

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

022510Orig1s000

PHARMACOLOGY REVIEW(S)



DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACOLOGY/TOXICOLOGY REVIEW AND EVALUATION

NDA NUMBER: 22-510
SERIAL NUMBER: 000
DATE RECEIVED BY CENTER: 8/5/09
PRODUCT: Abstral (fentanyl citrate (b) (4) tablet)
INTENDED CLINICAL POPULATION: for the management of breakthrough cancer pain in opioid-tolerant cancer patients
SPONSOR: ProStrakan, Inc.
DOCUMENTS REVIEWED: All nonclinical information in the above submission
REVIEW DIVISION: Division of Anesthesia, Analgesia, and Rheumatology Products (HFD-170)
PHARM/TOX REVIEWER: Elizabeth A. Bolan, Ph.D.
PHARM/TOX SUPERVISOR: R. Daniel Mellon, Ph.D.
DIVISION DIRECTOR: Bob Rappaport, M.D.
PROJECT MANAGER: Kimberly Compton

Date of review submission to DARRTS: March 11, 2010

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EXECUTIVE SUMMARY

I. Recommendations

A. Recommendation on approvability

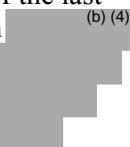
This NDA can be approved from a nonclinical pharmacology/toxicology perspective.

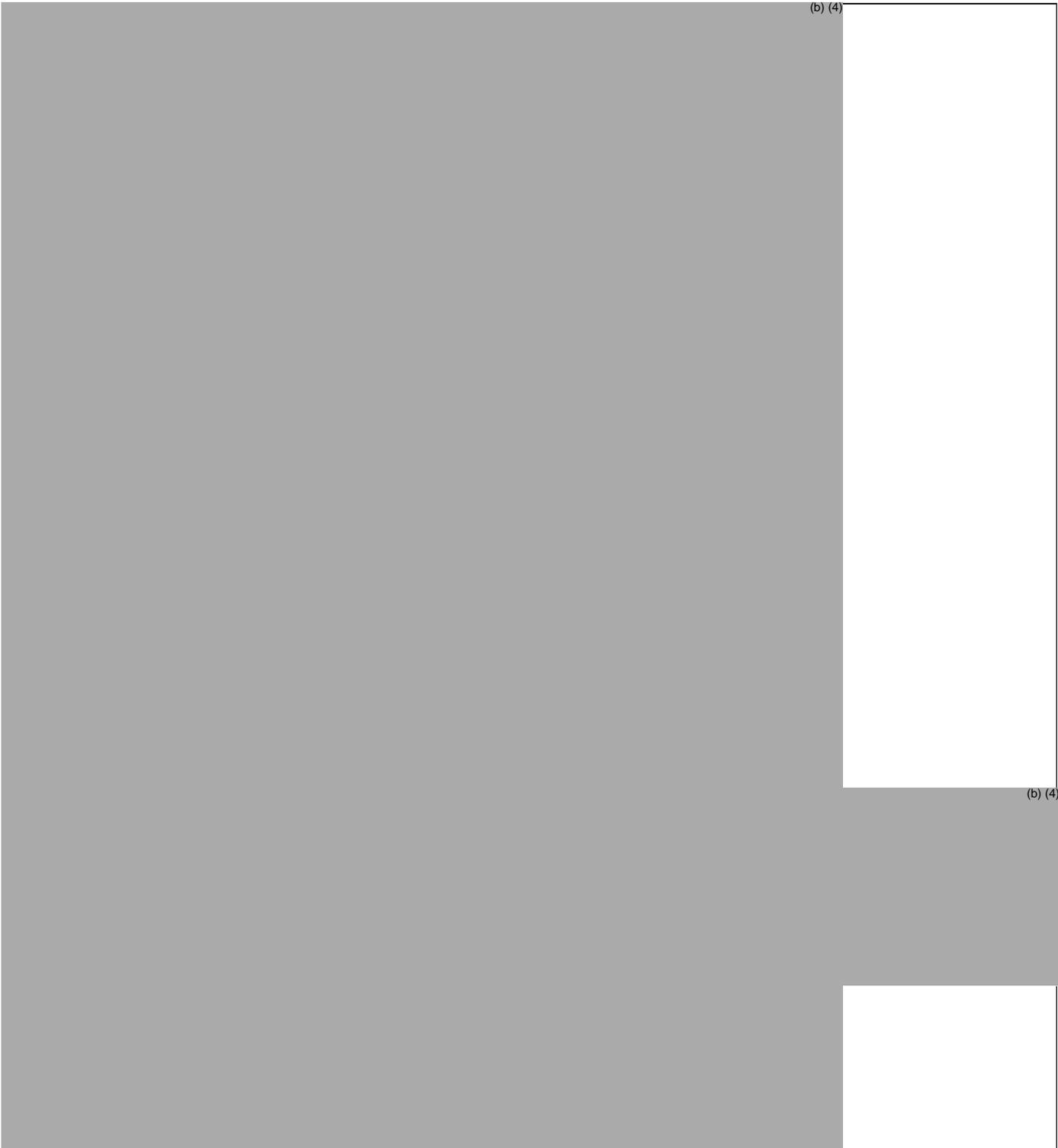
B. Recommendation for nonclinical studies

There are no recommendations for nonclinical studies.

C. Recommendations on labeling

The table below contains the draft labeling submitted by the Applicant, the proposed changes and the rationale for the proposed changes. For the final version of the label, please refer to the Action Letter. Note: The recommended changes from the proposed labeling are in red or strikeout font.

	<p>(b) (4)</p> <p>Rationale for changes</p>
	<p>This section is identical to the current Actiq label with the exception of minor edits (in red), the appropriate exposure margins for Abstral and the deletion of the last paragraph </p>



13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
Long-term studies in animals have not been performed to evaluate the

13 NONCLINICAL TOXICOLOGY
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Long-term studies in animals have not been performed to evaluate the

With the exception of minor edits (in red), this section is

<p>carcinogenic potential of fentanyl.</p> <p>Fentanyl citrate was not mutagenic in the <i>in vitro</i> Ames reverse mutation assay in <i>S. typhimurium</i> or <i>E. coli</i>, or the mouse lymphoma mutagenesis assay, and was not clastogenic in the <i>in vivo</i> mouse micronucleus assay.</p> <p>Fentanyl has been shown to impair fertility in rats at doses of 30 mcg/kg IV and 160 mcg/kg subcutaneously. Conversion to the human equivalent doses indicates that this is within the range of the human recommended dosing for ABSTRAL.</p>	<p>carcinogenic potential of fentanyl.</p> <p>Fentanyl citrate was not mutagenic in the <i>in vitro</i> Ames reverse mutation assay in <i>S. typhimurium</i> or <i>E. coli</i>, or the mouse lymphoma mutagenesis assay, and was not clastogenic in the <i>in vivo</i> mouse micronucleus assay.</p> <p>Fentanyl has been shown to impair fertility in rats at doses of 30 mcg/kg IV intravenously and 160 mcg/kg subcutaneously. Conversion to the human equivalent doses indicates that this is within the range of the human recommended dosing for ABSTRAL.</p>	<p>identical to the Actiq label.</p>
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II. Summary of nonclinical findings

A. Brief overview of nonclinical findings

The applicant is relying on the Agency’s findings of safety and efficacy and the pharmacology, pharmacokinetics, and toxicology information in the label of Actiq. One oral single-dose toxicity study in dog was conducted by the applicant in order to assess the toxicity of accidentally swallowed fentanyl. The findings observed in this study were consistent with acute toxicity of a mu opioid and no novel findings were seen.

Several pharmacokinetic studies in rat and dog were conducted to compare oral, sublingual, and intravenous administration of fentanyl. In both rat and dog, fentanyl has very low oral bioavailability and bioavailability of sublingually administered fentanyl is considerably higher. A tissue penetration study in rat using whole body autoradiography with sublingually administered ³H-fentanyl was also conducted. ³H-fentanyl was shown to be absorbed and distributed throughout the body. The radiolabeled fentanyl rapidly disappeared and no organs were seen to contain residual radioactivity.

An Ames test and an *in vitro* chromosome aberration assay with the fentanyl impurity/degradation product (b) (4) were conducted. The applicant has reduced the levels of (b) (4) in the drug substance and drug product to acceptable levels therefore the studies to qualify (b) (4) are not needed for approval. The Ames test with (b) (4) was deemed invalid. In the *in vitro* chromosomal aberration study with human peripheral blood lymphocytes, (b) (4) did not cause structural chromosomal aberrations. However, an equivocal result for increased levels of polyploid cells were seen in cultures treated with (b) (4) in the presence of S9.

Although not required for approval, the applicant submitted supportive data to evaluate the local toxicity of fentanyl and the Abstral formulation excipients in the oral mucosa of guinea pig and hamster. Fentanyl was tested in the oral mucosa of guinea pigs for four

days and under the conditions tested it did not appear to be an irritant. The excipients in the Abstral formulation were evaluated in a 28-day hamster cheek pouch local toxicity study and did not appear to be irritants. However, both studies are of questionable utility. The fentanyl study was not conducted according to GLP. Of the excipients evaluated in the hamster cheek pouch model, only one was tested at a higher concentration than found in the 800 mcg Abstral formulation. With the limited data provided, it appears that the potential for local toxicity of the oral mucosa for the Abstral product is relatively low.

The results of the submitted pharmacology and toxicology studies with fentanyl were consistent with acute effects of a mu opioid agonist and no novel findings were seen. The impurities/degradants are controlled at acceptable levels in both the drug substance and drug product. The excipients used in the Abstral formulation have been previously approved and do not pose any toxicologic concerns. There are no outstanding pharmacology/toxicology issues with this NDA.

B. Pharmacologic activity

Fentanyl is a potent mu opioid agonist with a rapid onset and short duration of action.

C. Nonclinical safety issues relevant to clinical use

There are no unique nonclinical issues with this product as compared to other approved fentanyl products.

2.6 PHARMACOLOGY/TOXICOLOGY REVIEW

2.6.1 INTRODUCTION AND DRUG HISTORY

NDA number: 22-510

Review number: 1

Sequence number/date/type of submission: 000/August 5, 2009/original NDA submission

Information to sponsor: Yes () No (X)

Sponsor and/or agent: Prostrakan, Inc.

Manufacturer for drug substance: [REDACTED] (b) (4)

Reviewer name: Elizabeth A. Bolan, Ph.D.

Division name: Division of Anesthesia, Analgesia and Rheumatology Products

HFD #: 170

Review completion date: March 11, 2010

Drug:

Trade name: Abstral

Generic name: fentanyl citrate

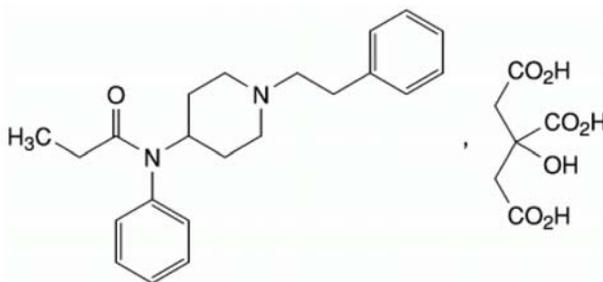
Code name: referred to as Rapinyl in the IND

Chemical name: N-phenyl-N-[1-(2-phenylethyl)-4-piperidinyl] propanamide, 2-hydroxy-1,2,3-propanetricarboxylate

CAS registry number: 990-73-8

Molecular formula/molecular weight: $C_{22}H_{28}N_2O \cdot C_6H_8O_7$ MW=528.59 (336.47 as free base)

Structure:



Relevant INDs/NDAs/DMFs:

<i>IND/NDA/MF</i>	<i>drug/compound</i>	<i>Sponsor</i>	<i>Division</i>	<i>status</i>
IND 69,190	Rapinyl	ProStrakan	DAARP	active
NDA 20-747	Actiq (referenced drug)	Cephalon	DAARP	approved 11/4/98
(b) (4)				

*The status of MF (b) (4) is currently inadequate. CMC recommends approval pending adequate resolution of requests. The CMC requests are delineated in the NDA review by Dr. Muthukumar Ramaswamy (dated 2/26/10). None of the pending CMC requests affect the approvability of this NDA from the pharmacology/toxicology perspective.

#As per the NDA supplement dated March 10, 2010 (b) (4) will be the sole commercial supplier for fentanyl. Fentanyl supplied by (b) (4) was used during product development but will not be used in the commercial batches.

Drug class: Fentanyl is a mu opioid receptor agonist.

Intended clinical population: Abstral is indicated for the management of breakthrough cancer pain in patients 16 years and older with malignancies who are already receiving and who are tolerant to opioid therapy for their underlying persistent cancer pain.

Clinical formulation: The Abstral drug product is a formulation of fentanyl intended for sublingual use. The Applicant refers to the product as an (b) (4) and states that “the Abstral formulation is designed for rapid disintegration in the small amount of saliva available sublingually. The tablet disintegrates to small mucoadhesive units that reduce the swallowing of the active ingredient”. Although the applicant refers to the formulation as an (b) (4) the Division states that it meets the criteria for a sublingual tablet and will be labeled as such. Abstral contains the active ingredient fentanyl citrate at the strengths of 100, 200, 300, 400, 600, and 800 mcg.

As per product labeling for Actiq, for the management of breakthrough cancer pain, dosing should not exceed 4 per day; therefore, the maximum daily dose (MDD) of fentanyl via this product is 3.2 mg/day. Levels of all excipients in the Abstral formulation calculated for use at the MDD of 3.2 mg/day of fentanyl can be found in approved drug products at equal or greater levels and do not pose any unique toxicological concerns. Refer to Table 1 for the composition of Abstral.

Table 1. Composition of Abstral (table is reproduced from NDA)

Composition (mg)	Reference	Tablet strength					
		100 µg	200 µg	300 µg	400 µg	600 µg	800 µg
Fentanyl citrate	USP PhEur	(b) (4)					
Mannitol	USP PhEur						
Silicified microcrystalline cellulose	NF PhEur						
Croscarmellose sodium	NF PhEur						
Magnesium stearate	NF PhEur						
Tablet weight (mg):		70	70	70	70	105	140

Impurities in the drug substance

The MDD of fentanyl via this product (3.2 mg/day) is ≤ 2 g/day, therefore the qualification threshold according to the ICH Q3A(R2) guideline for impurities in the drug substances is (b) (4) intake, whichever is lower. The applicant has monitored and controlled for four impurities in the drug substance (Tables 2 and 3). The applicant has set the specifications for the impurities in the fentanyl drug substance obtained from (b) (4) at NMT (b) (4) or less and no further qualification will be necessary (Table 3). The (b) (4) contains a structural alert for mutagenicity. (b) (4) is a synthesis intermediate in the manufacture of fentanyl citrate in the drug substance supplied by (b) (4) only and is a degradation product of fentanyl. A specification to reflect NMT (b) (4) should be set for genotoxic or potentially genotoxic residual intermediates/impurities. The applicant has set the specification (b) (4) in the drug substance at NMT (b) (4). At the specification of (b) (4) with a MTDD of 3.2 mg of fentanyl the total daily intake (b) (4). This is below the limit of NMT (b) (4) and is considered acceptable. The specification of (b) (4) has been set for the drug substance from (b) (4) (Table 3). The specifications set (b) (4) for the fentanyl drug substance impurities as outlined in Table 3 are acceptable from a pharmacology/toxicology perspective. (b) (4) is used as a starting material in the synthesis of fentanyl. It contains a structural alert for mutagenicity and is a known rat carcinogen (National Toxicology Program, 1978). Levels in the drug substance should therefore be controlled to reflect NMT (b) (4) total daily intake (b) (4). No specification is currently set for (b) (4) in the drug substances obtained (b) (4). Representative batches of fentanyl citrate (b) (4) have been tested and found to contain (b) (4) respectively. (b) (4). Although no specification is set, the levels of (b) (4) consistently detected in the drug substance are acceptable to the chemist (Dr. Muthukumar Ramaswamy) and are acceptable from a pharmacology/toxicology perspective.

It should be noted that the applicant submitted a computational toxicology assessment (MultiCase report 4.2.3.3.1), an Ames Test and an *in vitro* chromosome aberration assay

and with (b) (4). The discussion of the MultiCase report is below and the review of the Ames Test and *in vitro* chromosome aberration assay are under the Genetic Toxicology section of this NDA review. The applicant has reduced the levels (b) (4) in the drug substance and drug product to acceptable levels therefore the studies to qualify (b) (4) are not needed for approval. The MultiCASE report submitted by the applicant predicted that (b) (4) did not possess potential for mutagenicity or clastogenicity. Internal computational toxicology analysis of (b) (4) by FDA did not reach the same conclusions (see MultiCase Evaluation (b) (4) below). The Ames test with (b) (4) conducted by the applicant was invalid (see review for discussion). (b) (4) did not cause structural chromosomal aberrations in the *in vitro* chromosomal aberration study with human peripheral blood lymphocytes, however, an equivocal result for increased levels of polyploid cells were seen in cultures treated with (b) (4) in the presence of S9.



Impurities in the drug product

The MDD of fentanyl of 3.2 mg in the Abstral drug product is < 10 mg/day, therefore the qualification threshold according to the ICH Q3B(R2) guidelines for impurities/degradants is (b) (4), whichever is lower. The applicant has monitored and controlled for three impurities in the drug product. The applicant has set the specifications for the impurities in the fentanyl drug product (b) (4) and no further qualification will be necessary (Table 4). The specification for (b) (4) is set at NMT (b) (4). At this specification for the MDD of fentanyl the total daily intake (b) (4) would be (b) (4). In order to meet the currently accepted specification of (b) (4) for a potentially genotoxic impurity the specification would have to be set at (b) (4). The specification of (b) (4) as well as the other drug product specifications listed in Table 4 are considered acceptable from a pharmacology/toxicology perspective.

**MultiCASE Evaluation**

(b) (4)
The applicant submitted a computational analysis of (b) (4) (*MultiCASE report for the MC4PC predicted genotoxic activity* (b) (4) dated November 7, 2007; 4.2.3.3.1) which predicted that (b) (4) did not possess potential for mutagenicity or clastogenicity. The structure of (b) (4) was submitted to the FDA Informatics and Computational Safety Analysis Staff (ICSAS) for evaluation of the potential for genotoxicity. Although the ICSAS report concurred with the negative prediction for mutagenicity in the applicant's MultiCASE report, the ICSAS report predicted a positive result for clastogenicity for the *in vivo* micronucleus assay. The applicant's MultiCASE report was submitted to the ICSAS group for evaluation. The ICSAS staff identified several deficiencies in the applicant's MultiCASE evaluation which may explain the discrepancies between the two analyses. These findings are described briefly in a summary provided to us by Dr. Naomi Kruhlak of the ICSAS staff. This report is reproduced verbatim below.

The following is an evaluation of a MultiCASE report for the MC4PC predicted genotoxic activity of (b) (4), dated November 7, 2007:

MultiCASE screened (b) (4) using 2007 versions of the computational toxicology modules designed to be used with their MC4PC

software listed below. All modules used were reported by MultiCASE to give negative predictions.

- 1) FDA/ICSAS module A7O to assess hgprrt
- 2) FDA/ICSAS module A7S to assess micronucleus *in vivo*
- 3) MultiCASE module A61 to assess chromosome aberrations *in vitro*
- 4) FDA/ICSAS module A7P to assess chromosome aberrations *in vivo*

Based on FDA/ICSAS' evaluation of MultiCASE's report, it is ICSAS' conclusion that there are four major discrepancies between the analyses done by MultiCASE and ICSAS:

- 1) The version numbers of the modules used – MultiCASE used 2007 versions and ICSAS uses 2008 versions.
- 2) The way in which the modules were run – MultiCASE used single modules for the prediction of activity at each endpoint, whereas ICSAS uses a set of modules for micronucleus *in vivo*.
- 3) The modules that were deemed to have adequate predictive performance – MultiCASE reported predictions for chromosome aberrations *in vivo* with module A7P but ICSAS has determined that MC4PC modules for this endpoint have too low sensitivity for routine analysis.
- 4) The modules selected for the analysis – Module A61 is a MultiCASE module and is not part of ICSAS' standard battery.

These discrepancies resulted in different predicted outcomes by MultiCASE as compared to those obtained by FDA/ICSAS. ICSAS found that the hgprrt module gave a negative prediction but the micronucleus *in vivo* modules gave a positive prediction. No MC4PC prediction was made by ICSAS for chromosome aberrations *in vivo* or *in vitro*.

ICSAS attempted to replicate the 2007 model-based predictions in the MultiCASE report using 2008 models, and the negative prediction for hgprrt was confirmed by the 2008 model. In contrast, the negative prediction for micronucleus *in vivo* was not confirmed by the 2008 modules. When ICSAS ran the 2007 A7S module by itself it gave a negative prediction for micronucleus *in vivo*, but using the 2008 module either alone (A7S) or in combination with the other two modules (A7S, A7T, and A8J) it consistently gave positive predictions for micronucleus *in vivo* for (b) (4)

It can be concluded that the difference between the MultiCASE reported predictions and internal FDA/ICSAS predictions is due to several differences in methodology, including the version and types of genetic toxicity modules used. It is also concluded that the FDA/ICSAS-created modules run by MultiCASE were not used in the manner in which they were intended to be used by FDA/ICSAS.

Route of administration: sublingual

Disclaimer: Tabular and graphical information are constructed by the reviewer unless cited otherwise.

Data reliance: Except as specifically identified below, all data and information discussed below and necessary for approval of NDA 22-510 are owned by ProStrakan, Inc. or are data for which ProStrakan, Inc. has obtained a written right of reference. Any information or data necessary for approval of NDA 22-510 that ProStrakan, Inc. does not own or have a written right to reference constitutes one of the following: (1) published literature, or (2) a prior FDA finding of safety or effectiveness for a listed drug, as described in the drug's approved labeling. Any data or information described or referenced below from a previously approved application that ProStrakan, Inc. does not own (or from FDA reviews or summaries of a previously approved application) is for descriptive purposes only and is not relied upon for approval of NDA 22-510.

This NDA for Abstral (b) (4) Tablets is being filed under Section 505(b)(2) of the FD&C Act. Abstral contains fentanyl citrate, the same active ingredient as Actiq oral transmucosal lozenge (NDA 20-747). Actiq is the referenced drug for this NDA. Actiq is indicated for the management of breakthrough cancer pain in patients 16 years and older with malignancies who are already receiving and who are tolerant to opioid therapy for their underlying persistent cancer pain. The applicant is relying on the Agency's findings of safety and efficacy and the pharmacology, pharmacokinetics, and toxicology information in the label of Actiq.

Studies reviewed within this submission:

<i>Study number</i>	<i>eCTD location</i>	<i>Study Title</i>
SBL26-85	4.2.1.3	A Safety Pharmacology Study of Fentanyl Citrate on the Cardiovascular and Respiratory Systems in Conscious Dogs
D-04-177	4.2.2.2	Disposition of Fentanyl after Sublingual, Oral or Intravenous Administration of Fentanyl Citrate to Rats
04-054	4.2.2.2	Pharmacokinetics of Fentanyl in Dogs after Sublingual Administration, Oral Administration, and Intravenous Administration
D-05-129	4.2.2.3	Whole Body Autoradiography after Sublingual Administration of ³ H-Fentanyl Citrate to Rats
SBL26-84	4.2.3.1	A Single Dose Toxicity Study of Fentanyl Citrate in Dogs
MD-64-07	4.2.3.3	Reverse Ames Testing (b) (4)
EN3267-703	4.2.3.3	Computational Assessment of Mutagenicity Structural Alerts of (b) (4) an Impurity in Fentanyl Citrate, with MC4PC
8212994	4.2.3.3	Induction of Chromosome Aberration in Cultured Human Peripheral Blood Lymphocytes
10797-01	4.2.3.6	OX 22 - Oral Irritation Test in the Syrian Hamster
I-2019	4.2.3.6	Oral Mucosal Irritation Study of KW-2246 in Guinea Pigs

Studies not reviewed within this submission:

All submitted studies were reviewed.

2.6.2 PHARMACOLOGY**2.6.2.1 Brief summary**

Fentanyl is a synthetic phenylpiperidine opioid analgesic which acts as an agonist on the mu opioid receptor. The analgesic properties of fentanyl are similar to that of morphine and other mu opioids. Fentanyl is more lipid soluble than morphine and is roughly 100 times more potent than morphine as an analgesic. Time to peak analgesia of fentanyl is rapid and the duration of action is short (Goodman and Gilman, 2006). The safety concerns of fentanyl are similar to those of other potent opiates with the major concerns being respiratory depression and the potential for abuse.

2.6.2.2 Primary pharmacodynamics

Mechanism of action: Fentanyl is an opioid agonist which exerts its analgesic effects primarily through the mu opioid receptor subtype.

Drug activity related to proposed indication: Fentanyl is a potent opioid and with SL administration, first-pass metabolism is avoided resulting in a higher bioavailability than orally administered fentanyl. Fentanyl is lipophilic and rapidly crosses the blood brain barrier resulting in a rapid onset of action, an important factor for the relief of breakthrough pain episodes in cancer patients.

2.6.2.3 Secondary pharmacodynamics

No secondary pharmacology studies were conducted

2.6.2.4 Safety pharmacology

The safety of sublingually administered fentanyl pertaining to the current NDA is similar to those of systemically administered potent opioids. The major concern is respiratory depression which can occur in humans at plasma concentrations between 2 to 4 ng/mL. One safety pharmacology study was submitted in support of NDA 22-510. The applicant conducted a study to evaluate the effects of IV-administered fentanyl on cardiovascular and respiratory function in unanesthetized dogs (Study SBL26-85). The results of the study are summarized below.

Cardiovascular effects: Fentanyl has been shown to inhibit the activity of the cardiac HERG K⁺ channel with an IC₅₀ of 1.8 uM (Katchman et al., 2002). This finding is considered to be without clinical significance because the HERG IC₅₀ is approximately 400 fold higher than the concentration achieved with the highest dose of Abstral (1.5 ng/mL).

Fentanyl citrate was administered sequentially to telemetered dogs at doses of 0.003, 0.01, and 0.03 mg/kg with a 6-day washout between doses (Study SBL26-85). BP, HR, ECG, RR were continuously monitored for 24 h after fentanyl administration. Arterial blood gasses (pH, PaO₂ and PaCO₂) and hemoglobin oxygen saturation were measured 1 and 24 h after fentanyl administration. The plasma concentration of fentanyl was also measured.

At the mid and high dose significant increases in systolic blood pressure values were seen. The high dose showed a decrease of heart rate at 0.5 and 1 h post dosing (61% and 79%, respectively). Mean QT interval was also higher from 0.5 to 2 h post dose at the high dose. When corrected for heart rate (Matsunaga's Formula), QTc was still significantly increased. The increases were small (mean increase \leq 33 msec from baseline) and transient and are most likely not of any physiological significance. No CV effects were seen at the low dose.

Pulmonary effects: A reduction in arterial pH and an increase in arterial CO₂ partial pressure was seen at the mid and high doses. Both effects were reversible. No effects were seen on respiration rate, arterial partial pressure and hemoglobin oxygen saturation at any dose. No respiratory effects were seen at the low dose.

Neurological effects: Effects arising from CNS suppression including decreased spontaneous motor activity, sedation, anastasia, decreased muscle tone, miosis, and bradypnea were observed but disappeared by 4 h postdose for the high dose and by 1 h post dose for the mid and low doses. Severity of the effects was dose dependent. All observations were typical CNS effects of an opioid agonist.

Renal effects: not assessed

Gastrointestinal effects: not assessed

Abuse liability: Fentanyl is classified by the DEA as a Schedule II drug (DEA #9807). No abuse liability issues unique to this fentanyl product were identified.

2.6.2.5 Pharmacodynamic drug interactions No new studies were conducted.

2.6.3 PHARMACOLOGY TABULATED SUMMARY

Not provided by the applicant.

2.6.4 PHARMACOKINETICS/TOXICOKINETICS

2.6.4.1 Brief summary

The applicant conducted several ADME studies in rat and dog to compare oral, sublingual, and intravenous administration of fentanyl. A tissue penetration study in rat using whole body autoradiography with sublingually administered ³H-fentanyl was also conducted. The studies are summarized below.

2.6.4.2 Methods of Analysis

Methods are described under the individual heading.

2.6.4.3 Absorption

The absorption, bioavailability and pharmacokinetic profile of fentanyl were investigated in non-fasting male dogs following single dose SL, PO or IV administration (Study 04-054; Tables 1 and 3).

Intravenous administration of 0.04 mg/kg of fentanyl to dogs exhibited biphasic elimination and showed a $T_{1/2}$ of 3.7 +/- 1.25 h. Refer to Table 1 for C_{max} and $AUC_{0-\infty}$ values. The V_d and CL at SS were 0.429 +/- 0.17 L/h/kg and 1.01 +/- 0.1 L/kg, respectively.

Sublingual administration of fentanyl to dogs (100-400 mcg/dog) showed a T_{max} in the range of 0.15-0.18 h and exhibited biphasic elimination. The $T_{1/2}$ was 4.18 +/- 1.32 h. Refer to Table 1 for C_{max} and $AUC_{0-\infty}$ values. The pharmacokinetics were dose linear within the range tested and bioavailability with the SL route was very close to 100% (114.4 +/- 18.1%).

Oral administration of fentanyl to dogs at a dose of 1 mg/dog reached T_{max} at 0.83 +/- 0.29 h postadministration. Refer to Table 1 for C_{max} and $AUC_{0-\infty}$ values. Elimination was biphasic and oral bioavailability was very low at 3.5 +/- 0.8%.

Table 1. $AUC_{0-\infty}$ and C_{max} values following IV, PO or SL fentanyl administration in dogs (Study 04-054)			
ROA	dose	$AUC_{0-\infty}$ (ng*h/mL)	C_{max} ng/mL
IV	0.04 mg/kg	11.7 ± 2.5	-
PO	1 mg/kg	10.2 ± 2.2	3.15 ± 0.73
SL	100 mcg/dog	2.79 ± 0.22	2.41 ± 0.47
	200 mcg/dog	5.83 ± 1.44	4.96 ± 1.09
	400 mcg/dog	13.9 ± 1.8	9.60 ± 2.12

The absorption, bioavailability and pharmacokinetic profile of fentanyl were investigated in rats following single dose SL, PO or IV administration (Study D-04-177; Tables 2 and 4).

Intravenous administration of 0.01 mg/kg of fentanyl to male rats exhibited monophasic elimination. Refer to Table 2 for C_{max} and $AUC_{0-\infty}$ values. The V_d and CL at SS were 3.08 +/- 0.52 L/h/kg and 4.44 +/- 0.52 L/kg, respectively.

Sublingual administration of fentanyl to anesthetized male and female rats in the dosing range of 0.01-0.2 mg/kg showed a T_{max} at 0.5-0.83 h and exhibited biphasic elimination. The C_{max} and AUC values (Table 2) increased roughly proportionally for the doses tested.

Large individual fluctuations of fentanyl plasma levels were observed within the study. No statistically significant differences were observed between males and females. The bioavailability for SL administration ranged between 36.6-72.9% for the range of doses tested in this study.

Oral administration of fentanyl to male rats at doses of 0.2 and 2.0 mg/kg reached T_{max} at 1.2-2.2 h postadministration. Refer to Table 2 for C_{max} and $AUC_{0-\infty}$ values. The bioavailability with oral administration was very low at 5%.

Table 2. $AUC_{0-\infty}$ and C_{max} values following IV, PO or SL fentanyl administration in rats (Study D-04-177)			
ROA	dose mg/kg	$AUC_{0-\infty}$ (ng*h/mL)	C_{max} ng/mL
IV	0.01	3.32 ± 0.62	-
PO	0.2	3.23*	0.99 ± 1.4
	2.0	7.48 ± 0.35	0.78 ± 0.35
SL	0.01	2.42 ± 1.87	1.32 ± 1.26
	0.03	3.64 ± 0.34	1.68 ± 0.23
	0.1	16.4 ± 2.0	7.34 ± 2.00
	0.2	33.6 ± 14.6	13.2 ± 6.4

*n=2

The plasma binding of fentanyl has been reported in the literature to be between 57-62% in dog (Hug, Jr. and Murphy, 1979; Murphy et al., 1979) and 72-84% in human (Lehmann et al., 1983; Meuldermans et al., 1982).

2.6.4.4 Distribution

The tissue penetration characteristics of fentanyl were evaluated using whole body autoradiography after SL administration of 3H -fentanyl citrate to rats (Study D-05-129). Tissue radioactivity was quantified using radioluminography at 0.5, 2, 24 and 48 h post administration.

At 0.5 h the greatest tissue levels of 3H -fentanyl were in the liver (3.3 times the intracardiac blood level) followed by the medulla of the kidney, cortex of the kidney, spleen, pancreas and submaxillary gland which ranged from 1.0-2.4 times the intracardiac blood level. Lower levels (between 0.2-0.9 times the intracardiac blood level) were seen in the lung, Harderian gland, thymus, heart, posterior vena cava, bone marrow, muscle, brain and testis. Radioactivity was lowest in the eyeball (0.2 times the intracardiac blood level).

The applicant states that at 2 h postadministration the tissue/blood levels were not calculated because the intracardiac blood radioactive concentration and surrounding tissue luminescence intensity were the same level. However, they list the following organs which showed the highest tissue radioactivity at this time point: submaxillary

gland, liver, spleen, pancreas, lung, testis, heart, muscle, posterior vena cava, brain and eyeball. From 24 to 48 h postadministration radioactivity was not observed in any tissue. Sublingually administered ^3H -fentanyl citrate was absorbed and distributed throughout the body. The radioactivity rapidly disappeared and no organs were seen to contain residual radioactivity.

2.6.4.5 Metabolism No new studies were conducted.

2.6.4.6 Excretion No new studies were conducted.

2.6.4.7 Pharmacokinetic drug interactions No new studies were conducted.

2.6.4.8 Other Pharmacokinetic Studies No new studies were conducted.

2.6.4.9 Discussion and Conclusions

Several pharmacokinetic studies in rat and dog were conducted to evaluate oral, sublingual, and intravenous administration of fentanyl. In both rats and dogs, fentanyl has very low oral bioavailability and bioavailability of sublingually administered fentanyl is considerably higher. C_{\max} and AUC values are presented in Tables 1 (dog) and 2 (rat). In a tissue penetration study using whole body autoradiography in rat, sublingually administered ^3H -fentanyl was shown to be absorbed and distributed throughout the body. The radiolabeled fentanyl rapidly disappeared and no organs were seen to contain residual radioactivity.

2.6.4.10 Tables and figures to include comparative TK summary

Table 3. PK Parameters of fentanyl following single-dose IV, SL and PO administration to non-fasting dogs (Study 04-054; table reproduced from NDA)

Route	Dose		T_{\max} (h)	C_{\max} (ng/mL)	$t_{1/2}$ (h)	AUC _{0-∞} (ng•h/mL)	F (%)
	(mg/kg)	($\mu\text{g}/\text{body}$)					
IV	0.04	-	-	-	3.70±1.25	11.7±2.5	-
SL	-	100	0.18±0.03	2.41±0.47	4.18±1.32	2.79±0.22	-
	-	200	0.17±0.03	4.96±1.09	2.93±0.86	5.83±1.44	-
	-	400	0.15±0.05	9.60±2.12	3.14±1.53	13.9±1.8	114.1±18.0
PO	1.0	-	0.83±0.29	3.15±0.73	4.47±1.12	10.2±2.2	3.5±0.8

F=bioavailability; IV=intravenous administration; PO=oral administration; SL=sublingual administration

Note: Values are the means \pm SD of three animals.

Table 4. PK parameters of fentanyl following single-dose IV, SL and PO administration to rats (Study D-04-177; table reproduced from NDA)

Route	Dose (mg/kg)	C _{max} (ng/mL)	t _{1/2} (h)	AUC _{0-∞} (ng•h/mL)	F (%)
IV	0.01	-	1.27±0.14	3.32±0.62	-
SL	0.01	1.32±1.26	4.40±2.86	2.42±1.87	73
	0.03	1.68±0.23	1.62±0.28	3.64±0.34	-
	0.1	7.34±2.00	2.18±0.1	16.4±2.0	-
	0.2	13.2±6.4	2.99±1.16	33.6±14.6	-
PO	0.2	0.98±1.39	34.2*	3.23*	-
	2.0	0.78±0.35	4.49±1.9	7.48±2.8	-

n=3; F=bioavailability; IV=intravenous administration; PO=oral administration; SL=sublingual administration
 Note: Values are the means ± SD of three animals. * Mean of two animals.

2.6.5 PHARMACOKINETICS TABULATED SUMMARY

2.6.6 TOXICOLOGY

2.6.6.1 Overall toxicology summary

General toxicology: A single-dose toxicity study in dogs was conducted by the applicant. Two dogs were administered 35 mg/kg fentanyl orally. The behavioral findings observed in this study were consistent with acute toxicity of a mu opioid and no novel findings were seen. Large variations in TK were observed between the two dogs with differences in C_{max} >30 fold and AUC >20 fold.

Genetic toxicology: Genetic toxicology studies with fentanyl are described in the FDA approved label for the referenced product, Actiq. No new genetic toxicology studies with fentanyl were submitted by the applicant. The applicant conducted an Ames test and an *in vitro* chromosome aberration assay with the fentanyl impurity/degradation product (b) (4). The applicant has reduced the levels of (b) (4) in the drug substance and drug product to acceptable levels therefore the studies to qualify (b) (4) are not needed for approval. The Ames test with (b) (4) conducted by the applicant was invalid (see review). In the *in vitro* chromosomal aberration study with human peripheral blood lymphocytes, (b) (4) did not cause structural chromosomal aberrations. However, an equivocal result for increased levels of polyploid cells were seen in cultures treated with (b) (4) in the presence of S9.

Carcinogenicity: No carcinogenicity studies were conducted for this NDA.

Reproductive toxicology: No new reproductive toxicology studies were conducted. Fentanyl is currently a Pregnancy Category C. It has been evaluated in several animal studies which appear in the referenced label for this product.

Special toxicology: Although not required for approval, the applicant submitted supportive data to evaluate the local toxicity in the oral mucosa of fentanyl and several excipients found in the Abstral formulation. Under the conditions tested, fentanyl and the various excipients tested did not appear to show irritation in the oral mucosa. However, the studies are of questionable utility for the following reasons: the fentanyl study was not conducted according to GLP, and only one of the excipients evaluated was tested at a higher concentration than found in the 800 mcg Abstral formulation.

2.6.6.2 Single-dose toxicity

The applicant conducted a single-dose toxicology study with fentanyl (35 mg/kg orally) in dogs (n=2) with toxicokinetics (Study SBL 26-84). The purpose of the study was to investigate the toxicity of fentanyl if mistakenly swallowed. No deaths were seen in the study. Observations in both dogs after test article administration included anastasia (inability to stand up), bradypnea, flaccid muscle tone, lateral position, pale oral mucosa and conjunctiva, and loss of responsiveness to sound and touch. One of the dogs showed ataxic gait, tonic convulsions, twitching, mydriasis, coma, loss of light reflex and sedated condition and the other dog showed miosis and somnolence. On day 2 postadministration the observations of anastasia, reduced muscle tone, tonic convulsions, mydriasis, lateral or sitting position, loss of response to sound, decreased light reflex, sedated condition, and salivation in one dog and drowsiness and anastasia in the other dog were still observed. These observations disappeared by day 4.

Significant individual differences in TK were seen for the two dogs in this study. The C_{max} differed by 38 times and the AUC_{0-48h} differed by 26 times between the two dogs.

The T_{max} for both dogs was 30 min and drug concentration decreased over time however fentanyl was still detectable 48 h postadministration. In one of the dogs the plasma fentanyl concentration at 8 and 24 h were higher than measured at 4 h postadministration. This finding corresponded with bradycardia which had disappeared by 4 h but reappeared at 8 h. The applicant proposes that these changes in plasma levels may be due to enterohepatic circulation of fentanyl.

The behavioral observations in this study are consistent with that of a high dose of a mu opioid. No novel findings were observed.

2.6.6.3 Repeat-dose toxicity No repeat-dose studies were conducted.

2.6.6.4 Genetic toxicology

An Ames test and an *in vitro* chromosomal aberration assay were conducted with the impurity/degradant (b) (4). No genetic toxicology studies were conducted with fentanyl.

Study title: Salmonella Escherichia coli/Mammalian-Microsome Reverse Mutation Assay

Key findings: (b) (4) is not mutagenic in *S. typhimurium* strains TA98, TA100, TA1535, and TA1537 and *E. coli* strain WP2PuvrA in either the presence or absence of S9.

Study no.: 7718-112

Volume #, and page #: Module 4.2.3.3.1 (Study Report MD-64-07)

Conducting laboratory and location: (b) (4)

Date of study initiation: July 10, 2007

GLP compliance: Yes, but see exceptions

- Exceptions:
- 1) documentation of the stability, purity, and/or characterization of the test article was not provided by the Sponsor.
 - 2) the stability, homogeneity, and/or concentration of the dosing preparations were not analyzed.

QA reports: yes (X) no ()

Drug, lot #, and % purity: (b) (4); raw material number: 24516; purity not given

Methods

The Applicant evaluated (b) (4) in a bacterial mutagenicity assay based on the method of Maron and Ames (Maron and Ames, 1983). Six concentrations of test article as well as water vehicle and positive controls were plated in triplicate with overnight cultures of *Salmonella typhimurium* strains TA98, TA100, TA1535, and TA1537 (Ames et al., 1975) and *Escherichia coli* strains WP2uvrA (Green and Muriel, 1976) on selective minimal agar in the presence and absence of S9 prepared from Aroclor-induced rat liver using the plate incorporation method. The positive controls utilized were appropriate for each tester strain and metabolic activation condition. Five-hundred μL of S9 or sham mix, 100 μL of tester strain and 100 μL of vehicle, test article dilution or positive control were added to melted selective top agar, vortexed and overlaid onto the surface of 25 mL Vogel-Bonner minimal medium (Vogel and Bonner, 1956). After solidification of the overlay, plates were inverted and incubated for approximately 54 hours at 37°C. Following examination for contamination, revertant colonies for a given tester strain and activation condition were counted by hand or with an automated colony counter.

The criteria for a valid assay outlined by the applicant were as follows:

All *Salmonella* strains must exhibit sensitivity to crystal violet, demonstrating the presence of the *rfa* wall mutation. TA98 and TA100 strains must exhibit resistance to ampicillin, demonstrating the presence of the pKM101 plasmid. All strains must exhibit a characteristic number of spontaneous revertants per plate when plated under selective conditions. These ranges are outlined in Table 1. The density of all strains must be $>0.05 \times 10^9$ bacteria/mL. All positive controls evaluated in the presence and absence of

S9 must exhibit at least a 3-fold increase in the number of revertants as compared to concurrent vehicle controls. A minimum of three non-toxic doses were required to evaluate the assay. Cytotoxicity was defined as a detectable decrease in the number of revertants per plate and/or by a thinning or disappearance of the background lawn. A thinning of the bacterial lawn that was not accompanied by a reduction in the number of revertants per plate was not considered an indication of cytotoxicity.

For a test article to be considered positive it must produce at least a 2-fold increase (for TA98, TA100 and WP2*uvrA*) or a 3-fold increase (for TA1535 and TA1537) in the mean revertants per plate of at least one of the test strains. The increase in the mean number of revertants per plate must be accompanied by a dose response to increasing concentrations of the test article. The criteria provided by the applicant for a valid and positive assay are acceptable.

<i>strain</i>	<i>revertants</i>
TA98	8-60
TA100	60-240
TA1535	4-45
TA1537	2-25
WP2 <i>uvrA</i>	5-40

Strains/species/cell line: *S. typhimurium* histidine auxotrophs utilized included: TA98, TA100, TA1535 and TA1537. *E. coli* tryptophan auxotroph utilized: WP2*uvrA*.

Doses used in definitive study: The doses used for TA98, TA100, TA1535, TA1537, and WP2*uvrA* in the studies with both the presence and absence of S9 are: 156, 313, 625, 1250, 2500 and 5000 mcg/plate. DMSO was used as the vehicle for all conditions.

Basis of dose selection: The initial assay used tester strains TA100 and WP2*uvrA* only. Ten concentrations over a range of 6.67 mcg to 5000 mcg per plate of (b) (4) in DMSO vehicle ±S9 were tested using the plate incorporation method. Cytotoxicity, as evidenced by bacterial lawn clearing as well as a reduction in revertants, was observed at 3300 mcg and above in the absence of S9. No cytotoxicity was observed up to 5000 mcg in the presence of S9. Precipitate was observed at 5000 mcg in the absence of S9.

Negative controls: A negative control was not used in this study.

Positive controls: The positive controls utilized for the respective strains are indicated in Table 2.

Table 1. Positive Controls (table reproduced from NDA)

Tester Strain	S9 Mix	Positive Control	Dose ($\mu\text{g}/\text{plate}$)
TA98	+	benzo[a]pyrene	2.5
TA98	-	2-nitrofluorene	1.0
TA100	+	2-aminoanthracene	2.5
TA100	-	sodium azide	2.0
TA1535	+	2-aminoanthracene	2.5
TA1535	-	sodium azide	2.0
TA1537	+	2-aminoanthracene	2.5
TA1537	-	ICR-191	2.0
WP2uvrA	+	2-aminoanthracene	25.0
WP2uvrA	-	4-nitroquinoline-N-oxide	1.0

Incubation and sampling times: Plates were incubated for 54 hours at 37°C.

Results

Study validity (comment on replicates, counting method, criteria for positive results, etc.): The study is *invalid*. Three separate studies were conducted with each strain. Suitable numbers of replicate plates and appropriate counting methods were utilized. The positive controls demonstrated clear increases in tester strain revertants while the vehicle control was within historical range for the tester strains for this vehicle. However, no lot number or purity data were provided for the (b) (4) was also not analyzed for stability or homogeneity and the concentrations of the dosing preparations were not analyzed. Since cytotoxicity was demonstrated for all strains in both the presence and absence of S9 for at least one concentration the lack of analysis of the dosing preparations would not necessarily invalidate the study. However, no COA documenting the identity and purity and no stability data or other characterization of the test article used in the study were provided. For these reasons, the study will be considered invalid.

Study outcome: Assuming the study actually tested purified (b) (4) it is concluded that under conditions of the assays conducted, (b) (4) is not mutagenic in *S. typhimurium* strains TA98, TA100, TA1535, and TA 1537 and *E. coli* strain WP2uvrA in either the presence or absence of S9. The results of the confirmative assay are summarized in Table 3 (table reproduced from NDA). A reduction in the bacterial lawn was seen in the absence of S9 for strains TA98 and TA100 at concentrations of 1250 mcg and above and for all strains above 2500 mcg. A reduction in the bacterial lawn was seen in the presence of S9 for all strains at 5000 mcg. For all strains, at least three concentrations of test article were able to be evaluated. All of the strains at all of the concentrations tested showed negative mutagenic responses in the presence and absence of exogenous metabolic activation with S9 (Table 3). However, note that the study is invalid due to the reasons stated above.

Table 3. Data from the definitive study: Mutagenicity Assay Results Summary (table reproduced from NDA)

Test Article ID: [REDACTED] ^{(b) (4)}

Assay No.: 29369-0-409

Trial No.: B1

Date Plated: 10-Aug-07

Vehicle: DMSO

Date Counted: 13-Aug-07

Plating Aliquot: 50 µL

	Dose/Plate	Mean Revertants Per Plate with Standard Deviation										Back-ground Lawn ^a
		TA98		TA100		TA1535		TA1537		WP2uvrA		
		Mean	S.D.	Mean	S.D.	Mean	S.D.	Mean	S.D.	Mean	S.D.	
Microsomes: Rat Liver												
Vehicle Control		22	3	114	13	11	4	10	2	16	2	N
Test Article	156 µg	27	4	98	5	16	3	6	2	12	3	N
	313 µg	24	6	104	16	11	5	7	4	12	7	N
	625 µg	24	1	90	16	14	7	6	2	9	2	N
	1250 µg	24	5	85	6	12	3	4	3	5	2	N
	2500 µg	19	2	64	21	5	1	3	1	2	1	N
5000 µg	15	5	22	5	4	2	0	1	5	2	R	
Positive Control ^b		614	31	1035	149	143	13	94	11	615	90	N
Microsomes: None												
Vehicle Control		17	2	78	7	14	5	8	1	14	5	N
Test Article	156 µg	17	7	80	2	9	2	7	1	8	2	N
	313 µg	18	1	69	6	11	2	7	3	10	5	N
	625 µg	10	1	70	15	10	4	7	3	8	3	N
	1250 µg	11	1	70	10	7	1	6	3	6	1	N/R ^d
	2500 µg	7	5	47	3	6	2	4	3	2	2	R
5000 µg	4	2	14	5	2	1	2	4	1	1	R/RP ^e	
Positive Control ^c		345	97	1256	32	1015	23	525	58	315	70	N

^a Background Lawn Evaluation Codes:

N = normal R = reduced O = obscured A = absent P = precipitate

^b TA98	benzo[a]pyrene	2.5 µg/plate	^c TA98	2-nitrofluorene	1.0 µg/plate
TA100	2-aminoanthracene	2.5 µg/plate	TA100	sodium azide	2.0 µg/plate
TA1535	2-aminoanthracene	2.5 µg/plate	TA1535	sodium azide	2.0 µg/plate
TA1537	2-aminoanthracene	2.5 µg/plate	TA1537	ICR-191	2.0 µg/plate
WP2uvrA	2-aminoanthracene	25.0 µg/plate	WP2uvrA	4-nitroquinoline-N-oxide	1.0 µg/plate

^d The first entry is the lawn evaluation for tester strains TA1535, TA1537, and WP2uvrA.

The second entry is the lawn evaluation for tester strains TA98 and TA100.

^e The first entry is the lawn evaluation for tester strains TA1535 and WP2uvrA.

The second entry is the lawn evaluation for tester strains TA98, TA100, and TA1537.

Study title: (b) (4) **Induction of Chromosomal Aberrations in Cultured Human Peripheral Blood Lymphocytes**

Key findings: Under the conditions of the assay, (b) (4) does not induce structural chromosomal aberrations *in vitro* with human peripheral blood lymphocytes. However, increased levels of polyploid cells were seen in cultures treated with (b) (4) in the presence of S9 at concentrations of 375 and 450 mcg/mL in two separate assays. Although not all of the criteria stated by the applicant for a positive clastogenic result were met, there appears to be a signal of increased polyploidy. The result of (b) (4) induced polyploidy will be considered equivocal.

Study no.: 8212994

Volume #, and page #: Module 4.2.3.3.1

Conducting laboratory and location: (b) (4)

Date of study initiation: June 29, 2009

GLP compliance: Yes

QA reports: yes (X) no ()

Drug, lot #, and % purity: (b) (4) Batch #
030303; purity: 100.1%;

Methods

Strains/species/cell line: Human peripheral blood lymphocytes

Doses used in definitive studies: See Table 1

Basis of dose selection: In the dose range finding and two main study experiments several concentrations of (b) (4) in the presence or absence of S9 activation were tested (Table 1). The cultures were incubated with test article for 3 hours followed by a 17 hour recovery or for 20 hours with no recovery. In both main study assays, the highest concentrations selected for chromosomal aberration analysis were limited by cytotoxicity and reductions in mitotic activity. The assay parameters and concentrations at which cytotoxicity was observed are described in Table 1.

<i>Assay</i>	<i>S9</i>	<i>treatment with test article, h</i>	<i>concentrations tested (concentrations evaluated), mcg/mL</i>	<i>cytotoxicity, mcg/mL</i>	<i>precipitate</i>
dose range finding	-	3	4.4 to 1200	<259 ≥432	≥156
	+	3		<259 ≥432	
	-	20		<33.6 ≥93.3	
Assay 1	-	3	75 to 500 (75, 200, 350)	≥375	≥156
	+	3	75 to 500 (275, 300, 350)	≥375	
Assay 2	-	20	5 to 500 (30, 60, 80)	≥80	≥150
	+	3	5 to 500 (350, 375, 450)	≥450	

The applicant states that the procedures and assay design comply with the recommendations of the OECD guideline 473 and the ICH Tripartite Harmonized Guideline on Genotoxicity: Specific Aspects of Regulatory Tests (1995).

Negative controls: The negative control was DMSO.

Positive controls: 4-Nitroquinolone 1-oxide (NQO) was used as the positive control at 2.5 and 5.0 mcg/mL in the absence of S9 activation and cyclophosphamide (CPH) was used at 6.25 and 12.5 mcg/mL in the presence of S9 activation.

Incubation and sampling times: See Table 1.

Cytotoxicity:

Slides from each treatment group were scored to determine whether test article-induced mitotic inhibition had occurred. Mitotic inhibition is defined as a clear decrease in mitotic index compared with negative controls, (based on at least 1000 cells counted, where possible), and is preferably concentration-related (see formula below). A suitable range of concentrations was selected for the main study experiments based on the toxicity data (Table 1).

Mitotic inhibition (MIH) is calculated as:

$$\text{MIH (\%)} = [1 - (\text{mean MI}_T / \text{mean MI}_C)] \times 100\%$$

(where T = treatment and C = negative control)

Structural and Numerical Chromosomal Aberrations:

For the analysis of chromosomal aberrations, three parameters were evaluated. The parameters are listed below:

1. cells with structural aberrations including gaps
2. cells with structural aberrations excluding gaps
3. polyploid, endoreduplicated or hyperdiploid cells

The statistical method used was Fisher's exact test and probability values of $p \leq 0.05$ were accepted as significant.

The applicant's criteria for a valid assay are as follows:

1. The binomial dispersion test demonstrated acceptable heterogeneity between replicate cultures
2. The proportion of cells with structural aberrations (excluding gaps) in negative control cultures fell within the normal range
3. At least 160 cells out of an intended 200 were suitable for analysis at each concentration, unless 10 or more cells showing structural aberrations (per slide) other than gaps only were observed during analysis
4. The positive control chemicals induced statistically significant increases in the proportion of cells with structural aberrations.

The test article was considered to induce clastogenicity if all of the criteria below are met. Conversely, the test article was considered negative if none of the criteria are met. The applicant's criteria for a positive assay are as follows:

1. A proportion of cells with structural aberrations at one or more concentrations that exceeded the normal range was observed in both replicate cultures
2. A statistically significant increase in the proportion of cells with structural aberrations (excluding gaps) was observed ($p \leq 0.05$)
3. There was a concentration-related trend in the proportion of cells with structural aberrations (excluding gaps). Evidence of a concentration-related effect was considered useful but not essential in the evaluation of a positive result.

Results

Study validity: This study is valid. It utilizes appropriate replicates and cell counting/viability methodology. The vehicles and positive controls for the S9-activated and non-activated groups are within the range of the historical data set. The positive controls are higher than vehicle controls for all groups.

Study outcome: It is concluded that (b) (4) does not induce chromosome breaks *in vitro* with human peripheral blood lymphocytes under conditions of the assays conducted. However, increased levels of polyploid cells were found in cultures treated with (b) (4) in the presence of S9 at concentrations of 375 and 450 mcg/mL in two separate assays (Tables 2 and 3). These increases were outside of historical controls but not statistically significant or dose dependent. The result will be considered equivocal.

In the main study experiments (assays 1 and 2) cultures treated with (b) (4) at a range of concentrations. Three (b) (4) concentrations were evaluated in each condition for

structural and numerical aberrations at concentrations showing ~50% reduction in mean mitotic inhibition. In assay 1 in the absence of S9, the concentrations that were scored showed mean mitotic inhibition of 9%, 24% and 43% at 75, 200, and 350 mcg/mL, respectively (3 hour incubation with test article; Table 2). In assay 1 in the presence of S9, the concentrations that were scored showed mean mitotic inhibition of 34%, 29% and 51% at 275, 300, and 375 mcg/mL, respectively (3 hour incubation with test article; Table 2). All concentrations in assay 1 contained precipitate. In assay 2 in the absence of S9, the concentrations that were scored showed mean mitotic inhibition of 4%, 41% and 52% at 30, 60, and 80 mcg/mL, respectively (20 hour incubation with test article; Table 3). In assay 2 in the presence of S9, the concentrations that were scored showed mean mitotic inhibition of 2%, 31% and 57% at 350, 375, and 450 mcg/mL, respectively (3 hour incubation with test article; Table 3). Concentrations in assay 2 in the presence of S9 only (3 hour incubation with test article) contained precipitate. The applicant states that the precipitate did not interfere with the scoring in any case. No significant effects on osmolality or pH were observed at any concentration. In cultures treated with (b) (4) no structural aberrations greater than vehicle control were observed for any condition (Tables 2 and 3). The vehicle in assays 1 and 2 showed 1.5% and 0.5% polyploid cells, respectively. Cultures treated with concentrations of (b) (4) (375 and 450 mcg/mL) in the presence of S9 showed 3.8% and 3.4%, respectively (Tables 2 and 3). The historical negative control mean for polyploid cells in the presence of S9 was between 1 and 3%. The 95% reference range for polyploid cells in the presence of S9 was between 0 and 1%. The concentrations of 375 and 450 were considered equivocal for increases in polyploidy because the number of polyploidy cells fell outside the historical control range as well as the 95% reference range. However, several of the control values for polyploidy were also outside the 95% reference range. Historical negative control and 95% reference range data are presented in Table 4. Statistical significance (Fisher's exact test) was reached for the mean aberrant cell frequency for the positive control groups in each condition (Tables 2 and 3). No other statistical significance was noted.

Conclusions

No increases above control were seen for structural aberrations with (b) (4) in either the presence or absence of S9. It is concluded that (b) (4) does not induce structural chromosomal aberrations *in vitro* with human peripheral blood lymphocytes under conditions of the assays conducted. However, increased levels of polyploid cells were seen in cultures treated with (b) (4) in the presence of S9 at concentrations of 375 and 450 mcg/mL in two separate assays.

Although not all of the criteria stated by the applicant for a positive result were met, there appears to be a signal of increased polyploidy in the presence of S9 at the highest dose tested. The result will be considered equivocal.

Table 2. Assay 1: (b) (4) **: Mean chromosomal and numerical aberrations and mitotic inhibition**

Concentration, mcg/mL	time, h	S9	Mean Aberrant Cell Frequency, % (excluding gaps)	Mean Mitotic Inhibition, %	Polyploid Cells, %
Vehicle	3	-	0	-	0.5
75	3	-	0.5	9	0.5
200	3	-	0.5	24	0
350	3	-	0	43	1.0
NQO, 2.5	3	-	13*	NC	1.7
Vehicle	3	+	0	100	1.5
275	3	+	0	34	1.5
300	3	+	0	29	2.9
375	3	+	0	51	3.8#
NQO, 2.5	3	+	32*	NC	2.3

NC: not calculated; * $p \leq 0.001$; #outside historical control range

Table 3. Assay 2: (b) (4) **: Mean chromosomal and numerical aberrations and mitotic inhibition**

Concentration, mcg/mL	time, h	S9	Mean Aberrant Cell Frequency, % (excluding gaps)	Mean Mitotic Inhibition, %	Polyploid Cells, %
Vehicle	3	+	0	100	0.5
350	3	+	1.5	2	2.9
375	3	+	1.5	31	1.5
450	3	+	4.5	57	3.4#
CPA, 6.25	3	+	63*	NC	0.9
Vehicle	20	-	0.5	100	1.5
30	20	-	1.5	4	1.5
60	20	-	0.5	41	2.9
80	20	-	0.5	52	3.8#
NQO, 2.5	20	-	74*	NC	2.3

NC: not calculated; * $p \leq 0.001$; #outside historical control range

Table 4. Historical Negative Control Data (reproduced from NDA submission)

		Structural aberrations observed on 100 cells scored		Numerical aberrations observed during scoring of structural aberrations	
		Structural aberrations including gaps	Structural aberrations excluding gaps	Polyploid cells	Numerical aberrations (H+E+P)
-S9	Number of studies	63	63	63	63
	Number of cultures	274	274	274	274
	Median	1	0	0	0
	Mean	1.18	0.79	0.20	0.29
	SD	1.33	1.02	0.44	0.55
	Observed range	0 – 8	0 – 5	0 – 2	0 – 3
	95% reference range	0 – 5	0 – 3	0 – 1	0 – 2
+S9	Number of studies	63	63	63	63
	Number of cultures	245	245	245	245
	Median	1	0	0	0
	Mean	1.07	0.71	0.24	0.37
	SD	1.18	0.94	0.49	0.63
	Observed range	0 – 6	0 – 5	0 – 3	0 – 3
	95% reference range	0 – 4	0 – 3	0 – 1	0 – 2

H = Hyperdiploid, E=Endoreduplicated, P = Polyploid
Reference ranges are calculated from percentiles of the observed distributions.

Calculated in January 2009 by CLEH Statistics, from audited report data of studies started between January 2006 and July 2008.

2.6.6.5 Carcinogenicity

No carcinogenicity studies were conducted.

2.6.6.6 Reproductive and developmental toxicology

No reproductive and developmental toxicology studies were conducted.

2.6.6.7 Local tolerance

Study title: Oral Mucosal Irritation Study of KW-2246 in Guinea Pigs

Key study findings: It is concluded that fentanyl is not a mucosal irritant under the conditions of this study.

Study no.: I-2019

Volume #, and page #: 4.2.3.6

Conducting laboratory and location:

(b) (4)

Date of study initiation: September 10, 2003**GLP compliance:** No. The study was conducted in accordance with the CFTA method of the American Cosmetic Toiletry and Fragrance Association and under the following guidelines (reproduced from NDA):

"Ministry ordinance concerning conducting non-clinical study regarding safety of drugs" (Ministry of Health and Welfare Ordinance No. 21: dated March 26, 1997)

and

"With respect to implementing ministry ordinance concerning conducting non-clinical study regarding safety of drugs" (Yakuhatsu No. 424: Notification of the director of the department of Drug Affairs of the Ministry of Health and Welfare dated March 27, 1997)

QA reports: yes () no (X)**Drug, lot #, and % purity:** fentanyl (code name KW-2246); lot # D03010; 101.5%**Formulation/vehicle:** Not stated

The objective of the study was to investigate oral mucosal membrane irritation of fentanyl in guinea pigs.

Methods**Doses:** Four applications/day for 4 days of 400 mcg of fentanyl was used in this study.

Study design: One tablet of 400 mcg fentanyl or vehicle was placed in the mandibular oral vestibule of Hartley white female guinea pigs (5/group). The composition of the tablet and vehicle tablet are not described. One hundred microliters of water was used to dissolve the tablet followed by brushing for 30 s with a paintbrush four times/day for four consecutive days. Sodium dodecyl sulfate (2% w/v) and water for injection were used as the positive and negative controls, respectively. Irritation of the incisor gingival and labial mucosa was assessed daily and two days after the last dose by visual inspection and local histopathology (H&E stain) was assessed at the completion of dosing and three days later. The evaluation of the severity of irritation of the oral mucosa was by assigning an irritancy score (Table 1). General condition and body weight were also assessed daily and two days after the last dose.

Table 1. Evaluation of Irritancy

Irritancy score	Classification
0-0.4	Extremely weak irritation
0.5-1.0	Weak irritation
1.1-2.0	Moderate irritation
Above 2.1	Strong irritation

Results: For the first hour after treatment, all animals in the test article group demonstrated behaviors typical of opiate effects: crouching position, sedation, decreased locomotion, mydriasis, tremor, lacrimation and salivation. Decreased defecation was observed in the test article group after day 2. Body weights were also reduced after day 1 for the test article group. No changes in general condition or body weight were observed for the negative control, positive control, or control groups. No irritation was observed for the incisor gingival or labial mucosa for any animals in the test article, negative control or control groups. All irritancy scores at all time points for these groups were 0 (data not shown). The positive control group showed a positive irritation response with a mean irritancy score of 3.9. Histopathological findings are presented in Table 2. Slight cell infiltration was observed in one test article animal in the epithelium of the lip region. No other histopathological findings were observed in the test article group and no histopathological findings were seen in the negative control or control groups. The positive control group showed slight to moderate ulcers and slight to mild cell infiltration or fibrosis of the lamina propria in all animals.

Conclusions: It is concluded that fentanyl is not a mucosal irritant under the conditions of this study.

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Table 2. Histopathological findings

Findings	Test substance																			
	KW-2246 (Test article application group)					KW-2246 placebo (Control article application group)					SDS (Positive control article application group)					Water for injection (Negative control article application group)				
	Number of animals : 5					Number of animals : 5					Number of animals : 5					Number of animals : 5				
	0	1	2	3	4	0	1	2	3	4	0	1	2	3	4	0	1	2	3	4
Animals sacrificed on day 4																				
Ulcer	5					5					2	2	1			5				
Regeneration, epithelial, focal	5					5					2	3				5				
Cell infiltration, lamina propria, focal	5					5					1	4				5				
Cell infiltration, epithelial, focal	4	1				5					5					5				
Animals sacrificed on day 6																				
Ulcer	5					5					4	1				5				
Regeneration, epithelial, focal	5					5					5					5				
Cell infiltration, lamina propria, focal	5					5					3	2				5				
Fibrosis, lamina propria, focal	5					5					3	2				5				
0 : Not remarkable change																				
1 : slight																				
2 : mild																				
3 : moderate																				
4 : severe																				

2.6.6.8 Special toxicology studies

Study title: OX-22: Oral Irritation Test in the Syrian Hamster

Key study findings: Several excipients at concentrations similar to those contained in the Abstral drug product did not produce local irritation in the hamster cheek pouch model

Study no.: 10797/01 (b) (4)

Volume #, and page #: 4.2.3.6

Conducting laboratory and location: (b) (4)

Date of study initiation: not given

GLP compliance: Yes

QA reports: yes (X) no ()

Drug, lot #, and % purity: placebo batch number RF1303P; no lot or purity information given

Formulation/vehicle: Refer to Table 1.

Methods

A repeat-dose local oral irritation study using the hamster cheek pouch model with a formulation of zolpidem tartrate was submitted by the applicant. The placebo used in this study contained several inactive ingredients also found in the Abstral formulation. The applicant states that the study provides experimental support that there is no concern with the local tolerability of the inactive ingredients. The placebo in this study contained levels of mannitol and silicified microcrystalline cellulose which were lower than levels found in the 800 mcg Abstral tablet. Levels of croscarmellose sodium were about two-fold higher in the placebo used in the study as compared to the 800 mcg Abstral tablet. Levels of magnesium stearate were the same in the two formulations. Refer to Table 1 for comparison of the amounts of inactive ingredients between the 800 mcg Abstral tablet and the placebo used in the study. Note that the levels of all excipients in the Abstral formulation are found in approved drug products at equal or greater levels and therefore do not require qualification for approval. The summary of Study 10797/01 below will only discuss the placebo versus the untreated control and not the groups using the zolpidem tartrate.

<i>Table 1. Comparison between excipients in the Abstral formulation and those tested in Study 10797/01</i>		
<i>ingredient</i>	<i>amount in 800 mcg Abstral tablet formulation (mg)</i>	<i>amount tested for local tolerance in study 10797/01 (mg)</i>
mannitol		(b) (4)
silicified microcrystalline cellulose		
silicon dioxide, colloidal		
croscarmellose sodium		
saccharin sodium		
magnesium stearate		

Doses: The placebo was compared to the untreated control. Refer to Table 1 for composition of the placebo.

Study design: The placebo was administered to each guinea pig daily for 28 days into the left hamster cheek pouch (6 animals/sex); the right cheek pouch was used as the untreated control. Each day the cheek pouches were examined macroscopically using an otoscope prior to the daily administration of the placebo as well as at the termination of the study on day 29. An Irritation Index with numerical scores representing level of irritation (none: 0, minimal: 1-4, mild: 5-8, moderate: 9-11 and severe: 12-16) was used to

quantitate the observed irritation. Following the macroscopic evaluation on Day 29, the cheek pouches were processed for histological examination and evaluated. A grading system for histologic examination from 0-4 was used for each of the following four observations: epithelial status, leukocyte infiltration, vascular congestion and edema. A group "Irritation Score" was obtained by subtracting the mean score of the control pouches (right side) from the mean score of the treated pouches (left side).

Results: Macroscopic examination of the untreated control males and females and placebo-treated males showed a similar incidence of "very slight erythema" that were graded a minimal (Table 2). Half of the females (3/6) in the placebo-treated group showed minimal "very slight erythema" (Table 2). No histopathologic findings were observed in either sex for either placebo-treated or control groups (Table 2). Since the macroscopic finding of "very slight erythema" in females was of minimal severity and was not accompanied by histopathologic findings and similar findings were observed in untreated controls it will not be considered toxicologically significant.

<i>Table 2. Incidence of macroscopic and histologic findings in the placebo and control groups of Study 10797/01</i>				
<i>group</i>	<i>macroscopic score*</i>		<i>histological score</i>	
	<i>males</i>	<i>females</i>	<i>males</i>	<i>females</i>
Placebo-treated cheek pouch (left)	1/6	3/6	0/6	0/6
Untreated cheek pouch (right)	1/6	1/6	0/6	0/6

*in all cases the severity of the finding in the macroscopic evaluation was that of "minimal very slight erythema"

Conclusions: Macroscopic and microscopic examination revealed no treatment-related changes in the placebo-treated cheek pouches as compared to untreated control cheek pouches. At the levels tested in this assay, the components of the placebo did not appear to cause local irritation.

2.6.6.9 Discussion and Conclusions

An oral single-dose toxicity study in dogs was conducted by the applicant. The behavioral findings observed in this study were consistent with acute toxicity of a mu opioid and no novel findings were seen.

The applicant conducted an Ames test and an *in vitro* chromosome aberration assay with the fentanyl impurity/degradation product (b) (4). The applicant has reduced the levels of (b) (4) in the drug substance and drug product to acceptable levels therefore the studies to qualify (b) (4) are not needed for approval. The Ames test with (b) (4) was deemed invalid (see review). In the *in vitro* chromosomal aberration study with human peripheral blood lymphocytes, (b) (4) did not cause structural chromosomal aberrations. However, an equivocal result for increased levels of polyploid cells were seen in cultures treated with (b) (4) in the presence of S9. The applicant also submitted a computational toxicology evaluation of (b) (4) which concluded that (b) (4) was not

a mutagen or clastogen. Internal FDA analysis did not agree with the applicant's assessment.

Although not required for approval, the applicant submitted supportive data to evaluate the local toxicity in the oral mucosa of fentanyl and several excipients found in the Abstral formulation. Under the conditions tested, fentanyl and the various excipients tested did not show irritation in the oral mucosa. However, the studies are of questionable utility. The fentanyl study was not conducted according to GLP. The composition of the tablet (other than fentanyl concentration) and placebo were not stated and a COA for fentanyl was not provided. Of the excipients evaluated in the hamster cheek pouch model, only the croscarmellose sodium was tested at a higher concentration than found in the 800 mcg Abstral formulation. The other excipients tested were at the same (magnesium stearate) or lower (mannitol and silicified microcrystalline cellulose) levels than found in the 800 mcg Abstral formulation. However, with the limited data provided, it appears that the potential for local toxicity of the oral mucosa for the Abstral product is relatively low.

The results of the submitted pharmacology and toxicology studies with fentanyl were consistent with acute effects of a mu opioid agonist and no novel findings were seen. The impurities/degradants are controlled at acceptable levels in both the drug substance and drug product. The excipients used in the Abstral formulation have all been previously approved and do not pose any toxicologic concerns.

2.6.6.10 Tables and Figures

2.6.7 TOXICOLOGY TABULATED SUMMARY

[pivotal studies pertinent to the primary indication and core pharmacology studies relevant to the primary pharmacodynamic effect, as available and as provided by the sponsor]

OVERALL CONCLUSIONS AND RECOMMENDATIONS

Conclusions: The results of the submitted pharmacology and toxicology studies with fentanyl were consistent with acute effects of a mu opioid agonist and no novel findings were seen. The impurities/degradants are controlled at acceptable levels in both the drug substance and drug product. The excipients used in the Abstral formulation have all been previously approved and do not pose any toxicologic concerns.

Unresolved toxicology issues (if any): There are no unique nonclinical issues with this product as compared to other approved fentanyl products.

Recommendations: This NDA can be approved from a nonclinical pharmacology/toxicology perspective.

Suggested labeling: See executive summary

Signatures (optional):

Reviewer Signature _Elizabeth A. Bolan, Ph.D._____

Supervisor Signature __R. Daniel Mellon, Ph.D._____ Concurrence Yes _X_ No ____

APPENDIX/ATTACHMENTS

Reference List

Ames BN, Mccann J, Yamasaki E (1975) Methods for detecting carcinogens and mutagens with the Salmonella/mammalian-microsome mutagenicity test. *Mutat Res* 31:347-364.

Goodman, Gilman (2006) Goodman and Gilman's The Pharmacological Basis of Therapeutics. New York, NY: McGraw-Hill.

Green MH, Muriel WJ (1976) Mutagen testing using TRP+ reversion in *Escherichia coli*. *Mutat Res* 38:3-32.

Hug CC, Jr., Murphy MR (1979) Fentanyl disposition in cerebrospinal fluid and plasma and its relationship to ventilatory depression in the dog. *Anesthesiology* 50:342-349.

Katchman AN, McGroary KA, Kilborn MJ, Kornick CA, Manfredi PL, Woosley RL, Ebert SN (2002) Influence of opioid agonists on cardiac human ether-a-go-go-related gene K(+) currents. *J Pharmacol Exp Ther* 303:688-694.

Lehmann KA, Schmitz KF, Daub D (1983) [Disposition of fentanyl in human blood]. *Anaesthesist* 32:329-334.

Maron DM, Ames BN (1983) Revised methods for the Salmonella mutagenicity test. *Mutat Res* 113:173-215.

Meuldermans WE, Hurkmans RM, Heykants JJ (1982) Plasma protein binding and distribution of fentanyl, sufentanil, alfentanil and lofentanil in blood. *Arch Int Pharmacodyn Ther* 257:4-19.

Murphy MR, Olson WA, Hug CC, Jr. (1979) Pharmacokinetics of 3H-fentanyl in the dog anesthetized with enflurane. *Anesthesiology* 50:13-19.

National Toxicology Program (1978) Report of the Rodent Bioassay of Aniline for Carcinogenicity to Rodents. Technical Report 130.

Vogel H, Bonner D (1956) Acetylornithinase of *Escherichia coli*: partial purification and some properties. *J Biol Chem* 218:97-106.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22510	ORIG-1	PROSTRAKAN INC	Abstral (fentanyl citrate) (b) (4) tablets

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/s/

ELIZABETH BOLAN
03/11/2010

RICHARD D MELLON
03/11/2010

I concur with Dr. Bolan's recommendation that NDA 22510 may be approved from the nonclinical perspective. I also concur with Dr. Bolan's labeling recommendations.

**PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR
NDA/BLA or Supplement**

NDA Number: 22-510

Applicant: ProStrakan

Stamp Date: 8/5/2009

Drug Name: ABSTRAL

NDA/BLA Type: 505(b)(2)

On **initial** overview of the NDA/BLA application for filing: Filable

	Content Parameter	Yes	No	Comment
1	Is the pharmacology/toxicology section organized in accord with current regulations and guidelines for format and content in a manner to allow substantive review to begin?	X		
2	Is the pharmacology/toxicology section indexed and paginated in a manner allowing substantive review to begin?	X		
3	Is the pharmacology/toxicology section legible so that substantive review can begin?	X		
4	Are all required (*) and requested IND studies (in accord with 505 b1 and b2 including referenced literature) completed and submitted (carcinogenicity, mutagenicity, teratogenicity, effects on fertility, juvenile studies, acute and repeat dose adult animal studies, animal ADME studies, safety pharmacology, etc)?	X		
5	If the formulation to be marketed is different from the formulation used in the toxicology studies, have studies by the appropriate route been conducted with appropriate formulations? (For other than the oral route, some studies may be by routes different from the clinical route intentionally and by desire of the FDA).	X		
6	Does the route of administration used in the animal studies appear to be the same as the intended human exposure route? If not, has the applicant <u>submitted</u> a rationale to justify the alternative route?	X		
7	Has the applicant <u>submitted</u> a statement(s) that all of the pivotal pharm/tox studies have been performed in accordance with the GLP regulations (21 CFR 58) <u>or</u> an explanation for any significant deviations?	X		
8	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?	X		

PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	Comment
9	Are the proposed labeling sections relative to pharmacology/toxicology appropriate (including human dose multiples expressed in either mg/m ² or comparative serum/plasma levels) and in accordance with 201.57?	X		Referenced label is Actiq
10	Have any impurity – etc. issues been addressed? (New toxicity studies may not be needed.)		X	<ul style="list-style-type: none"> • Sponsor lowered limit on (b) (4) in DS to (b) (4) – acceptable • Sponsor has not justified safety of (b) (4) spec in DS, which exceeds ICHQ3A. Cites USP, should be able to be tightened. Will need to include this in 74-day letter. • Spec for (b) (4) in DP is NMT (b) (4) for a MDD of 3200 mcg/day – acceptable.
11	Has the applicant addressed any abuse potential issues in the submission?			See CSS review and REMS program. Fentanyl is already scheduled by DEA.
12	If this NDA/BLA is to support a Rx to OTC switch, have all relevant studies been submitted?			N/A

IS THE PHARMACOLOGY/TOXICOLOGY SECTION OF THE APPLICATION FILEABLE? Yes

If the NDA/BLA is not fileable from the pharmacology/toxicology perspective, state the reasons and provide comments to be sent to the Applicant.

As per current policy, since the outstanding issue related to the impurity (see below) could be addressed via tightening the specification, this will not be deemed a filing issue.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

1. Your proposed drug substance specification for the (b) (4) of fentanyl exceeds ICHQ3A(R2) qualification threshold. Reference to a USP specification does not provide the Agency with adequate justification for the safety of this impurity specification. You must either submit a minimal genetic toxicology screen and a 90-day repeat dose toxicology study for the isolated impurity or reduce the specification to NMT (b) (4) unless otherwise justified.

R. Daniel Mellon, Ph.D. (PT Supervisor)

9/16/2009

Reviewing Pharmacologist

Date

Team Leader/Supervisor

Date

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

/s/

RICHARD D MELLON
09/16/2009