CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20747

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA: 20-747 **RELATED IND:**
NAME: Actiq™ (Oral Transmucosal Fentanyl Citrate) 200, 400, 600, 800, 1200, and 1600 μg
SPONSOR: Anesta Corp., 4745 Wiley Post Way, Plaza 6, Suite 650, Salt Lake City, Utah
TYPE OF SUBMISSION: Original NDA **SUBMISSION DATE:** November 11, 1996
REVIEWER: Suresh Doddapaneni, Ph.D. **REVIEW DATE:** April 22, 1997

SYNOPSIS

Actiq™ (Oral Transmucosal Fentanyl Citrate) is fentanyl incorporated into a sweetened matrix (lozenge on a stick) that is designed to provide pain relief in chronic pain patients and is proposed to be marketed in strengths of 200, 400, 600, 800, 1200, and 1600 μg. The dosage units are manufactured in a base of sucrose, liquid glucose, food color (off white), and raspberry flavor with fentanyl citrate and are designed to be sucked for 15 minutes for the complete release of fentanyl. Fentanyl Oralet®(OTFC), a similar dosage form, was approved for marketing in the United States in October of 1993 at lower strengths of 100, 200, 300, and 400 μg for use in adults and children as an anesthetic premedication in the operating room setting, and to induce conscious sedation prior to a diagnostic or therapeutic procedure in other monitored anesthesia care settings in the hospital (NDA 20-195). The use of OTFC for the management of chronic pain, particularly breakthrough pain, in patients who are already receiving and are tolerant to opioid therapy is a new indication for OTFC and is not approved for marketing in any country.

The pharmacokinetics of OTFC following single doses for use as anesthetic premedicant and conscious sedation have been characterized in healthy adults and children in NDA 20-195. In the current NDA, dose-proportionality of OTFC in the range of 200-1600 μg was demonstrated thus linking up the pharmacokinetics of Actiq™ with Fentanyl Oralet®. *In vitro* drug metabolism studies showed that fentanyl metabolism to its major inactive metabolite, norfentanyl is mediated by cytochrome P450 3A4 isozyme. A bioequivalency study was conducted to demonstrate equivalency between the red, raspberry formulation used in Fentanyl Oralet® and off white, lemon formulation developed to be used in Actiq™, although the final formulation used in Actiq™ involved only a change in color because of manufacturing problems. A multiple dose pharmacokinetic study was conducted to investigate the potential for accumulation. However, inadequate study design in terms of not mimicking the clinical use situation did not permit the evaluation of true multiple dose pharmacokinetics under real life use conditions. The dosage regimen used in this study (three consecutive doses of 800 μg doses at 6 hour intervals) does not reflect the true usage of this product in terms of the dose (Out of 25,160 OTFC units used to treat 21,758 breakthrough pain episodes, 1600 μg unit dose represented the most commonly used unit (22.5% of the total units)), or the dosing interval ((maximum total dose was 7200 μg administered over 3-3/4 hours in chronic pain trials) to evaluate the altered absorption pharmacokinetics or the potential for accumulation. Direct evidence of the safety of this product under these conditions has to be derived from these chronic pain trials.

RECOMMENDATION

Section 6 of NDA 20-747 is acceptable from the viewpoint of Office of Clinical Pharmacology and Biopharmaceutics. Revised pharmacokinetic section of the package insert should be sent to the sponsor.

/S/ 6/12/97

Suresh Doddapaneni, Ph.D.
Pharmacokineticist, DPE II/OCPB

RD initialed by Dale Conner, Pharm.D. on 5/1/97
FT initialed by Dale Conner, Pharm.D.: /S/ 6/12/97
CC:NDA 20-747 (Original), HFD-170 (Division files, MWright), HFD-850 (Lesko), HFD-870 (Doddapaneni, Mei-Ling Chen, Conner), HFD-340 (Viswanathan), CDER (Barbara Murphy).

TABLE OF CONTENTS

1.0. INTRODUCTION

Fentanyl is currently marketed as a Transdermal Patch by Alza (Duragesic®, NDA 19-813, 0.6, 1.2, 1.8, and 2.4mg/24hour), fentanyl citrate injection in a strength of 0.05 mg base/mL and Janssen- (NDA 16-619). It is available orally as Fentanyl Oralet®(Oral Transmucosal Fentanyl Citrate), which was approved for marketing in the United States in October of 1993 for use in adults and children as an anesthetic premedication in the operating room setting, and to induce conscious sedation prior to a diagnostic or therapeutic procedure in other monitored anesthesia care settings in the hospital (NDA 20-195). Fentanyl Oralet® is available in strengths of 100, 200, 300, and 400 µg. The use of OTFC for the management of chronic pain, particularly breakthrough pain, in cancer patients who are already receiving and are tolerant to opioid therapy is a new indication for OTFC (named Actiq™ for this indication) and is not approved for marketing in any country. Actiq is available in strengths of 200, 400, 600, 800, 1200, and 1600 µg. The rationale behind separating the anesthetic premedicant OTFC (Fentanyl Oralet®) and cancer pain OTFC (Actiq) which are almost identically formulated (except for the color), as two distinct products is to avoid potential medication errors where the higher strengths suitable for cancer pain relief could be accidentally prescribed for anesthetic premedication. OTFC's primary therapeutic value is the delivery of fast-acting, relatively short duration, non invasive, self-titratable drug in a convenient dosage form.

The pharmacokinetics of OTFC following single doses for use as anesthetic premedicant and conscious sedation have been characterized in healthy adults and children in NDA 20-195. Four pharmacokinetic studies were conducted in 48 healthy volunteers in this NDA. Pharmacokinetic trials were designed; (1) To characterize the *in vitro* drug metabolism of fentanyl (2) To demonstrate that multiple dosing does not alter absorption pharmacokinetics in volunteers (3) To demonstrate dose-proportionality of 200 to 1600 µg OTFC and (4) To demonstrate bioequivalence of two OTFC formulations - an off white lemon formulation and a red raspberry formulation.

2.0. OVERVIEW OF THE PHARMACOKINETIC CHARACTERISTICS OF OTFC

The different strengths of Actiq™ have the same unit weight (same inactive ingredients ratio) with the fentanyl amount comprising less than 1% of the total unit weight. Since dose-proportionality was demonstrated at the higher strengths for Actiq™, sponsor used the following pharmacokinetic information developed for NDA 20-195 in support of the current NDA.

Fentanyl is highly lipophilic and is therefore conjugated with citric acid to impart water solubility. The pKa of fentanyl is 8.4. At physiologic pH, fentanyl exists primarily in the ionized state (less than 10% unionized).

After intravenous injection, the pharmacokinetics of fentanyl have been described by both three and two compartment models. Fentanyl exhibits a high total body clearance (13.3 mL/kg/minute) with liver as the principal site of metabolism. Seventy-five percent of an iv dose is recovered in the urine with less than 10% as unchanged fentanyl. Approximately 9% of the dose is recovered in the feces, mainly as metabolites. Norfentanyl, which was inactive in animal studies, is the major metabolite. The volume of distribution is 4 liter/kg. The plasma protein binding of fentanyl is 80-85%. Binding to plasma proteins is pH dependent with an increase in binding as pH rises. At a pH of 7.6, fentanyl is 90% protein bound.

Oral administration of fentanyl results in poor bioavailability due to the first pass effect. The absorption pharmacokinetics of fentanyl from the oral transmucosal dosage form are a combination of an initial rapid absorption from the buccal mucosa and a more prolonged absorption of swallowed

fentanyl from the GI tract. Both the blood fentanyl profile and the bioavailability of fentanyl will vary depending on the fraction of the dose that is absorbed through the oral mucosa and the fraction swallowed. Normally, about 25% of the total dose is rapidly absorbed from the buccal mucosa and becomes systemically available. The remaining 75% of the total dose is swallowed with the saliva and then is slowly absorbed from the GI tract. Therefore, the generally absorbed 50% bioavailability of OTFC is divided equally between rapid transmucosal and slower GI absorption. Chewed or swallowed fentanyl contributes little to the peak concentration, but can contribute to the prolonged tail on the blood level profile as it is slowly absorbed, increasing the duration of action of OTFC.

In general, the pharmacokinetic profile of OTFC was similar in adult and pediatric patients. Opioid non-tolerant elderly patients have been shown to be twice as sensitive to the effects of fentanyl when administered intravenously compared with younger population. Fentanyl kinetics are known to be altered in both hepatic and renal disease, due to alterations in metabolic clearance and plasma proteins, although individualized doses of OTFC have been used successfully in anesthesia in both kinds of disorders. For these reasons, reduced doses are recommended in the elderly, and in patients with severe hepatic disease and/or renal disease.

3.0. *IN VITRO* METABOLISM OF FENTANYL

The biotransformation of fentanyl was studied in human hepatic and duodenal microsomal preparations in order to isolate and characterize the primary route(s) and identify the predominant P450 isoform(s) responsible for human fentanyl metabolism. Since, Actiq® is proposed to be used for treating breakthrough pain in patients who are already receiving steady doses of other analgesics (opioids), potential drug-drug metabolic interactions can be isolated if the metabolism of fentanyl and these other opioids is mediated by the same cytochrome P450 isoform.

Piperidine N-deaklyation to norfentanyl was found to be the predominant pathway of human liver and duodenal microsomal fentanyl metabolism. Amide hydrolysis to despropionylfentanyl and alkyl hydroxylation to hydroxyfentanyl were minor pathways. The average rate of norfentanyl formation in the duodenum was approximately half that of hepatic microsomal metabolism. The mechanism-based CYP3A4 inhibitor troleandomycin and the CYP3A4 substrate and competitive inhibitor midazolam significantly inhibited norfentanyl formation. Of the six expressed human P450 isoforms, CYP3A4 was the only one to exhibit significant catalytic activity towards fentanyl dealkylation to norfentanyl.

The clinical implications of these results is that (1) The fraction of fentanyl that is swallowed during OTFC administration likely undergoes significant pre-hepatic first-pass metabolism in the intestine and (2) Both intestinal and hepatic first-pass metabolism may also be subject to individual variability in CYP3A4 expression and to drug interactions involving CYP3A4.

A large number of clinically important drugs act as substrates of the cytochrome CYP3A which comprises as much as 60% of the total cytochrome P450 content of the liver. The potential for metabolism based drug-drug interactions associated with the use of OTFC involves both first pass effects on swallowed fentanyl and clearance effects on fentanyl which has reached the systemic circulation. However, CYP3A4 is not involved in the metabolism of morphine (glucuronidation), oxycodone (CYP2D6), hydromorphone (primarily glucuronidation) which are the most commonly used opioid drugs for chronic cancer pain. The sponsor reportedly conducted a comprehensive Medline literature search involving fentanyl and various substrates, inhibitors, and inducers of CYP3A4 which did not yield any clinically relevant reports. See study summary for a detailed list of inhibitors, inducers and substrates of CYP3A4 isozyme.

Results from this study support the labeling claim of "Fentanyl is metabolized primarily in the liver, and to a lesser extent in the intestinal mucosa to norfentanyl by cytochrome P450 3A4 isoform. Norfentanyl is not pharmacologically active".

4.0. DOSE-PROPORTIONALITY OF OTFC

This study was an open-label, randomized, four-period, single-dose, complete cross over design to evaluate the dose proportionality of four dose levels of OTFC (200, 400, 800, 1600 µg fentanyl citrate) in 12 healthy male subjects (protocol AC 200/009).

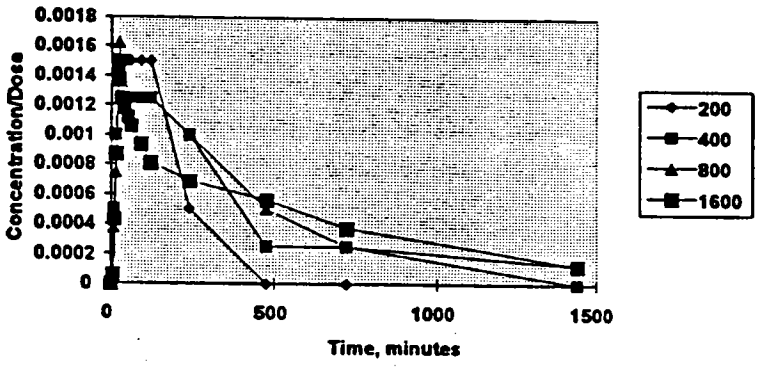


Figure 1. Dose normalized mean serum concentration-time profiles of fentanyl after the administration of 200, 400, 800, and 1600 µg OTFC.

The dose-normalized, mean serum concentration-time profiles of fentanyl after the administration of the four doses of OTFC show that the profiles for the four doses in general appear to be similar but they do not completely overlap each other in the distributive and terminal phases. The smallest dose, 200 µg, appears to separate itself out with the 400, 800, and 1600 µg doses appearing to be more closer to each other.

Table 1 shows the mean pharmacokinetic parameters for the four treatments. Mean C_{max} and $AUC_{0-\infty}$ increased in a dose proportional manner that was approximately proportional to the OTFC administered dose level. The mean $t_{1/2}$ for the 400, 800, and 1600 µg doses was similar (358-386 minutes) but that of the 200 µg dose was smaller (193 minutes) resulting in a statistically significant difference between the doses. In dose-proportionality studies, it is common to find that the lowest dose tested (especially if the resulting concentrations are relatively low) dose appears to deviate from dose-proportionality. The half-life at the lower dose of 200 µg of OTFC could have been affected by the concentrations in the terminal phase being close to the limit of quantification and therefore resulting in the incomplete characterization of the terminal phase.

Results from this study support the labeling claim of "Dose proportionality among four of the available strengths of Actiq® (200, 400, 800, and 1600 µg) has been demonstrated in healthy volunteers. Mean serum fentanyl levels following these four doses of Actiq® are shown in Figure 2. The curves for each dose level are similar in shape with increasing dose levels producing increasing serum fentanyl levels. C_{max} and $AUC_{0-\infty}$ increased in a dose-dependent manner that is

approximately proportional to the Actiq® administered dose level".

Table 1. Pharmacokinetic parameter values of fentanyl after the administration of 200, 400, 800, and 1600 µg OTFC (mean (% CV)).

Pharmacokinetic Parameter	200 µg	400 µg	800 µg	1600 µg
Dose (µg/kg)	2.61 (13)	5.24 (13)	10.5 (13)	20.9 (12)
T_{max}, minute	61 (70)	55 (118)	44 (89)	61 (216)
C_{max}, ng/mL	0.39 (23)	0.75 (33)	1.55 (30)	2.51 (23)
AUC_{0-1440}, ng/mL minute	102 (65)	243 (67)	573 (64)	1026 (67)
$AUC_{0-\infty}$, ng/mL minute	130 (49)	308 (84)	661 (72)	1153 (74)
$t_{1/2}$, minute	193 (48)	386 (115)	381 (55)	358 (45)

5.0. PHARMACOKINETIC PROFILE AFTER ADMINISTRATION OF MULTIPLE DOSES OF OTFC

This was an open-label, randomized, complete crossover study with an OTFC phase and an intravenous phase conducted in 12 healthy subjects (5 females and 7 males). In the OTFC phase of the study, the pharmacokinetics and safety of multiple administration (3 doses) of 800 µg OTFC in adult healthy volunteers was evaluated (protocol AC 200/005). The subjects received three separate OTFC units with 6-hour interval between administrations. In the intravenous phase of the study, the subjects received one fentanyl infusion of 15 µg/kg (50 µg/minute). The intent of the study was to examine if absorption pharmacokinetics are altered and accumulation occurs upon multiple dosing.

The design of this study does not reflect the clinical use situation. The terminal half-life of fentanyl when administered as OTFC dosage form is about 6-7 hours. Although the intent was to examine multiple dose pharmacokinetics, only three consecutive doses of 800 µg OTFC at 6 hour intervals were administered in this study and as such, the study design did not permit the evaluation of the pharmacokinetics of fentanyl under true multiple dosing conditions. According to the labeling instructions, four or fewer units per day is the maximum recommended dosage. During titration phase, redosing for ongoing episodes may start 15 minutes after the previous unit has been completed. In fact, in the chronic pain trials, patients were exposed to larger doses of OTFC in shorter intervals (maximum total dose was 7200 µg administered over 3-3/4 hours) than what was tested in the current study. Ideally, the study should have characterized the multiple dose pharmacokinetics at the highest strength (1600 µg) and at 15 minute intervals for four doses. If patients needed more than four units per day, the labeling instructs the physician to increase the around-the-clock opioid dose used for persistent pain in patients experiencing more than four breakthrough pain episodes daily.

The increasing values of C_{360} concentrations over the three OTFC administrations confirmed that steady state was not reached in this study (Table 2). The AUC's were also slightly higher in the second and third administrations relative to the first administration. Therefore, the sponsor resorted to indirect techniques to evaluate if absorption pharmacokinetics are altered along with the potential for accumulation (sponsor states that none of these methods by themselves are ideal, but viewed as

a group, they indicate that absorption pharmacokinetics are not affected by multiple dosing). This involved;

(i). Simple inspection of raw serum fentanyl concentration-time data for all individual subjects. Conclusion was that there was no obvious alteration in the concentration-time profile with multiple dosing.

(ii). Inspection of serum concentration-time profiles to see if there are any gross alterations in the concentration-time profile. Conclusion was that peak concentrations and time to peak concentration were similar among administrations indicating that absorption kinetics did not change after multiple dosing.

(iii). Compartmental modeling to fit the serum fentanyl concentration-time profiles for both the OTFC and fentanyl data. Conclusion from this approach was that K_a (first order absorption rate constant) and F (bioavailability) did not appear to change with the dosing regimen used in this study.

The above approaches would detect only gross alterations in the pharmacokinetics of fentanyl. Since proportionality at single doses was already demonstrated up to 1600 µg and only three doses were administered at intervals of one terminal half-life (i.e., doses were not administered high enough, quick enough, or long enough), it is not surprising that no obvious alterations in the pharmacokinetics were observed. The information from this study is only supportive at best and no firm conclusions on the multiple dose pharmacokinetics should be made. However, direct evidence of the safety of this product under real life multiple dosing situations is available from the chronic pain clinical trials where patients were exposed to doses up to 7200 µg over 3-3/4 hours. There were no reports of respiratory depression or hypoventilation at these doses. Since this is the only study that included female subjects in this NDA, gender effect on the pharmacokinetics was examined. No statistically significant gender differences were found in the pharmacokinetics of fentanyl.

Table 2. Summary of pharmacokinetic parameter values after the administration of three consecutive doses of 800 µg OTFC at 6 hour intervals.

Pharmacokinetic Parameter	First Dose	Second Dose	Third Dose
Time period, minutes	0-360	360-720	720-2160
T_{max}, minute	42 (95)	40 (158)	44 (143)
C_{max}, ng/mL	2.10 (28)	2.05 (25)	1.92 (36)
C_{360}, ng/mL	0.61 (44)	0.79 (42)	0.89 (52)
AUC_{0-360}, ng/mL minute	343 (23)	393 (28)	409 (37)
$AUC_{0-\infty}$, ng/mL minute	744 (40)	893 (41)	893 (56)
$t_{1/2}$, minute	-	-	7.2 (30)

Poor design of this study does not permit the sponsor's following labeling claims of "Multiple dosing of Actiq® at 6 hour intervals in healthy volunteers does not alter absorption pharmacokinetics and the drug did not accumulate" from this study. The dosage regimen used in this study does not reflect the true usage of this product in terms of the dose (Out of 25,160 OTFC

units used to treat 21,758 breakthrough pain episodes, 1600 µg unit dose represented the most commonly used unit (22.5% of the total units)), or the dosing interval ((maximum total dose was 7200 µg administered over 3-3/4 hours in chronic pain trials) to evaluate the altered absorption pharmacokinetics or the potential for accumulation.

6.0. BIOEQUIVALENCE OF TWO FORMULATIONS OF OTFC

The objective of this randomized, two-way cross-over study conducted in 24 healthy volunteers was to determine the bioequivalency of white, lemon flavored and red, raspberry flavored formulations of 800 µg OTFC (AC 200/008). The rationale behind the change over from the red, raspberry (fentanyl Oralet®) to white, lemon flavored (at one time proposed to be used in Actiq®) formulation is that the raspberry flavor might present an undesirable flavor in cancer patients and its attractive red color might result in an abuse potential in the children. According to the regulations, the sponsor need not have conducted this study for these minor changes in inactive ingredients of flavor and color. The sponsor chose to conduct this study without obtaining input from the Agency on this matter.

Based on the geometric mean of the log differences of the AUC, the bioavailability of lemon formulation to the raspberry formulation was 103.8%. The 90% confidence intervals for the log transformed C_{max} and AUC ratios were within the limits of 0.8-1.25 indicating that the two formulations are bioequivalent to each other..

After the off-white lemon flavored formulation was used in several clinical studies, the manufacturer, Abbott laboratories experienced difficulties in the manufacturing scale-ups, resulting in the inability to produce an acceptable product. After several attempts to utilize a lemon flavoring product failed, the sponsor decided to use an off-white raspberry flavored formulation for chronic pain. In January 1995, the sponsor contacted the Agency regarding the need to do an *in vivo* bioequivalence study for the minor change in formulation of replacing lemon flavor with raspberry flavor. The sponsor was informed by Office of Clinical Pharmacology and Biopharmaceutics (formerly Division of Biopharmaceutics) that such an *in vivo* bioequivalence test can be waived according to the regulation, 21 CFR 320.22 (d) (4) (e). However, the sponsor was requested to submit dissolution data (not officially required by the Agency for this product) on the to-be-marketed formulation with the already marketed formulation.

The dissolution data for the all the strengths of the to-be-marketed formulation meets the specified dissolution criteria of 50% dissolved in 7 minutes or less. Therefore, the sponsor fulfilled the obligation set forth for granting the waiver from conducting the *in vivo* bioequivalence study comparing the clinical formulation to the to-be-marketed formulation. Besides, the product passed bioequivalency criteria when both the color and flavor were changed, therefore, there is no reason to believe that the product would not have passed the bioequivalency criteria when only the flavor is changed. No labeling claims were made from this study.

7.0. CONCLUSIONS

1. Under single dose conditions, OTFC delivers fentanyl in a dose-dependent manner over the range 200-1600 µg.
2. Fentanyl is metabolized to norfentanyl by cytochrome P4503A4 isoform.
3. The red, raspberry OTFC formulation (used in the premedication product) and an off white, lemon OTFC formulation (anticipated for use in cancer) were bioequivalent. However, because of manufacturing difficulties, the OTFC product for use in cancer is now manufactured as off

white, raspberry formulation.

4. Pharmacokinetics of 800 µg OTFC are similar in males and females.
5. Three consecutive doses of 800 µg OTFC given at 6-hour intervals in adult volunteers did not permit the evaluation of altered absorption pharmacokinetics or accumulation potential under real life dosing conditions.

8.0. PROPOSED PACKAGE INSERT

Pharmacokinetics (see Figures and Table)

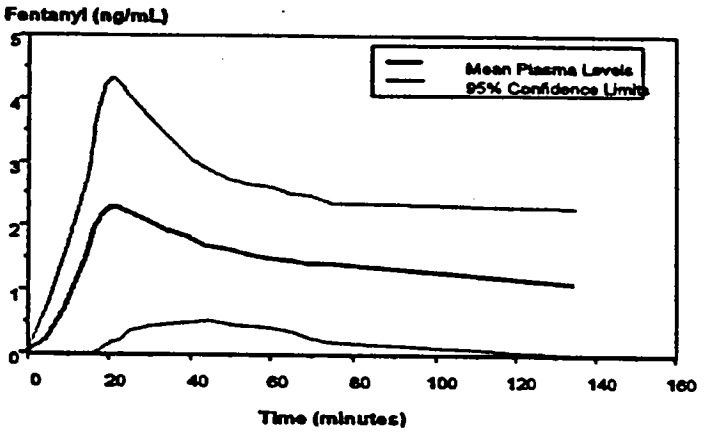
As with all opioids, the ***Actiq*** dose must be individualized to each patient's specific requirements (see DOSAGE AND ADMINISTRATION).

Absorption

The absorption pharmacokinetics of fentanyl from the oral transmucosal dosage form are a combination of an initial rapid absorption from the buccal mucosa and a more prolonged absorption of swallowed fentanyl from the gastrointestinal tract (see Figure 1). Both the blood fentanyl profile and the bioavaialbility of fentanyl will vary depending on the fraction of the dose that is absorbed through the oral mucosa and the fraction swallowed.

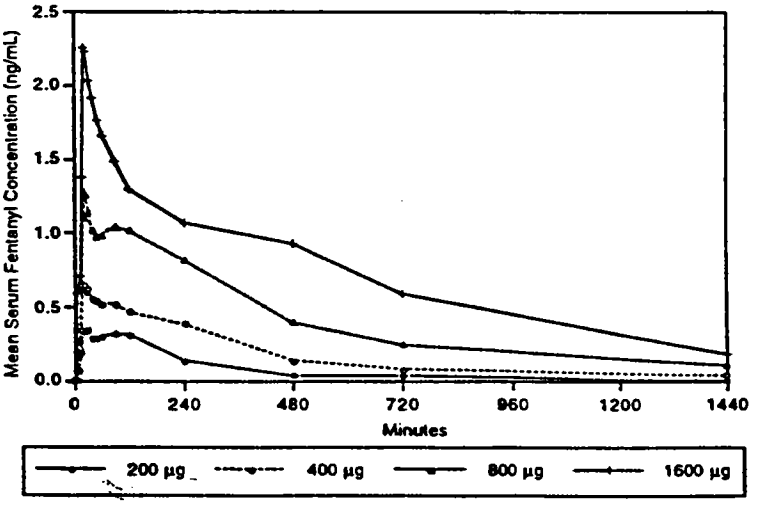
Normally, approximately 25% of the total dose of ***Actiq*** is rapidly absorbed from the buccal mucosa and becomes systemically available. The remaining 75% of the total dose is swallowed with the saliva and then is slowly reabsorbed from the GI tract. About 1/3 of this amount (25% of the total dose) escapes hepatic and intestinal first-pass elimination and becomes systemically available. Therefore, the generally observed 50% bioavailability of ***Actiq*** is divided equally between rapid oral transmucosal and slower GI absorption. Chewed or swallowed fentanyl contributes little to the peak concentration, but can contribute to the prolonged tail on the blood level profile as it is slowly absorbed, increasing the duration of action of ***Actiq***.

Figure 1.
Plasma Fentanyl Levels
Healthy volunteers
(OTFC - 15 mcg/kg)



Dose proportionality among four of the available strengths of *Actiq* (200, 400, 800, and 1600 mcg) has been demonstrated in healthy volunteers. Mean serum fentanyl levels following these four doses of *Actiq* are shown in Figure 2. The curves for each dose level are similar in shape with increasing dose levels producing increasing serum fentanyl levels. C_{max} and $AUC_{0-\infty}$ increased in a dose-dependent manner that is approximately proportional to the *Actiq* administered dose level.

Figure 2.
Mean Serum Fentanyl Concentration (ng/mL)
Healthy Volunteers



In healthy male volunteers given 15 mcg/kg, the mean C_{max} is 2.7 ng/mL (Table 1). The median time of maximum plasma concentration (T_{max}) is 23 minutes. Absolute bioavailability, as determined by area under the concentration-time curve, of 15 mcg/kg in 12 healthy male volunteers was 50% compared to iv fentanyl.

Table 1.
Pharmacokinetic Parameters in
Opioid Non-Tolerant Adults Receiving 15 mcg/kg.

Parameter	Unit	N=12
C_{max} (ng/mL)	Mean	2.7
	Range	
T_{max} (minutes)	Median	23
	Range	
Bioavailability (percent)	Mean	50
	Range	
$t_{1/2}$ (hours)	Median	6.6
	Range	

Distribution

Fentanyl is highly lipophilic. Following absorption, fentanyl is rapidly distributed to the brain, heart, lungs, kidneys and spleen followed by a slower redistribution to muscles and fat. The plasma protein binding of fentanyl is 80-85%. The main binding protein is alpha-1-acid glycoprotein, but both albumin and lipoproteins contribute to some extent. The free fraction of fentanyl increases with acidosis. The mean volume of distribution at steady state (Vss) was 4 L/kg.

Metabolism

Fentanyl is metabolized primarily in the liver, and to a lesser extent in the intestinal mucosa to norfentanyl by cytochrome P450 3A4 isoform. Norfentanyl was not found to be pharmacologically active in animal studies.

Elimination

Fentanyl is primarily (more than 90%) eliminated by biotransformation to N-dealkylated and hydroxylated inactive metabolites. Less than 7% of the dose is excreted unchanged in the urine and only about 1% is excreted unchanged in the feces. The metabolites are mainly excreted in the urine, while fecal excretion is less important. The terminal elimination half-life after OTFC adminsitration is about 7 hours.

Special populations

Elderly:

Elderly patients have been shown to be twice as sensitive to the effects of fentanyl when administered intravenously, compared with younger population.

In the 257 opioid tolerant patients studied with ***Actiq***, approximately 20% were over age 65 years. There was no difference in the safety profile in this group compared to those aged less than 65 years, though

they did titrate to lower doses than younger patients (see PRECAUTIONS).

Renal and Hepatic Impairment:

Actiq should be administered with caution to patients with liver and kidney dysfunction because of the importance of these organs in the metabolism and excretion of drugs and effects on plasma binding proteins (see PRECAUTIONS).

Although fentanyl kinetics are known to be altered in both hepatic and renal diseases due to alterations in metabolic clearance and plasma proteins, individualized doses of ***Actiq*** have been used successfully in anesthesia in both kinds of disorders. This is because the duration of effect for the intial dose is determined by redistribution of the drug, such that diminished metabolic clearance will only become significant with repeated dosing or with excessively large single doses. For these reasons, while doses titrated to clinical effect are recommended for all patients, special care should be taken in patients with severe hepatic and/or renal disease.

Gender:

Both male and female patients were studied for the management of chronic pain. No clinically relevant differences were noted between dosage requirement nor adverse event reporting.

APPENDIX
STUDY I

STUDY TYPE: *In Vitro* metabolism
STUDY TITLE: Human Fentanyl Biotransformation: Identification of responsible Cytochrome P450 Isoforms.
NDA:20-747 SUBMISSION DATE:11/11/96 VOLUME:1.12 STUDY: CR/FC/96/001
CLINICAL
INVESTIGATOR:

LABELLING CLAIMS: Fentanyl is metabolized primarily in the liver, and to a lesser extent in the intestinal mucosa to norfentanyl by cytochrome P450 3A4 isoform. Norfentanyl is not pharmacologically active.

OBJECTIVE

To completely characterize the human metabolism of fentanyl.

RESULTS AND DISCUSSION

The biotransformation of fentanyl was studied in human hepatic and duodenal micorsomal preparations in order to isolate and characterize the primary route(s) and identify the predominant P450 isoform(s) responsible for human fentanyl metabolism.

Piperidine N-deaklyation to norfentanyl was found to be the predominant pathway of human liver and duodenal microsomal fentanyl metabolism. Amide hydrolysis to despropionylfentanyl and alkyl hydroxylation to hydroxyfentanyl were minor pathways. The average rate of norfentanyl formation in the duodenum was approximately half that of hepatic microsomal metabolism. The mechanism-based P4503A4 inhibitor troleandomycin and the P4503A4 substrate and competitive inhibitor midazolam significantly inhibited norfentanyl formation. Of six expressed human P450 isoforms, P4503A4 was the only one to exhibit significant catalytic activity towards fentanyl dealkylation to norfentanyl.

The clinical implications of these results is that (1) The fraction of fentanyl that is swallowed during OTFC administration likely undergoes significant pre-hepatic first-pass metabolism in the intestine and (2) Both intestinal and hepatic first-pass metabolism may also be subject to individual variability in P4503A4 expression and to drug interactions involving P4503A4.

A large number of clinically important drugs act as substrates of the cytochrome P450 3A which comprises as much as 60% of the total cytochrome P450 content of the liver. The potential for metabolism based drug-drug interactions associated with the use of OTFC involves both first pass effects on swallowed fentanyl and clearance effects on fentanyl which has reached the systemic circulation. Table 1 lists the drugs identified as inducers, substrates and inhibitors of cytochrome P450 3A4. It is noticeable that this table does not mention morphine (glucuronidation), oxycodone (P450 2D6), hydromorphone (primarily glucuronidation) which are the most commonly used opioid drugs for chronic cancer pain. The sponsor conducted a comprehensive Medline literature search involving fentanyl and various substrates, inhibitors, and inducers of P450 3A4 which did not yield any clinically relevant reports.

The metabolite norfentanyl reportedly was not found to be pharmacologically active in animal studies.

Table 1. Cytochrome P450 3A4 substrates and Inhibitors

Cytochrome P450 3A4 Inducers	Cytochrome P450 3A4 Substrates/Inhibitors
Carbamazepine, phenobarbital, phenytoin, rifampin, R-warfarin (10-OH)	Alprazolam, amiodarone, astemizole, azithromycin, calcium antagonist (diltiazem, nifedipine, verapamil), carbamazepine, cimetidine, cisapride, clarithromycin, clotrimazole, cocaine, cyclosporin, dexamethasone, dextromethorphan, diazepam, erythromycin, estradiol, ethynlestradiol, etoposide, fluconazole, fluoxetine*, fluvoxamine*, gestodene, itraconazole, granisetron, josamycin, ketoconozole, letoconazole, lidocaine, lovastatin, micanozole, midazolam, midecamycin, nefazodone*, ondansetron, paroxetine*, quinidine, sertraline*, tamoxifen, tapson, teniposide, terfenadine, testosterone, theophyline, tricyclic antidepressants (amitriptyline, clopipramine, imipramine), triazolam, troleandomycin, vinblastine, vincristine, and zonisamide.

* suspected but not confirmed

APPEARS THIS WAY
ON ORIGINAL

STUDY II

STUDY TYPE: Dose-Proportionality
STUDY TITLE: An Open Label, Randomized, Crossover, Pharmacokinetic Study of the Dose Proportionality of Four Doses of Oral Transmucosal Fentanyl Citrate (OTFC) in Normal Healthy Volunteers.
NDA:20-747 **SUBMISSION DATE:**11/11/96 **VOLUME:**1.11 **STUDY:** AC 200/009

STUDY DESIGN:
CLINICAL INVESTIGATOR: ANALYTICAL INVESTIGATOR

SINGLE DOSE: Yes **CROSS-OVER:** Four-way **OTHER DESIGN:**Open, randomized
WASHOUT PERIOD: At least 72 hours

SUBJECT BREAKDOWN:
Normal Yes Young Yes Number= 12 Male= 12
Weight; Mean 78 Range 65-100 kg
Age; Mean 25 Range 19-34 yrs

FORMULATION:

Treatment groups	Dose	Dosage Form	Strength	Lot
200 µg OTFC	200 µg	Lozenge on a stick	200 µg	88-905-DH
400 µg OTFC	400 µg	Lozenge on a stick	400 µg	88-906-DH
800 µg OTFC	800 µg	Lozenge on a stick	800 µg	88-908-DH
1600 µg OTFC	1600 µg	Lozenge on a stick	1600 µg	88-910-DH

PLASMA SAMPLING TIMES: Eight (8) mL venous blood samples were collected at zero, 5, 10, 15, 20, 25, 30, 40, 50, 60, 90, 120, 240, 480, 720, and 1440 minutes.
ASSAY METHOD:
ASSAY SENSITIVITY: Quantitation limit was 0.1 ng/mL. The assay was linear in the range of ng/mL.
ASSAY ACCURACY: The assay validation parameters were within acceptable limits.
LABELLING CLAIMS: Dose proportionality among four of the available strengths of Actiq (200, 400, 800, and 1600 µg) has been demonstrated in healthy volunteers. Mean serum fentanyl levels following these four doses of Actiq are shown in Figure 2. The curves for each dose level are similar in shape with increasing dose levels producing increasing serum fentanyl levels. C_{max} and $AUC_{0-\infty}$ increased in a dose-dependent manner that is approximately proportional to the Actiq administered dose level.

OBJECTIVES

To evaluate the dose-proportionality and safety of four strengths of OTFC; 200, 400, 800, and 1600 µg fentanyl citrate.

RESULTS AND DISCUSSION

Figure 1 shows the dose-normalized, mean plasma concentration-time profiles of fentanyl after the administration of the four doses of OTFC. The profiles for the four doses appear to be similar but they do not completely overlap each other in the distributive and terminal phases. The smallest dose 200 µg appears separate itself out, with the 400, 800, and 1600 µg doses appearing to be more closer to each other.

Table 1 shows the mean pharmacokinetic parameter values for the four treatments. Mean C_{max} and $AUC_{0-\infty}$ increased in a dose proportional manner that was approximately proportional to the OTFC administered dose level. The mean $t_{1/2}$ for the 400, 800, and 1600 µg doses was similar (358-386 minutes) but that of the 200 µg dose was smaller (193 minutes) resulting in a statistically significant difference between the doses. The half-life at the lower dose of 200 µg could have been affected by the concentrations in the terminal phase being close to the limit of quantification.

CONCLUSIONS

The C_{max} and $AUC_{0-\infty}$ show approximate dose-proportionality in the range of 400-1600 µg of OTFC. Therefore, the results support the labeling claims from this study.

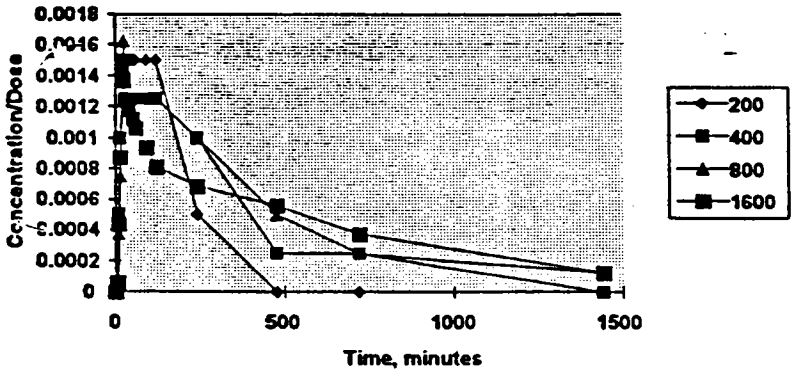


Figure 1. Dose normalized mean concentration-time profiles of fentanyl after the administration of 200, 400, 800, and 1600 µg OTFC.

Table 1. Pharmacokinetic parameter values of fentanyl after the administration of 200, 400, 800, and 1600 µg OTFC (mean (% CV)).

Pharmacokinetic Parameter	200 µg	400 µg	800 µg	1600 µg
Dose (µg/kg)	2.61 (13)	5.24 (13)	10.5 (13)	20.9 (12)
T_{max}, minute	61 (70)	55 (118)	44 (89)	61 (216)
C_{max}, ng/mL	0.39 (23)	0.75 (33)	1.55 (30)	2.51 (23)
C_{max}/dose	0.00195	0.001875	0.001938	0.00157
$AUC_{0\text{-}1440}$, ng/mL minute	102 (65)	243 (67)	573 (64)	1026 (67)
$AUC_{0\text{-}1440}$/dose	0.51	0.61	0.72	0.64
$AUC_{0\text{-}\infty}$, ng/mL minute	130 (49)	308 (84)	661 (72)	1153 (74)
$AUC_{0\text{-}\infty}$/dose	0.65	0.77	0.82	0.72
$t_{1/2}$, minute	193 (48)	386 (115)	381 (55)	358 (45)

STUDY III

STUDY TYPE: Multiple dose Pharmacokinetics.
STUDY TITLE: Determination of the pharmacokinetic and safety profile for chronic administration of oral transmucosal fentanyl citrate (OTFC) in normal human volunteers.
NDA:20-747 SUBMISSION DATE:11/11/96 VOLUME:1.10 STUDY: AC 200/005

STUDY DESIGN:
CLINICAL INVESTIGATOR:
ANALYTICAL INVESTIGATOR

MULTIPLE DOSE: Yes
OTHER DESIGN: Open, randomized
CROSS-OVER: Three-way
WASHOUT PERIOD: Not applicable

SUBJECT BREAKDOWN:
Normal Yes Young Yes Number= 12 Male= 7 Female= 5

Weight;	**Mean 79**	**Range 66-86 kg**	**Weight;**	**Mean 68**	**Range 51-85 kg**
Age;	**Mean 28**	**Range 24-36 yrs**	**Age;**	**Mean 28**	**Range 23-31 yrs**

FORMULATION:

Treatment Groups	Dose	Dosage Form	Strength	Lot
Administration 1	800 µg	Lozenge on a stick	800 µg	60-838-DH
Administration 2	800 µg	Lozenge on a stick	800 µg	60-838-DH
Administration 3	800 µg	Lozenge on a stick	800 µg	60-838-DH

PLASMA SAMPLING TIMES: Seventy three (73) arterial blood samples were obtained (during a span of 36 hours) during the administration of the three doses of OTFC with the sampling schedule covering 6 hours of the concentration-time profile for the first two doses and 24 hours for the third dose
ASSAY METHOD:
ASSAY SENSITIVITY: Quantitation limit of 0.2 ng/mL. Assay was linear in the range of ng/mL.
ASSAY ACCURACY AND PRECISION: Both intra-day and inter-day precision and accuracy values were less than 10% coefficient of variation.
LABELLING CLAIMS: Multiple dosing of Actiq at 6 hour intervals in healthy volunteers does not alter absorption pharmacokinetics and the drug did not accumulate.

OBJECTIVES

To evaluate the pharmacokinetic and safety profile of multiple administration of 800 µg OTFC.

STUDY DESIGN

This was an open-label, randomized, complete crossover study with an OTFC phase and an intravenous phase conducted in 12 healthy subjects (5 females and 7 males). In the OTFC phase of

the study, the pharmacokinetics and safety of multiple administration (3 doses) of 800 µg OTFC in adult healthy volunteers was evaluated (protocol AC 200/005). The subjects received three separate OTFC units with 6-hour interval between administrations. In the intravenous phase of the study, the subjects received one fentanyl infusion of 15 µg/kg (50 µg/minute). A washout period of at least 14 days separated the two phases of the study.

RESULTS AND DISCUSSION

The design of this study does not reflect the clinical use situation. The terminal half-life of fentanyl when administered as OTFC dosage form is about 6-7 hours. Although the intent was to examine multiple dose pharmacokinetics, only three consecutive doses of 800 µg OTFC at 6 hour intervals were administered in this study and as such, the study design did not permit the evaluation of the pharmacokinetics of fentanyl under true multiple dosing conditions. According to the labeling instructions, four or fewer units per day is the maximum recommended dosage. During titration phase, redosing for ongoing episodes may start 15 minutes after the previous unit has been completed. In fact, in the chronic pain trials, patients were exposed to larger doses of OTFC in shorter intervals (maximum total dose was 7200 µg administered over 3-3/4 hours) than what was tested in the current study. Ideally, the study should have characterized the multiple dose pharmacokinetics at the highest strength (1600 µg) and at 15 minute intervals for four doses. If patients needed more than four units per day, the labeling instructs the physician to increase the around-the-clock opioid dose used for persistent pain in patients experiencing more than four breakthrough pain episodes daily.

The increasing values of C_{360} concentrations over the three OTFC administrations confirmed that steady state was not reached in this study. The AUC's were also slightly higher in the second and third administrations relative to the first administration. Therefore, the sponsor resorted to indirect techniques to evaluate if absorption pharmacokinetics are altered along with the potential for accumulation (sponsor states that none of these methods by themselves are ideal, but viewed as a group, they indicate that absorption pharmacokinetics are not affected by multiple dosing). This involved;

(I). Simple inspection of raw serum fentanyl concentration-time data for all individual subjects. Conclusion was that there was no obvious alteration in the concentration-time profile with multiple dosing.

(ii). Inspection of serum concentration-time profiles to see if there are any gross alterations in the concentration-time profile. Conclusion was that peak concentrations and time to peak concentration were similar among administrations indicating that absorption kinetics did not change after multiple dosing.

(iii). Compartmental modeling to fit the serum fentanyl concentration-time profiles for both the OTFC and fentanyl data. Conclusion from this approach was that K_a (first order absorption rate constant) and F (bioavailability) did not appear to change with the dosing regimen used in this study.

The above approaches would detect only gross alterations in the pharmacokinetics of fentanyl. Since proportionality at single doses was already demonstrated up to 1600 µg and only three doses were administered at intervals of one terminal half-life, it is not surprising that no obvious alterations in the pharmacokinetics were observed. The information from this study is only supportive at best and no firm conclusions on the multiple dose pharmacokinetics should be made. Direct evidence of the safety of this product under real life multiple dosing situations can be derived from the chronic pain clinical trials where patients were exposed to doses up to 7200 µg over 3-3/4

hours. There were no reports of respiratory depression or hypoventilation at these doses. Since this is the only study that included female subjects in this NDA, gender effect on the pharmacokinetics was examined. No significant gender differences were found in the pharmacokinetics of fentanyl. The sponsor came to the same conclusion from the analysis of integrated safety and efficacy data. No clinically relevant differences were noted between dosage requirements nor adverse event reporting.

CONCLUSIONS

The dosage regimen used in this study does not reflect the true usage of this product in terms of the dose (Out of 25,160 OTFC units used to treat 21,758 breakthrough pain episodes, 1600 µg unit dose represented the most commonly used unit (22.5% of the total units)), or the dosing interval ((maximum total dose was 7200 µg administered over 3-3/4 hours in chronic pain trials) to evaluate the altered absorption pharmacokinetics or the potential for accumulation. Sponsor's labeling claims form this study are not appropriate.

Table 1. Summary of pharmacokinetic parameter values after the administration of three consecutive doses of 800 µg OTFC at 6 hour intervals.

Pharmacokinetic Parameter	First Dose	Second Dose	Third Dose
Time period, minutes	0-360	360-720	720-2160
T_{max}, minute	42 (95)	40 (158)	44 (143)
C_{max}, ng/mL	2.10 (28)	2.05 (25)	1.92 (36)
C_{360}, ng/mL	0.61 (44)	0.79 (42)	0.89 (52)
AUC_{0-360}, ng/mL minute	343 (23)	393 (28)	409 (37)
$AUC_{0-\infty}$, ng/mL minute	744 (40)	893 (41)	893 (56)
$t_{1/2}$, minute	-	-	7.2 (30)

STUDY IV

STUDY TYPE: Bioequivalency
STUDY TITLE: Bioequivalence of "Cancer Pain" Formulation and "Premedication" Formulation of Fentanyl Oralet.
NDA:20-747 SUBMISSION DATE:11/11/96 VOLUME:1.12 STUDY: AC 200/008

STUDY DESIGN:
CLINICAL [**ANALYTICAL** [
INVESTIGATOR: **INVESTIGATOR**

SINGLE DOSE: Yes **CROSS-OVER:**Two-way **OTHER DESIGN:**Open, randomized
WASHOUT PERIOD: Yes, 72 hours

SUBJECT BREAKDOWN:
Normal Yes **Young** Yes **Number=** 24 **Male=**24
Weight; **Mean** 75 **Range** 63-91 kg
Age; **Mean** 34 **Range** 21-50 yrs

FORMULATION:

Treatment Groups	Dose	Dosage Form	Strength	Lot
Lemon Flavor	800 μg	Lozenge on a stick	800 μg	73-883-DH
Raspberry Flavor	800 μg	Lozenge on a stick	800 μg	66-865-DH

PLASMA SAMPLING TIMES: Seven (7) mL samples of blood were collected at pre-dose and at 5, 10, 15, 17.5, 20, 22.5, 25, 27.5, 30, 35, 40, 45, 55, 65, 75, 120, 240, 360, 480, 600, 720, and 1440 minutes following the dose
ASSAY METHOD: [
ASSAY SENSITIVITY: The assay was linear in the range of] ng/mL with a quantitation limit of 0.1 ng/mL.
ASSAY ACCURACY: The accuracy and precision parameters were within acceptable limits.
LABELLING CLAIMS: None
OBJECTIVES

To determine the bioequivalency of off white, lemon flavored and red, raspberry flavored formulations of 800 μg OTFC. The rationale behind the change over from the red, raspberry to white, lemon flavored formulation is that the raspberry flavor might present an undesirable flavor in cancer patients and its attractive red color might result in an abuse potential in the children.

RESULTS AND DISCUSSION

The mean pharmacokinetic parameter values of AUC and C_{max} were also very close between the two formulations (Table 1). Based on the geometric mean of the log differences of the AUC, the bioavailability of lemon formulation to the raspberry formulation was 103.8%. The 90% confidence intervals on the C_{max} and AUC ratio were within limits (Table 2).

After the off-white lemon flavored formulation was used in several clinical studies, the manufacturer, Abbott laboratories experienced difficulties in the manufacturing scale-ups, resulting

in the inability to produce an acceptable product. After several attempts to utilize a lemon flavoring product failed, the sponsor decided to use an off-white raspberry flavored formulation for the chronic pain. In January 1995, the sponsor contacted the Agency regarding the need to do an *in vivo* bioequivalence study for the minor change in formulation of replacing lemon flavor with raspberry flavor. This was discussed by the reviewing pharmacokineticist at that time, Ruth Stevens, Ph.D. with the Pilot Drug Evaluation Staff Chemist, Pramoda Maturu, Ph.D., and Division of Biopharmaceutics Branch Chief II, Mei-Ling Chen, Ph.D. The sponsor was informed that such an *in vivo* bioequivalence test can be waived according to the regulation, 21 CFR 320.22 (d) (4) (e). However, the sponsor was requested to submit dissolution data on the to-be-marketed formulation with the already marketed formulation.

The dissolution data for the all the strengths of the to-be-marketed formulation meets the approved dissolution criteria of 50% dissolved in 7 minutes or less. Therefore, the sponsor fulfilled the obligation set forth for granting the waiver from conducting the *in vivo* bioequivalence study comparing the clinical formulation to the to-be-marketed formulation.

CONCLUSIONS

The lemon flavored and the raspberry flavored OTFC formulations were bioequivalent with respect to C_{max} and AUC_{0-24}.

Table 1. Summary of pharmacokinetic data (mean (CV)).

Pharmacokinetic Parameter	Red, Raspberry Formulation	Off White Lemon, Formulation
C_{max}, ng/mL	1.27 (36)	1.30 (38)
AUC_{0-24}, ng/mL.minute	373.1 (54)	373.2 (47)
T_{max}, minute	67 (93)	71 (124)

Table 2. Summary of bioequivalence test for C_{max} and AUC.

Pharmacokinetic Parameter	Red, Raspberry Formulation	Off White, Lemon Formulation	90% Confidence Intervals
C_{max}, ng/mL	0.165	0.197	0.94-1.14
AUC_{0-24}, ng/mL.minute	5.76	5.81	0.91-1.18

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA: 20-747 RELATED IND: **NAME:** Actiq™ (Oral Transmucosal Fentanyl Citrate)
STRENGTHS: Fentanyl citrate 200, 400, 600, 800, 1200, and 1600 μg
SPONSOR: Anesta Corp., 4745 Wiley Post Way, Plaza 6, Suite 650, Salt Lake City, Utah
TYPE OF SUBMISSION: Original NDA **SUBMISSION DATE:** November 11, 1996
REVIEWER: Suresh Doddapaneni, Ph.D. **NDA FILING DATE:** December 20, 1996

NDA FILING MEMORANDUM

I. BACKGROUND

Actiq™ (Oral Transmucosal Fentanyl Citrate) is fentanyl incorporated into a sweetened matrix (lozenge on a stick) that is designed to provide pain relief in cancer patients. The dosage units are manufactured in a base of sucrose, liquid glucose, food color, and raspberry flavor with fentanyl citrate and are designed to be sucked for the release of the drug. Fentanyl Oralet®(OTFC), which is a similar dosage form, is approved for marketing in the United States in October 1993 for use in adults and children as an anesthetic premedication in the operating room setting, and to induce conscious sedation prior to a diagnostic or therapeutic procedure in other monitored anesthesia care settings in the hospital (NDA 20-195). The main difference between Fentanyl Oralet® and Actiq™ is in the dose range of use. Fentanyl Oralet® is used in the range of 200 - 400 μg and Actiq™ is used in the range of 200 - 1600 μg. The use of OTFC for the management of chronic pain, particularly breakthrough pain, in patients who are already receiving and are tolerant to opioid therapy is a new indication for OTFC and is not approved for marketing in any country. OTFC's primary therapeutic value is the delivery of fast-acting, relatively short duration, non invasive, self-titratable drug in a convenient dosage form.

II. STUDY SUMMARIES

The bioavailability of OTFC following single doses in healthy adults has been described in NDA 20-195. Pharmacokinetic trials in this NDA were designed 1) to demonstrate that multiple dosing does not alter absorption pharmacokinetics in volunteers; 2) to demonstrate dose proportionality in volunteers; 3) to demonstrate the bioequivalence of two OTFC formulations; and 4) to more completely investigate the *in vitro* human metabolism of fentanyl. The studies are briefly summarized below;

(1) In Vitro Metabolism of Fentanyl (Study CR/FC/96/001):

In this *in vitro* study, the cytochrome P450 isozyme responsible for the metabolism of fentanyl was identified. Of the six expressed human P450 isoforms, P4503A4 was the only one to exhibit significant catalytic activity towards fentanyl dealkylation to norfentanyl (inactive metabolite) in both hepatic and duodenal microsomes. The clinical implications of this is that both intestinal and hepatic first-pass metabolism may be subject to individual variability in P4503A4 expression and to drug interactions involving P4503A4.

(2) Dose-Proportionality of OTFC (Study AC 200/009):

Dose-proportionality of 200, 400, 800, and 1600 μg OTFC was demonstrated in an open-label, randomized, four-period, single-dose, complete cross-over design in 12 healthy male subjects with respect to both C_{max} and $AUC_{0-\infty}$.

(3) Pharmacokinetic Profile after Administration of Multiple Doses of OTFC (Study AC 200/005):

The pharmacokinetic profile after administration of three consecutive doses of 800 μg OTFC at 6 hour intervals was investigated in 12 healthy male and female subjects. A major limitation of this study is that because only three consecutive doses were administered, plasma concentrations achieved were not at steady state. As such, any conclusive analysis of steady state pharmacokinetics of OTFC is not possible. The sponsor concluded from the analysis of the available data that the absorption pharmacokinetics of OTFC are not affected by multiple dosing of OTFC (information regarding elimination pharmacokinetics of fentanyl not being affected after long-term fentanyl administration was quoted from literature).

(4) Bioequivalence of Two Formulations of OTFC (Study AC 200/008):

The two formulations differ in flavor and color. The lemon flavored unit is off white and the raspberry flavored unit is red colored. The rationale behind the change over from the red, raspberry (used in children for anesthetic pre-medication-NDA 20-195) to white, lemon flavored formulation is that the raspberry flavor might present an undesirable flavor in cancer patients and its attractive red color might result in an abuse potential in the children. Bioequivalency in terms of both C_{max} and AUC was demonstrated between the two formulations.

After the off-white lemon flavored formulation was used in several clinical studies, the manufacturer, Abbott laboratories experienced difficulties in the manufacturing scale-ups, resulting in the inability to produce an acceptable product. After several attempts to utilize a lemon flavoring product failed, the sponsor decided to use an off-white raspberry flavored formulation for the chronic pain. In January 1995, the sponsor contacted the Agency regarding the need to do an *in vivo* bioequivalence study for the minor change in formulation of replacing lemon flavor with raspberry flavor (relative to the product in NDA 20-195). This was discussed by the reviewing pharmacokineticist at that time, Ruth Stevens, Ph.D. with the Pilot Drug Evaluation Staff Chemist, Pramoda Maturu, Ph.D., and Division of Biopharmaceutics Branch Chief II, Mei-Ling Chen, Ph.D. The sponsor was informed that such an *in vivo* bioequivalence test can be waived according to the regulation, 21 CFR 320.22 (d) (4) (e).

III. PROPOSED PACKAGE INSERT

The pharmacokinetics section of the proposed package insert is organized according to the ADME format and covers the relevant information that is usually contained in this section.

IV. RECOMMENDATION

No major deficiencies have been found that limit the review of the information presented in the Human Pharmacokinetics and Bioavailability section of the NDA 20-747. Therefore, Section 6 of NDA 20-747 is fileable.

/S/ 12/18/96

Suresh Doddapaneni, Ph.D.
Pharmacokineticist
DPE II/OCPB

RD initialed by Dale Conner, Pharm.D.
FT initialed by Dale Conner, Pharm.D.: /S/ 12/18/96

CC:
NDA 20-747 (Original), HFD-170 (Millie Wright), HFD-850 (Lesko), HFD-870 (Doddapaneni, Mei-Ling Chen, Conner, Chron, Drug, Reviewer), HFD-340 (Viswanathan).