CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

022569Orig1s000

PHARMACOLOGY REVIEW(S)

FDA Center for Drug Evaluation and Research
Division of Anesthesia, Analgesia and Addiction Products
10903 New Hampshire Avenue, Silver Spring, MD 20993

MEMO TO FILE

PHARMACOLOGY TOXICOLOGY

NDA number:	**22569**
Drug:	**Lazanda (intranasal fentanyl citrate)**
Indication:	for the management of breakthrough cancer pain in opioid-tolerant cancer patients
Applicant:	Archimedes Development Ltd.
Date of Memo:	June 20, 2011
Reviewer name:	Elizabeth A. Bolan, Ph.D.
Supervisor name:	R. Daniel Mellon, Ph.D.
Division name:	Division of Anesthesia, Analgesia and Addiction Products

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This memo serves to document the rationale behind the nonclinical exposure margin in the Pregnancy section of the Lazanda label. Lazanda (NDA 22569) is an intranasal fentanyl citrate product indicated for the management of breakthrough cancer pain in opioid-tolerant cancer patients. NDA 22569 is a 505(b)(2) application and the referenced product is Actiq (oral transmucosal fentanyl citrate lozenge).

Data from a publically-available literature reference describing a rat study appear in the Pregnancy section of the label of Actiq and products that use Actiq as their 505(b)(2) reference (Table 1). In the literature reference, the doses of fentanyl administered to the rat were given in mcg/kg and no pharmacokinetic data was provided. Because no pharmacokinetic data was available for the rat study, the exposure comparison to the human data in the Actiq label could not be based on AUC values. In the Actiq label, the rat and human exposure comparisons of mg/kg dosing were made on a mg/m^2 basis which takes into consideration body surface area scaling of the two species. The rat dose of 500 mcg/kg and the human dose of 1600 mcg per pain episode of Actiq were used for the exposure ratio. On a mg/m^2

basis the exposure ratio for these values is three. Refer to the calculations below for details.

In human pharmacokinetic studies, Lazanda was shown to have higher fentanyl bioavailability than Actiq. The two products have differing dosage forms and labeled maximum daily doses. The systemic exposure from a dose of 800 mcg of Lazanda (intranasal administration) was roughly equal to the systemic exposure from a dose of 1600 mcg of Actiq (buccal administration). The human dose of 800 mcg per pain episode was used for the exposure comparison in the Lazanda label (Table 1). A dose of 1600 mcg per pain episode, to be consistent with the Actiq label, could not be used in the Lazanda label because the two products are dosed differently and the labeled maximum dose per pain episode for Lazanda is 800 mcg. Using the human dose of 800 mcg of Lazanda would result in an exposure ratio of six based on body surface area comparisons in mg/m^2 (see calculations below). We did not want to use an exposure margin of six and falsely imply that Lazanda has a higher exposure margin than Actiq or other fentanyl products and is therefore a "safer" alternative. Therefore, we kept the exposure ratio of three from the Actiq label because the *systemic exposure* per pain episode for Lazanda and Actiq are equal even though the *dose* per pain episode differs (800 mcg vs. 1600 mcg). Using an exposure ratio of three for both products accurately reflects the equivalent systemic exposures of Actiq and Lazanda even though the exposure ratio it is not technically correct based on the ratio of the administered dose in mg/m^2. The wording from the Actiq and Lazanda labels is detailed in Table 1.

Body surface area conversion to mg/m^2

Rat: 500 mcg/kg x 6 = **3 mg/m^2**

Human (Actiq): 1600 mcg/60 kg = 0.027 mg/kg x 37 = **1 mg/m^2**
Rat/human (Actiq) exposure ratio: 3 mg/m^2 / 1 mg/m^2 = **3**

Human (Lazanda): 800 mcg/60 kg = 0.013 mg/kg x 37 = **0.5 mg/m^2**
Rat/human (Lazanda) exposure ratio: 3 mg/m^2 / 0.5 mg/m^2 = **6**

Note: 6 and 37 are the k_m values for rat and human, respectively, which are used in the conversion of mg/kg to mg/m^2 for human equivalent dosing based on body surface area scaling according to the FDA guidance *Estimating the Maximum Safe Starting Dose in Initial Clinical Trials for Therapeutics in Adult Healthy Volunteers (2005).*

Table 1. Excerpts from the Pregnancy section of the Actiq and Lazanda labels

Actiq label	***Lazanda label***
Published studies demonstrated that	Published studies demonstrated that

administration of fentanyl (10, 100, or 500 mcg/kg/day) to pregnant rats from day 7 to 21, of their 21 day gestation, via implanted microosmotic minipumps was not teratogenic. The high dose was approximately 3 times the human dose of 1600 mcg per pain episode on a mg/m^2 basis. Intravenous administration of fentanyl (10 or 30 mcg/kg) to pregnant female rats from gestation days 6 to 18 was embryo or fetal toxic and caused a slightly increased mean delivery time in the 30 mcg/kg/day group, but it was not teratogenic.	administration of fentanyl (10, 100, or 500 mcg/kg/day) to pregnant rats from day 7 to 21, of their 21 day gestation, via implanted microosmotic minipumps was not teratogenic. The high dose was approximately 3 times the human dose of 800 mcg per pain episode on a mg/m^2 basis. Intravenous administration of fentanyl (10 or 30 mcg/kg) to pregnant female rats from gestation days 6 to 18 was embryo or fetal toxic and caused a slightly increased mean delivery time in the 30 mcg/kg/day group, but it was not teratogenic.

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/s/

ELIZABETH BOLAN
06/20/2011

RICHARD D MELLON
06/20/2011

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ADDENDUM TO NDA 22-569 PHARMACOLOGY TOXICOLOGY REVIEW

NDA number:	**22-569**
Product:	PecFent (intranasal fentanyl citrate)
Date Received by Center:	April 20, 2010
Sponsor:	Archimedes Development Ltd.

Reviewer name:	Elizabeth A. Bolan, Ph.D.
Division name:	Division of Anesthesia and Analgesia Products
HFD #:	170
Review completion date:	April 28, 2010

Overall Recommendation: The impurity [(b) (4)] has been adequately qualified for genotoxic potential and may be regulated as a standard impurity to levels set in ICH Q3A(R2) and Q3B(R2). The recommendation from Pharmacology/Toxicology (P/T) is that NDA 22-569 may be approved with no Post-marketing studies.

Background: In the NDA filing letter for NDA 22-569 the Division noted that the drug substance and drug product specifications for [(b) (4)] were unacceptable. The [(b) (4)] [(b) (4)] contains a structural alert for mutagenicity. [(b) (4)] [(b) (4)] A specification to reflect NMT [(b) (4)] must be set for genotoxic or potentially genotoxic residual intermediates/impurities or the impurities must be qualified by conducting a minimal genotoxic screen. The specifications set by the applicant exceeded this level and it was noted as a deficiency in the NDA review. On the basis of this deficiency, the original recommendation from P/T was to not recommend approval of NDA 22-569 (See PT review finalized on 4/9/2010).

In this amendment, the applicant has submitted an Ames Test and an *in vitro* Chromosomal Aberration Assay with [(b) (4)]. Both studies are valid and show a negative result. The impurity/degradation product [(b) (4)] can be considered qualified for genotoxic potential with the minimal genotoxic screen. This issue was the only deficiency noted from the P/T

perspective and with these new studies the recommendation from P/T is that NDA 22-569 may be approved. The review of the studies is below.

The applicant also submitted additional information which is described below. Other than the two genetic toxicology studies with (b) (4), the information submitted does not have any impact on the NDA review that was submitted on April 9, 2010.

The applicant submitted an amendment (submitted date: April 19, 2010; received date April 19, 2020) to NDA 22-569 which contained the following information:

1. Final study report of a Bacterial Reverse Mutation (Ames) Assay with (b) (4)
2. Final study report of an In Vitro Chromosomal Aberration Assay with (b) (4)
3. Updated version of Tables 2.6.6.34 and 2.6.6.3-5.
4. A summary of results from two carcinogenicity bioassays with fentanyl from the Effentora EPAR procedural steps document (European Registration).

Data were provided in order to update the rat toxicokinetic data summarized in Tables 2.6.6.34 and 2.6.6.3-5 (from study WFEN/P37/05). The applicant states that the changes made to were to correct "a number of transcription errors". It should be noted that the study report submitted to the NDA was the final study report and it was quality assured. The modifications made by the applicant in this submission do not change the interpretation of the study findings in the original NDA review (dated April 9, 2010).

The applicant also added information describing the results from two carcinogenicity assessments with fentanyl to the Nonclinical Overview and Nonclinical Written and Tabulated Summary sections of the NDA. No study reports were submitted to this NDA. The results of a 26-week dermal bioassay with fentanyl in Tg.AC mice and a two-year subcutaneous fentanyl carcinogenicity assessment in rats showing that fentanyl did not demonstrate oncogenic potential were described. The source of this information is a document from the EMEA describing updates to the label of Effentora, the EU version of Fentora. It is stated on the document that "the reproduction of this information is authorized provided the source is acknowledged". It should be noted that although this information is appropriate for the nonclinical summary sections of the NDA as part of a review of the fentanyl literature and publicly available information, (b) (4) The submission of this summary information in this amendment does not change the conclusions in the original NDA review (dated April 9, 2010) and is not required or taken into consideration in terms of the nonclinical recommendations.

2.6.6.4 Genetic toxicology

An Ames test and an *in vitro* chromosomal aberration assay were conducted with the impurity/degradant (b) (4)

Study title: Reverse Mutation in Five Histidine-Requiring Strains of *Salmonella Typhimurium*

Key findings: [redacted] is not mutagenic in *S. typhimurium* strains TA98, TA100, TA1535, TA1537 and TA102 in either the presence or absence of S9.

Study no.: 8221663
Volume #, and page #: Module 4.2.3.3.1
Conducting laboratory and location: [redacted]
Date of study initiation: January 12, 2010
GLP compliance: Yes
QA reports: yes (X) no ( )
Drug, lot #, and % purity: [redacted] batch number 528.04.09.03; 99.9%

Methods
The Applicant evaluated [redacted] in a bacterial mutagenicity assay based on the method of Maron and Ames (Maron and Ames, 1983). The test article was diluted into DMSO and DMSO was used as the vehicle. Six concentrations of test article as well as negative (vehicle) and positive controls were plated with overnight cultures of *Salmonella typhimurium* strains TA98, TA100, TA1535, and TA1537 and TA102 (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 1). Five plates were plated for vehicle control groups and three plates were plated for test article and positive control groups. 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 72 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.
A pre-incubation step (1 h at 37°C) with the test article or vehicle was included in Experiments 2 and 3. Due to potential toxicity of the DMSO vehicle during the pre-incubation, the added volumes for Experiments 2 and 3 were reduced from 100 µL to 50 µL.

The assay was considered valid if the following criteria were met (as outlined by the applicant):
1. the negative control counts fell within the normal historical ranges as defined in Table 6,
2. the positive controls induced clear increases in revertant numbers confirming discrimination between different strains, and an active S-9 preparation, and
3. no more than 5% of the plates were lost through contamination or some other unforeseen event.

The assay was considered positive if the following criteria were met (as outlined by the applicant):

1. Dunnett's test gave a significant response ($p \leq 0.01$) which was concentration related, and
2. the positive trend/effects described above were reproducible.

The test article was considered as negative in this assay if none of the above criteria were met.

Reviewer's note:
The following criteria for a positive assay are added by the reviewer:
For a test article to be considered positive it must produce at least a 2-fold increase (for TA98, TA100 and WP2*uvr*A) or a 3-fold increase (for TA1535, TA1537 and TA102) 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.

With the additions made by the reviewer, the criteria as defined by the applicant for a valid and positive assay are considered acceptable

Strains/species/cell line: *S. typhimurium* histidine auxotrophs utilized included: TA98, TA100, TA1535, TA1537 and TA102

Concentrations used in definitive study: Refer to Tables 2-5 for concentrations used in the definitive studies. DMSO was used as the vehicle for all conditions.

Basis of concentration selection: Concentration selection was based on an initial study conducted in strain TA100 only in the presence and absence of S9 using the concentrations 1.6, 8, 40, 200, 1000 and 5000 mcg/plate. Toxicity was seen at 1000 mcg/plate and above in the presence and absence of S9. The same concentration ranges were used in Experiment 1 in all strains in the presence and absence of S9. For Experiment 2, a preincubation step with (b) (4) (b) (4) or vehicle was included and due to potential for increased cytotoxicity of the test article and/or the DMSO vehicle the maximum concentration of (b) (4) was decreased. Excessive cytotoxicity was observed in strains TA98 and TA1535 in the presence of S9 and less than three concentrations were able to be evaluated for mutagenicity. Experiment 3 was conducted with these strains in the presence of S9 and the maximum concentration of (b) (4) was decreased. The presence or absence of precipitate was noted for all strains.

Negative controls: The negative control used in this study was the vehicle, DMSO.

Positive controls: The positive controls utilized for the respective strains are indicated in Table 1.

Table 1. Positive Controls (table reproduced from NDA)

Chemical***	Stock * concentration (µg/mL)	Final concentration (µg/plate)	Strain(s)	S-9
2-nitrofluorene (2NF)	50	5.0	TA98	–
Sodium azide (NaN_3)	20	2.0	TA100, TA1535	–
9-aminoacridine (AAC)	500	50.0	TA1537	–
Mitomycin C (MMC)	2	0.2	TA102	–
Benzo[a]pyrene (B[a]P)	100**	10.0	TA98	+
2-aminoanthracene (AAN)	50**	5.0	TA100, TA1535, TA1537	+
	200**	20.0	TA102	+

* Stock solutions were formulated in water (NaN_3 and MMC), or in DMSO (2NF, AAC, AAN and B[a]P). All stock solutions were stored in aliquots at 1-10°C in the dark, with the exception of B[a]P which was stored in aliquots at −80ºC nominal, in the dark and MMC which was prepared freshly on the day of use or stored in aliquots at −80ºC nominal in the dark.

** Concentrations were twice that stated for the pre-incubation methodology (0.05 mL per plate).

*** Obtained from Sigma-Aldrich Chemical Co, Poole, UK.

Incubation and sampling times: Plates were incubated for 72 hours at 37°C.

Results

Study validity (comment on replicates, counting method, criteria for positive results, etc.): The study is valid. Three separate studies were conducted. 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.

An initial dose ranging study was conducted in strain TA100 only in the presence and absence of S9 using the concentrations 1.6, 8, 40, 200, 1000 and 5000 mcg/plate. Toxicity was seen at 1000 mcg/plate and above in the presence and absence of S9. The same concentration ranges were used in Experiment 1 in all strains in the presence and absence of S9. In Experiment 1, evidence of toxicity was observed in all strains at 1000 mcg/plate and/or 5000 mcg/plate in the presence and absence of S9. Refer to Table 2 for cytotoxicity and mutagenicity results from Experiment 1. No increases in revertants for the test article conditions either in the presence or absence of S9 were observed. The positive controls for each strain showed appropriate increases.

In Experiment 2, the maximum concentration for strain TA1535 in the presence and absence of S9 and TA98 in the absence of S9 remained 5000 mcg/plate because only minimal toxicity was demonstrated at this concentration for these strains (Tables 3 and 4). Due to toxicity observed in Experiment 1, the maximum concentration used was reduced to 1250 for the other strains in both the presence and absence of S9. The concentration range was narrowed for all strains. A pre-incubation with (b) (4) or vehicle in the S9 conditions was included in

Experiment 2. Although toxicity was observed, all strains in both the presence and absence of S9, with the exception of TA98 and TA1535 in the presence of S9, had at least three evaluable concentrations and no increase in revertants was seen (Tables 3 and 4). The positive controls for each strain showed appropriate increases. Strains TA98 and TA1535 in the presence of S9 were not able to be evaluated due to toxicity at all but the lowest concentration so a third study was conducted with these strains using 1250 as the maximum concentration. In Experiment 3, strains TA98 and TA1535 in the presence of S9 with 1250 mcg/plate used as the maximum concentration were evaluated. Slight cytotoxicity was observed at the higher concentrations but at least three concentrations were able to be evaluated and no increases in revertants were observed (Table 5). The positive controls for each strain showed appropriate increases.

No statistically significant increases in revertants were observed for any concentration of (b) (4) (b) (4) in all strains tested in either the presence or absence of S9.

Study outcome: It is concluded that under conditions of the assays conducted, (b) (4) is not mutagenic in *S. typhimurium* strains TA98, TA100, TA1535, TA1537, and TA102 in either the presence or absence of S9. The results of the definitive assays are summarized in Tables 2-5. The experiments conducted for this study are deemed valid. For all strains in either the presence or absence of S9, 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 (Tables 2-5).

Table 2. Data from Experiment 1: Mutagenicity Assay Results Summary in the Absence and Presence of S9												
strain:			***TA98***		***TA100***		***TA1535***		***TA1537***		***TA102***	
	S9	***conc, mcg***	***mean***	***S.D.***	***mean***	***S.D.***	***mean***	***S.D.***	***mean***	***S.D.***	***mean***	***S.D.***
vehicle	-	***0***	27.0	7.7	100.6	4.2	15.8	5.4	6.8	2.5	253.0	13.8
	-	***1.6***	18.0	3.5	112.0	6.6	18.3	3.2	9.0	3.0	245.3	28.0
(b) (4)	-	***8***	20.7	2.9	105.0	6.2	13.7	4.2	5.3	1.5	251.7	14.2
	-	***40***	22.7	2.1	104.3	8.6	14.3	2.1	6.0	1.0	247.3	9.3
	-	***200***	19.3	11.2	99.7	13.7	11.3	2.3	4.0	2.0	228.0	8.5
	-	***1000***	16.0	4.0	79.7 **S**	15.5	8.0	2.6	5.7 **S**	4.0	89.3 **S**	7.5
	-	***5000***	**T,P**	-	**T,P**	-	2.3 **S**	1.5	**T,P**	-	**T,P**	-
positive control	-	*******	736.7	39.1	669.3	18.6	599.3	29.7	77.0	13.0	791.3	11.0
vehicle	+	***0***	30.4	8.5	96.8	13.2	14.6	6.3	14.6	3.2	240.6	11.6
	+	***1.6***	32.7	5.8	99.0	6.6	14.3	2.1	15.3	3.5	244.3	25.4
	+	***8***	31.3	6.4	101.0	2.6	12.7	2.9	20.0	1.0	262.0	14.7
(b) (4)	+	***40***	30.7	6.0	101.7	9.5	11.7	3.1	13.0	5.2	238.7	9.5
	+	***200***	33.0	6.1	95.3	4.9	10.3	0.6	14.7	4.6	213.0	15.0
	+	***1000***	27.7	9.8	70.3 **S**	10.1	13.0	2.6	9.7 **S**	5.5	85.7 **S**	6.0
	+	***5000***	3.3 **S,P**	1.2	**T,P**	-	1.0 **S**	0.0	**T,P**	-	**T,P**	-
positive control	+	*******	313.0	10.5	1034.3	15.3	205.3	77.5	95.0	2.6	1253.7	71.3

Mean: mean number or revertants (n=5 for vehicle, n=3 for test article and positive control)
S.D.: standard deviation
*: refer to Table 1 for concentration of appropriate positive control
S: slightly thinned bacterial lawn
T: toxic, no revertant colonies
P: precipitate

Table 3. Data from Experiment 2: Mutagenicity Assay Results Summary in the Absence of S9													
strain:			***TA98***		***TA100***		***TA1537***		***TA102***			***TA1535***	
	S9	***conc, mcg***	***mean***	***S.D.***	***mean***	***S.D.***	***mean***	***S.D.***	***mean***	***S.D.***	***conc, mcg***	***mean***	***S.D.***
vehicle	-	***0***	19.8	5.3	105.6	9.9	10.4	3.0	272.2	10.0	***0***	10.0	3.3
	-	***39.06***	19.0	8.2	91.7	14.6	4.3	2.5	261.7	29.5	***156.3***	14.3	3.8
	-	***78.13***	12.3	4.0	105.0	7.2	9.0	1.7	269.7	6.4	***312.5***	13.3	2.3
(b) (4)	-	***156.3***	21.7	3.8	96.0	7.9	6.3	3.2	246.7	11.8	***625***	10.0	1.0
	-	***312.5***	24.3	7.6	112.0	9.5	9.7	6.0	194.7	4.0	***1250***	9.3 **S,P**	6.4
	-	***625***	16.3	4.0	79.3	3.8	6.0	3.6	132.3	7.8	***2500***	10.7 **S,P**	1.5
	-	***1250***	14.7 **S,P**	2.3	76.3 **S,P**	6.0	5.3 **S,P**	1.2	71.3 **S,P**	12.7	***5000***	**T,P**	-
positive control	-	*	575.0	72.3	548.7	21.1	107.7	11.7	751.7	12.6	*	538.3	28.5

Mean: mean number or revertants (n=5 for vehicle, n=3 for test article and positive control)
S.D.: standard deviation
*: refer to Table 1 for concentration of appropriate positive control
S: slightly thinned bacterial lawn
T: toxic, no revertant colonies
P: precipitate

Table 4. Data from Experiment 2: Mutagenicity Assay Results Summary in the Presence of S9													
strain:			***TA100***		***TA1537***		***TA102***			***TA98***		***TA1535***	
	S9	***conc, mcg***	***mean***	***S.D.***	***mean***	***S.D.***	***mean***	***S.D.***	***conc, mcg***	***mean***	***S.D.***	***mean***	***S.D.***
vehicle	+	***0***	113.0	17.5	13.8	2.0	196.6	56.3	***0***	27.8	8.5	14.6	4.6
	+	***39.06***	80.7	4.5	14.7	4.0	187.7	20.3	***156.3***	29.0	6.6	17.0	2.0
	+	***78.13***	105.0	7.0	17.7	5.5	187.7	25.5	***312.5***	29.0 **S**	8.5	10.0 **S**	1.0
(b) (4)	+	***156.3***	90.0	7.2	6.7	2.1	203.0	14.7	***625***	19.0 **S**	3.6	6.0 **S**	4.0
	+	***312.5***	70.7 **S**	7.6	7.3 **S**	5.7	151.7 **S**	16.5	***1250***	19.0 **S,P**	4.4	8.3 **S,P**	2.3
	+	***625***	67.7 **S**	5.9	10.3 **S**	9.2	133.7 **S**	50.5	***2500***	12.3 **V,P**	5.8	4.7 **V,P**	0.6
	+	***1250***	48.3 **S,P**	5.1	9.0 **S,P**	3.6	53.0 **V,P**	7.9	***5000***	9.0 **V,P**	5.2	**T,P**	-
positive control	+	*	989.3	196.3	149.7	10.8	1597.7	510.0	*	278.3	33.3	249.3	20.8

Mean: mean number or revertants (n=5 for vehicle, n=3 for test article and positive control)

S.D.: standard deviation
*: refer to Table 1 for concentration of appropriate positive control
S: slightly thinned bacterial lawn
V: very thin bacterial lawn
T: toxic, no revertant colonies
P: precipitate

Table 5. Data from Experiment 3: Mutagenicity Assay Results Summary in the Presence of S9						
strain:			***TA98***		***TA1535***	
	S9	***conc, mcg***	***mean***	***S.D.***	***mean***	***S.D.***
vehicle	+	***0***	29.0	5.0	16.6	2.4
[redacted] (b) (4)	+	***39.06***	34.3	5.7	10.0	4.6
	+	***78.13***	27.7	4.0	16.0	3.6
	+	***156.3***	37.3	10.3	15.7	7.5
	+	***312.5***	38.0 **S**	3.0	12.7S	2.9
	+	***612***	21.7 **S**	5.1	7.3 **S**	1.2
	+	***1250***	24.7 **S**	4.7	10.0 **S**	2.6
positive control	+	*******	390.3	48.7	301.7	18.6

Mean: mean number or revertants (n=5 for vehicle, n=3 for test article and positive control)
S.D.: standard deviation
*: refer to Table 1 for concentration of appropriate positive control
S: slightly thinned bacterial lawn

Table 6. Historical Negative Control Data (reproduced from NDA submission)

Strain	S-9	No. of studies	No. of plates	Mean	Revertant numbers for individual plates: 99% reference range[1]	99% confidence interval for group mean of: 4 values [2]	5 values [2]	6 values [2]
TA98	-	50	503	25	10.0-43.0	16.4-33.3	17.1-32.3	17.7-31.5
TA98	+	50	525	35	15.0-56.0	24.7-46.2	25.6-44.9	26.4-44.0
TA100	-	50	572	111	72.0-160.0	88.8-134.1	90.9-131.5	92.6-129.6
TA100	+	50	588	119	77.0-178.0	92.9-145.4	95.4-142.4	97.2-140.1
TA1535	-	50	505	17	5.0-33.0	9.8-24.8	10.4-23.9	10.9-23.2
TA1535	+	50	524	19	6.0-35.0	11.6-26.8	12.2-25.9	12.7-25.2
TA1537	-	50	512	11	2.0-27.0	5.4-17.7	5.9-16.9	6.2-16.3
TA1537	+	50	534	15	4.0-32.0	8.3-22.9	8.9-21.9	9.4-21.2
TA102	-	48	475	281	178.0-435.0	222.8-342.7	228.5-335.7	232.7-330.6
TA102	+	48	499	238	152.0-341.0	194.4-283.4	198.7-278.3	201.9-274.6

[1] Reference ranges are calculated from percentiles of the observed distributions.
[2] Calculated from square-root transformed data.

Ranges calculated in August 2008 by [redacted] (b) (4) using data selected without bias from studies# started during the periods given below:

S.typhimurium strains (except TA102) Mar 07 to Oct 07
S.typhimurium strain TA102 Feb 07 to Oct 07

All studies had been audited prior to data collection.

Study title: **Induction of Chromosome Aberrations in Cultured Human Peripheral Blood Lymphocytes**

Key findings: Under the conditions of the assay, [redacted] (b) (4) does not induce structural chromosomal aberrations *in vitro* with human peripheral blood lymphocytes. However, levels of polyploid cells outside the historical control 95% range were seen in cultures treated with [redacted] (b) (4) in the absence and presence of S9. The criteria for a positive result were not met,

however, there appears to be a signal of increased polyploidy in the absence and presence of S9 at the higher doses tested.

Study no.: 8221664
Volume #, and page #: Module 4.2.3.3.1
Conducting laboratory and location: (b) (4)
Date of study initiation: January 7, 2010
GLP compliance: Yes
QA reports: yes (X) no ( )
Drug, lot #, and % purity: (b) (4) (b) (4) (b) (4) lot number 528.04.09.03; 99.9%

Methods
Strains/species/cell line: Human peripheral blood lymphocytes

Concentrations used in definitive studies: See Table 1

Basis of concentration selection: 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 concentration ranges tested and the final concentration ranges that were evaluated are outlined in Table 1.

Table 1. (b) (4) ***concentration ranges used in Study 8221664***

Experiment	Treatment	Concentration range (mg/mL)			Final concentration range (µg/mL)		
Range-Finder	3+17, -S-9	0.5079	to	140.0	5.079	to	1400
	3+17, +S-9	0.5079	to	140.0	5.079	to	1400
	20+0, -S-9	0.5079	to	140.0	5.079	to	1400
Experiment 1	3+17, -S-9	2.500	to	60.00	25.00	to	600.0
	3+17, +S-9	5.000	to	75.00	50.00	to	750.0
Experiment 2	20+0, -S-9	1.000	to	12.50	10.00	to	125.0
	3+17, +S-9	5.000	to	50.00	50.00	to	500.0

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 5 mcg/mL in the absence of S9 activation and cyclophosphamide (CPA) was used at 12.5 mcg/mL in the presence of S9 activation.

Incubation and sampling times: See Table 2.

Table 2. Numbers of cultures and incubation times for Experiments 1 and 2

Number of cultures						
Treatment	S-9	Cytotoxicity Range-Finder		Experiment 1	Experiment 2	
		3+17*	20+0*	3+17*	3+17*	20+0*
Negative control	-	2	2	4		4
	+	2		4	4	
Test article	-	1	1	2		2
	+	1		2	2	
Positive controls	-			2		2
	+			2	2	

* Hours treatment + hours recovery

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:

$$MIH\ (\%) = [1 - (\text{mean } MI_T / \text{mean } MI_C)] \times 100\%$$

(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, and
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 ($p \leq 0.05$), and
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 a concentration of 300 mcg/mL (Tables 2 and 3). This increase was outside of historical controls but not statistically significant or dose dependent. Several other concentrations showed numbers of polyploid cells outside the historical control 95% range but not outside the historical control observed range. These increases were very small and occurred in the presence of cytotoxicity in most cases. The result for polyploidy will be considered equivocal.

In the main study experiments (Experiments 1 and 2) cultures were treated with (b) (4) at a range of concentrations. Three or four (b) (4) concentrations were evaluated in each condition for structural and numerical aberrations at concentrations showing ~50% or less reduction in mean mitotic inhibition. In Experiment 1 in the absence of S9, the concentrations that were scored showed mean mitotic inhibition of 11%, 27%, 60% and 40% at 150, 250, 346.2 and 350 mcg/mL, respectively (3 hour incubation with test article; Table 2). In Experiment 1 in the presence of S9, the concentrations that were scored showed mean mitotic

inhibition of 0%, 33% and 63% at 150, 346.2 and 400 mcg/mL, respectively (3 hour incubation with test article; Table 2). All concentrations in Experiment 1 contained precipitate at the beginning of the incubation, but not at the end of the treatment. In Experiment 2 in the absence of S9, the concentrations that were scored showed mean mitotic inhibition of 12%, 22% and 50% at 30, 50, and 55 mcg/mL, respectively (20 hour incubation with test article; Table 3). In Experiment 2 in the presence of S9, the concentrations that were scored showed mean mitotic inhibition of 0%, 16%, 41% and 54% at 100, 150, 200, and 300 mcg/mL, respectively (3 hour incubation with test article; Table 3). All concentrations in Experiment 2 in the absence of S9 and at the top two concentrations in the presence of S9 contained precipitate at the beginning of the incubation, but not at the end of the treatment. 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). In Experiment 2, cultures treated with 300 mcg/mL (b) (4) in the presence of S9 showed 6.5% polyploid cells (Table 3). The historical negative control observed range for polyploid cells in the presence of S9 is between 0 and 3% and is between 0 and 2% in the absence of S9. The historical control 95% reference range for polyploid cells is between 0 and 1% in both the presence and absence of S9. The concentrations of 300 mcg/mL in the presence of S9 is considered positive for increases in polyploidy because the number of polyploidy cells falls outside the historical control range (as well as the 95% reference range) but the overall result of the chromosomal aberration assay will be considered negative as the criteria for a positive assay were not met. Several other concentrations in both the presence and absence of S9 showed increases in polyploidy that were outside the 95% reference range but not outside the observed range (Tables 2 and 3). Historical negative control observed range and 95% reference range data are presented in Table 4. Statistical significance (Fisher's exact test) was reached for the mean structural aberration 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, levels of polyploid cells outside the historical control 95% range were seen in cultures treated with (b) (4) in the absence and presence of S9.
The criteria stated by the applicant for a positive result were not met, however, there appears to be a signal of increased polyploidy in the absence and presence of S9 at the higher doses tested. This effect did not demonstrate a consistent concentration relationship and generally occurred at concentrations that are not deemed biologically relevant for a drug product impurity. Further the finding of polyploidy has not been demonstrated to have clinical significance.

Table 2. Experiment 1: (b) (4) : Mean chromosomal structural aberrations, mitotic inhibition and polyploid cells					
Concentration, mcg/mL	time, h	S9	Mean Structural Aberration Frequency, % (excluding gaps)	Mean Mitotic Inhibition, %	Mean Polyploid Cells, %
Vehicle	3	-	0.5	-	1.0
150	3	-	0.5	11	0.5
250	3	-	0	27	0
346.2	3	-	0.5	60	**1.1#**
350	3	-	0.6	40	0.6
NQO, 5	3	-	32.2*	NC	0.8
Vehicle	3	+	0	-	0
150	3	+	0	0	0.5
346.2	3	+	0.5	33	**1.5#**
400.0	3	+	1.8	63	**2.4#**
CPA, 12.5	3	+	70.5*	NC	0

NC: not calculated; *p≤ 0.001 (calculated for structural aberrations raw data only)
#outside historical control 95% reference range

Table 3. Experiment 2: (b) (4) Mean chromosomal structural aberrations, mitotic inhibition and polyploid cells					
Concentration, mcg/mL	time, h	S9	Mean Structural Aberration Frequency, % (excluding gaps)	Mean Mitotic Inhibition, %	Mean Polyploid Cells, %
Vehicle	3	+	1	0	0.5
100	3	+	1	0	1
150	3	+	0	16	**1.5#**
200	3	+	0	41	0.5
300	3	+	0.5	54	**6.5#, ##**
CPA, 12.5	3	+	42.9*	NC	0
Vehicle	20	-	0.5	-	0.5
30	20	-	0	12	0.5
50	20	-	1	22	**2#**
55	20	-	0	50	**2#**
NQO, 5	20	-	42.6*	NC	0

NC: not calculated; *p≤ 0.001 (calculated for structural aberrations raw data only);
#outside historical control 95% reference range
##outside historical control observed 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 (b) (4) from audited report data of studies started between January 2006 and July 2008.

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.

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

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-22569	ORIG-1	ARCHIMEDES DEVELOPMENT LTD	(b) (4) (fentanyl nasal spray)

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
04/29/2010

RICHARD D MELLON
04/30/2010
I concur with Dr. Bolan. From a nonclinical pharmacology toxicology perspective, NDA 22569 may be approved.

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:	**22-569**
SERIAL NUMBER:	**000**
DATE RECEIVED BY CENTER:	**8/31/09**
PRODUCT:	**PecFent (intranasal fentanyl citrate)**
INTENDED CLINICAL POPULATION:	**for the management of breakthrough cancer pain in opioid-tolerant cancer patients**
SPONSOR:	**Archimedes Development Ltd.**
DOCUMENTS REVIEWED:	**All nonclinical information in the above submission**
REVIEW DIVISION:	**Division of Anesthesia and Analgesia Products**
PHARM/TOX REVIEWER:	**Elizabeth A. Bolan, Ph.D.**
PHARM/TOX SUPERVISOR:	**R. Daniel Mellon, Ph.D.**
DIVISION DIRECTOR:	**Bob Rappaport, M.D.**
PROJECT MANAGER:	**Matthew Sullivan**

Date of review submission to Division File System (DFS): April 9, 2010

TABLE OF CONTENTS

EXECUTIVE SUMMARY

I. Recommendations

A. Recommendation on approvability

This NDA may not be approved from a nonclinical pharmacology/toxicology perspective.

B. Recommendation for nonclinical studies

In order to qualify the potentially genotoxic impurity (b) (4), we recommend that the applicant conduct the minimal genotoxic screen which consists of two *in vitro* genetic toxicology studies, e.g., one point mutation assay and one chromosome aberration assay, with the isolated impurity, tested up to the limit dose for the assay.

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.

(b) (4)

1 PAGE OF DRAFT LABELING HAS BEEN WITHHELD IN FULL AS b4 (CCI/TS) IMMEDIATELY FOLLOWING THIS PAGE

(b) (4)

II. Summary of nonclinical findings

A. Brief overview of nonclinical findings

The excipients in the PecFent formulation can be considered qualified via the intranasal route from the pharmacology/toxicology perspective. All of the excipients in the PecFent formulation can be found in products approved for intranasal use or have been adequately qualified in the toxicology studies submitted in this NDA.

With the exception of (b) (4) the specifications for impurities/degradation products in the drug substance and drug product are acceptable. (b) (4) which contains a structural alert for mutagenicity. A specification to reflect NMT 1.5 mcg/day should be set for genotoxic or potentially genotoxic residual intermediates/impurities. The current proposed specifications for (b) (4) in the drug substance and drug product are unacceptable. The applicant stated that they are currently conducting genetic toxicology studies in order to qualify (b) (4). Until the studies are submitted and formally reviewed the recommendation from a pharmacology/toxicology

perspective will be not to approve this product on the basis of unacceptable specifications for (b) (4) in the drug substance and drug product.

The applicant conducted 3-month and 6-month toxicology studies in the rat and a 9-month toxicology study in the dog with the clinical formulation of PecFent via intranasal administration. All three studies adequately assessed the toxicologic potential of the PecFent formulation and included thorough evaluations of the local tissues including the nasal cavity, nasopharynx and lung. Central nervous system-related clinical signs consistent with the pharmacology of fentanyl were observed in all studies and do not pose any toxicologic concern. No test article-related toxicity was noted in the dog study but the rat studies showed some histopathologic changes in the local tissues. These changes were also observed in the control and placebo groups and are most likely not due to the test article.

Administration of fentanyl by the intranasal route in the dog and rat does not present any unique toxicities. No outstanding nonclinical toxicities were seen that would preclude approval of this product. However, until the potentially genotoxic impurity/degradation product (b) (4) is either reduced to acceptable levels in the drug substance and drug product or toxicologically qualified, the recommendation from the pharmacology/toxicology perspective will be to not approve 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 associated with this product as compared to other approved fentanyl products.

2.6 PHARMACOLOGY/TOXICOLOGY REVIEW

2.6.1 INTRODUCTION AND DRUG HISTORY

NDA number: 22-569
Review number: 1
Sequence number/date/type of submission: 000/August 28, 2009/Original submission
Information to sponsor: Yes ( ) No (X)
Sponsor and/or agent: Archimedes Development, Ltd. Nottingham, UK
Manufacturer for drug substance: (b) (4)

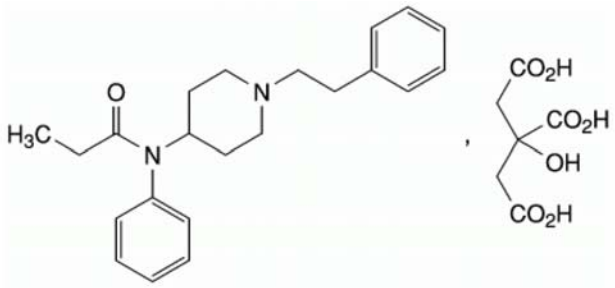
Reviewer name: Elizabeth A. Bolan, Ph.D.
Division name: Division of Anesthesia and Analgesia Products

HFD #: 170

Review completion date: April 8, 2010

Drug:

Trade name: PecFent (approved trade name undecided)
Generic name: fentanyl citrate
Code name: referred to as NasalFent in 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: $C_{22}H_{28}N_2O.C_6H_8O_7$ MW=528.59 (336.47 as free base)
Structure:



Relevant INDs/NDAs/DMFs:

IND/NDA/MF	*drug/compound*	*Sponsor*	*Division*	*status*
IND 70,854	NasalFent (intranasal fentanyl citrate)	Archimedes	DAAP	active
NDA 20-747	Actiq (referenced drug)	Cephalon	DAAP	approved 11/4/98
	(b) (4)			

Drug class: Fentanyl is a mu opioid receptor agonist.

Intended clinical population: PecFent 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.

Clinical formulation: The PecFent drug product is a formulation of fentanyl intended for intranasal use. PecFent is an aqueous solution which contains 100 mcg (1.0 mg/mL) or 400 mcg (4.0 mg/mL) of fentanyl per 0.1 mL actuation. (b) (4) Mannitol is added (b) (4) and phenylethyl alcohol and propylparaben are used as (b) (4) The solution is delivered to the nasal mucosa via a (b) (4) metered-dose pump. As per product labeling for Actiq, for the management of breakthrough cancer pain, dosing should not exceed 4 per day; therefore, the MDD of fentanyl via this product is 3.2 mg/day. Levels of all excipients in the PecFent 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 or have been adequately qualified with nonclinical toxicology studies and do not pose any unique toxicological concerns. Refer to Table 1 for the description and composition of PecFent and Table 2 for the maximum levels of each excipient in the 400 mcg strength when used at the MDD of fentanyl.

Table 1. Composition of PecFent (table reproduced from NDA)

Component	Reference to Standard	Function	Quantity per mL (mg)	
			FNS 1.0 mg/mL	FNS 4.0 mg/mL
Fentanyl citrate	Ph.Eur./USP	Active	1.570[1]	6.280[2]
(b) (4)				
Mannitol	Ph.Eur./USP	(b) (4)		(b) (4)
Phenylethyl alcohol	USP			
Propylparaben	Ph.Eur./NF			
Hydrochloric acid or sodium hydroxide	Ph.Eur./NF			
(b) (4)				

[1] Equivalent to 1.000 mg fentanyl base

[2] Equivalent to 4.000 mg fentanyl base

(b) (4)

Table 2. Levels of PecFent Excipients* at the MDD of Fentanyl (3.2 mg/day)

Excipient	*mg*	*Acceptable?*
(b) (4)		YES
Mannitol	(b) (4)	YES
Phenylethyl alcohol		YES
Propylparaben		YES

*levels of excipients are calculated for 8 actuations (3.2 mg fentanyl) of the 400 mcg strength

Excipients

With the exception of (b) (4) and mannitol, all of the excipients can be found at higher levels in products approved for intranasal use. (b) (4) Mannitol is a sugar alcohol used in (b) (4) Pectin, (b) (4) and mannitol are food products/additives as well as commonly used pharmaceutical excipients approved for use via the oral route. However, pectin, (b) (4) and mannitol have not been approved for intranasal use. In order to assess the safety of the formulation via the intrasnasal route, the applicant conducted repeat-dose toxicology studies in rat (3-month, WFEN/P34/05 and 6-month, WFEN/P37/05) and dog (9-month, WFEN/P36/05) with the final PecFent formulation. Each study utilized saline and drug-free formulation controls and included detailed histopathological assessments of the nasal cavity, nasopharynx and lung. No

unique toxicities due to the drug-free formulation were observed in any of the studies (see below for formal review).

Because of its relatively high molecular weight, pectin is not likely to be absorbed in the nasal mucosa. The local concentration of pectin in the nasal cavity (mg/cm^2) assessed in the repeat-dose studies was roughly equivalent to the human for the rat and 2-fold higher in the dog.

All of the excipients are approved for oral use at levels higher than found in this product when it is used at the MDD of fentanyl. Pectin is GRAS in food products with no limitations other than good manufacturing practice (21CFR §184.1588). If the PecFent product is mistakenly swallowed the excipients in the formulation will not present any toxicologic concerns.

The repeat-dose toxicology studies conducted by the applicant did not identify any unique toxicities due to the excipients. The components of the PecFent formulation can be considered qualified via the intranasal route from the pharmacology/toxicology perspective.

Impurities in the drug substance

The MDD of fentanyl (3.2 mg/day) is $\leq$ 2 g/day, therefore the qualification threshold according to the ICH Q3A(R2) guideline for impurities in the drug substances is 0.15% or 1 mg/day intake, whichever is lower. The applicant has set the specifications for the impurities in the fentanyl drug substance obtained from (b) (4) at NMT (b) (4) (Table 3). (b) (4) has been deemed adequate to support numerous NDAs and ANDAs. Recently, several drug substance impurities were evaluated for potential structural alerts for mutagenicity, as summarized below.

The (b) (4) contains a structural alert for mutagenicity. (b) (4) A specification to reflect NMT (b) (4) should be set for genotoxic or potentially genotoxic residual intermediates/impurities. At the current specification of (b) (4) with a MDD of 3.2 mg of fentanyl the total daily intake of (b) (4). This is above the limit of NMT (b) (4) and is not considered acceptable. The applicant conducted a computational toxicology analysis of (b) (4) (*DEREK* for Windows 11.0.0) which predicted that (b) (4) did not possess genotoxic or carcinogenic potential. However, internal analysis did not reach the same conclusions. Refer to discussion of the (b) (4) computational toxicology below. The applicant's analysis is not considered adequate and levels of (b) (4) must either be reduced or the compound must be qualified by conducting a minimal genotoxic screen. The applicant states that they are currently conducting genetic toxicology studies in order to qualify (b) (4). Until the studies are submitted and formally reviewed the recommendation from a pharmacology/toxicology perspective will be not to approve this product. With the exception of the specification for (b) (4), the specifications set by (b) (4) for the fentanyl drug substance impurities as outlined in Table 3 are

acceptable from a pharmacology/toxicology perspective. The adequacy of the drug substance specification for (b) (4) will be determined upon review of pending genetic toxicology studies.

(b) (4). 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). However, no specifications have been set for (b) (4) in the drug substances obtained from (b) (4) or other fentanyl suppliers. Dr. Sheldon Markofsky (CMC) has requested that the DMF holder monitor for levels of (b) (4) in the drug substance. Levels should not exceed (b) (4) in order to remain below the acceptable level of (b) (4) for a genotoxic impurity.

No specification in the drug substance was set for the structural alert-containing fentanyl synthesis impurity (b) (4) After examination of the (b) (4) synthesis scheme for fentanyl by Dr Sheldon Markofsky (CMC reviewer) it was determined that (b) (4) would not be formed and that a specification in the drug substance would not be necessary.

Table 3	***Specifications of fentanyl citrate drug substance impurities from (b) (4)***	
Impurity	***Specification***	***Acceptable?***
(b) (4)	NMT (b) (4)	**NO**
	NMT	YES
	NMT	YES
	NMT	YES
	NMT	YES

Impurities in the drug product

The MDD of fentanyl of 3.2 mg in the PecFent drug product is < 10 mg/day, therefore the qualification threshold according to the ICH Q3B(R2) guidelines for impurities/degradants is 1.0% or (b) (4), whichever is lower. The applicant has set the specifications for the individual unspecified impurities in the fentanyl drug product at (b) (4) and no further qualification will be necessary (Table 4). The specification for (b) (4) (b) (4) The (b) (4) contains a structural alert for mutagenicity. (b) (4) At the current specification of (b) (4) for the MDD of fentanyl the total daily intake of (b) (4). In order to meet the currently accepted specification of 1.5 mcg/day for a potentially genotoxic impurity the specification would have to be set at (b) (4). The current specification of (b) (4) (b) (4) is unacceptable. The applicant is currently conducting genetic toxicology studies to qualify (b) (4). Until the studies are formally reviewed the recommendation from a pharmacology/toxicology perspective will be not to approve this product. With the exception of the specification for (b) (4), the specifications for the fentanyl drug

product impurities as outlined in Table 4 are acceptable from a pharmacology/toxicology perspective.

Table 4	***Specifications of PecFent drug product impurities/degradants***	
Impurity/degradant	***Stability specification***	***Acceptable?***
(b) (4)	NMT (b) (4)	**NO**
individual unspecified	NMT	YES

Computational toxicology evaluation of the genotoxic and carcinogenic potential (b) (4) (b) (4)

The applicant submitted a computational toxicology analysis of (b) (4) (*DEREK* for Windows 11.0.0) which predicted that (b) (4) did not possess genotoxic or carcinogenic potential. The structure of (b) (4) was also submitted to the FDA Informatics and Computational Safety Analysis Staff (ICSAS) for evaluation of the potential for genotoxicity and carcinogenicity. The ICSAS evaluation predicted a negative result for mutagenicity and a positive result for clastogenicity in the *in vivo* micronucleus assay using the A7J: Rodent mutation *in vivo* composite module. The ICSAS report also predicted a positive result for carcinogenicity using the *MC4PC* format, however, the *MDL-QSAR* format predicted a negative result for carcinogenicity. Carcinogenicity studies are not required for this indication. The applicant's analysis of the genotoxic potential of (b) (4) is not considered adequate and levels must either be reduced to NMT (b) (4) or the compound must be adequately qualified by conducting a minimal genotoxic screen. The minimal genotoxic screen consists of two *in vitro* genetic toxicology studies, e.g., one point mutation assay and one chromosome aberration assay, with the isolated impurity, tested up to the limit dose for the assay. In a teleconference with the applicant on December 3, 2009, the applicant stated that they are conducting an Ames Test and an *in vitro* chromosomal aberration assay with (b) (4) and the reports will be submitted at a later date. Until the studies are received by FDA and formally reviewed the recommendation from a pharmacology/toxicology perspective will be not to approve this product.

Route of administration: intranasal

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 22-569 are owned by Archimedes or are data for which Archimedes has obtained a written right of reference. Any information or data necessary for approval of NDA 22-569 that Archimedes 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 Archimedes 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 22-569.

This NDA for PecFent is being filed under Section 505(b)(2) of the FD&C Act. PecFent 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:

Study number	***eCTD location***	***Study Title***
WFEN/R07/02	4.2.2.2	Evaluation of Nasal Formulations of Fentanyl Citrate in Sheep
WPEC/R06/03	4.2.2.2	Effect of Pectin Concentration on the Intranasal Absorption of Fentanyl in Sheep
AD1001 R70/08	4.2.2.2	Pharmacokinetics of Fentanyl in the Dog Compared with Human Subjects Following Administration of Fentanyl Citrate Nasal Spray
AD1001 R71/08	4.2.2.2	Pharmacokinetics of Fentanyl in the Rat Compared with Human Subjects Following Administration of Fentanyl Citrate Nasal Spray
DBS-PEC-R02-99	4.2.2.7	Investigation of the Nasal Clearance of Pectin Formulations in Sheep
WFEN/P34/05	4.2.3.2	Fentanyl Citrate Nasal Spray: 90-Day Intranasal Administration Toxicity Study in the Rat Followed by a 28-Day Treatment-Free Period
WFEN/P37/05	4.2.3.2	Six Month Repeated Dose Intranasal Chronic Toxicity Study in the Rat with 28-Day Recovery Phase
WFEN/P36/05	4.2.3.2	Fentanyl Citrate Nasal Spray: 39-Week Intranasal Administration Toxicity Study in the Dog Including a 13-Week Interim Kill Which is Followed by a 28-Day Treatment-Free Period
AD1001-R68-08	4.2.3.7	Investigation of the Gelling Properties of (b) (4) Pectin in the Rat Nasal Cavity

Studies <u>not</u> reviewed within this submission:

Study number	***eCTD location***	***Study Title***
WFEN/R01/02	4.2.2.2	Nasal Fentanyl Citrate Dose-Ranging Study in Sheep
WFEN/P35/05	4.2.3.2	Fentanyl Citrate Nasal Spray: Maximum Tolerated Dose (MTD) Followed by a 10-Day Fixed Dose Intranasal Administration Toxicity Study in the Dog
WFEN/P33/05	4.2.3.2	Fentanyl: 7-Day Intranasal Administration Toxicity Study in the Rat (Dose-Ranging Study)

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 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.

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 intranasal 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 new studies were conducted.

2.6.2.4 Safety pharmacology No new studies were conducted.
Refer to review by Dr. John Gong of the Controlled Substances Staff for an evaluation of the abuse potential of this product.

2.6.2.5 Pharmacodynamic drug interactions No new studies were conducted.

2.6.3 PHARMACOLOGY TABULATED SUMMARY

2.6.4 PHARMACOKINETICS/TOXICOKINETICS

The PecFent drug product is an intranasal fentanyl formulation based on the applicant's proprietary PecSys™ (b) (4) pectin) technology. (b) (4) . For the PecFent product, the divalent calcium cations in the nasal fluid serve to gel the (b) (4) pectin. The applicant hypothesizes that the pectin gel will delay the normal process of mucocilliary clearance and increase residency time of the drug in the nasal passages. This could increase the systemic absorption of the drug or the duration of action of locally administered drugs. The applicant conducted a study to investigate the gelling properties of pectin in the rat nasal cavity and to demonstrate that (b) (4) pectin formulations gel *in vivo* (AD1001-R68-08). The study is summarized below.

A single dose of fifty microliters of (b) (4) pectin: sucrose) or saline was administered intranasally to anesthetized rats (3 per group).

All solutions contained blue food dye to aid in visualization *in situ*. Ten minutes post-administration rats were euthanized and the nasal mucosa was exposed and examined to confirm the presence of the pectin gel. Wide spread blue coloration of the nasal mucosa extending from the nostrils to the nasopharynx was observed in all animals. In the treated groups, small plaques of gel were present in the medial section of the nasal respiratory region with larger plaques observed in the posterior regions of the nasopharynx and nasal cavity. The gel tended to form plaques rather than a contiguous mass. No differences were observed between the two concentrations of pectin. No gel was observed in the saline group. These observations demonstrate that the pectin formulations can form a gel in the rat nasal cavity. The study was not designed to assess safety or local toxicity of pectin.

The applicant conducted Study DBS-PEC-R02-99 to evaluate nasal clearance rates of pectin in the sheep. The study showed that pectin-based formulations (10%, 15% and 20% pectin) slowed nasal clearance rates as compared to controls when administered intranasally to sheep. No differences were seen between the concentrations of pectin.

2.6.4.1 Brief summary

Two pharmacokinetic studies in sheep were conducted. In Study WFEN/R07/02, a single dose of fentanyl (300 mcg) was administered intranasally to sheep (n=2) in formulations with and without the excipient chitosan. (b) (4) The results showed that the intranasal absorption of fentanyl was rapid and not modified by the presence of the chitosan. A second PK study in sheep (Study WPEC/R06/03) evaluated the effect of several different concentrations of (b) (4) Pectin on intranasal absorption of fentanyl. A single dose of fentanyl (200 mcg) in formulations containing 0, 5, 10, 20, and 40 mg/mL (b) (4) Pectin was administered intranasally to sheep (n=5). A trend toward decreased C_{max} and AUC values was noted with formulations containing the higher concentrations of (b) (4) Pectin but this trend was not evident at lower concentrations. It could not be definitively shown that the concentration of (b) (4) Pectin modifies absorption characteristics of intranasally administered fentanyl.

Two pharmacokinetic studies using the PecFent formulation in rat and dog were submitted by the applicant (Studies AD1001/R71/08 and AD1001/R70/084, respectively). These studies were not new PK studies but compared existing toxicokinetic data from the chronic toxicology studies conducted in rat and dog (refer to Studies WFEN/P34/05, WFEN/P37/05 and WFEN/P36/05). In both evaluations, the rat and dog data were compared to human data from the Phase 1 clinical trial Study CP37/02. In Study CP37/02, naltrexone-blocked human healthy volunteers were administered a single dose of one of three intranasal formulations containing 100 mcg fentanyl or 200 mcg Actiq lozenge (buccal administration). In addition to fentanyl, the three formulations contained: chitosan, pectin or a chitosan/poloxamer 188 combination. Only data from the pectin-containing formulation were compared with the nonclinical data. Blood samples were taken at 0, 5, 10, 15, 20, 30, 45, 60, 90, 120, 180, 240, 360, 480, 720 and 1440 min post dosing.

The studies concluded that the absorption profile of intranasally administered fentanyl was comparable in the rat, dog and human with a sharp early peak followed by an initial rapid decline with a further steady decline in plasma concentrations.

2.6.4.2 Methods of Analysis

2.6.4.3 Absorption

2.6.4.4 Distribution

2.6.4.5 Metabolism

2.6.4.6 Excretion

2.6.4.7 Pharmacokinetic drug interactions

2.6.4.8 Other Pharmacokinetic Studies

2.6.4.9 Discussion and Conclusions

The applicant has demonstrated that the pectin-containing excipient forms gel plaques when administered to the nasal mucosa of rat. Further evaluation of various pectin concentrations in the sheep demonstrated that the presence of pectin in the nasal cavity slows the nasal clearance rate. No dose-dependency with pectin was seen in either study. Two PK studies in sheep showed that the intranasal absorption of fentanyl is rapid and that although a trend toward decreased C_{max} and AUC values was noted with formulations containing the higher concentrations of (b) (4) Pectin it could not be definitively shown that the concentration of (b) (4) Pectin modifies absorption characteristics of intranasally administered fentanyl. Toxicokinetic studies in rat and dog concluded that the absorption profile of intranasally administered fentanyl was comparable to human with a sharp early peak followed by an initial rapid decline with a further steady decline in plasma concentrations.

2.6.4.10 Tables and figures to include comparative TK summary

Table 5 represents exposure margins calculated by the reviewer using the toxicokinetic data from the repeat-dose toxicology studies in rat (3-month, WFEN/P34/05 and 6-month, WFEN/P37/05) and dog (9-month, WFEN/P36/05) and human pharmacokinetic data from study CP047. The pharmacokinetic data from study CP047 appear in the draft label of PecFent.

Table 5 Species comparisons of fentanyl exposure margins

study	***dose***	***AUC animal/human ratio***	***C_{max} animal/human ratio***
3-month rat (WFEN P34/05)	0.26 mg/kg	2.9	1.7
6-month rat (WFEN P36/05)	0.48 mg/kg	1.5	0.80

9-month dog* (WFEN P37/05)	0.96 mg/kg	12.0	5.4

Note: human data is from study CP047
*the dog AUC value used in the ratio is $AUC_{6.5\text{-}24h}$, all other AUC values are $AUC_{0\text{-}24h}$

2.6.5 PHARMACOKINETICS TABULATED SUMMARY

2.6.6 TOXICOLOGY

2.6.6.1 Overall toxicology summary

General toxicology: The applicant conducted 3-month and 6-month toxicology studies in the rat and a 9-month toxicology study in the dog with the clinical formulation of PecFent via intranasal administration. All three studies adequately assessed the toxicologic potential of the PecFent formulation and included thorough evaluations of the local tissues including the nasal cavity, nasopharynx and lung. No test article-related toxicity was noted in the dog study but the rat studies showed some histopathologic changes in the local tissues. These changes were also observed in the control and placebo groups and are most likely not due to the test article. Refer to review of the studies and Discussion and Conclusions section for further discussion.

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.

Carcinogenicity: No carcinogenicity studies were required 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: No special toxicology studies were conducted.

2.6.6.2 Single-dose toxicity No new studies were conducted.

2.6.6.3 Repeat-dose toxicity

Study title: Fentanyl Citrate Nasal Spray: 39-Week Intranasal Administration Toxicity Study in the Dog Including a 13-Week Interim Kill which is Followed by a 28-Day Treatment-free Period

Key study findings:

- Several CNS-related clinical signs consistent with a mu opioid in dog were observed. Findings were dose-dependent with incidence and severity decreasing with time.

- Treatment-related decreases in body weights with concurrent decreases in food intake were observed during the study.

- Slight increases in heart rate were seen in weeks 12, 25 and 38 in all treated groups. No changes were observed in the recovery groups.

- At the interim kill only, an increase in cortical vacuolation of the adrenal was seen in both sexes at the MD and HD. No microscopic findings were seen at any dose in the terminal kill or recovery groups.

Study no.: WFEN/P36/05
Volume #, and page #: 4.2.3.2
Conducting laboratory and location: (b) (4)

Date of study initiation: July 13, 2005
GLP compliance: Yes
QA report: yes (X) no ( )
Drug, lot #, and % purity: fentanyl citrate nasal spray 6.28 mg/mL (clinical formulation); 95.5% and placebo (clinical formulation without the fentanyl citrate)

Methods

Doses: control, placebo, 0.16, 0.48, 0.96 mg/kg/day with a four-day build up period of 0.16 mg/kg/day for treatment groups prior to start of dosing; doses were divided into four intranasal administrations per day in both build up and main study phases. Saline was used as the control and the formulation without the active ingredient was used as the placebo. Doses were selected based on the results of a dose range finding study in the dog (Study 2550/003).

Species/strain: beagle dog

Number/sex/group or time point (main study): 4/sex/dose for 39-week terminal kill, 3/sex/dose for 13-week interim kill

Route, formulation, volume, and infusion rate: intranasal with a (b) (4) nasal spray device which administers 0.1 mL per actuation, clinical formulation containing 6.28 mg/mL fentanyl citrate (equivalent to 4 mg/mL fentanyl base per actuation); control (6 actuations), placebo (6 actuations), 0.16 (1 actuation), 0.48 (3 actuations), 0.96 (6 actuations) mg/kg/day; refer to Table 1 for details of the formulation.

Satellite groups used for toxicokinetics or recovery: 28-day recovery: 2/sex for the control, placebo and high dose groups

Age: 23-37 weeks old

Weight: males: 8.7-13.7 kg; females: 6.1-13.7 kg

Sampling times: Blood samples for toxicokinetic analysis were obtained from all animals at approximately 6.5, 12 and 24 hours after the first dose on day 1 and in weeks 13 and 38.

Unique study design or methodology (if any): In order to allow for higher dosing of fentanyl, a four-day build up phase using the low dose was employed for all treatment groups.

Methods and Results

Mortality: One animal from the MD was euthanized on day 2. This animal had received four doses of test article on day 1 and three doses on day 2. The animal showed clinical signs similar to the other dogs in this group on the first day of dosing (e.g. subdued behavior post-dosing) but on the second day salivation and convulsion were noted about 20 minutes after dose 2 and salivation, convulsion, vocalization and body tremors were noted about 30 minutes after dose 3. The animal was examined by a veterinarian and euthanized after its condition had declined further (prostration and reluctance/inability to move). Macroscopic findings consisted of minor reddening of areas of the heart and gastrointestinal tract. Following microscopic evaluation, the cause of death was not determined, but findings were generally similar to those in animals surviving to the interim kill, or were related to terminal events (e.g. convulsions). Due to the timing of the clinical signs relative to dosing, an association with the test article cannot be ruled out. However, no pathological evidence of test article toxicity as a cause of death and no other animal in the study exhibited convulsions during the study.

Clinical signs: Animals in the main study were observed for signs of ill heath or overt toxicity and given physical examinations daily. Weekly physical examinations were conducted on animals in the recovery groups.
The treatment-related clinical signs observed in this study were mostly CNS-related signs. These signs included subdued behavior, salivation, vomiting, and tremors. Incidence and severity increased with increasing doses with the highest incidence of the clinical signs seen in the first week of dosing. Most signs disappeared by week 6 in the LD, week 11 in the MD and week 14 in the HD. The clinical signs are attributed to the pharmacologic effect of fentanyl and are consistent with clinical signs observed after administration of a mu opioid.

Body weights: Individual body weights were recorded weekly during the main study and recovery period. Body weights were also recorded prior to treatment of the build-up phase and the treatment period as well as on the day of scheduled necropsy.
Males and females in the treated groups showed a mean body weight decrease during the build up phase and week 1. Male group mean body weights were reduced as compared to placebo until the middle of the study (~week 26) when weight changes were similar to controls. For females, weight gain was steady for the first half of the study and after week 26 weight gain slowed. For males, overall body weight gain was lower in the treated groups with statistical significance reached for the HD. For females, overall body weight gain for the HD was lower than the placebo with the LD and MD being higher than placebo. Statistical significance was not reached in any case. For both sexes, the weight decreases correlate with reduced food consumption. Recovery groups for both sexes in all treated groups showed a steady increase in weights.

Food consumption: The amount of food consumed by each animal was determined weekly. Dose dependent reductions in group mean food consumption were seen in the first 8 weeks of the study for all treated groups for both sexes. From week 13 onwards reductions in food consumption in the treated groups were less than in the beginning of the study although levels were still lower than control groups.

Ophthalmoscopy: Ophthalmoscopic investigations were performed on all animals pre-treatment and in weeks 12, 25 and 38 and on the recovery animals. No test article-related changes in ophthalmoscopic parameters were noted.

EKG: Electrocardiographic investigations were performed on all animals pre-treatment and in weeks 12, 25 and 38 and on the recovery animals. At weeks 12, 25 and 38, slight increases in heart rate were seen in all dose groups for males and females when compared with the placebo control group. Several of these differences reached statistical significance. No changes were seen in the recovery groups.

Hematology: Blood samples (0.5 mL) for evaluation of hematologic parameters were obtained from all animals pre-treatment, weeks 13, 26, 39 and from the recovery animals. Samples were collected from the jugular vein prior to dosing and after an overnight period without food. No toxicologically significant changes in hematologic parameters were seen.

Clinical chemistry: Blood samples (0.5 mL) for clinical chemistry analysis were obtained from all animals pre-treatment, weeks 13, 26, 39 and from the recovery animals. Samples were collected from the jugular vein prior to dosing and after an overnight period without food. No toxicologically significant changes in clinical chemistry parameters were seen.

Urinalysis: Urine samples were collected from all animals by direct catheterization of the bladder pre-treatment, in weeks 12, 26, 39 and from recovery animals. No toxicologically significant changes in urinalysis parameters were seen.

Gross pathology: The scheduled necropsies were performed after an overnight period without food. Animals were euthanized by intravenous overdose of sodium thiopentone followed by severing of a major blood vessel in order to exsanguinate the animal. A full macroscopic examination was performed under the general supervision of a pathologist and all lesions were recorded. Bone marrow smears were prepared at necropsy and fixed in methanol. The applicant notes that bone marrow smears were not evaluated. No test toxicologically significant macroscopic findings were seen.

Organ weights (see histopathology table): At the terminal kill, increased adjusted adrenal weight for the male MD was seen. This finding achieved statistical significance ($P<0.05$). Group mean increases in adjusted weight were in the range 18 to 34% above the control value. The absolute adrenal weights in males were within the historical control range and no microscopic findings in the adrenal were seen in the terminal kill

groups. No changes were noted in females. No other test article-related changes in organ weights were seen.

Histopathology: Adequate Battery: yes (X), no ( )—explain
Peer review: yes (X), no ( )
The battery of organs sampled for histopathologic analysis is detailed in the histopathology table.
At the interim kill, an increase in cortical vacuolation of the adrenal was seen in males and females at the MD and HD. The vacuolation was characterized by a minor increase in coarse, clear vacuoles, predominantly in the zona glomerulosa. Microscopic findings were not seen in any dose at the terminal kill. No increases in adrenal weight were seen in the interim kill or recovery groups.

Toxicokinetics: Blood samples (0.5 mL) for toxicokinetic analysis were obtained from all animals at approximately 6.5, 12 and 24 hours after the first dose on day 1 and in weeks 13 and 38. Blood samples were collected from a cephalic/saphenous vein into lithium heparin anticoagulant.

C_{max} and $AUC_{6.5\text{-}24h}$ were generally dose proportional in both males and females. No gender differences were seen. Slight accumulation in males and females based on $AUC_{6.5\text{-}24h}$ was seen at week 38 in the MD and HD. Slight accumulation in males and females was also noted with C_{max} values at all dose levels. For most conditions, the applicant states that the T_{max} is 6.5 h (Table 6). However, 6.5 h was the first time point measured. The value of 6.5 h as the actual T_{max} of fentanyl in the dog may not necessarily be accurate. The AUC, $C_{max,}$ and T_{max} values are presented in Table 6.
The applicant calculated the area under the curve between the time points of 6.5 and 24 h in this study. The 6.5 h time point was 30 min after the administration of the last dose. The applicant notes the following:

> It should be noted that by using $AUC_{(6.5\text{-}24h)}$, this represents an underestimate of the actual exposure to fentanyl compared to values if a full AUC (i.e. 0-24 h) were available. All inter-group comparisons within the study are still valid as the values were all calculated in the same way, however, care should be taken with any comparisons with other data.

This incomplete toxicokinetic data is of limited utility and, as stated by the applicant, care should be taken with comparisons of these exposure data to other studies. The first time point measured in this study was 6.5 h. Fentanyl has a rapid onset of action and this time point may have missed the peak plasma levels of fentanyl. The T_{max} as well as the C_{max} values are most likely inaccurate and should not be used. However, the AUC values demonstrate that the dogs showed systemic exposure to fentanyl and although the study was not conducted optimally the data can be used to estimate exposure margins with the understanding that the $AUC_{6.5\text{-}24h}$ provides an underestimate of the actual exposure.

Table 6. TK parameters from the 39-week dog chronic toxicology study (WFEN P36/05)							
dose group, mg/kg/day	***parameter***	***males***			***females***		
		Day 1	***Week 13***	***Week 26***	***Day 1***	***Week 13***	***Week 26***
0.16	C_{max}* ***ng/mL***	2.7	2.4	2.7	13.4	1.8	2.2
	$AUC_{6.5-24}$ ***ng.h/mL***	11.1	13.8	12.4	10.4	7.4	9.8
	T_{max}*, ***h***	6.5	7.9	6.5	6.5	6.5	6.5
0.48	C_{max}* ***ng/mL***	6.3	4.6	9.3	4.6	4.0	7.8
	$AUC_{6.5-24}$ ***ng.h/mL***	31.7	20.6	37.7	23.5	18.3	30.6
	T_{max}*, ***h***	6.5	6.5	6.5	6.5	6.5	6.5
0.96	C_{max}* ***ng/mL***	10.7	9.5	15.1	15.0	13.2	16.6
	$AUC_{6.5-24}$ ***ng.h/mL***	83.6	47.4	79.6	86.1	63.7	77.8
	T_{max}*, ***h***	7.8	6.5	6.5	7.8	6.5	6.5

*See discussion above regarding the accuracy of these values

Conclusions: Several CNS-related clinical signs including subdued behavior, salivation, vomiting and tremors were observed during the study. The incidence and severity of the signs were generally dose dependent and decreased with time. The observations are consistent with the pharmacology of an opioid in dogs and do not pose any unique toxicologic concern. One animal showed convulsions and was euthanized on day 2 of the study. Treatment-related decreases in body weights were observed during the study. These changes correlated with decreases in food intake which were attributed to the pharmacologic effect of fentanyl. At several time points during the study, slight increases in heart rate were seen in the treated groups. Changes in heart rate were not seen in the recovery groups. At the interim kill, an increase in cortical vacuolation of the adrenal was seen in males and females at the MD and HD. These changes did not correlate with organ weight changes and were not seen in the terminal kill or recovery groups. Increased adrenal weights were seen in the MD group in males in the terminal kill only. No microscopic findings were seen in any dose at the terminal kill. No treatment-related changes were seen in the nasal cavity, nasopharynx, and lung tissues.

The findings in this study were either known pharmacologic effects of fentanyl or of low severity and toxicologic concern. Administration of fentanyl by the nasal route in the dog does not present any unique toxicities. Although the collection of the toxicokinetic data was not optimal, the data show that the animals were exposed to the drug. Thorough analysis of the relevant local tissues was conducted and the study is deemed a valid assessment of the toxicity including local toxicity of this fentanyl product. No outstanding nonclinical toxicities were seen that would preclude approval of this product.

Histopathology inventory

Histopathology Inventory			
Study: 39-week intranasal toxicology study (WFEN/P36/05)			
Species: dog			
Adipose tissue		Nasopharyngeal duct	X
Adrenals	X*	Optic nerves	X
Aorta	X	Ovaries, oviducts	X*
Bone marrow smear	X	Pancreas	X
Bone (femur)	X	Parathyroid	X
Brain	X*	Peripheral nerve	
Cecum	X	Peyer's Patch	X
Colon	X	Pharynx	
Duodenum	X	Pituitary	X*
Epididymis	X*	posterior pharyngeal wall	X
Esophagus	X	Prostate	X*
Eye	X	Rectum	X
Fallopian tube		Salivary glands	X
Gall bladder	X	Sciatic nerve	X
Gross lesions	X	Seminal vesicles	**X**
Harderian gland		Skeletal muscle	X
Heart	X*	Skin	X
Ileum	X	Spinal cord (C, T, L)	X
Injection site		Spleen	X*
Jejunum	X	Sternum	X
Kidneys	X*	Stomach	X
Joint (tibiofemoral)		Testes	X*
Lachrymal gland	X	Thymus	X*
Larynx incl. epiglottis	X	Thyroid	X*
Liver	X*	Tongue	X
Lungs with mainstem bronchi and bronchioles	X*	Trachea and trachea bifurcation	X
Lymph nodes, bronchial	X	Urinary bladder	X
Lymph nodes, mandibular	X	Uterus incl. cervix	X*
Lymph nodes, mesenteric	X	Ureters	X
Mammary gland	X	Vagina	X
Nasal cavity	X		

X, histopathology performed
*, organ weight obtained

Study title: Fentanyl Citrate Nasal Spray: 90-Day Intranasal Administration Toxicity Study in the Rat Followed by a 28-Day Treatment-Free Period

Key study findings:

- Treatment-related clinical signs included lethargy, exophthalmos, hyperactivity, chewing of bedding and fast heart rate. With the exception of exophthalmos and chewing of the bedding which were seen until the end of the main study period,

the signs decreased in frequency with repeated dosing. No treatment-related clinical signs were observed in the recovery groups

- A slightly higher incidence of foamy histiocytes in the lung was observed at the HD in males and females

- No drug-related microscopic findings in the nasal cavity or nasopharynx were seen

Study no.: WFEN/P34/05
Volume #, and page #: 4.2.3.2
Conducting laboratory and location: (b) (4)

Date of study initiation: April 19, 2005
GLP compliance: Yes
QA report: yes (X) no ( )
Drug, lot #, and % purity: fentanyl citrate nasal spray 6.28 mg/mL (clinical formulation; batch WFEN/010/F); 95.5% and placebo (clinical formulation without the fentanyl citrate; batch WFEN/009F)

Methods

Doses: control, placebo, 0.08, 0.16, 0.26 mg/kg/day; doses were divided into two intranasal administrations per day

Species/strain: Rat/Han Wistar Crl:WI (GLX/BRL/Han) IGS BR

Number/sex/group or time point (main study): 10/sex/dose

Route, formulation, volume, and infusion rate: intranasal instillation with a syringe pump, 6.28 mg/mL fentanyl citrate (equivalent to 4 mg/mL fentanyl base); Refer to Table 1 for details of the formulation.

Satellite groups used for toxicokinetics or recovery: 28-day recovery: 5/sex for the control, placebo and high dose groups; TK: 3/sex for control and placebo groups and 6/sex/treatment group

Weight: males: mean 213.6 g; females: mean 158.6 g

Age: 28-35 days old

Sampling times: Blood samples for toxicokinetic analysis were obtained from all animals at approximately 0.1, 0.5, 1.0, 3.0, 6.0 and 24 hours after the first dose on days 1, 45 and 89.

Methods and Results

Mortality: There were three unscheduled deaths in this study. Three males from the HD showed clinical signs including tremor, prostration, coldness to the touch, hunched posture, labored breathing, lethargy, blue coloration, and liquid feces. One of animal was found dead (week 2) and the other two were euthanized (weeks 4 and 5). Gastrointestinal inflammation/lesions were observed in these animals and thought to be treatment-related because such findings were not seen in the control, placebo LD or MD groups.

Clinical signs: Individual clinical observations were performed one hour post-dosing. Weekly physical examinations were conducted on animals in the main study and recovery groups. Treatment-related clinical signs included lethargy, exophthalmos (protruding of the eyes), hyperactivity, chewing of bedding and fast heart rate. With the exception of exophthalmos and chewing of the bedding which were seen until the end of the main study period, the signs decreased in frequency with repeated dosing. None of the signs were observed during the recovery phase.

Body weights: Individual body weights were recorded on the day before the initiation of dosing and twice weekly during the main study and recovery period and at terminal kill. Males at the HD showed reductions in body weight gain as compared to controls in the first four weeks of the study after which body weight gains were comparable to controls. No effects on body weight gains were seen for females during the study.

Food consumption: The amount of food consumed by each animal was determined weekly. No test article-related changes in food consumption were observed in the study.

Ophthalmoscopy: Ophthalmoscopic investigations were performed on main study animals from the control, placebo and HD groups. Examinations were conducted pre-treatment and in week 13. No test article-related changes in ophthalmoscopic parameters were noted.

Hematology: Blood samples for evaluation of hematologic parameters were obtained from half of the animals (the other half were sampled for clinical chemistry) prior to dosing on day 2 and during week 13. Samples were also taken from the recovery group animals. No toxicologically relevant changes in hematologic parameters were seen.

Clinical chemistry: Blood samples for clinical chemistry analysis were obtained from half of the animals (the other half were sampled for hematology) prior to dosing on day two and during week 13. Samples were also taken from the recovery group animals. On day 2, very slight increases in AST were seen in males at the HD and females at the MD and HD. All increases were < 0.5 fold and were not seen at week 13. No increases in ALT or changes in liver weights/histopathology were observed. No other toxicologically relevant changes in clinical chemistry parameters were seen.

Urinalysis: Urine samples were collected from all groups including recovery groups during week 12 by housing the animals overnight in metabolism cages. No test article-related changes in urinalysis parameters were seen.

Gross pathology: Animals were euthanized by intravenous overdose of sodium pentobarbitone followed by exsanguination. A full macroscopic examination was performed and all lesions were recorded. No toxicologically relevant macroscopic findings were seen.

Organ weights (see histopathology table): No toxicologically relevant changes in organ weights were seen

Histopathology: Adequate Battery: yes (X), no ( )—explain
Peer review: yes (X), no ( )
The battery of organs sampled for histopathologic analysis is detailed in the histopathology table. Tissues were examined from Control and HD animals with the exception of the nasal cavities, nasopharynx and lungs which were examined in all groups. The nasal cavities were sampled at four levels which are detailed below.

Level A (anterior turbinate) - taken between posterior side of front incisors and 2 to 4 mm in front of anterior edge of first palatine fold
Level B (anterior) - immediately behind level A to approx 1 mm behind the edge of the first palatine fold
Level C (posterior turbinate) – between first and second palatine fold
Level D (posterior) - between posterior edge of second palatine fold and anterior edge of third palatine fold

A slightly higher incidence of foamy histiocytes was observed at the HD in males and females as compared to controls. No other toxicologically relevant changes in histopathology were seen. No drug-related microscopic findings in the nasal cavity, nasopharynx were seen.

Lung
Foamy histocytes and inflammatory cell foci were observed in the lung of all animals including control and placebo in both the terminal kill and recovery groups (Table 7). A slightly higher incidence of foamy histiocytes was observed at the HD in males and females. Levels at the HD in males were similar to placebo.

Nasal cavities
Goblet cell hypertrophy/hyperplasia in the nasal cavity was observed all groups including placebo and control in both the terminal kill and recovery groups (Table 7). A slightly higher incidence was observed at the LD, MD and HD females but levels were similar to placebo.

Table 7. Rat 3-Month Study: Microscopic Lesions in Males and Females (WFEN/P34/05)

organ	*microscopic finding*	*Control 1*	*Placebo*	*0.08 mcg*	*0.16 mcg*	*0.26 mcg*
Lung	*foamy histiocytes*	M: 2/10; R: 2/5 F: 4/10; R: 1/5	M: 4/9; R: 3/5 F: 3/10; R: 2/5	M: 4/10 F: 4/10	M: 2/10; R: 1/5 F: 4/10; R: 3/5	M: 4/9; R: 2/3 F: 6/10; R: 2/5
	inflammatory cell foci	M: 2/10; R: 4/5 F: 3/10; R: 1/5	M: 4/10; R: 2/5 F: 3/10; R: 1/5	M: 3/10 F: 1/10	M: 3/10; R: 2/5 F: 2/10; R: 0/5	M: 3/9; R: 0/3 F: 1/10; R: 1/5
Nasal Cavity	*goblet cell hypertrophy/ hyperplasia*	M: 9/10; R: 2/5 F: 5/10; R: 1/5	M: 7/10; R: 2/5 F: 7/10; R: 3/5	M: 4/10 F: 8/10	M: 8/10; R: 2/5 F: 9/10; R: 2/5	M: 9/9; R: 2/3 F: 9/10; R: 1/5

R= 28-day recovery group

Toxicokinetics: Blood samples for toxicokinetic analysis were obtained from all animals at approximately 0.1, 0.5, 1.0, 3.0, 6.0 and 24 hours after the first dose on days 1, 45 and 89. C_{max} and $AUC_{0.167-24h}$ increased with greater-than-dose-proportionality with larger differences seen in females. C_{max} and AUC values were higher on day 1 than on days 45 and 89. AUC values were typically higher in females at the higher doses. T_{max} values ranged between 0.167 and 1 h and were generally similar for males and females. Refer to Table 8 for a summary of the toxicokinetic data.

Table 8. Toxicokinetic analysis of fentanyl in the rat (study WFEN/P34/05; reproduced from NDA)

Dose Group	Dose (mg/kg/dose)	Day	C_{max} (ng/mL)		$AUC_{(0.167-24h)}$ (ng.h/mL)		T_{max} (hour)	
			Male	Female	Male	Female	Male	Female
3	0.08	1	3.08	2.70	4.54	5.31	0.5	0.5
		45	1.15	1.01	4.01	3.22	0.5	0.5
		89	0.91	1.01	4.07	3.58	0.5	0.5
4	0.16	1	3.45	5.85	9.08	17.33	0.5	0.5
		45	2.14	2.83	6.22	10.25	0.167	0.5
		89	3.01	4.24	15.02	13.73	0.5	0.5
5	0.26	1	8.45	17.01	27.33	41.37	1	1
		45	4.83	5.09	11.05	14.27	0.5	0.167
		89	4.50	6.69	12.82	25.99	0.5	0.5

Conclusions

Several treatment-related clinical signs including lethargy, exophthalmos, hyperactivity, chewing of bedding and fast heart rate were noted during the study. With the exception of exophthalmos and chewing of the bedding which were seen until the end of the main study period, the signs decreased in frequency with repeated dosing. No treatment-related clinical signs were noted in the recovery groups. The clinical signs are attributed to the pharmacologic effects of fentanyl in the rat. A slightly higher incidence of foamy histiocytes in the lung was observed at the HD in males and females. Goblet cell hypertrophy/hyperplasia in the nasal cavity was observed all groups including placebo and control and most likely represents a local reaction to the presence of a high volume of liquid in the nasal cavity and not a toxicologic effect of the test article. No other microscopic findings were noted and no drug-related microscopic findings in the nasal cavity or nasopharynx were seen. No other microscopic or other toxicologically relevant findings were noted.

This study adequately assessed the toxicity of the test article. The local toxicity of the test article was conducted via a thorough evaluation of four levels of the nasal cavity as well as the nasopharynx and lung in all groups. The study is deemed a valid assessment of the toxicity including local toxicity of this fentanyl product. No outstanding nonclinical toxicities were seen that would preclude approval of this product.

Goblet cells secrete mucous as a normal response to aid in removing foreign particles from the nasal cavity. Rats, as obligate nose breathers, are more susceptible to respiratory pathogens than other species such as dogs and humans (Briggs GB and Oehme FW, 1980).

Histopathology inventory

Histopathology Inventory			
Study: 3-month intranasal toxicology study (WFEN/P34/05)			
Species: rat			
Adipose tissue		Nares	X
Adrenals	X*	Optic nerves	X
Aorta	X	Ovaries, oviducts	X*
Bone marrow smear	X	Pancreas	X
Bone (femur)	X	Parathyroid	X
Brain	X*	Peripheral nerve	
Cecum	X	Peyer's Patch	
Colon	X	Pharynx	
Duodenum	X	Pituitary	X*
Epididymis	X*	posterior pharyngeal wall	X
Esophagus	X	Prostate	X*
Eye	X	Rectum	X
Fallopian tube		Salivary glands (submax.)	X
Gall bladder	X	Sciatic nerve	X
Gross lesions	X	Seminal vesicles	X
Harderian gland	X	Skeletal muscle	X
Heart	X*	Skin (hind limb)	X
Ileum	X	Spinal cord (C,L,T)	X
Injection site		Spleen	X*
Jejunum	X	Sternum	X
Kidneys	X*	Stomach	X
Joint (tibiofemoral)		Testes	X*
Lachrymal gland	X	Thymus	X*
Larynx incl. epiglottis	X	Thyroid	X*
Liver	X*	Tongue	X
Lungs with mainstem bronchi	X	Trachea and trachea bifurcation	X
Lymph nodes, bronchial	X	Urinary bladder	X
Lymph nodes, mandibular	X	Uterus incl. cervix	X
Lymph nodes, mesenteric	X	Ureters	X
Mammary gland	X	Vagina	X
Nasal cavity/nasopharynx	X	Zymbal gland	X

X, histopathology performed
*, organ weight obtained

Study title: Six Month Repeated Dose Intranasal Chronic Toxicity Study in the Rat with 28-Day Recovery Phase

Key study findings:

- Exophthalmos (protruding of the eyes), ploughing (pushing the snout along the cage bottom) and excitability were observed post-dosing in all treatment groups

- Minor decreases in hemoglobin, red blood cells and hematocrit were seen in both sexes and all treatment groups at week 13 but were not present at the terminal kill or in recovery groups.

- A higher incidence of groups of alveolar macrophages in the lung was seen for both sexes in the placebo as well as the three treatment groups.

- Goblet cell hypertrophy/hyperplasia was observed in the first level of the nasal cavity in males (placebo, LD, MD, HD) and in the first level and second level in females at the HD. Levels in the recovery groups were similar to control.

Study no.: WFEN/P37/05
Volume #, and page #: 4.2.3.2
Conducting laboratory and location: (b) (4)
Date of study initiation: November 7, 2005
GLP compliance: Yes
QA report: yes (X) no ( )
Drug, lot #, and % purity: fentanyl citrate nasal spray 6.28 mg/mL (clinical formulation; batch WFEN/016/F); 95.5% and placebo (clinical formulation without the fentanyl citrate; batch WFEN/017F)

Methods

Doses: control, placebo, 0.16, 0.32, 0.48 mg/kg/day with a four-day build up period of 0.16 mg/kg/day for treatment groups prior to start of dosing; doses were divided into two intranasal administrations per day in both build up and main study phases

Species/strain: Rat/Han Wistar Crl:WI (GLX/BRL/Han) IGS BR

Number/sex/group or time point (main study): 20/sex/dose

Route, formulation, volume, and infusion rate: intranasal instillation with a syringe pump, 6.28 mg/mL fentanyl citrate (equivalent to 4 mg/mL fentanyl base); Refer to Table 1 for details of the formulation.

Satellite groups used for toxicokinetics or recovery: 28-day recovery: 5/sex for the control, placebo and high dose groups; TK: 3/sex for control and placebo groups and 6/sex/treatment group

Weight: males: 215-278 g; females: 154-216 g

Sampling times: Blood samples for toxicokinetic analysis were obtained from all animals at approximately 0.5, 1.5 and 24 hours after the first dose on days 1, 85 and 181.

Unique study design or methodology (if any): A four-day build up phase using a lower dose was employed since fentanyl is a very potent opioid.

Methods and Results

Mortality: There were six unscheduled deaths in this study. Three males from the HD (0.64 mg/kg) died on day 1 and the HD was subsequently reduced to 0.48 mg/kg for the remainder of the study. Two males and one female at the MD died or were euthanized on study days 25, 63, or 182, respectively. The applicant states that sufficient evidence for renal and liver or bladder pathology was noted and most likely contributed to the deaths of these animals. The deaths may be treatment-related although no pathologies relating to liver, kidney or bladder were observed in the study at any dose.

Clinical signs: Individual clinical observations were performed immediately prior to dosing and one hour post-dosing. Weekly physical examinations were conducted on animals in the main study and recovery groups. Exophthalmos (protruding of the eyes) and excitability were noted post-dosing in all treatment groups in a dose-dependent manner. Ploughing (pushing the snout along the cage bottom) was also observed in the treated groups. The applicant hypothesizes that this behavior may be due to palatability of the test article since it was typically observed post-dosing. Generalized hair loss and staining of the fur was sporadically observed in all groups.

Body weights: Individual body weights were recorded weekly during the main study and recovery period and at terminal kill. No test article-related changes in body weight were observed in the study.

Food consumption: The amount of food consumed by each animal was determined weekly. No test article-related changes in food consumption were observed in the study.

Ophthalmoscopy: Ophthalmoscopic investigations were performed on ten males and females from the control, placebo and HD groups. Examinations were conducted pre-treatment and in weeks 13 and 25. No test article-related changes in ophthalmoscopic parameters were noted.

Hematology: Blood samples for evaluation of hematologic parameters were obtained from ten males and females from each group during week 13 and at the end of the treatment period (week 26). Samples were also taken from the recovery group animals. At week 13, both sexes in all treatment groups showed small but significant reductions in hemoglobin, red blood cells and hematocrit. No changes were seen at week 26 or in the recovery groups. No other toxicologically relevant changes in hematologic parameters were seen.

Clinical chemistry: Blood samples for clinical chemistry analysis were obtained from ten males and females from each group during week 13 and at the end of the treatment period (week 26). Samples were also taken from the recovery group animals. No toxicologically relevant changes in clinical chemistry parameters were seen.

Urinalysis: Urine samples were collected from all groups including recovery groups during week 13 and week 25 by housing the animals overnight in metabolism cages. No test article-related changes in urinalysis parameters were seen.

Gross pathology: Animals were euthanized by intravenous overdose of sodium pentobarbitone followed by exsanguination. A full macroscopic examination was performed and all lesions were recorded. No toxicologically relevant macroscopic findings were seen.

Organ weights (see histopathology table): Females at the HD showed a statistically significant increase in absolute and relative ovary weights in comparison to both placebo and control. The change was not present in the recovery group. No histopathological changes in the ovary were noted. No other test article-related changes in organ weights were seen.

Histopathology: Adequate Battery: yes (X), no ( )—explain
Peer review: yes (X), no ( )
The battery of organs sampled for histopathologic analysis is detailed in the histopathology table. In addition, the nasal cavity was sampled at four levels. The levels are described below.

First Level (anterior turbinate): between posterior side of front incisors and 2 to 4 mm in front of the anterior edge of the palantine fold
Second Level (anterior): immediately behind first level to ~1 mm behind the edge of the palantine fold
Third Level (posterior turbinate): between the first and second palatine folds
Fourth Level (posterior): between the posterior edge of the second palantine fold and the anterior edge of the third palantine fold

Lung
A higher incidence of groups of alveolar macrophages was seen for both sexes in the placebo as well as the three treatment groups. Severity was increased at the MD and HD (Table 9). There applicant states that were no significant inflammatory or other changes in either the airways or the lung parenchyma.

Nasal cavities
Goblet cell hypertrophy/hyperplasia was observed in the first level of the nasal cavity in males (placebo, LD, MD, HD) and in females at the HD with increasing severity at the HD in both sexes. In the control recovery groups, 2/5 animals showed minimal goblet cell hypertrophy/hyperplasia. Recovery groups at the HD were similar to control. In the second level of the nasal cavity, increased incidence was seen in females at the HD only and the observation was reversible (Table 9). The severity in all cases was minimal to slight. No other toxicologically relevant changes in histopathology were noted.

Table 9.	*Rat 6-Month Study: Microscopic Lesions in Males and Females (WFEN/P37/05)*						
organ	***microscopic finding***	***gender***	***Control 1***	***Placebo***	***0.16 mcg***	***0.32 mcg***	***0.48 mcg***
Lung	***groups of alveolar macrophages***	***male***	1/20 min 1/20 slight; R: 1/5 min	5/20 min; R: 1/5 min	3/20 min	8/18 min 2/18 slight	8/18 min 2/18 slight; R: 1/4 min
		female	11/20 min; R: 1/5	10/20 min; R: 1/5 min	13/20 min	11/20 min 1/20 slight	12/20 min 3/20 slight; R: 2/5 min 1/5 slight
Nasal Cavity	***goblet cell hypertrophy/ hyperplasia first level***	***male***	1/20 min; R: 2/5 min	4/20 min; R: 1/5 min	2/20 min 1/20 slight	3/18 min	1/18 min; R: 1/4 min 1/4 slight
		female	0/20 min; R: 2/5 min	1/20 min; R: 0/5	2/20 min	0/20	5/20 min 4/20 slight; R: 0/5
	second level	***female***	0/20; R: 0/5	1/20 min; R: 0/5	2/20 min	0/19	11/20 min; R: 0/5

R= 28-day recovery group

Toxicokinetics: Blood samples for toxicokinetic analysis were obtained from all animals at approximately 0.5, 1.5 and 24 hours after the first dose on day 1 and in weeks 85 and 181.

Generally C_{max} and $AUC_{0.5\text{-}24h}$ were variable at all doses and time points and both greater than- and less than- dose proportionality was seen in males and females. Several anomalous values were also observed in the study (i.e. extremely high AUC values of 42.27 and 147.12 for LD males at week 13 and HD females at week 13, respectively). T_{max} values ranged between 0.5 and 1 h and were generally similar for males and females. One T_{max} value of 24 h was seen at week 13 for females at the HD. Although the toxicokinetics in this study were not optimal, systemic exposure was demonstrated in all treatment conditions and no fentanyl was seen in either the control or placebo groups. Refer to Table 10 for a summary of the toxicokinetic data.

Table 10. Toxicokinetic analysis of fentanyl in the rat (study WFEN/P37/05; table reproduced from NDA)

Dose Group (mg/kg/day)	Sampling time:	Males			Females		
		Day 1	Wk 13	Wk 26	Day 1	Wk 13	Wk 26
0.16	Cmax (ng/ml)	0.87	3.46	0.80	0.75	0.79	1.09
	tmax	0.5 h	5 h	0.5 h	0.5 h	5 h	0.5 h
	AUC (ng.h/ml)	6.61	42.27	6.26	4.10	11.70	5.33
	AUC (norm)	41.29	264.16	39.13	25.62	73.11	33.31
0.32	Cmax (ng/ml)	2.01	1.88	1.39	3.14	2.07	2.76
	tmax	1 h	0.5 h	1 h	1 h	1 h	0.5 h
	AUC (ng.h/ml)	7.34	9.06	7.43	11.31	10.19	8.73
	AUC (norm)	45.88	28.31	23.23	70.69	31.85	27.28
(0.64 -Day 1 only) 0.48	Cmax (ng/ml)	7.62	2.72	2.24	3.72	13.3	2.52
	tmax	0.5 h	0.5 h	0.5 h	1 h	24 h	0.5 h
	AUC (ng.h/ml)	20.80	11.14	8.91	16.76	147.12	11.85
	AUC (norm)	32.50	23.20	18.56	26.19	306.49	24.69

Key:

AUC (0.5-24 h) Area under the plasma concentration-time curve at 0.5, 1, 5 and 24 hours post the first dose on Day 1 Week 13 and Week 26.

$\mathbf{C_{max}}$ Maximum observed plasma concentration on Day 1, Week 13 and Week 26

$\mathbf{t_{max}}$ Time of maximum observed plasma concentration on Day 1, Week 13 and Week 26

AUC (0.5-24 h) (norm) = AUC [ng.h/ml] / dose [mg/kg/day]

Conclusions

Several treatment-related clinical signs were noted during the study. Exophthalmos (protruding of the eyes) and excitability were observed post-dosing in all treatment groups in a dose-dependent manner. These are known pharmacologic effects of a mu opioid in rat. Ploughing (pushing the snout along the cage bottom) was also observed in the treated groups. The applicant hypothesizes that this behavior may be due to palatability of the test article since it was typically observed post-dosing. However, the described ploughing behavior may be analogous to the burrowing behavior of rodents in bedding. Burrowing behavior is a typical stress response in rodents akin to creating a refuge from predators. Minor decreases in hemoglobin, red blood cells and hematocrit were seen at in both sexes and all treatment groups at week 13 were not present at the terminal kill or in recovery groups. Alveolar macrophages in the lung (minimal to slight severity) were seen for both sexes in all groups including control but with a higher incidence in the placebo and treatment groups. Levels in the recovery groups were similar to controls. No inflammatory or other changes in either the airways or the lung parenchyma were observed. Slight to minimal goblet cell hypertrophy/hyperplasia was observed in the first level of the nasal cavity in males (placebo, LD, MD, HD) and in the first level and second level in females at the HD. Levels in the recovery groups were similar to control.

This study adequately assessed the toxicity of the test article. The local toxicity of the test article was conducted via a thorough evaluation of four levels of the nasal cavity as

well as the nasopharynx and lung in all groups. The study is deemed a valid assessment of the toxicity including local toxicity of this fentanyl product. No outstanding nonclinical toxicities were seen that would preclude approval of this product.

Histopathology inventory

Histopathology Inventory			
Study: 6-month intranasal toxicology study (WFEN/P37/05)			
Species: rat			
Adipose tissue		Nasopharyngeal duct	X
Adrenals	X*	Optic nerves	X
Aorta	X	Ovaries, oviducts	X*
Bone marrow smear	X	Pancreas	X
Bone (femur)	X	Parathyroid	X
Brain	X*	Peripheral nerve	
Cecum	X	Peyer's Patch	
Colon	X	Pharynx	
Duodenum	X	Pituitary	X*
Epididymis	X*	posterior pharyngeal wall	X
Esophagus	X	Prostate	X*
Eye	X	Rectum	X
Fallopian tube		Salivary glands (submax.)	X
Gall bladder	X	Sciatic nerve	X
Gross lesions	X	Seminal vesicles	**X**
Harderian gland		Skeletal muscle	X
Heart	X*	Skin (hind limb)	X
Ileum	X	Spinal cord (cervical)	X
Injection site		Spleen	X*
Jejunum	X	Sternum	X
Kidneys	X*	Stomach	X
Joint (tibiofemoral)		Testes	X*
Lachrymal gland	X	Thymus	X
Larynx incl. epiglottis	X	Thyroid	X
Liver	X*	Tongue	X
Lungs with bronchi	X	Trachea and trachea bifurcation	X
Lymph nodes, bronchial		Urinary bladder	X
Lymph nodes, cervical	X	Uterus incl. cervix	X
Lymph nodes, mesenteric	X	Ureters	X
Mammary gland	X	Vagina	X
Nasal cavity/nasopharynx	X		

X, histopathology performed
*, organ weight obtained

2.6.6.4 Genetic toxicology

Genetic toxicology studies were not conducted.

2.6.6.5 Carcinogenicity
Carcinogenicity studies were not conducted.

2.6.6.6 Reproductive and developmental toxicology
Reproductive and developmental toxicology studies were not conducted.

2.6.6.7 Local tolerance
Local tolerance studies were not conducted.

2.6.6.8 Special toxicology studies
Special toxicology studies were not conducted.

2.6.6.9 Discussion and Conclusions
The applicant conducted 3-month and 6-month toxicology studies in the rat and a 9-month toxicology study in the dog with the clinical formulation of PecFent via intranasal administration. All three studies adequately assessed the toxicologic potential of the PecFent formulation and included thorough evaluations of the local tissues including the nasal cavity, nasopharynx and lung.

Central nervous system-related clinical signs were observed in all studies and usually decreased with subsequent dosing. The observations are consistent with the pharmacology of fentanyl and do not pose any toxicologic concern.

No toxicologically relevant findings were identified in the 9-month dog study. In the 3-month rat study, a slightly higher incidence of foamy histiocytes was observed at the HD in both sexes as compared to controls. No other toxicologically relevant changes in histopathology were seen. No drug-related microscopic findings in the nasal cavity or nasopharynx were seen. In the 6-month rat study a higher incidence of groups of alveolar macrophages was seen for both sexes in the placebo as well as the three treatment groups. Severity, although slight, was increased at the MD and HD. No significant inflammatory or other changes in either the airways or the lung parenchyma were noted. Goblet cell hypertrophy/hyperplasia in the nasal cavity was observed at varying incidences and severities in all groups including control and placebo in the terminal kill and recovery groups of both the 3-month and 6-month rat studies. In the 6-month study goblet cell hypertrophy/hyperplasia increased in incidence and severity at the higher doses. In all cases the severity was minimal to slight.

Rats, as obligate nose breathers, are more susceptible to respiratory pathogens than other species such as dogs and humans (REF Briggs). Alveolar macrophages in the lung function to remove foreign particles. Goblet cells serve a similar role in the nasal cavity and secrete mucous as a normal response to trap and clear foreign particles. The histopathologic findings in the lung and nasal cavity in the rat most likely reflect an adaptive response to the intranasal solution. Findings were observed in all groups including control and placebo. No observations indicative of a respiratory toxicant including loss of cilia, epithelial erosion or degeneration/ulceration or necrosis of the nasal epithelium were observed. Taken together with the lack of histopathologic changes in the local tissues in

the 9-month dog study, the observations most likely reflect an adaptive response to the intranasal route of administration specific to the rat and not toxicity due to the test article.

The findings in these studies were either known pharmacologic effects of fentanyl or of low severity and toxicologic significance. Administration of fentanyl by the intranasal route in the dog and rat does not present any unique toxicities. No outstanding nonclinical toxicities were seen that would preclude approval of this product.

2.6.6.10 Tables and Figures

2.6.7 TOXICOLOGY TABULATED SUMMARY

OVERALL CONCLUSIONS AND RECOMMENDATIONS

Conclusions: The results of the submitted pharmacology and toxicology studies with fentanyl and the PecFent formulation were consistent with effects of a mu opioid agonist and no novel findings were seen. The excipients used in the PecFent formulation have all been previously approved or adequately qualified and do not pose any toxicologic concerns. With the exception of the levels of (b) (4), The impurities/degradants are controlled at acceptable levels in both the drug substance and drug product.

Unresolved toxicology issues (if any): The specifications in the drug substance and drug product for (b) (4) are not acceptable. In order to qualify the potentially genotoxic impurity (b) (4), we recommend that the applicant conduct the minimal genotoxic screen which consists of two *in vitro* genetic toxicology studies, e.g., one point mutation assay and one chromosome aberration assay, with the isolated impurity, tested up to the limit dose for the assay. These concerns were noted in the 74-day letter and are being addressed by the Sponsor; however, the results of the genetic toxicology studies have not been submitted to the NDA as of the date of this review.

Recommendations: This NDA may not be approved from a nonclinical pharmacology/toxicology perspective.

Suggested labeling: See executive summary.

Signatures (optional):

Reviewer Signature _Elizabeth A. Bolan, PhD_____

Supervisor Signature_____ Concurrence Yes ___ No ___

APPENDIX/ATTACHMENTS

Reference List

Briggs GB, Oehme FW (1980) Toxicology. In: The Laboratory Rat pp 103-118.

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

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

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22569	ORIG-1	ARCHIMEDES DEVELOPMENT LTD	(b) (4) (fentanyl nasal spray)

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/s/

ELIZABETH BOLAN
04/09/2010

RICHARD D MELLON
04/09/2010
I concur.

PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR NDA/BLA or Supplement

NDA/BLA Number: 22-569 **Applicant: Archimedes** **Stamp Date: 8/31/09**

Drug Name: PecFent **NDA/BLA Type: 505(b)(2)**

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)?	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 submitted a rationale to justify the alternative route?	X		
7	Has the applicant submitted a statement(s) that all of the pivotal pharm/tox studies have been performed in accordance with the GLP regulations (21 CFR 58) or 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/m2 or comparative serum/plasma levels) and in accordance with 201.57?	X		
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?			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.

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

Comments for the 74-day letter:

Your proposed drug product specification for (b) (4) may be inadequate. We note that your justification for the proposed levels of (b) (4) includes a structure-activity assessment which did not reveal the presence of structural alerts for genotoxicity, mutagenicity or carcinogenicity. In contrast, a computational toxicology assessment (b) (4) (b) (4) conducted internally suggests that (b) (4) may be clastogenic. Provide further justification to support your conclusion that (b) (4) is not potentially genotoxic or carcinogenic. In the absence of adequate justification, (b) (4) must be regulated to a level of NMT (b) (4) in the drug substance and drug product.

We recognize that there are literature reports suggesting that (b) (4) may be a (b) (4) metabolite. Significant metabolites are generally deemed adequately qualified for safety. Include in the justification mentioned above a quantitative assessment of (b) (4) metabolite at the maximum daily dose of fentanyl for your product. This assessment may include a literature review and copies of referenced citations. The presence of (b) (4) metabolite at significant levels could render the need for qualification unnecessary.

Please be advised that as a 505(b)(2) submission, which relies on the Agency's previous findings of safety and efficacy, we can not legally use information contained within a Summary Basis of Approval to support your application unless you have right of reference to the underlying data.

PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR NDA/BLA or Supplement

Elizabeth A. Bolan, Ph.D.	10/27/09
Reviewing Pharmacologist	Date
R. Daniel Mellon, Ph.D.	10/29/09
Team Leader/Supervisor	Date

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/s/

ELIZABETH BOLAN
10/28/2009

RICHARD D MELLON
10/29/2009
I concur.