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APPLICATION NUMBER:
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PHARMACOLOGY REVIEW(S)

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

PHARMACOLOGY/TOXICOLOGY NDA REVIEW AND EVALUATION

Application number: NDA 202788
Supporting document/s: EDR Original Serial 000
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Product: Fentanyl Sublingual Spray
Indication: Management of breakthrough cancer pain in patients [REDACTED] (b) (4) [REDACTED] who are already receiving and who are tolerant to opioid therapy for their underlying persistent cancer pain
Applicant: Insys Therapeutics, Inc.
Review Division: Division of Anesthesia, Analgesia and Addiction Products (DAAAP)
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1 Executive Summary

1.1 Introduction

Insys Therapeutics, Inc. has submitted NDA 202788 for Fentanyl Sublingual Spray (FSS), a formulation of fentanyl base intended for sublingual delivery for the treatment of breakthrough cancer pain. Fentanyl Sublingual Spray is packaged as a unit dose spray device that delivers one actuation per vial. Each actuation delivers (b) (4) with 100, 200, 400, 600 or 800 mcg of fentanyl. Doses of 100, 200, 400, 600, 800, 1200, and 1600 mcg of fentanyl are intended to be used.

This application was submitted via the 505(b)(2) regulatory pathway and 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 (NDA 20747).

1.2 Brief Discussion of Nonclinical Findings

The pharmacology and toxicology of fentanyl have been well characterized. No nonclinical toxicology studies were deemed necessary to characterize the safety of fentanyl for this product unless abnormalities arose during monitoring of pulmonary function in the clinical studies. No abnormalities in pulmonary function were noted in the clinical studies therefore, no nonclinical studies with fentanyl were conducted.

The excipients used in the FSS formulation are all found at higher levels in drugs previously approved by FDA and do not pose any toxicologic concerns. Extractable and leachable assessments were conducted with the (b) (4) material from the FSS container closure system. Drug Master File (b) (4) for the (b) (4) is referenced by the Applicant. The (b) (4) are used in over 150 approved drugs, many with similar aqueous formulations to FSS. The Agency's previous finding of safety for the (b) (4) material will be relied on in order to support its safety.

The impurities/degradants in the drug substance and drug product are controlled at acceptable levels. A structural alert for mutagenicity was identified in the drug product degradant (b) (4) (b) (4). The Applicant conducted an Ames Assay which showed a negative result for mutagenicity, therefore (b) (4) can be regulated as a typical non-genotoxic impurity according to ICH Q3B(R2). The drug product specification set for (b) (4) in this NDA is acceptable.

There are no unique nonclinical issues associated with this product compared to the referenced fentanyl product. There are no outstanding concerns with this NDA that would preclude approval. The recommendation from Pharmacology/Toxicology is that NDA 202788 be approved with no post-marketing requirements.

1.3 Recommendations

1.3.1 Approvability

The recommendation from Pharmacology/Toxicology is that NDA 202788 be approved with no post-marketing studies.

1.3.2 Additional Non Clinical Recommendations

None

1.3.3 Labeling

The table below contains the draft labeling submitted by the Applicant, the changes proposed by the reviewer 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.

Applicant's proposed labeling	Reviewer's proposed changes	Rationale for changes
--------------------------------------	------------------------------------	------------------------------

(b) (4)



2 Page(s) of Draft Labeling has been Withheld in Full as B4 (CCI/TS) immediately following this page

(b) (4)

2 Drug Information

2.1 Drug

CAS Registry Number

437-38-7

Generic Name

Fentanyl base

Code Name

NA

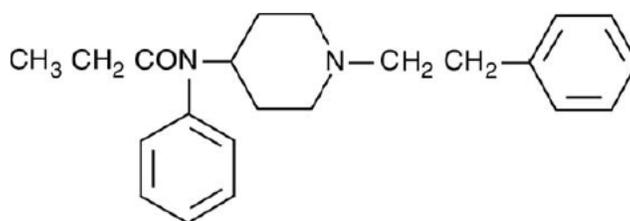
Chemical Name

N-phenyl-N-[1-(2-phenylethyl)-4-piperidiny] propanamide; N-(1-phenethylpiperidin-4-yl)-N-phenylpropanamide

Molecular Formula/Molecular Weight

C₂₂H₂₈N₂O; MW=336.47 (free base)

Figure 1. Structure of Fentanyl Base



Pharmacologic Class

Opioid Agonist (FDA Established Pharmacologic Class)

2.2 Relevant INDs, NDAs, and DMFs

IND/NDA/MF	drug/compound	Sponsor	Division/Office	status
IND 72411	Fentanyl Sublingual Spray	Insys	DAAAP	active
NDA 20747	Actiq (referenced drug)	Cephalon	DAAAP	approved 11/4/98
MF (b) (4)	(b) (4)	(b) (4)	ONDQA	adequate
MF (b) (4)	(b) (4)	(b) (4)	ONDQA	adequate

2.3 Drug Formulation

Fentanyl Sublingual Spray is packaged as a unit dose spray device that delivers one actuation per vial. Each actuation delivers a volume of (b) (4) containing 100, 200, 400, 600 or 800 mcg of fentanyl. Doses of 100, 200, 400, 600, 800, 1200, and 1600 mcg are intended to be used. The two highest doses of 1200 and 1600 mcg require actuation of two units of the 600 mcg and 800 mcg strengths, respectively.

Fentanyl Sublingual Spray is labeled to be used at a maximum of four doses per day. The two highest doses of 1200 mcg and 1600 mcg require actuation of two units to achieve the dose therefore the maximum number of units actuated per day is eight. With (b) (4) per actuation for eight actuations, (b) (4) will be used as the total daily volume of drug product consumed. The excipient levels and leachable assessments will be based on the volume of (b) (4) per day. The maximum daily dose (MDD) of the fentanyl drug substance for this product is 6.4 mg (1600 mcg x 4 doses).

(b) (4) Total daily intake of excipients as well as the amount of the excipient in drugs previously approved for sublingual, buccal or oral use as listed in the FDA Inactive Ingredients Guide is outlined in Table 1. With the use of (b) (4) of FSS, total levels of all excipients are below levels previously approved by FDA and are therefore considered acceptable.

Table 1. Levels and Acceptability of Fentanyl Sublingual Spray Excipients

Excipient	TDI, mg	Amount in IIG*, mg	Acceptable?
Dehydrated alcohol	(b) (4)	196	YES
Propylene glycol	(b) (4)	52	YES
L-Menthol	(b) (4)	10	YES
Xylitol	(b) (4)	72	YES

*FDA Inactive Ingredients Guide

2.4 Comments on Novel Excipients

There are no novel excipients in FSS.

2.5 Comments on Impurities/Degradants of Concern

Impurities in the drug substance

The MDD of fentanyl (6.4 mg) is ≤ 2 g/day, therefore the qualification threshold according to the ICH Q3A(R2) guideline for impurities in the drug substance is 0.15% or 1 mg/day intake, whichever is lower. The Applicant is obtaining the fentanyl base drug substance from (b) (4) (DMF (b) (4)). The specifications for the drug substance impurities are listed in Table 2 and the structures are presented in Figure 2.

The Applicant has set the specifications in the drug substance for (b) (4), (b) (4) at (b) (4), which are considered acceptable (Table 2). Four impurities in the drug substance obtained from (b) (4) contain moieties which are considered structural alerts for mutagenicity. (b) (4)

Specifications to reflect NMT (b) (4) should be set for genotoxic or potentially genotoxic residual intermediates/impurities. For a MDD of 6.4 mg of fentanyl, the specifications set by the Applicant for the impurities containing structural alerts would yield a total daily intake of <1.5 mcg of each impurity and are therefore considered acceptable (Table 2).

Figure 2. Structures of Fentanyl Drug Substance Impurities (reproduced from NDA)

(b) (4)



Table 2. Specifications of Fentanyl Base Drug Substance Impurities

Impurity	Specification	Acceptable
(b) (4)	(b) (4)	YES
	(b) (4)	YES

*structural alert for mutagenicity

Impurities in the drug product

The MDD of fentanyl of 6.4 mg in the FSS drug product is <10 mg/day, therefore the qualification threshold according to the ICH Q3B(R2) guidelines for impurities/degradants in the drug product is 1.0% or 50 mcg TDI, whichever is lower. The Applicant has identified (b) (4) (b) (4) as the only degradant (Table 3).

(b) (4) (b) (4)

The Applicant considered (b) (4) a potential structural alert and conducted a computational toxicology analysis using the MultiCase and Leadscope modeling programs (see reports in section 3.2.P.5.5 of NDA). The Applicant's analysis predicted that (b) (4) did not show potential for mutagenicity in either program. The Applicant evaluated several other parameters (*i.e.* clastogenicity and DNA damage) in the computational toxicology analysis but those parameters have not been validated and the results will not be discussed in this review. In 2009, an internal computational toxicology analysis using two programs was conducted by the FDA Informatics and Computational Safety Analysis Staff (ICSAS) for the potential for genotoxicity of (b) (4). The ICSAS analysis found that the MultiCase (MC4PC) program predicted negative mutagenicity for *Salmonella* and *E. coli* and the MDL-QSAR program predicted a positive result for *Salmonella* mutagenicity and a negative result for *E. coli* mutagenicity. Other endpoints were analyzed in the ICSAS report, but only results relevant to *Salmonella* and *E. coli* mutagenicity will be discussed here. In order to be certain that the most current computational toxicology databases were used, the structure of (b) (4) was resubmitted in 2011 to ICSAS for evaluation of mutagenicity. The *Salmonella* mutagenicity endpoint was analyzed by ICSAS using four different programs. No structural alerts for (b) (4) were identified using DEREK for Windows and negative predictions were obtained with MultiCase (MC4PC) and Leadscope programs. The negative predictions with the MultiCase and Leadscope programs are consistent with the negative result from the 2009 ICSAS analysis. The SciQSAR program predicted a positive result for *Salmonella* mutagenicity which replicated the positive result from the MDL-QSAR in the 2009 ICSAS analysis. The names MDL-QSAR and SciQSAR refer to the same program and the name was changed to current SciQSAR when the program was sold to a new company. For the 2011 ICSAS analysis, the overall call of positive

for *Salmonella* mutagenicity for (b) (4) was made by the director of ICSAS, Dr. Daniel Benz. Below is an excerpt from the 2011 ICSAS report.

“Based on the OND mandate for us to maximize sensitivity (avoid false negatives), we have predicted that (b) (4) will be positive for *Salmonella* mutagenesis based solely on a moderately positive call by only one of the four programs we used.”

The Division considered (b) (4) to be potentially mutagenic and requested that the Applicant either reduce the specification to reflect a TDI of NMT (b) (4) or conduct an Ames Assay. The Division held a tcon with the Applicant on 8/9/11 to discuss the positive prediction of the computational toxicology analysis for (b) (4). The Division explained to the Applicant that in an internal computational toxicology analysis by FDA ICSAS, the SciQSAR program predicted a positive result for *Salmonella* mutagenesis for the drug product degradant (b) (4). The Division requested that the Applicant conduct an Ames Assay with (b) (4) in order to definitively define the potential for mutagenicity. Since there has been confusion in the past with different compounds being referred to as (b) (4) the Division clarified that the CAS number of (b) (4) is (b) (4). The Applicant agreed to conduct an Ames Assay with (b) (4) and submit it to the NDA.

The Applicant has conducted an Ames Assay with the impurity (b) (4). The study is reviewed below (Section 7.1) and found to be valid and negative. (b) (4) can be considered to be adequately qualified for mutagenic potential and may be regulated as a standard impurity to levels set in ICH Q3B(R2). The Applicant’s current drug product specification for (b) (4) is acceptable.

Figure 3. Structure of (b) (4) (reproduced from NDA)



Table 3. Specifications of Fentanyl Sublingual Spray Drug Product Impurities/Degradants

<i>Impurity/degradant</i>	<i>Stability specification</i>	<i>Acceptable</i>
(b) (4)	(b) (4)	YES

2.6 Proposed Clinical Population and Dosing Regimen

Fentanyl Sublingual Spray is indicated for the management of breakthrough cancer pain in patients (b) (4) who are already receiving and who are tolerant to opioid therapy for their underlying persistent cancer pain. Fentanyl Sublingual Spray is labeled to be used at a maximum of four doses per day.

2.7 Regulatory Background

A PIND meeting with Insys Therapeutics, Inc. for IND 72411 was held on 8/25/05. The Division determined that no additional nonclinical studies would be required to characterize the safety of the fentanyl drug substance unless abnormalities arose during monitoring of pulmonary function in the clinical studies. It was also communicated to the Applicant that the NDA submission should include the identification and toxicity information of potential leachables and extractable from the drug delivery system. Guidance regarding adequate qualification of drug substance and drug product impurities/degradants as well as submission of an NDA via the 505(b)(2) regulatory pathway were provided to the Applicant. The IND was submitted in early 2007 and the 30-date safety date was 2/2/07. The proposed clinical protocol was allowed to proceed. End-of-phase 2 and PNDA meetings were held on 12/07/07 and 8/17/10, respectively. The comments regarding extractable/leachable evaluation and specifications of impurities were reiterated to the Applicant at these meetings. No abnormalities in pulmonary function were noted in the clinical studies, therefore, no nonclinical studies to characterize the safety of fentanyl were deemed necessary.

3 Studies Submitted

3.1 Studies Reviewed

Table 4. Studies Reviewed

Study number	eCTD location	Study Title
158333	4.2.2.2	Bacterial Mutagenicity Test- Ames Assay ((b) (4))
TTP-IOX-M0026	4.3	Safety Assessment of Extractables and Leachables from (b) (4)
NA	3.2.P.5.5	Computational Assessment of Genotoxicity of (b) (4) with MC4PC
NA	3.2.P.5.5	Computational Toxicity Assessment Using the Leadscope FDA Model for Test Structure ((b) (4))

3.2 Studies Not Reviewed

All submitted studies have been reviewed.

3.3 Previous Reviews Referenced

No previous reviews are referenced.

4 Pharmacology

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 as an analgesic than morphine. Time to peak analgesia of fentanyl is rapid and the duration of action is short (Gutstein HB and Akil H, 2006). The safety concerns of fentanyl are similar to those of other potent opioids with the major concerns being respiratory depression and the potential for abuse.

5 Pharmacokinetics/ADME/Toxicokinetics

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 sublingual 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.

6 General Toxicology

No general toxicology studies were required for this NDA and none were submitted by the Applicant.

7 Genetic Toxicology

Genetic toxicology studies with fentanyl are described in the label of the referenced product, Actiq. No new genetic toxicology studies with fentanyl were required for this NDA and none were submitted by the Applicant. It was determined through computational toxicology analysis that the fentanyl degradant (b) (4) contains a structural alert for mutagenicity. The Applicant conducted an Ames Assay with (b) (4) which is reviewed below. The degradant (b) (4) was found to be negative in the Ames Assay.

7.1 *In Vitro* Reverse Mutation Assay in Bacterial Cells (Ames) with

(b) (4)

Study title: Bacterial Mutagenicity Test- Ames Assay

Study no.: 158333
 Study report location: EDR 4.2.3.3.1
 Conducting laboratory and location: (b) (4)
 Date of study initiation: 8/26/11
 GLP compliance: Yes
 QA statement: Yes
 Drug, lot #, and % purity: (b) (4) CAS# (b) (4); Lot#
 S813990; 100%

Key Study Findings

(b) (4) *is not mutagenic in S. typhimurium strains TA97a, TA98, TA100, TA102, and TA1535 in either the presence or absence of S9.*

Methods

Strains: TA97a, TA98, TA100, TA102, TA1535
 Concentrations in definitive study: 0.0501, 0.158, 0.501, 1.582, 5.00 mg/plate
 Basis of concentration selection: dose range finding study
 Negative control: DMSO
 Positive control: see Table 5 (reproduced from NDA)
 Formulation/Vehicle: DMSO
 Incubation & sampling time: incubation time: 48-72 h

Study Validity

The study is *valid*. Suitable numbers of replicate plates and appropriate counting methods were utilized. The five strains utilized in this study are considered adequate for routine testing as per ICH S2A. 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.

Methods

The Applicant evaluated (b) (4) in a bacterial mutagenicity assay based on the method of Maron and Ames (Maron and Ames, 1983). Five concentrations of test article as well as DMSO vehicle and positive controls were plated in triplicate with overnight cultures of *Salmonella typhimurium* strains TA97a, TA98, TA100, TA102, TA1535 (Ames, et al., 1975) 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 (Table 5).

Results

No substantial reductions in the background lawns or precipitate were noted at any concentration of test article. For each strain, all five concentrations in the presence and absence of S9 were able to be evaluated. The colony count data for each strain in the presence and absence of S9 are presented in Tables 6 through 10 (reproduced from NDA). The fold increase of the mean test article colony count value over the mean vehicle control colony count value is presented in the column with the heading "FI" (Tables 6-10). 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.

Study outcome: It is concluded that under conditions of the assays conducted, (b) (4) is not mutagenic in *S. typhimurium* strains TA97a, TA98, TA100, TA102, and TA1535 in either the presence or absence of S9.

Table 5. Positive Controls

CONTROL	STRAIN	METABOLIC ACTIVATION	CONCENTRATION	LOT NUMBER
ICR-191 Acridine	TA97a	No	1.0 µg/plate	TDSG4685
2-nitrofluorene	TA98	No	10.0 µg/plate	TDSG4659
Sodium azide	TA100 and TA1535	No	1.5 µg/plate	TDSG4493
Cumene	TA102	No	200.0 µg/plate	TDSG4686
2-aminoanthracene	all strains (except TA1535)	Yes	10.0 µg/plate	TDSG4494
2-aminoanthracene	TA1535	Yes	1.6 µg/plate	TDSG4495

Table 6. TA97a Colony Count Data

With S9 Activation							Without S9 Activation						
Dose	Rep 1	Rep 2	Rep 3	Avg.	SD	FI	Dose	Rep 1	Rep 2	Rep 3	Avg.	SD	FI
5.00 mg/plate	80	72	63	72	8.5	1.1	5.00 mg/plate	91	72	109	91	18.5	0.9
1.582 mg/plate	65	93	121	93	28.0	1.4	1.582 mg/plate	109	108	124	114	9.0	1.2
0.501 mg/plate	64	66	64	65	1.2	1.0	0.501 mg/plate	102	112	120	111	9.0	1.1
0.158 mg/plate	75	81	85	80	5.0	1.2	0.158 mg/plate	126	89	105	107	18.6	1.1
0.0501 mg/plate	68	67	76	70	4.9	1.1	0.0501 mg/plate	108	111	96	105	7.9	1.1
DMSO	59	60	77	65	10.1	NA	DMSO	92	104	98	98	6.0	NA
2-aminoanthracene*	1348	1011	944	1101	216.5	16.9	ICR-191*	1579	1512	1636	1576	62.1	16.1

*Positive control response is two fold or greater than the negative control.

Table 7. TA98 Colony Count Data

With S9 Activation							Without S9 Activation						
Dose	Rep 1	Rep 2	Rep 3	Avg.	SD	FI	Dose	Rep 1	Rep 2	Rep 3	Avg.	SD	FI
5.00 mg/plate	26	28	32	29	3.1	1.0	5.00 mg/plate	31	29	30	30	1.0	1.0
1.582 mg/plate	30	38	27	32	5.7	1.1	1.582 mg/plate	25	24	30	26	3.2	0.9
0.501 mg/plate	38	28	27	31	6.1	1.1	0.501 mg/plate	25	30	25	27	2.9	0.9
0.158 mg/plate	39	27	37	34	6.4	1.2	0.158 mg/plate	29	33	24	29	4.5	1.0
0.0501 mg/plate	41	25	41	36	9.2	1.2	0.0501 mg/plate	36	32	20	29	8.3	1.0
DMSO	26	36	26	29	5.8	NA	DMSO	22	36	28	29	7.0	NA
2-aminoanthracene*	657	479	492	543	99.2	18.5	2-NF*	1002	1032	1113	1049	57.4	36.6

*Positive control response is two fold or greater than the negative control.

Table 8. TA100 Colony Count Data

With S9 Activation							Without S9 Activation						
Dose	Rep 1	Rep 2	Rep 3	Avg.	SD	FI	Dose	Rep 1	Rep 2	Rep 3	Avg.	SD	FI
5.00 mg/plate	81	90	84	85	4.6	0.7	5.00 mg/plate	88	72	74	78	8.7	0.7
1.582 mg/plate	110	92	86	96	12.5	0.8	1.582 mg/plate	102	85	89	92	8.9	0.9
0.501 mg/plate	132	114	115	120	10.1	1.0	0.501 mg/plate	118	124	89	110	18.7	1.0
0.158 mg/plate	115	122	121	119	3.8	1.0	0.158 mg/plate	132	114	147	131	16.5	1.2
0.0501 mg/plate	123	115	122	120	4.4	1.0	0.0501 mg/plate	96	108	103	102	6.0	1.0
DMSO	129	126	110	122	10.2	NA	DMSO	112	103	105	107	4.7	NA
2-aminoanthracene*	1063	1205	1020	1096	96.8	9.0	Sodium Azide*	492	457	500	483	22.9	4.5

*Positive control response is two fold or greater than the negative control.

Table 9. TA1535 Colony Count Data

With S9 Activation							Without S9 Activation						
Dose	Rep 1	Rep 2	Rep 3	Avg.	SD	FI	Dose	Rep 1	Rep 2	Rep 3	Avg.	SD	FI
5.00 mg/plate	17	15	14	15	1.5	1.0	5.00 mg/plate	21	15	30	22	7.5	1.2
1.582 mg/plate	18	16	16	17	1.2	1.1	1.582 mg/plate	13	22	25	20	6.2	1.1
0.501 mg/plate	16	17	13	15	2.1	1.0	0.501 mg/plate	15	18	17	17	1.5	0.9
0.158 mg/plate	16	19	22	19	3.0	1.2	0.158 mg/plate	11	12	12	12	0.6	0.6
0.0501 mg/plate	16	15	18	16	1.5	1.0	0.0501 mg/plate	14	14	17	15	1.7	0.8
DMSO	18	15	14	16	2.1	NA	DMSO	24	20	11	18	6.7	NA
2-aminoanthracene*	191	221	242	218	25.6	13.9	Sodium Azide*	500	526	579	535	40.3	29.2

*Positive control response is two fold or greater than the negative control.

Table 10. TA102 Colony Count Data

With S9 Activation							Without S9 Activation						
Dose	Rep 1	Rep 2	Rep 3	Avg.	SD	FI	Dose	Rep 1	Rep 2	Rep 3	Avg.	SD	FI
5.00 mg/plate	220	207	275	234	36.1	0.9	5.00 mg/plate	133	147	196	159	33.1	0.7
1.582 mg/plate	198	259	243	233	31.6	0.9	1.582 mg/plate	217	230	233	227	8.5	1.0
0.501 mg/plate	234	236	250	240	8.7	0.9	0.501 mg/plate	245	223	216	228	15.1	1.0
0.158 mg/plate	249	241	252	247	5.7	1.0	0.158 mg/plate	241	220	230	230	10.5	1.0
0.0501 mg/plate	184	245	271	233	44.7	0.9	0.0501 mg/plate	246	240	241	242	3.2	1.0
DMSO	257	285	235	259	25.1	NA	DMSO	220	241	233	231	10.6	NA
2-aminoanthracene*	1558	1502	1298	1453	136.8	5.6	Cumene*	926	898	870	898	28.0	3.9

*Positive control response is two fold or greater than the negative control.

8 Carcinogenicity

No carcinogenicity studies were required for this NDA and none were submitted by the Applicant.

9 Reproductive and Developmental Toxicology

No reproductive toxicology studies were required for this NDA and none were conducted. Fentanyl is currently a Pregnancy Category C. It has been evaluated in several animal studies which appear in the label of the referenced product, Actiq.

10 Special Toxicology Studies

The FSS device is a single-dose stoppered glass vial assembled into a delivery device to be used as a sublingual spray. The NDA references DMF (b) (4) for the (b) (4) material. This DMF has been reviewed by ONDQA and found to be adequate. The Applicant conducted extractable and leachable studies with the (b) (4) (b) (4). The DMF for the (b) (4) (b) (4) has been referenced by many NDAs for products approved by FDA and no safety concerns with leachables have arisen.

Fentanyl Sublingual Spray is labeled to be used at a maximum of four doses per day. The label reads: "Once a successful dose is found, patients should limit consumption to four or fewer doses per day". The two highest doses of 1200 mcg and 1600 mcg require actuation of two units to achieve the dose. Each unit can be actuated only once. Therefore, with a maximum of four doses per day with the two highest doses requiring two actuations, the maximum number of units actuated per day would be eight. With (b) (4) per actuation for eight actuations, (b) (4) is the total daily volume of drug product consumed. The volume of (b) (4) will be used in the extractable and leachable assessments in order to calculate total daily intake of any identified compounds.

An extractables assessment was conducted with the (b) (4) used in the FSS device (report # TTP-IOX-M0026). Extractions with the (b) (4) were performed with water and 100% ethanol. Several compounds were identified at very low levels. A leachable assessment with the (b) (4) with the drug product was also conducted using 1-3 year stability samples (report # TTP-IOX-M0026). The most abundant leachable identified was (b) (4) (b) (4) at a level which would yield (b) (4). Several other compounds were identified in the leachable study at very low levels. The (b) (4) (b) (4) are used in over 150 approved drugs, many with similar aqueous formulations to FSS. We are unaware of any safety signals that have arisen for these products due to the use of the (b) (4). The Agency's previous finding of safety for the material will be relied on in order to support its safety.

11 Integrated Summary and Safety Evaluation

Fentanyl is a well-characterized mu opioid. No pharmacology or toxicology data with fentanyl were required for this NDA and no data with fentanyl were submitted. The excipients used in the FSS formulation are all found at higher levels in drugs previously approved by FDA for sublingual, buccal or oral use and do not pose any unique toxicologic concerns. There are no concerns with extractables or leachables from the (b) (4) material for this product. The impurities/degradants in the drug substance and drug product are controlled at acceptable levels. There are no outstanding concerns with this NDA that would preclude approval. The recommendation from Pharmacology/Toxicology is that NDA 202788 be approved with no post-marketing requirements.

12 Appendix/Attachments

Reference List

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

Gutstein HB and Akil H (2006) Goodman and Gilman's The Pharmacological Basis of Therapeutics, (Laurence L.Brunton ed) McGraw-Hill, New York, NY.

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

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/s/

ELIZABETH BOLAN
11/30/2011

RICHARD D MELLON
11/30/2011
I concur.

PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR NDA/BLA or Supplement

NDA/BLA Number: 202-788 Applicant: Insys Therapeutics, Inc. Stamp Date: March 4, 2011

Drug Name: Fentanyl NDA/BLA Type: 505(b)(2)
Sublingual Spray

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

	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)?			N/A No studies were required or requested and none were submitted.
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).			N/A No toxicology studies were required and none were submitted.
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?			N/A No animal studies were required and none were submitted.
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?			N/A No pharmacology/toxicology studies were required and none were submitted.
8	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?	X		

File name: 5_Pharmacology_Toxicology Filing Checklist for NDA_BLA or Supplement
010908

**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	The proposed label will need to be updated. This is not a filing issue.
10	Have any impurity – etc. issues been addressed? (New toxicity studies may not be needed.)	X		
11	Has the applicant addressed any abuse potential issues in the submission?			Refer to Controlled Substances Staff review
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___

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

We have no issues for the 74-day letter.

Elizabeth A. Bolan, Ph.D.	4/15/2011
_____ Reviewing Pharmacologist	_____ Date
R. Daniel Mellon, Ph.D.	4/15/2011
_____ 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/

ELIZABETH BOLAN
04/15/2011

RICHARD D MELLON
04/15/2011