125.8±62.04	327.92±124.3	38.36	26.14-50.58
Trough (ng/mL)	1.37±0.42	1.01±0.29		
T_{ss} (d)	3	3		

[a]Ratio(%) (Test mean/Reference mean) of least square means (ANOVA) derived from logarithmic-transformed values of AUC_t and C_{max}.
[b]90% confidence interval (CI) of the LSM ratio.

Figure 3: Mean plasma hydromorphone concentrations (ng/mL) and Mean subjects drug effect (VAS, mm) following HHCR 12 mg.



Concentration (ng/ml) Patient Drug Effects (VAS)

Figure 4: Mean plasma hydromorphone concentrations (ng/mL) and Mean subjects drug effect (VAS, mm) following HHIR 3 mg. Symbols are the same as Figure 3.

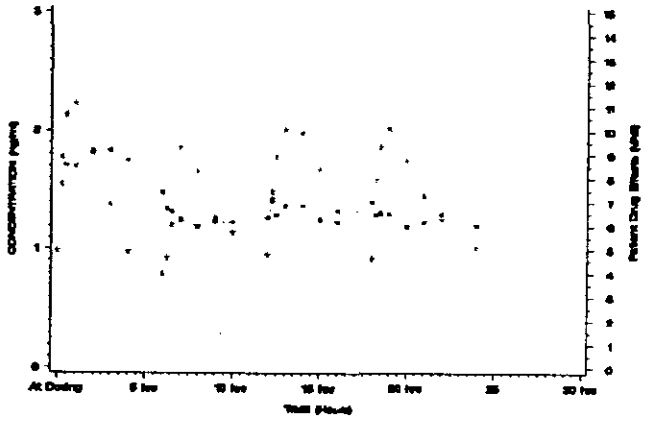
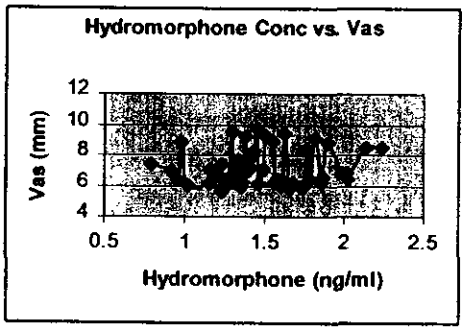


Figure 5: Hydromorphone concentration *vs.* Drug effect (VAS) from pooled data (*i.e.*, HHCR and HHIR)



Conclusions:

- Comparison of AUC_{ss},(0-24) indicated that the two treatments were bioequivalent with respect to extent of absorption (but not with respect to $C_{ss,max}$).
- The profile for each HHCR concentration-time curve resulted in a relatively rapid rise to an initial early peak concentration followed by a second broader peak with plateau concentrations being maintained beyond 24 hours.
- Consistent with controlled-release characteristics, HHCR capsules produced a lower $C_{ss,max}$, a longer $t_{ss,max}$, higher C_{min} and less % fluctuation.
- Steady state appeared to have been reached between day 3 and 4 for both treatments (C_{min} was similar between 3rd and 4th day, however, steady state assessment was not done by statistical analysis).
- Accumulation factor for HHCR was < 2 (based on simulation $C_{1,min}$ using average single dose PK parameter values, see Table 1, page 5 and $C_{ss,min}$, Table 1)
- There was no significant difference in "drug effect" between treatments (Figure 2).

HD95-0801 and HD95-0802: Double-Blind, Randomized, Two-Period Crossover Study Comparing the Efficacy, Safety and Pharmacokinetic and Pharmacodynamic Profiles of Oral Administration of Hydromorphone Hydrochloride Controlled-Release Capsules (qAM) and Hydromorphone Hydrochloride Immediate-Release Tablet (qid) for Cancer-Related or Chronic Nonmalignant Pain.

Reference: Volume 37-47 (HD95-0801) and 48- (HD95-0802)
Investigators: Multi-investigators
Study Center: Multi-center
[redacted] (Assay; HD95-0801)
Purdue Research Center Laboratory, Yonkers, NY 10701 (Assay; HD95-0802)

Formulation:

Dosage Form	Dose	Unit Strength	Lot #
Test Product: HHCR Capsule (qd)	12-84 mg/day	12 mg	CB25-33
Reference Product: HHIR Tablet (qid)	12-84 mg/day	3 mg	CB25-37
Rescue medication: HHIR Tablet (q4-6h prn)	2-12 mg/day	2 mg	CB25-38

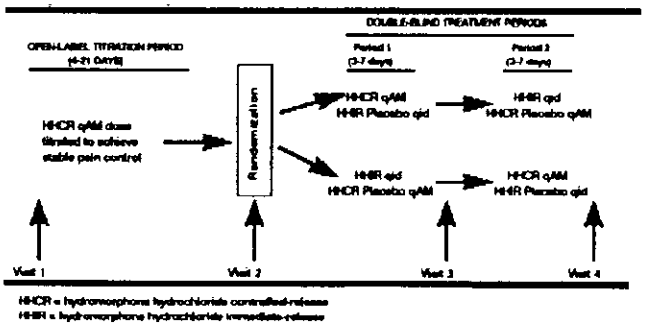
Objective:

To determine the efficacy, safety, plasma concentration, and pharmacodynamic effect of oral administration of HHCR capsules qd as compared with HHIR tablets qid in the treatment of cancer-related or chronic nonmalignant pain.

Objective of Amendment No. 1: To determine if patients could discriminate between a lower dose of oral hydromorphone (or placebo) and the dose of hydromorphone that previously provided stable pain control in the treatment of their cancer-related pain.

Study Design:

A multi-center study with a double-blind (double-dummy), randomized, two-period (Periods 1 and 2) crossover design to compare HHCR qd (maximum 84 mg daily) with HHIR qid. Daily dose was determined by a prior nonrandomized, open-label titration period with HHCR qd. A schematic diagram of the study design and over view of the treatments administered are presented in the below.



Schedule of Oral Dosing in the Open-Label and Double-Blind Periods

Open-Label Period	Double-Blind Periods	
Titration (4 to 21 days, ending on the day of Visit 2)	Period 1 (3 to 7 days, ending on the day of Visit 3)	Period 2 (3 to 7 days, ending on the day of Visit 4)
	Active Test → Active Reference	
HHCR qd[a] Rescue[e]	HHCR qd[a] + HHIR placebo qid[c] Rescue[e]	HHCR placebo qd[b] + HHIR qid[d] Rescue[e]
	Active Reference → Active Test	
	HHCR placebo qd[b] + HHIR qid[d] Rescue[e]	HHCR qd[a] + HHIR placebo qid[c] Rescue[e]

HHCR = hydromorphone hydrochloride controlled-release
HHIR = hydromorphone hydrochloride immediate-release

[a]Capsule(s) containing 12 mg hydromorphone hydrochloride taken at 0800 hours ± 1 hour.
[b]Matching placebo capsule(s) taken at 0800 hours ± 1 hour.
[c]Matching placebo tablet(s) taken at 0800 hours ± 1 hour, 1300 hours ± 1 hour, 1800 hours ± 1 hour, and bedtime (at least 4 hours after the 1800 hours dose).
[d]Tablet(s) containing 3 mg hydromorphone hydrochloride taken at 0800 hours ± 1 hour, 1300 hours ± 1 hour, 1800 hours ± 1 hour, and bedtime (at least 4 hours after the 1800 hours dose).
[e]Rescue tablet(s) containing 2 mg hydromorphone hydrochloride taken every 4 to 6 hours as needed for incident and breakthrough pain except from the midnight preceding the last day of each double-blind period until completion of the pharmacokinetic blood sampling just before the second dose (1300 hours ± 1 hour) on the last day of each double-blind period.

Number of Patients: 174 patients were enrolled; 106 were randomized into the double-blind period; 104 were included in the intent-to-treat population; 89 completed and 67 were included in the efficacy analysis; 174 were included in the safety analysis. Only 7 patients were enrolled for amendment No. 1 study.

Pharmacokinetic: Studies HD95- 0801 and HD95 0802 were identical in design. Therefore all data was pooled to generate adequate numbers of patients in each of the studied subgroups. Following titration of dose to achieve optimal pain control, all subjects were administered the test regimen for between 3-7 days prior to blood sampling. All subjects were scheduled for 5 blood collections for at least 5-6 hours with optional 24 hour blood samples. In the HHCR treated period, 135 subjects were evaluable for pharmacokinetic assessments. Note: AUC_{0-6} is considered valuable (even though AUC_{0-24} is preferred) since most subjects did not have 24 hour blood draws (*i.e.*, completed the 6 hour portion of the sampling scheme). Because of the relatively flat plasma concentration curves at steady-state for HHCR, pharmacokinetic metrics of C_{min} and AUC_{0-6} were good indicators for exposure and for comparison between subgroups. Therefore AUC_{0-6} (and C_{min}/C_{max}) can serve as indicators for comparison between subgroups.

Criteria for Evaluation:

Pharmacokinetic: Area under the plasma concentration curve (AUC_{0-6}, AUC_{0-24} when available), maximum plasma concentration (C_{max}) and C_{min} (trough concentrations).

Others: Primary efficacy (pain intensity; drug effect), Secondary efficacy (average pain; amount of rescue per day; time of rescue; number of patients requiring rescues) and Safety

Analytical Methodology:

Plasma Sampling Times: At Visits 3 and 4, blood samples were collected at five time points: 0 hour, within 10 minutes before the AM dose (administered at 0800 hours ± 1 hour) and 1, 2, 3 and 5-6 hours after the AM dose. The 5-6 hour sample had to be drawn before the next dose (administered at 1300 hours ± 1 hour). A sixth, optional blood sample could be collected 22-24 hours after the AM dose (and, for Visit 3, before the next AM dose).

Assay Method: [redacted] (HD95-0801) and [redacted] assay (HD95-0802).

Assay Sensitivity: The limit of detection was [redacted] ng/ml with linear range of [redacted] ng/ml.

Assay Precision/Accuracy: Quality control samples inter-batch precision and accuracy ranged from [redacted] and [redacted] respectively regardless of concentration level (HD95-801). For HD95-

802; The inter-day quality control samples precision at low (—ng/ml), medium (— ng/ml) and high (— ng/ml) were [ ] and [ ], respectively. Accuracy for those QC samples were [ ] respectively.

Statistical methods:

Efficacy: All statistical tests were two-sided with a significance level of 0.05. Interaction and carryover effects were conducted at a significance level of 0.10. The standard crossover analysis of variance (ANOVA) model included treatment (double-blind), sequence, period, and patient nested within sequence. A 90% confidence interval analysis (two one-sided 95% confidence intervals) was conducted for the mean of the average pain intensity ratings on the last 2 days before the PK/PD day in the double-blind periods.

Results: The results are illustrated in figures and tables below.

Figure 1: Combined Studies H95-0801 and HD95-0802: Relationships between C_{max}, C_{min}, AUC_{0-6} and dose.

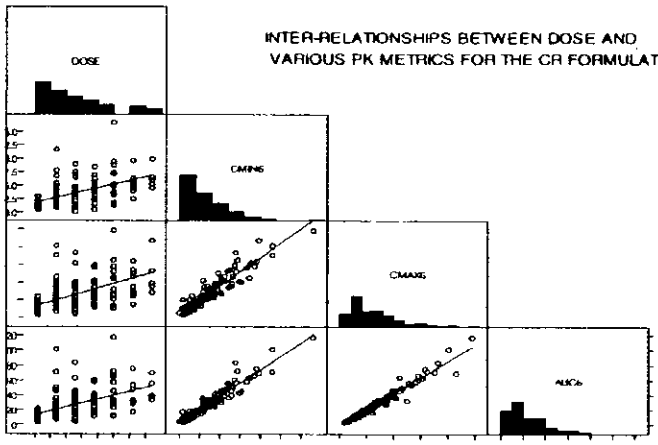


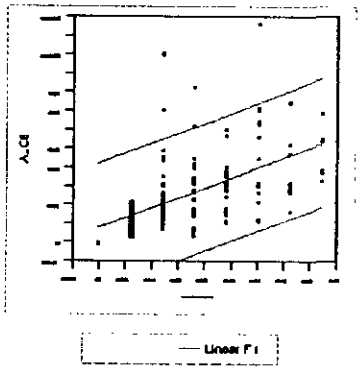
Table 2: Dose Adjusted Mean Pharmacokinetic Values At Steady-State in All Pharmacokinetically Evaluable Patients in Studies HD95-0801 and HD95-0802 (Mean (SD))

	HHCR	HHIR
Cmin	0.105 (0.07)	0.111 (0.09)
Cmax	0.206 (0.12)	0.302 (0.21
AUC	0.843 (0.54)	0.991 (0.76)

Table 3: HHCR Pharmacokinetics in HD95-0801 and HD95-0802: Dose Proportionality at Steady-State: Pooled Phase III Data [Mean (SD)] AUC_6

Metric	12 mg	24 mg	36 mg	48 mg	60 mg	72 mg	84 mg
Number of subjects	42	31	20	16	12	9	5
Cmin (ng/mL)	1.33 (0.59)	3.63 (2.67)	3.61 (2.38)	4.09 (2.05)	5.99 (4.26)	5.18 (1.98)	6.40 (2.09)
AUC0-6 (ng*hr/mL)	10.20 (4.26)	26.57 (19.51)	29.20 (19.58)	32.35 (13.54)	46.63 (30.31)	38.34 (17.51)	46.96 (15.09)

Figure 2: Dose proportionality of HHCR in Phase III studies HD95-0801 and HD95-0802



The linear fit was highly significant ($p<0.0001$) for AUC (also C_{max}, and C_{min}; not shown here).

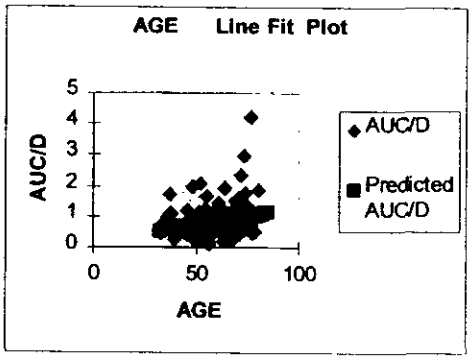
Special Population: From Phase III studies, HD95-0801 and HD95-0802, pharmacokinetic information was extracted for 'special population' subgroups.

Age: Age comparison for HHCR pharmacokinetics is presented in Table 4 and Figure 3.

Table 4: Age comparison at steady state [mean (SD)]

Age	N	AUC0-6/Dose (ng*hr/mL)	Cmin (ng/mL)
20-64 years	89	0.75 (0.40)	0.098 (0.06)
65-74 years	31	0.98 (0.58)	0.12 (0.09)
>75 years	15	1.14 (0.92)	0.16 (0.11)

Figure 3: Age and Dose-adjusted AUC_{0-6} with regression line



Predicted $AUC_{0-6} = 0.155 + 0.012$ x Age. The linear fit was significant ($p = 0.0014$).

Gender: There was no significant gender effect noted, as shown in Table 5.

Table 5: Gender comparison at steady state [mean (SD)]

Gender	N	AUC0-6 (ng*hr/mL)	Cmin (ng/mL)
Male	64	0.76 (0.40)	0.10 (0.06)
Female	71	0.92 (0.64)	0.12 (0.08)

Race: There was no clear or significant trend towards PK differences with race as shown in the table below.

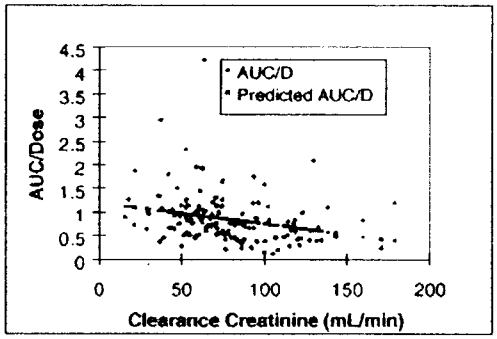
Race	N	AUC0-6 (ng*hr/mL)	Cmin (ng/mL)
White	120	0.94 (0.63)	0.11 (0.08)
Black	11	0.78 (0.36)	0.10 (0.05)
Hispanic	3	0.73 (0.28)	0.09 (0.04)
Other	1		

Renal impairment: Dose normalized AUC_{0-6} and C_{min6}, categorized by creatinine clearance (i.e., degree of renal impairment), are shown in the Table below;

Palladone XL™ Pharmacokinetics and Renal Function (mean (SD))			
Creatinine Clearance (mL/min)	n	C_{min}*/Dose (ng/mL/mg)	AUC*/Dose (ng•hr/mL/mg)
Normal (>80)	54	0.09 (0.06)	0.66 (0.40)
Mild (50-80)	61	0.12 (0.07)	0.93 (0.59)
Moderate (30-49)	15	0.14 (0.11)	1.07 (0.65)
Severe (<30)	5	0.16 (0.10)	1.08 (0.50)

* C_{min} and AUC values for 0-6 hours at steady-state

Figure 4: Calculated creatinine Clearance and Dose-adjusted AUC_{0-6}.



Predicted AUC_{0-6} = 1.19 - 0.004 x Clcr ($p = 0.0026$). A clear trend was observed in the regression analysis. However, since the slope is shallow, it may not be critical for hydromorphone clearance.

Hepatic impairment: The results of regression analysis with respect to hepatic function indices with AUC_{0-6} is presented in Table 6.

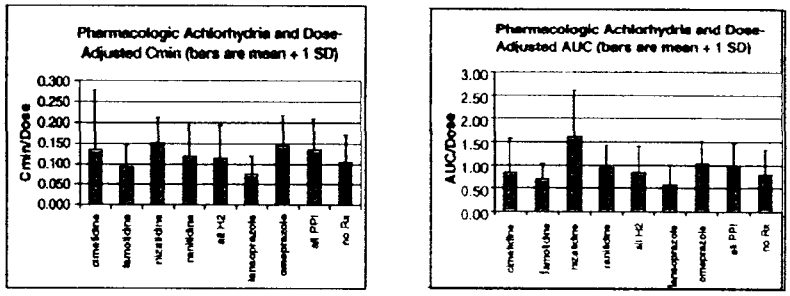
Table 6: Regression analysis: Hepatic function

Parameter	Mean	Max	N	F value	P value	R^2
GGT	107	1253	123	6.05	0.015	0.048
AST	23	90	132	8.21	0.005	0.059
ALT	25	159	126	0.38	0.540	0.003
Albumin	3.9	2.4[1]	130	4.01	0.047	0.030
Bilirubin	0.06	3.6	134	4.08	0.045	0.030

Several of these regressions resulted in statistically significant F values. However, the sponsor concluded that these associations are not clinically meaningful due to low coefficients of determination (e.g., highest value 0.059, AST). However, whether clinically meaningful or not could not be predicted solely by R^2 value alone (*i.e.*, need clinical data).

Drug interaction: The phase III data was analyzed to evaluate whether the HHCR controlled release formulation has any potential interactions with gastrointestinal tract modifying agents which could potentially modify release rates and drug absorption. The results (Figure 5) indicated that there were no significant interactions between hydromorphone and proton pump or H_2 blockers.

Figure 5



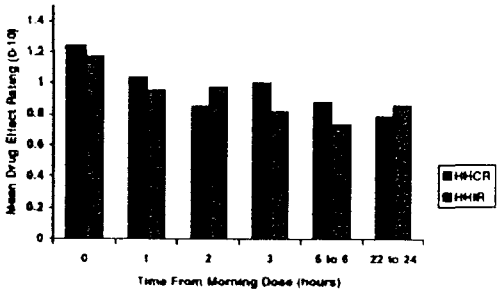
Efficacy: The results on average pain intensity (0-10 scale), mean drug effect and observed mean dose-adjusted plasma hydromorphone concentrations are presented in Table 9 and Figures 10-11. The sponsor reported that the number of rescue doses used was similar between HHCR and HHIR groups (1.38 ± 0.17and 1.36 ± 0.17, respectively).

Table 9: 90% CI analysis of the mean average pain intensity over the last 2 days before each PK/PD Day of the double-blind periods.

	mean[a](SE) average pain intensity		Difference	90% Confidence Interval	
	HHCR	HHIR	HHCR–HHIR	Lower Bound	Upper Bound
HD95-801	2.48 (0.07)	2.42 (0.07)	0.06	-0.11	0.23
HD95-802	2.59 (0.08)	2.58 (0.08)	0.01	-0.17	0.19

[a]Least squares mean

Figure 10: Mean Drug Effect rating (0-10 point scale) immediately before Each Phlebotomy; HD95-0801 (left) and HD95-0802 (right)



HHCR	N	62	61	61	60	60	14
	Mean	1.24	1.03	0.85	1.00	0.88	0.79
	SE	0.24	0.22	0.20	0.24	0.21	0.54
HHIR	N	59	61	61	61	60	14
	Mean	1.17	0.95	0.97	0.82	0.73	0.86
	SE	0.27	0.22	0.21	0.20	0.20	0.31

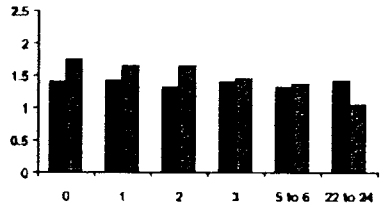
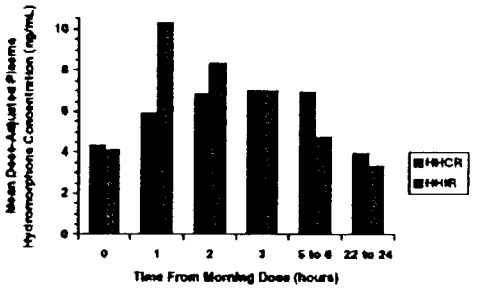
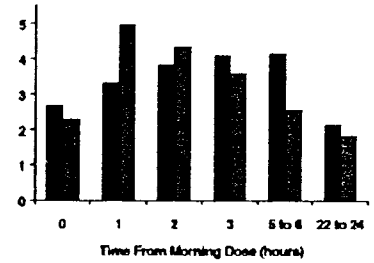


Figure 11: Mean Dose-Adjusted (to 36 mg) Plasma Hydromorphone Concentration at the Time of Each Phlebotomy; HD95-0801 (left) and HD95-0802 (right)

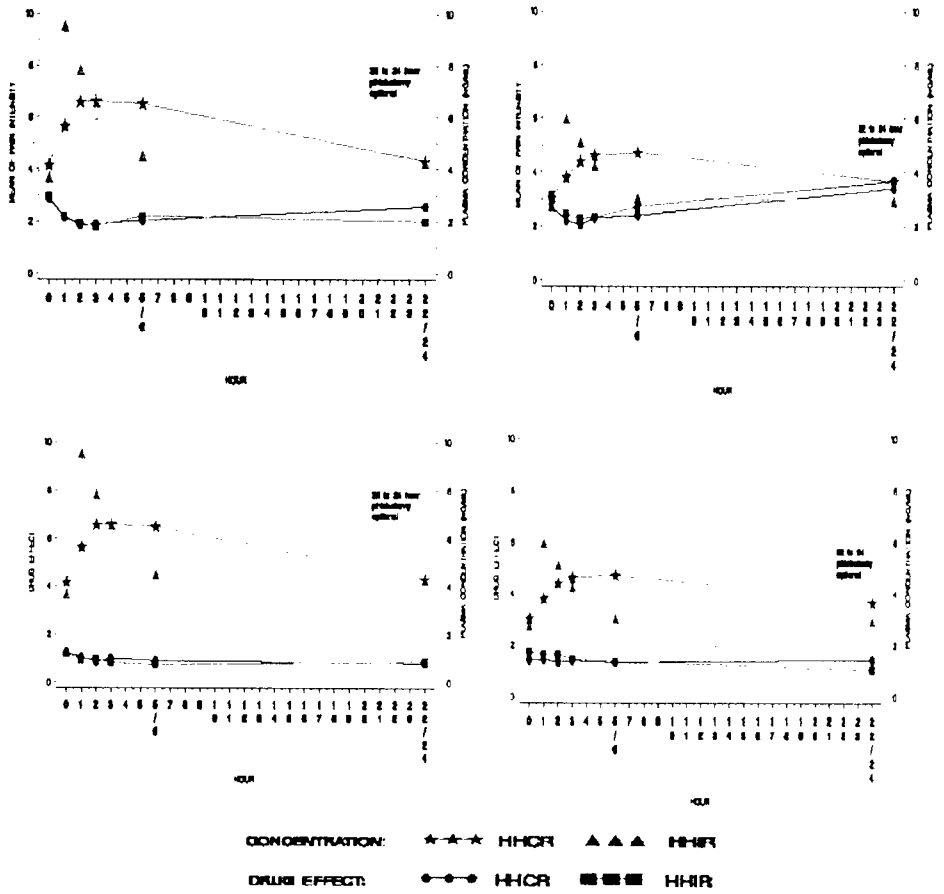


HHCR	N	56	56	57	56	56	13
	Mean	4.38	5.97	6.92	7.06	6.92	3.94
	SE	0.45	0.56	0.67	0.68	0.67	0.71
HHIR	N	52	55	55	54	55	13
	Mean	4.11	10.3	8.34	7.04	4.74	3.33
	SE	0.69	0.94	0.79	0.73	0.49	0.41



HHCR	N	82	82	81	82	81	19
	Mean	2.70	3.31	3.81	4.06	4.15	2.12
	SE	0.16	0.17	0.21	0.24	0.26	0.25
HHIR	N	82	82	82	81	82	22
	Mean	2.27	4.94	4.31	3.59	2.57	1.81
	SE	0.14	0.29	0.27	0.23	0.18	0.24

Figure 12: Mean pain intensity (upper panel) or Mean drug effect (lower panel) and mean plasma hydromorphone concentration (ng/ml) over time. Population: Evaluable for PK/PD. HD95-801 (left) and HD95-802 (right)



Rescue medication during double-blind periods (information from the medical officer).

The mean daily dose of rescue medication ranged from 6.51-9.86 mg (average of 8.89 mg) and 5.43-11.89 mg (average of 8.66 mg) for the HHCR and HHIR treatments, respectively. The mean pain intensity at these assessment times for the HHCR and HHIR were 2.89 and 2.63, respectively. The integrated pain intensity resulted in 57 (29%) of patients for whom no treatment was superior. There were 73 (38%) for whom the HHIR was superior and 64 (33%) who did better on the HHCR. The number and % of patients who used rescue medication during the combined double blind periods were 69 of 91 patients (76%) on HHCR and 66 of 91 patients (73%) on HHIR for the efficacy population. The corresponding results for the intent-to-treat population were 78% for HHCR and 74% for HHIR.

Conclusions:

- A good correlation was observed between C_{min}, AUC_{0-6}, C_{max} and dose (Figure 1).
- Dose-proportionality data over the range employed in the clinical studies has shown linearity in pharmacokinetics (Figure 1 and 2). Strictly speaking, pharmacokinetics are not exactly dose-proportional.
- The predicted linear fit between age and AUC_{0-6} was statistically significant ($p = 0.001$; Figure 3).
- No significant differences with respect to gender were noted in the HHCR treated groups.
- No significant differences in PK were found between different races. Note: Number of subjects of different race was low.
- A clear trend of increased AUC with decreased creatinine clearance was observed in the regression analysis with respect to the relationship between calculated creatinine clearance and AUC_{0-6} ($p = 0.0026$).
- Regression analysis between hepatic function indices and hydromorphone AUC_{0-6} resulted in statistically significant F values, yet very low R^2 values. The sponsor was asked to classify patients with hepatic impairment based on the severity of liver disease into mild, moderate and severe impairment. Based on the sponsor's response, it is clear that all the patients with hepatic impairment (n=10) had only mild elevations in any two measures of liver disease. No patients with moderate and severe disease were included.
- No drug interactions were noted in subjects receiving proton pump inhibitors or H_2 blockers.
- The mean (least squares mean) of average pain intensity (0-10 scale) over the last 2 days prior to the PK/PD day was 2.54 for the HHCR treatment group and 2.50 for the HHIR treatment group based on combined studies (HD95-0801 and 2).
- Observed mean-dose adjusted plasma hydromorphone concentrations fell within a similar range, except at 1hr time point, during HHCR and HHIR treatments (Figure 11). Therefore, the relationship of PK/PD between the two treatments is not surprising (i.e., similar concentrations resulted in similar pain intensity or 'drug effect').
- The number of rescue doses used was similar between the HHCR and HHIR groups ($1.38 \pm 0.17$and 1.36 ± 0.17, respectively).
- It appears that there is no obvious advantage (s) of taking HHCR over HHIR based on the results of comparison of total amount of rescue medication usage and pain scores. However, there is a subtle advantage of taking HHCR over HHIR; patients in HHCR need to take once a day *vs.* HHIR qid. Therefore, overall, it can be said that the performance of HHCR appears **not** worse than HHIR.

HD97-0502: A Single Dose, Four-Way, Randomized, Crossover Pharmacokinetic Study to Compare Hydromorphone HCl Controlled-Release 24 mg Capsule with Different Dissolution Profiles in Fasted Normal Volunteers to Establish an In-Vitro/In-Vivo Correlation.

Reference: Volume 29 - 30
Investigators: [redacted]
Study Location: [redacted]
Purdue Research Center Laboratory, Yonkers, NY 10701 (Analytical)

Formulation:

Dosage Form	Dose	Lot #
Test Product:		
HHCR Capsule (fast dissolving)	24 mg	CB26-15
HHCR Capsule (very slow dissolving)	24 mg	CB26-16
HHCR Capsule (slow dissolving - external validation)	24 mg	4L-B
Reference Product:		
HHCR Capsule (target)	24 mg	4L

Objective:

To correlate in vitro dissolution with in vivo absorption using four different HHCR 24-mg formulations with different dissolution profiles.

Study Design:

This was a single-dose, randomized, open-label, four-way crossover study with four HHCR formulations. Enrolled 12 subjects (male); 10 were included in the pharmacokinetic analysis (2 discontinued); 12 were included in the safety analysis.

Criteria for Evaluation:
Pharmacokinetic: Area under the curve to the last quantifiable plasma concentration (AUC_t), maximum plasma concentration (C_{max}), time to maximum plasma concentration (t_{max}), apparent terminal half-life ($t_{½}$), and mean residence time (MRT).
In Vitro/In Vivo Correlation: The data from the study together with the in-vitro dissolution data for the formulations tested were treated according to the FDA's Guidance For Industry-Extended Release Oral Dosage Forms: Development, Evaluation, and Application of In Vitro/In Vivo Correlation. Internal and external predictability was assessed.
Safety: Clinical laboratory tests, vital signs monitoring, physical examinations, electrocardiograms, and reports of adverse events.

Analytical Methodology:
Plasma Sampling Times: pre-dose (0 hour), 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 10, 12, 14, 18, 24, 36, 48, 60, 72 and 96 hours after dosing.
Assay Method: [redacted]
Assay Sensitivity: The limit of quantitation was — ng/mL with linear range of [redacted] ng/mL.
Assay Precision/Accuracy: The quality control sample precision and accuracy ranged from [redacted] and [redacted] respectively.

Statistical methods:

Bioequivalence was assessed by comparison of AUC_t and C_{max} values from the test treatment with those from the reference treatment by analysis of variance (ANOVA) using the appropriate model for this study design. Confidence intervals (90%) were estimated around ratios (test/reference) of least squares means derived from logarithmic-transformed values of AUC_t and C_{max}. Other metrics were reported as mean and standard deviation. Student's t-test was performed on changes in vital signs from predose values to 2, 4, 8, 12, 24, 48, and 72 hours postdose. Pharmacokinetic and dissolution model assignment was based on Akaike Information Criteria Assessment.

Results:

The mean hydromorphone concentration-time profile following each treatment is shown in Figure 1. Summary of PK metrics with statistical analysis is presented in Table 1. The sponsor's proposal for HHCR dissolution specifications is presented in Table 2.

Figure 1: Mean Plasma Hydromorphone Concentration-Time Curves of Four Formulations of HHCR.

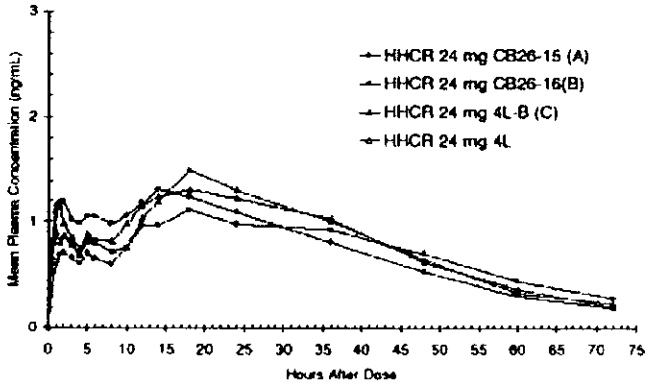


Table 1: Summary of Pharmacokinetic Metrics (Arithmetic Means and Standard Deviations)

Metric	CB26-15	4L	LSM Ratio(%)[a]	90% CI[b]
AUC_t (ng/mL•h)	54.1 ± 12.54	58.73 ± 15.84	93.29	85.81-101.43
C_{max} (ng/mL)	1.52 ± 0.34	1.58 ± 0.25	96.02	85.71-107.57
T_{max} (h)	12.9 ± 3.78	14.25 ± 10.97		
	CB26-16	4L		
AUC_t (ng/mL•h)	52.49 ± 12.16	58.73 ± 15.84	91.01	83.71-98.94
C_{max} (ng/mL)	1.2 ± 0.28	1.58 ± 0.25	75.14	67.07-84.18
T_{max} (h)	21.8 ± 10.09	14.25 ± 10.97		
	4L-B	4L		
AUC_t (ng/mL•h)	57.52 ± 18.48	58.73 ± 15.84	96.5	88.76-104.91
C_{max} (ng/mL)	1.49 ± 0.33	1.58 ± 0.25	92.4	82.47-103.51
T_{max} (h)	17.6 ± 7.65	14.25 ± 10.97		

LSM = least squares mean. [a]Ratio (%) (test/reference) of least square means (ANOVA) derived from logarithmic- transformed values of AUC_t and C_{max}.
[b]90% confidence interval (CI) around the least squares means (LSM) ratio.

Table 2: Sponsor proposed HHCR dissolution specifications (in their specification sheet).

Time (hours)	Lower	Upper
2		
8		
22		-

Conclusions:

- Comparisons of AUC_t data indicated that HHCR 24 mg test Lots CB26-15, CB26-16, and 4L-B were each bioequivalent to reference Lot 4L in terms of extent of absorption. However, the number of subjects in the study were few (may not have adequate power to declare bioequivalence).
- Comparisons of C_{max} data indicated that HHCR 24 mg test Lots CB26-15 and 4L-B were each bioequivalent to reference Lot 4L in terms of this metric. CB26-16 was not bioequivalent to 4L.
- The C_{max} of HHCR 24 mg test Lot CB26-16 was lower (CI = 67-84) and t_{max} longer (21.8 versus 14.3 hours) than those of reference Lot 4L.
- Mean MRT values for Lots CB26-15, CB26-16, 4L-B, and 4L were 26.02, 30.97, 27.85, and 27.87 hours, respectively.
- Dissolution specifications for HHCR were suggested (Table 2); however, this will be evaluated in the next section, "IVIVC".

In Vitro-In Vivo Correlation (IVIVC)

Objectives:

To develop an IVIVC for Hydromorphone HCl Controlled Release (HHCR), evaluate the IVIVC, and apply the IVIVC in order to justify dissolution specifications.

Methods:

Data Sets: Data from protocol number HD97-0502 was used. In this study, four formulations with differing dissolution profiles were evaluated (no immediate release reference or iv treatment was included). Their lot numbers were CB26-15, 4L, 4L-B, and CB26-16. Their relative rates of drug release were CB26-15 > 4L > 4L-B > CB26-16. Lot 4L is the market image product (*i.e.* reference product). Lot 4L-B is 4L capsules, which had been subjected to six months of elevated temperature and humidity. Composition of these formulations is shown in the table below;

Ingredient	4L	4L-B	CB26-15	CB26-16
Hydromorphone HCl	24.0 mg	24.0 mg	24.0 mg	24.0 mg
	[redacted]			
Stearyl alcohol				
Capsules	Size # 1 blue	Size # 1 blue	Size # 1 blue	Size # 1 blue
Total	240.0 mg	240.0 mg	240.0 mg	240.0 mg

Dissolution was performed using the USP basket method at 100 r.p.m. at 37°C in 900 ml of SIF(simulated intestinal fluid) without enzyme plus [redacted] of NaCl. At 8 hr, the mean percent dissolved for CB26-15, 4L, 4L-B, and CB26-16 was 67.7%, 56.7%, 40.5%, and 34.8%, respectively. Figure 1 shows dissolution profiles and the mean drug plasma concentration *vs* time profiles of 4 formulations.

Figure 1: Dissolution Profiles of HHCR products (left), and the mean drug plasma concentration *vs* time profiles (right).

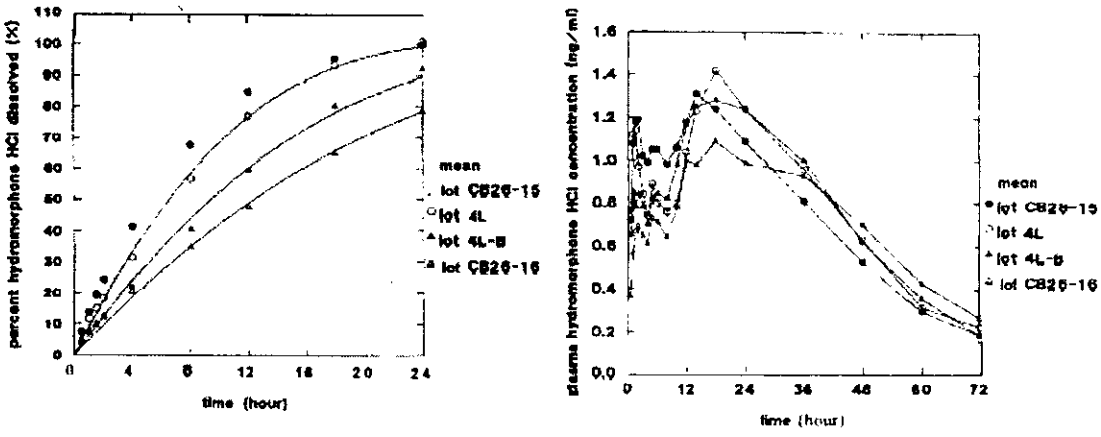


Table 1 lists C_{max} and AUC (0, last) values from each formulation's mean drug plasma concentration profile. Using all four formulations, C_{max}, a surrogate for rate, did not provide a rank-order agreement with dissolution due to CB26-15, which exhibited a lower C_{max} than 4L. Because C_{max} from CB26-15 did not follow the rank order agreement for C_{max} among the other three formulations, CB26-15 (the fastest release formulation) was not included in the development of the IVIVC.

Table 1: C_{max} and AUC (0, last) values from mean hydromorphone plasma concentration profile.

formulation	Cmax (ng/ml)	AUC(0,last) (ng · hr/ml)
CB26-15	1.31	54.2
4L	1.42	57.4
4L-B	1.28	57.5
CB26-16	1.09	52.9

Deconvolution of the mean plasma concentration profiles was performed using the Wagner-Nelson method[1]. The results are shown in figure 2, along with fraction absorbed vs. fraction dissolved plots.

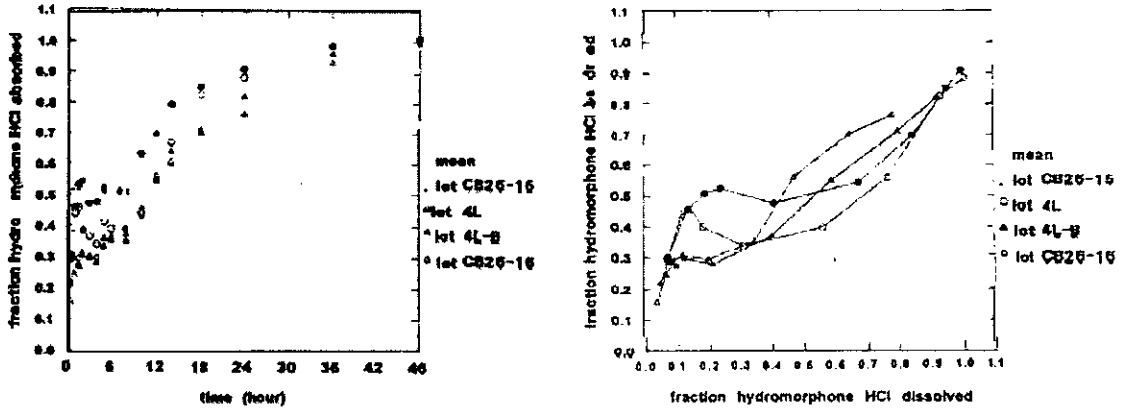


Figure 2: Fraction Absorbed Profiles according to Wagner-Nelson (left) and the fraction absorbed *versus* fraction dissolved (right).

IVIVC Predictability: Internal and External Predictability
In evaluating internal predictability, all three formulations (*i.e.* 4L, 4L-B, and CB26-16) were used in the development of the IVIVC. In evaluating external predictability, the 4L and CB26-16 were used to develop the IVIVC; 4L-B was used to externally evaluate the IVIVC's predictability. A convolution approach using PC-NONLIN to IVIVC was used and was performed in three phases (IVIVC development, IVIVC evaluation, and IVIVC application).
IVIVC development: The Akaike Information Criterion (AIC) was used to select the best fitting model, which represents the dissolution data for all formulations. The best fit model was then used in subsequent IVIVC development. To evaluate the internal predictability, the mean drug concentration plasma profiles of 4L, 4L-B, and CB26-16 were pooled into one data set, which was then used to ascertain a pharmacokinetic model. For the approach where external predictability was evaluated, the mean drug concentration plasma profiles of 4L and CB26-16 were pooled into one data set for pharmacokinetic model determination.

IVIVC Evaluation: Evaluation of IVIVC predictability was conducted through convolution of the dissolution profile, using the developed IVIVC pharmacokinetic model, and followed the criteria in the IVIVC guidance[2]. Internal as well as external IVIVC predictability was considered by the sponsor to be established if the average absolute percent prediction error (% *PE)* was 10% or less for C_{max} and AUC (0, last) and if % *PE* for each formulation did not exceed 15%. The % *PE was* determined by:

$$\% \ PE = \frac{Observed \quad value - Predicted \quad value}{Observed \quad value} \bullet 100$$

IVIVC Application: Lower limit dissolution specifications were determined from the two IVIVC models (*i.e.* one developed and evaluated from the internal predictability approach and one from external predictability approach). Lower specifications were identified such that the percent prediction difference from the observed lot 4L data (% PD_{obs}) were within 10% for C_{max} and AUC (0, last). Additionally, acceptable lower specifications required % PD_{obs} to be within *20%* of CB26-15.

$$\% PD_{obs} = \frac{observed \ reference \ value - predicted \ value \ at \ the \ specification \ limit}{observed \ reference \ value} 100\%$$

Upper limit dissolution specifications were primarily determined based upon the demonstrated bioequivalence of CB26-15 to 4L and CB26-15 to 4L-B and supported by the IVIVC's predicted bioequivalence of CB26-15 to lower dissolution limit specifications.

Results:

IVIVC Development: The Hixson-Crowell model was selected as the dissolution model for IVIVC development. The solid curves in Figure 1 are the Hixson-Crowell fits to 4L, 4L-B, and CB26-16. The Hixson-Crowell model, % dissolution, equation is;

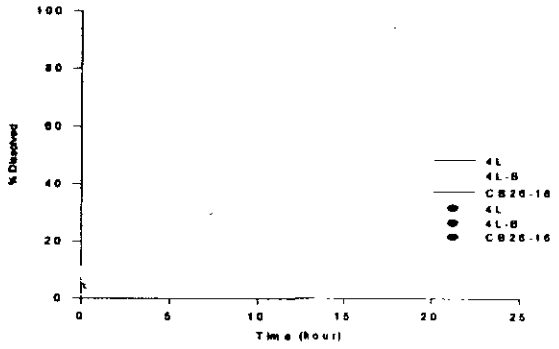
$$\% \ diss = 100[1-(1-{}^{kt}/_{dose^{1/3}})^3]$$

Table 2 lists fitted k values on four formulations and internal and external k values for the pooled dissolution data. Figure 3 is the fit of individual dissolution data using k values shown in Table 2.

Table 2: Fitted k parameter for the Hixson-Crowell function.

Formulation	k ($mg^{1/3}$/hr)
CB26-15	0.115 (±0.003)
4L	0.0908 (±0.0021)
4L-B	0.0633 (±0.0016)
CB26-16	0.0481 (±0.0010)
Internal	0.0654 (±0.0035)
External	0.0666 (±0.0053)

Figure 3: Fit of Hixson-Crowell model to observed dissolution Data: lines are obtained by simulations using k values in Table 2. Symbols are observed data.



PK model: One compartment with no lag time was chosen as the PK model for both the internal and external predictability. Pharmacokinetic model parameters are listed in Table 3 for Internal and external predictability.

Table 3: Internal and external Predictability approach: Fitted PK model parameters

Parameter	Fitted Value	
	Internal	External
V/F (L)	9410 (± 940)	10100 (± 1000)
K_e (hr^{-1})[a]	0.043 (± 0.0062)	0.0403 (± 0.0077)
K_p (hr^{-1})[b]	19.9 (± 211.7)	18.2 (± 235.1)

[a]terminal elimination rate constant. [b]absorption rate constant

IVIVC Evaluation: Internal and external IVIVC predictability are presented in Tables 4-5. The predicted plasma profiles for 4L, 4L-B and CB26-16 using Internal and External IVIVC are illustrated in Figure 4-5, respectively (Note: it appears that observed AUC_t or C_{max} values are obtained by the mean value at each sampling time point).

Table 4: Internal predictability approach: IVIVC evaluation for AUC (0,last) and C_{max}: IVIVC developed with 3 release rates.

Formulation	Observed AUC (ng•hr/ml)	Predicted[a] AUC (ng•hr/ml)	Predicted[b] AUC (ng•hr/ml)	% PE[a]	% PE[b]
4 L	57.4	55.6	55.38	3.1	3.5
CB26-16	52.9	53.3	53.41	-0.8	-1.0
4L-B	57.5	54.4	54.56	5.4	5.1
	Observed C_{max} (ng/ml)	Predicted C_{max} (ng/ml)	Predicted C_{max} (ng/ml)		
4 L	1.42	1.49	1.50	-4.9	-5.6
CB26-16	1.09	1.15	1.15	-5.5	-5.5
4L-B	1.28	1.30	1.30	-1.6	-1.6

[a]By the sponsor [b]By the reviewer

Figure 4: Observed and predicted plasma data using Internal IVIVC for 4L, 4L-B and CB26-16. (lines are by simulations and symbols are observed data)

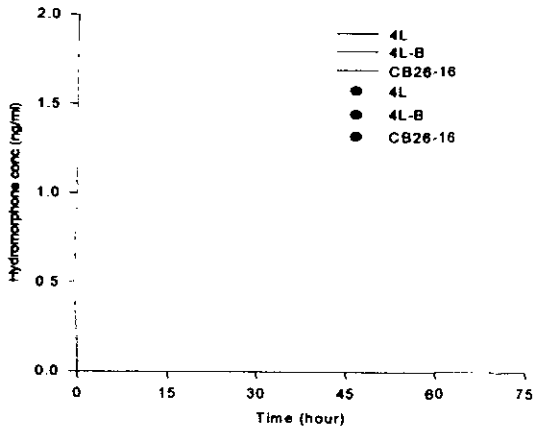
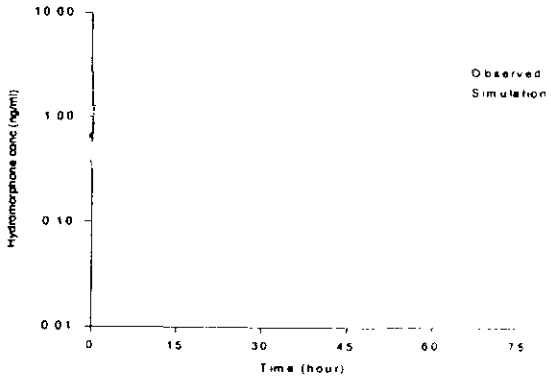


Table 5: The sponsor's external predictability approach: IVIVC evaluation for AUC (0,last) and C_{max}: IVIVC developed with 2 release rates.

		Internal		External	
Formulation	Observed AUC (ng•hr/ml)	Predicted AUC (ng•hr/ml)	% PE	Predicted AUC (ng•hr/ml)	% PE
4 L	57.4	55.6	3.1		
CB26-16	52.9	53.3	-0.8		
4L-B	57.5			53.4	7.1[a], 11.6[b]
	Observed C_{max} (ng/ml)	Predicted C_{max} (ng/ml)		Predicted C_{max} (ng/ml)	
4 L	1.42	1.49	-4.9		
CB26-16	1.09	1.15	-5.5		
4L-B	1.28			1.24	3.1[a], 5.5[b]

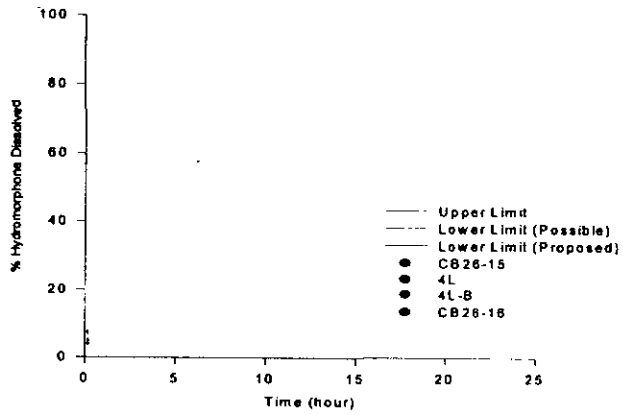
[a]sponsor's %PE [b]reviewer's %PE

Figure 5: Observed and predicted plasma data using External IVIVC for 4L-B.



IVIVC Application: The sponsor proposes dissolution specifications, referred to as "possible" or "proposed", based upon observed bioequivalence data and in vitro-in vivo correlation using a % PD_{obs} = 10% or 15%. "Possible" dissolution specification is defined as [redacted], (lower limit) and [redacted] (upper limit) at 2 hours; [redacted], (lower limit) and [redacted], (upper limit) at 8 hours; [redacted], (lower limit) at [redacted] ours. "Proposed" dissolution specification is the same as "possible" at 2 and 8 hours, but [redacted] (lower limit) at 22 hours. Comparison of the "possible" and "proposed" dissolution specifications to the study formulations are shown in Figure 6.

Figure 6: Comparison of the Possible and Proposed Dissolution Specifications; the fits of Hixson-Crowell model to the upper and lower specifications are drawn.



Dissolution Specifications justification Based upon IVIVC: In addition to the % prediction difference from the observed reference data (% PD_{obs}), the internally and externally validated IVIVC models each were assessed in terms of two other measures of IVIVC predictability; (a) the corrected % difference from the observed reference data (% PD'_{obs}), and (b) the % prediction difference from the predicted reference data (% PD_{pred}). Unless otherwise noted, the reference data was taken to be lot 4L, which is the market image formulation.

$$\% PD'_{obs} = \% PD_{obs} - PE_{app}$$

where % PE_{app} is the approximate % prediction error of the model and is taken to be the % PE from the closest formulation; 4L-B and CB26-15 were the formulations closest to the lower and upper dissolution specifications, respectively. % PD'_{pred} was determined from:

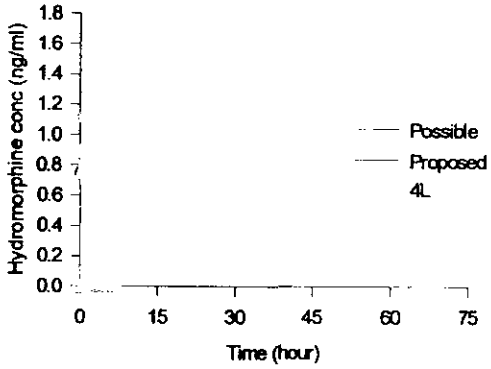
$$\% PD_{pred} = \frac{predicted\ reference\ value - predicted\ value\ at\ the\ specification\ limit}{predicted\ reference\ value} 100\%$$

(1) Lower limit specifications: Predicted plasma profiles are shown in Figure 7.

"Possible specification: Based on predicted values for AUC (0,last) and C_{max} from the internally validated model, the % PD_{obs} were [redacted] respectively. From the externally validated model, % PD_{obs} were [redacted] respectively. These results suggest that the potential lots with the possible dissolution specifications will be bioequivalent to 4L with respect to AUC (0,last) and C_{max}.

"Proposed specification: Based on predicted values for AUC (0,last) and C_{max} from the internally validated model, the % PD_{obs} were [ ] respectively. From the externally validated models they were [ ], respectively. Since the % PD_{obs} is — the specification needs to be tightened.

Figure 7: IVIVC Predictions for a Formulation at the "Possible" and "Proposed" Lower Dissolution Specification with 4L observed data.



(2) Upper limit specifications: Since the fast formulation was not included in the IVIVC development process, upper limit dissolution specifications were based upon the demonstrated bioequivalence of CB26-15 to 4L and CB26-15 to 4L-B.

Table 6: Summary of Pharmacokinetic Metrics (Arithmetic Means and Standard Deviations)

Metric	CB26-15	4L	LSM Ratio(%)[a]	90% CI[b]
AUC_t (ng/mL•h)	54.1 ± 12.54	58.73 ± 15.84	93.29	85.81-101.43
C_{max} (ng/mL)	1.52 ± 0.34	1.58 ± 0.25	96.02	85.71-107.57
T_{max} (h)	12.9 ± 3.78	14.25 ± 10.97		
	CB26-16	4L		
AUC_t (ng/mL•h)	52.49 ± 12.16	58.73 ± 15.84	91.01	83.71-98.94
C_{max} (ng/mL)	1.2 ± 0.28	1.58 ± 0.25	75.14	67.07-84.18
T_{max} (h)	21.8 ± 10.09	14.25 ± 10.97		
	4L-B	4L		
AUC_t (ng/mL•h)	57.52 ± 18.48	58.73 ± 15.84	96.5	88.76-104.91
C_{max} (ng/mL)	1.49 ± 0.33	1.58 ± 0.25	92.4	82.47-103.51
T_{max} (h)	17.6 ± 7.65	14.25 ± 10.97		

LSM = least squares mean. [a]Ratio (%) (test/reference) of least square means (ANOVA) derived from logarithmic- transformed values of AUC_t and C_{max}.
[b]90% confidence interval (CI) around the least squares means (LSM) ratio.

Based on observed bioequivalence data and the in vitro-in vivo correlation, the sponsor concluded that dissolution specification for HHCR 24 mg capsules are:

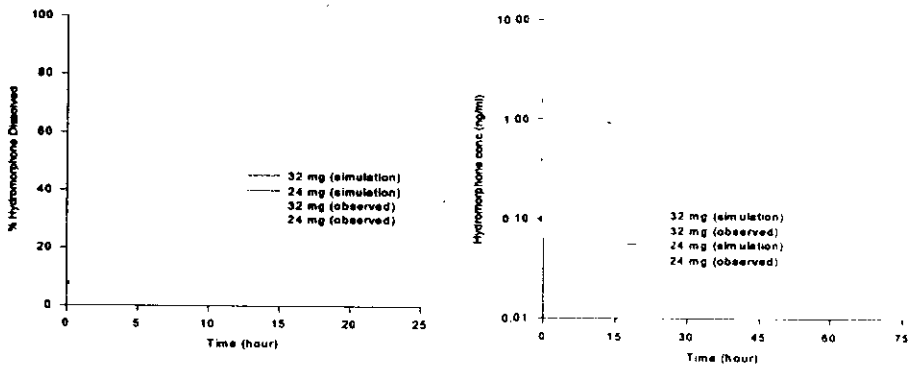
2 hours:
8 hours:
— hours:

Prediction for 24 and 32-mg strengths: Simulations were done by this reviewer using software called 'Simulation Control Program (ScoP)', developed by the Simulation Resources Inc.

Dissolution profiles: K parameter value of the Hixon-Crowell function for the observed dissolution data for 32-mg strength (data on page 65, Table 1) was — . Dissolution profile data for 24 mg (HD95-0701) was not provided, therefore it was assumed the dissolution profile would be similar to 4L (the to-be marketed formulation was used in this clinical trial). Predicted dissolution profile (along with observed dissolution data) using this k value is shown in Figure 8 (left panel).

Plasma concentrations: Predicted plasma hydromorphone concentrations following 24 and 32 mg dose (HD95-0805) using k values of — for 32 mg and — for 24 mg, and the same PK parameter values (which were used to develop IVIVC) are shown in Figure 8 (right panel) along with the observed data. The results show that 32 mg dose was under predicted (however, data for 32 mg strength may be confounded due to concomitant naltrexone administration). For 24-mg dose, % PE for C_{max} and AUC were [ ] respectively.

Figure 8: Fit of Hixon-Crowell model to the dissolution data (left) and Predictions of hydromorphone plasma concentrations following 24 and 32 mg dose (right).



Conclusions:

- Comparisons of AUC_t data indicated that all test lots were bioequivalent to the reference lot in terms of extent of absorption, although for Lot CB26-16 the mean C_{max} was lower and the mean t_{max} was longer than that of the reference lot.
- Plasma concentration-time profiles showed multiple peaks. However, data available does not indicate that multiple peaks are necessary for efficacy or safety of hydromorphone based on the data from clinical studies. Therefore IVIVC that predicts just one peak is considered reasonable for this product.
- While developing IVIVC, the fastest formulation was dropped, which makes the target formulation the fastest release rate studied in IVIVC, therefore there is no IVIVC data to cover upper range dissolution specification.
- It is not clear how the sponsor used IVIVC relationship in the model to evaluate IVIVC.
- It is not correct to use k values from the pooled data (always need to use individual formulation observed dissolution data). Also, it is not correct to use $\%PD'_{obs}$ or $\%PD_{pred}$.
- The sponsor needs to select only one model instead of two models (*i.e.*, external and internal model).

- The sponsor used two different 'KP' values, therefore, the sponsor needs to clarify the reason(s) for having two KP-values (simulation by the reviewer showed that KP did not affect the prediction of plasma hydromorphone concentration-time profile as long as KP >> k). Also, there should be only one-set of PK parameter values.
- Using the model/parameter values, the plasma hydromorphone concentration-time profile following a 32 mg dose was under predicted and that of 24 mg dose was over predicted.
- These comments were communicated to the sponsor via teleconference. The sponsor was requested to address these comments and provide (1) explanation of their IVIVC model and (2) external predictability evaluation of 12, 24 or 32 mg strength data.
- Since there are issues/questions to be answered by the sponsor, the IVIVC as well as dissolution specifications will be reviewed later, at appropriate time.

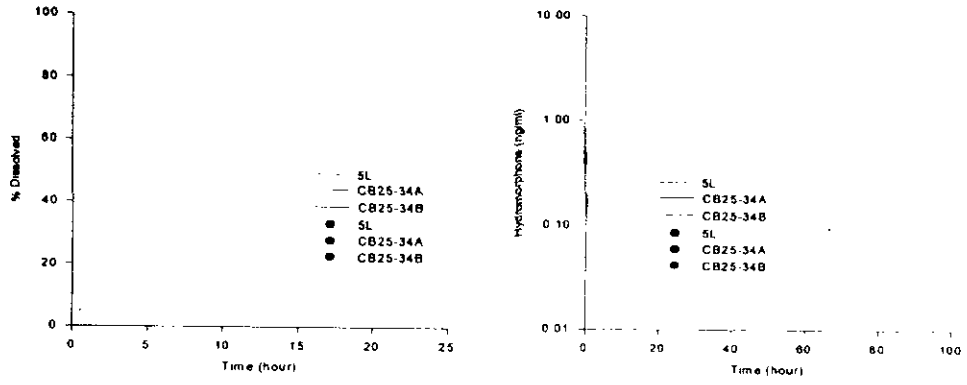
The following summarizes the submitted package from the sponsor (September 15, 1999) after the teleconference communication (*i.e.*, response received from the sponsor regarding our comments).

External validation of HHCR IVIVC Model using HD96-1206 study: The sponsor (and the reviewer) used a fixed value of KP, —, assumed a 1:1 relationship between dissolution and absorption, and used an internally validated IVIVC model (using 3 release rates) to predict the data from the study, HD96-1206 for 24 mg strength.

Dissolution profiles: K parameter values of the Hixon-Crowell function for the observed dissolution data for 5L, CB35-34A and 34B were [redacted] respectively. Predicted dissolution profiles (along with observed dissolution data) using these k values are shown in Figure 9 (left panel).

Plasma concentrations: Predicted plasma hydromorphone concentrations following HHCR (from 3 lots), using k values, above, and the same PK parameter values (which were used to develop IVIVC) are shown in Figure 9 (right panel) along with the observed data.

Figure 9: Fit of Hixon-Crowell model to the dissolution data (left) and Predictions of hydromorphone plasma concentrations from 3 lots (right).



The External validation of HHCR IVIVC model for 3 lots from the study HD96-1206 is shown in the table below:

		Sponsor		Reviewer	
Formulation	Observed[a] AUC (ng•hr/ml)	Predicted AUC (ng•hr/ml)	% PE	Predicted AUC (ng•hr/ml)	% PE
5 L	54.96	55.64	-1.2	55.44	-0.9
CB25-34A	58.03	55.23	4.8	55.30	4.7
CB25-34B	54.64	54.41	0.4	54.98	-0.6
	Observed[a] C_{max} (ng/ml)	Predicted C_{max} (ng/ml)	% PE	Predicted C_{max} (ng/ml)	% PE
5 L	1.27[a] or 1.4[b]	1.47	-15.7[a] or -5[b]	1.52	-19.7[a] or -8.6[b]
CB25-34A	1.34	1.41	-5.2	1.47	-10
CB25-34B	1.28	1.30	-1.6	1.39	-8.6

[a]Observed from the mean profile.
[b]Based on observed individual subject profiles

In addition, %PE for C_{max} for 4L, 4L-B and CB26-16 using Dmax model for the dissolution data and conventional (or numerical method) convolution method (simulations were done by P. Marroum and R. Uppoor), were 0.7, 4.0 and -3.2%, respectively. Percent PE (%PE) for AUC_{0-24} for 4L, 4L-B and CB26-16 were -6.8, 9.4 and 7.9%, respectively. Similarly, %PE (or $\%PD_{obs}$) for C_{max} and AUC_{0-24} for lower limit dissolution specifications (¯ at 2 hours, — at 8 hours and — at ¯hours) were — and — respectively.

Conclusion: It appears that IVIVC is satisfactorily established (limited to release rates lower than the to-be marketed product). Since %PE for lower limit dissolution specifications for both C_{max} and AUC_{0-last} were — the sponsor's 'Possible' lower limit dissolution specifications seem appropriate. Upper limit dissolution specifications are set to give a range of no more than — range (between lower and upper specifications) or — , from the target profile at each time point (since there is no established IVIVC at release rate faster than the to be marketed product). The agency, however agrees with the sponsor's dissolution method.

The (agency's) recommended dissolution specifications are:

Time (hours)	Lower	Upper
2		
8		
—	NLT	-

NLT = not less than

Comment: In future, if a major change is made to the HHCR product that requires a biostudy, IVIVC can be used to grant biowaiver only when the release rates are lower than the to-be marketed product. However, since bioequivalence has been shown between CB26-15 and 4L, it is possible to grant waivers within the dissolution range of CB26-15 and IVIVC (at 2 hrs: — at 8 hrs: — and at — hrs not less than —).

DISSOLUTION METHODOLOGY

Summary of Studied Dissolution Methods and Proposed Specification

Dosage Form:	Capsules
Strengths:	12, 16, 24, and 32 mg
Apparatus Type:	USP Apparatus I (Basket)
Media:	Simulated Intestinal Fluid (SIF), without enzyme plus — NaCl
Volume/ Temperature:	900 mL / 37 °C
Speed of Rotation:	100 rpm
Sampling time:	1, 2, 4, 8, 12, 18, 22 and 24 hours

Dissolution in different media and pH: The sponsor evaluated dissolution profiles in many different media, *i.e.*, SGF (USP), SIF (+ KH_2PO_4), SIF (USP), Sodium Phosphate and Potassium phosphate with different amounts of chloride ions. The sponsor reported that the results indicated that the concentration of chloride ion in the dissolution medium was critical in order to obtain the proper dissolution profile. Typical examples of the dissolution data of HHCR 12 mg capsules using dissolution media of SIF without enzyme at pH 7.5 containing [redacted] of NaCl/L are shown in Figure 1. Based on the dissolution profile shown in Figure 1, the sponsor determined that SIF without enzyme at pH 7.5 containing — of NaCl/L should be used as the dissolution medium. Additionally, the dissolution of HHCR in different pH varying from 1.7 to 7.5 was carried out (— NaCl/L in the same medium), and the results are shown in Figure 2. This graph indicates that the HHCR dissolution is pH independent.

Figure 1

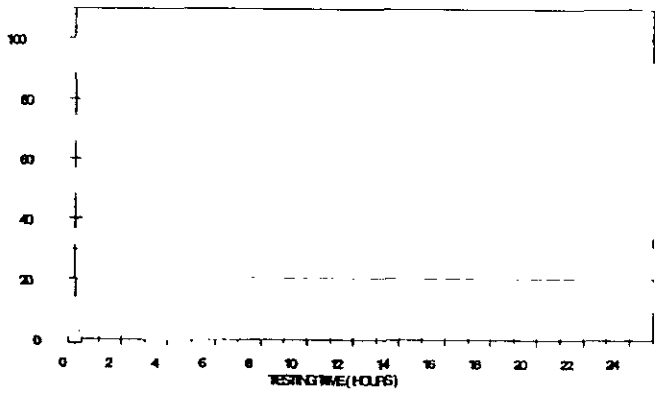


Figure 2

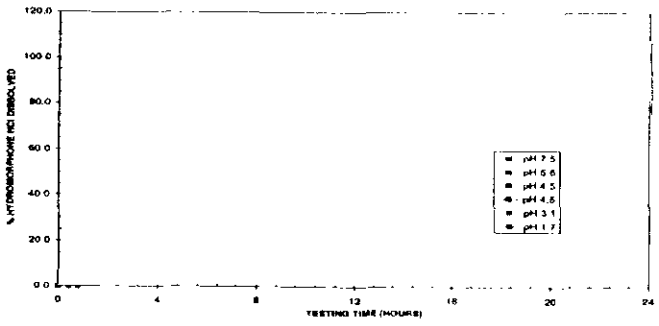


Table 1: Representative dissolution testing data for each strength and dosage formulation.

Date of Test	Dosage Strength Dosage Form	Lot Number	No. Units Tested	Collection Time (hours) / Range / Mean % Dissolved / RSD						
				1	2	4	6	12	18	24
10/11/96	12 mg capsule	9K [2]	12	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
				11.8	18.4	32.1	56.6	75.5	91.6	97.8
				4.9	4.7	3.9	4.6	3.7	2.8	2.8
10/16/96	16 mg capsule	1L [3]	12	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
				10.7	18.4	35.2	61.7	80.0	92.4	98.4
				5.0	6.0	6.0	4.1	2.9	2.8	2.4
7/14/97	24 mg capsule	4L [1,2]	12	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
				11.5	18.3	30.9	55.9	75.3	92.6	101.3
				2.7	3.4	3.2	3.0	2.5	1.6	1.9
9/4/97	24 mg capsule	4L [1,2]	12	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
				12.0	19.0	32.2	57.5	78.2	94.0	100.1
				3.0	2.3	4.8	7.3	3.3	2.5	2.4
7/15/97	24 mg capsule	4L-B [1]	12	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
				7.8	12.6	21.7	39.2	56.5	78.2	90.8
				2.9	2.1	2.7	2.1	2.5	2.4	2.2
9/5/97	24 mg capsule	4L-B [1]	12	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
				7.8	13.1	21.7	41.9	62.0	82.1	93.3
				4.6	3.6	2.8	2.7	1.9	1.9	1.8
6/30/97	24 mg capsule	CB26-15 [1]	12	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
				14.0	24.7	41.7	68.6	86.1	96.3	100.6
				3.0	2.5	2.8	3.1	2.2	1.8	1.6
9/22/97	24 mg capsule	CB26-15 [1]	6	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
				13.2	23.2	40.2	65.9	82.1	92.9	98.3
				0.6	1.2	1.1	1.3	0.7	1.2	0.7
7/2/97	24 mg capsule	CB26-16 [1]	12	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
				6.9	12.1	19.9	33.6	46.2	63.2	76.1
				4.9	2.2	2.3	2.0	1.8	2.4	2.7
9/22/97	24 mg capsule	CB26-16 [1]	6	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
				7.4	12.6	21.4	37.1	50.4	68.7	83.1
				3.1	2.0	1.6	1.2	1.3	1.6	1.3
10/22/96	32 mg capsule	8L [2]	12	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
				11.0	17.7	30.9	55.0	73.9	90.0	98.5
				2.9	3.7	3.2	4.8	2.8	1.9	1.4

[1] These lots were used in the 24 mg capsules in vivo bioequivalence study.
[2] These lots were used in the 32 mg capsules in vivo bioequivalence study.
[3] This lot was not used in either bioequivalence study

Sponsor proposed Dissolution Specification (in their specification sheet):

/ **at 2 hours**
at 8 hours
% at 22 hours.

Sponsor proposed dissolution specification based on IVIVC report:

/ **at 2 hours**
at 8 hours
at

The dissolution specification was determined based on IVIVC analysis and bioavailability/bioequivalence studies.

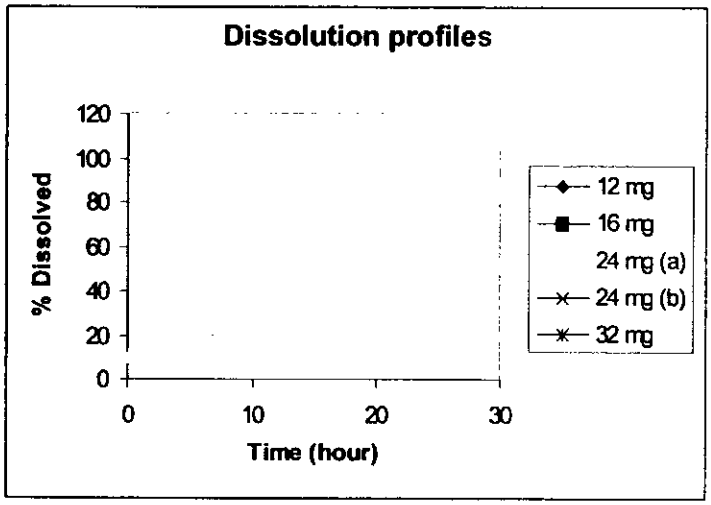
Conclusions:

The sponsor proposed dissolution method is acceptable. The (agency's) recommended dissolution specifications are (see pages 63-64 of this review):

/ **at 2 hours**
at 8 hours
Not less than **at**

BIO-WAIVER FOR THE SIXTEEN MG STRENGTH

Plot of dissolution profiles for different strengths (the data are shown on page 65) is shown below, including 16 mg strength (Note: 24 mg a and b refer to date tested a = 7/14/97; b = 9/4/97).

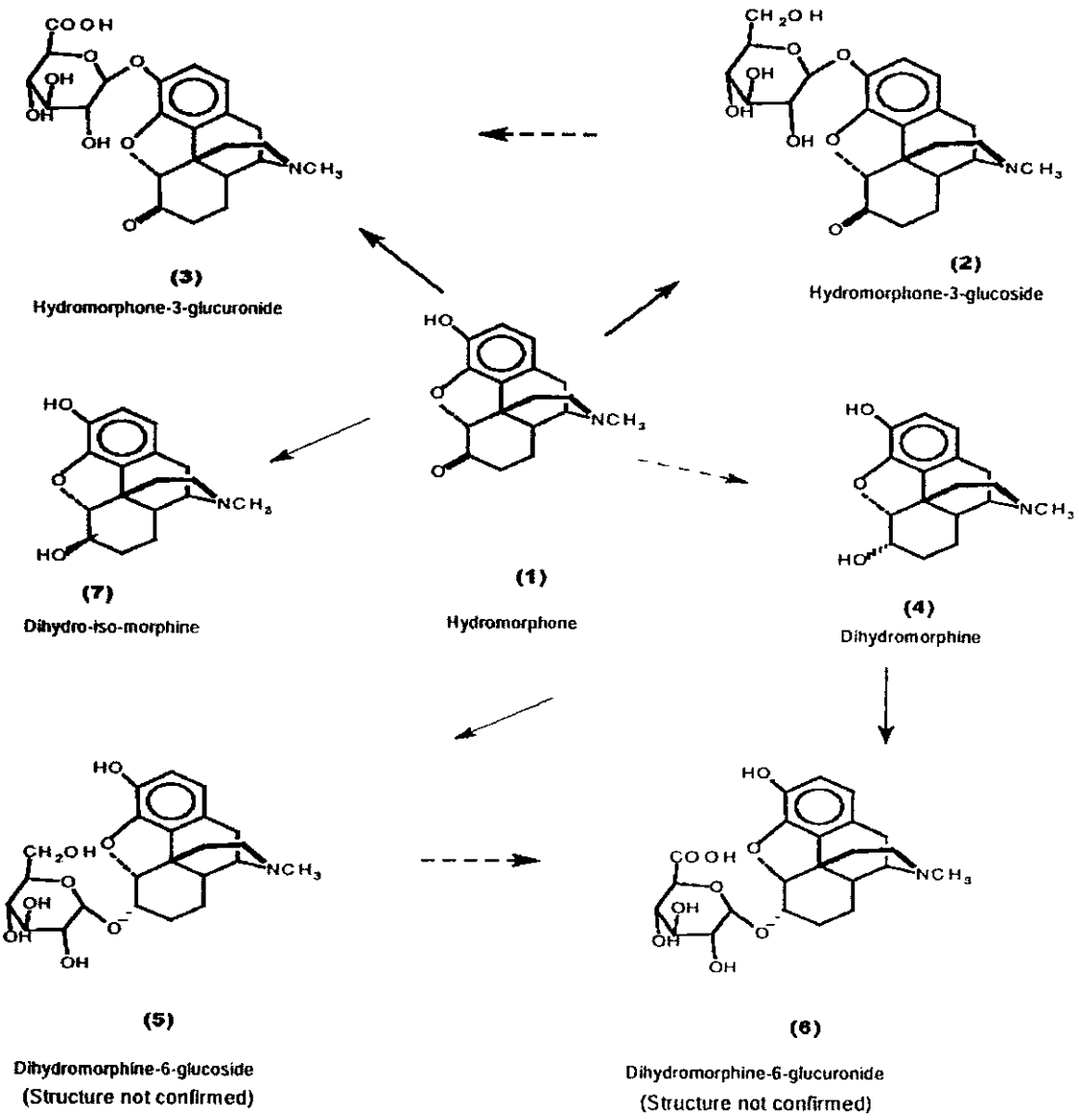


Bioequivalence was established on HHCR product for, 2 x 12 mg *vs.* 24 mg and 3 x 12 mg *vs.* 32 mg capsules. Sixteen-mg capsule strength was not evaluated, however, the only difference in capsule contents among the four strengths is incremental weights of common pellets. Thus, as expected dissolution profile for 16-mg strength is similar to other strengths (Figure above). In addition, f_2 factor between 16 mg and 24 mg (Lot tested on 7/14/97) is calculated to be 72.2, therefore, it can be said that dissolution profiles of these two are similar (and two strengths are considered bioequivalent). Note: Dissolution of HHCR is pH independent, therefore, comparison of this profile in one dissolution medium is sufficient.

Conclusion:

A biowaiver for 16-mg strength can be granted.

Proposed hydromorphone metabolism pathways



Since the metabolism of hydromorphone and most opioids is generally understood (6-ketoreduction and conjugation), hydromorphone and its metabolites in human plasma, urine and human hepatocyte incubations from HHCR formulation was compared to HHIR formulation using [ ] technology and where available, reference standards and NMR support. Results indicate that the metabolites identified from both controlled-release and immediate release formulations are the same. Therefore, it can be concluded that the hydromorphone metabolite profile from the HHCR formulation is not different from that generated by the HHIR formulation.

Reference: (1) Cone J and Darwin D (1978), Biomedical Mass Spec. Vol5, No.4; 291-296.
(2) Babul N. (1995), Letter, Vol 10 No. 5; 336-337