CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-947

CHEMISTRY REVIEW(S)

CMC Memorandum

Date: 28-June-2006
From: Jila H. Boal, Ph.D., Review Chemist, Branch V (Pre-marketing), ONDQA
To: NDA 21-947, ***FENTORA*** (Fentanyl Buccal Tablets)
Each tablet contains fentanyl citrate equivalent to fentanyl free base: 100, 200, 400, 600, or 800 mcg
Through: Ravi S. Harapanhalli, Ph.D., Branch Chief, Branch V (Pre-marketing), ONDQA

Subject: **Review of the following submissions:**
1. Editorial Corrections to CMC Review # 1, dated May 23, 2006.
2. Proposed Established Name.
3. Proposed Changes in the Color of Tablets.
4. Container and Carton Labels.

Background Information:

1. Editorial Corrections to CMC Review # 1:

- Page 7, Please note the typo error on consult to Pharm/Tox dated September 20, 2005. Impurity specifications were consulted with Dr. Dan Mellon, Pharm/Tox Team leader on June 20, 2006 and it was determined that the level of all of the specified identified impurities in the drug substance should be based on the ICH Q3 A recommendations. This includes reduction in the level of the specified identified impurity —— , i.e., the impurity to be reduced to NMT —— vs the currently proposed NMT —— The correction in the consult is incorporated into the final version of the table.

- Page 7, Please note that there is no alcohol dose dumping studies for these tablets in the NDA and it is not required either. Therefore, the comment on validation of the in-vitro method of dose dumping studies by the FDA labs is mute. A more accurate account on whether the analytical methods need validation by the FDA labs can be found in the table below.

- Methods Validation: The HPLC method for determination of related substances in fentanyl citrate tablets (100 and 200 mcg fentanyl base) indicates ——

The final edited table.

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	24 months expiration	May 30, 2006 and	Roswitha E, Kelly,

	dating period could be granted.	June 6, 2006	Ph.D.
EES	Overall Recommendation Acceptable	May 26, 2006	Shirnette Ferguson
Pharm/Tox	One impurity in the drug substance, — exceeds ICH Q3A threshold for qualification and has not been tested for potential genetic toxicity. However, — does not contain a structural alert for mutagenicity, has similar pharmacodynamic and toxicologic effects as fentanyl, — and has been present in the fentanyl drug substance used for the Actiq product controlled with a specification of NMT — As such, the specification of NMT — does not raise significant safety concerns; however, the Sponsor should either reduce the specification to NMT — or provide a minimal genetic toxicology screen to confirm safety for the current specification. This can be completed postapproval.	June 22, 2006	L. Steven Leshin, D.V.M., Ph.D. and R. Daniel Mellon, Ph.D.
Biopharm	Not consulted		
LNC	(Fentanyl Buccal Tablets)	May 22, 2006	Dr. Guiragos K, Poochikian, Chair of the LNC
Methods Validation	Under the ONDQA Method Validation Program Procedures		Jila Boal, Ph.D.

	(1/5/2005), the test methods for assay and related impurities qualify for evaluation by FDA method validation laboratory. This is because of the low concentration of the fentanyl citrate (microgram) quantity.		
ODS/DMETs	***FENTORA*** (Fentanyl Buccal Tablet) 100 mcg, 200 mcg, 400 mcg, 600 mg, and 800 mcg.	June 28, 2006	Kristina Arnwine DRUG SAFETY OFFICE REVIEWER
EA	Not applicable. Exclusion from assessment was granted		See the EA section in this review
Microbiology	NA		

2. Proposed Established Name.
   - On June 21, 2006 the division has received through an e-mail the applicant's desire to keep the term effervescent as part of the established name and for the FDA to consider the proposal ***fentanyl orally effervescent tablets***.

   The CMC discipline consulted the proposed established name with Dr. Guiragos K, Poochikian, chair of the LNC. The LNC chair disagreed with using the term ***orally effervescent,*** arguing that these are too specific and would not be acceptable in terms of formulation justification for the future generic brands of these tablets.

   The final conclusion on the established name is,
   FENTORA (Fentanyl Buccal Tablets)
   Each tablet contains fentanyl citrate equivalent to fentanyl base: 100, 200, 400, 600 and 800 mcg.

3. Proposed Changes in the Color of Tablets.
   - The applicant has proposed to change the color of all commercial strengths to white and to submit CMC information. Although the CMC discipline recommended retaining the tablet colors as originally presented, the Clinical division took a position and agreed with the firm to change the colors to all white. Therefore, description of commercial tablets are as follows:

Tablet Strength	**Description**
100 microgram:	White, [redacted] tablet. Debossed with "1"
200 microgram:	White [redacted] tablet. Debossed "2" [redacted]
400 microgram:	White. [redacted] tablet. Debossed

		"4"	
600 microgram:	White, with	"6"	tablet. Debossed
800 microgram:	White, with	"8"	tablet. Debossed

The blister packaging configuration remains the same as the one proposed in the NDA original submission. These are 7 blister cards with 4 tablets in each card, i.e., 28 buccal tablets per carton. Different colors have been decided for the flat side of the blister packaging of each strength. The blister and the carton colors of each strength are matched.

4. Container and Carton Labels.
   The label information on the blister and cartons are deemed accurate.

   The colors will be,

100 microgram:	Blue
200 microgram:	Orange
400 microgram:	Green
600 microgram	Pink
800 microgram	Yellow

DDMAC has reviewed the proposed product labeling (PI), proposed patient labeling (PPI), and proposed carton and container labeling for fentanyl effervescent buccal tablets in a consult request dated August 31, 2005. Their comments were conveyed to the applicant.

The CMC related portion of their comments in conjunction with the final responses received from the applicant are reviewed below.

PI

General

No CMC related comments for PI.

General

1. We recommend referring to DSRCS for their review of this proposed [redacted] for comments on formatting, order of presentation, consistency, and readability.

How should I store TRADE NAME?
1. "Store TRADE NAME at room temperature, 59° to 86° F (15° to 30° C) until ready to use."

We recommend adding the following statements to the above sentence —

This Reviewer's Evaluation and Comments:

- The tradename ***FENTORA*** is approved. See DMETS review of the tradename dated June 28, 2006 in DFS.
- It was concluded that white color for all strengths will be approved in the NDA and the deboosed information as indicated above will distinguish the different strengths, in addition the carton and blister labels of each strength will be in distinguished colors as mentioned on the above table.

The CMC Comments to be Conveyed to the Applicant in the Action Letter:

1. We remind you that you ought to reduce the specification for — impurity in active drug substance from — to NMT — by the end of December 2006 and updated in your first NDA Annual Report.

2. We acknowledge your statement of confirmation that following proposed change in the tablet color to white, the manufacturing process for all strengths will be similar to that of the 200-mcg tablets and you will provide three months of accelerated and long term stability data for at least one lot of each strength within six months from the date of NDA approval.

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

/s/

Jila Boal
6/28/2006 05:19:41 PM
CHEMIST

Ravi Harapanhalli
6/28/2006 05:28:05 PM
CHEMIST

NDA 21-947
Tradename (Fentanyl Buccal Tablets)
Each tablet contains fentanyl citrate equivalent to fentanyl free base :100, 200, 400, 600, or 800 mcg

Jila H. Boal, Ph. D.

Division of Pre-marketing Assessment III and Manufacturing Science, ONDQA

Table of Contents

Chemistry Review Data Sheet

1. NDA # 21-947

2. REVIEW #: 1

3. REVIEW DATE: May 23, 2006

4. REVIEWER: Jila H. Boal, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
IND 65,447 Telecon	November 5, 2002
IND 65,447, Type B, EOP2 Meeting Minutes	December 5, 2003
Information Request, Advice, & General Correspondence Letter	March 3, 2004
Pre-NDA Meeting Minutes	April 6, 2005

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
IND 65,447 Telecon	November 5, 2002
IND 65,447, Type B, EOP2 Meeting Minutes	December 5, 2003
Information Request, Advice, & General Correspondence Letter	March 3, 2004
Pre-NDA Meeting Minutes	April 6, 2005
Office of Drug Safety (ODS) Consult	August 10, 2005
N-0000 (Original Application)	August 31, 2005
N-000 BL	September 09, 2005
N-0000 BC (Stability Update)	January 20, 2006
N-0000 BC (Update on excipients specifications)	March 13, 2006
N-000 BL (Update on Label)	May 11, 2006
N-000 BC (updated stability data for the 100 microgram — tablets)	May 23, 2006
N-000 BC (12 months updated stability data for the site	May 31, 2006

specific registration batches)

7. NAME & ADDRESS OF APPLICANT:

Name: Cephalon Inc. c/o CIMA Labs

41 Moores Road

Frazer, PA 19355

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Pending
b) Non-Proprietary Name (USAN): Fentanyl Citrate Buccal Tablets
c) Code Name/# (ONDC only): None
d) Chem. Type / Submission Priority (ONDC only):
   - Chem. Type: 3 (new dosage form)
   - Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: 505 (b)(2)

10. PHARMACOL. CATEGORY: Management of Breakthrough pain in opioid tolerant patients with cancer.

11. DOSAGE FORM: Buccal tablet.

12. STRENGTH/POTENCY: 100, 200, 400, 600, and 800 microgram.

13. ROUTE OF ADMINISTRATION: Oral transmucosal (buccal)

14. Rx / OTC DISPENSED: _X_ Rx __ OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

_____ SPOTS product – Form Completed

Chemistry Review Data Sheet

____X___ Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Established Name: Fentanyl Citrate

Chemical Name:

- Propanamide, N-phenyl-N-[(1-(2-phenylethyl)-4-piperidinyl]-, 2-hydroxy-1,2,3-Propanetricarboxylate (1:1)

Or,

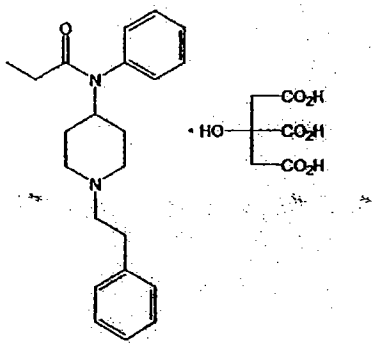
- N-(1-Phenethyl-4-piperidyl) propionanilide citrate (1:1)

CAS REGISTRY NUMBER: 990-73-8

MW:
The molecular weight of the citrate salt is: 528.59.
The molecular weight of the free base is: 336.48.

Molecular Formula: $C_{22}H_{28}N_2O \cdot C_6H_8O_7$

Structure of Fentanyl Citrate:



17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE	STATUS	DATE REVIEW COMPLETED	COMMENT

Chemistry Review Data Sheet

	II	Fentanyl Citrate	3 and 4	Adequate	January 3, 2005 and September 20, 2005	Reviewed by Jila H. Boal, P.h. D. Review # 7. and DMF's last submissions reviewed by Aloka Srinivasan, P.h. D. Review # 8
	III		1	Adequate	June 2, 2006	Reviewed by Jila H. Boal, P.h. D. Review # 1.
	III		3	Adequate	November 2, 2000	Martha R. Heimann, P.h.D.
	III		4	Adequate	June 16, 2006	Jila H. Boal, Ph.D.

[1] Action codes for DMF Table:
1–DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	65,447	OraVescent fentanyl citrate, OTFC
NDA	20 747	Actiq (Oral Transmucosal fentanyl citrate)

18. STATUS:

Chemistry Review Data Sheet

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	24 months expiration dating could be granted.	May 30, 2006 and June 6, 2006	Roswitha E, Kelly, Ph.D.
EES	Overall Recommendation Acceptable	May 26, 2006	Shirnette Ferguson
Pharm/Tox	Impurity specifications acceptable	September 20, 2005	Mamta De
Biopharm	Not consulted		
LNC	Fentanyl citrate buccal tablet	May 22, 2006	Dr. Guiragos K, Poochikian, Chair of the LNC
Methods Validation	Under the ONDQA Method Validation Program Procedures, none of the test methods qualify for evaluation by FDA method validation laboratory. However, since alcohol dose dumping studies showed reversal between in vitro prediction and in vivo dose dumping, the in vitro method will be evaluated at the FDA laboratories.		Jila Boal, Ph.D.
ODS/DMETs	Tradename unacceptable. Additional recommendations on carton and container labels.	April 12, 2006	Kristina Arnwine
EA	Not applicable. Exclusion from assessment was granted		See the EA section in this review
Microbiology	NA		

The Chemistry Review for NDA 21-897

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

All critical quality attributes of the drug substance and the drug product and the critical process parameters of the manufacture of the drug product have been identified and controlled adequately to assure tablet content uniformity and potency. All critical CMC issues identified during the earlier meetings were addressed adequately. An overall "acceptable" recommendation was entered into the EES by the Office of Compliance on May 26, 2006. The NDA is recommended for approval from CMC perspective. An expiration dating period of 24 months may be granted.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

The applicant has proposed to change the color of all commercial strengths to white and to submit CMC information as a phase IV commitment. Approval of this proposal is pending assessment from the medical division and the Division of risk management. From CMC perspective, we do not agree with this proposal and recommend that the tablets be distinguished by both embossed strengths as well as by their colors. If the Division concurs with this approach

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

Drug Product:

OraVescent® fentanyl citrate is a potent opioid analgesic tablet that employs a proprietary fast dissolve drug delivery technology called OraVescent®.

This product is indicated for the management of break through pain in patients who are already receiving and who are tolerant of opioid therapy for their underlying persistent breakthrough cancer pain. The tablet is placed between the cheek and gum. The effervescent reaction causes release of carbon dioxide and facilitates disintegration of the tablet and is hypothesized also to produce a decrease in pH in the microenvironment around the tablet, thus driving the fentanyl into solution. As the effervescent reaction continues and the other

pH modifying substances dissolve, a subsequent rise in pH increases the fraction of the fentanyl dose that is non-ionized and further facilitates its rapid absorption through the buccal mucosa. The effervescence property is suppose to facilitate absorption across the oral mucosa.

Tablets are available in 5 dosage strengths (100 µg, 200 µg, 400 µg, 600 µg and 800 µg expressed as fentanyl free base).

Description of Commercial Fentanyl Effervescent Buccal Tablets

Tablet Strength	Description
100 µg	tablet. Debossed with "1"
200 µg	White, tablet. Debossed with "2"
400 µg	tablet. Debossed with "4"
600 µg	tablet. Debossed with "6"
800 µg	tablet. Debossed with "8"

The excipients of the formulation were selected to [redacted] to ensure consistent manufacturability of the drug product, additional controls on physicochemical properties such as [redacted] excipients mannitol, citric acid, sodium carbonate and sodium bicarbonate were developed and appropriate specifications were established.

Drug Substance:

Fentanyl citrate, USP, is a [redacted] soluble in [redacted] but sparingly soluble in water. Octanol-water partition coefficient at pH 7.4 = 816:1. pKa values for the two tertiary nitrogens are 7.3 and 8.4. Milled fentanyl citrate has a low hygroscopicity.

Fentanyl citrate is supplied [redacted] from [redacted] DMF number [redacted] The DMF has been extensively reviewed in the past by this reviewer. The latest data in the DMF regarding [redacted] was reviewed by Aloka Srinivasan and this reviewer and was deemed acceptable. [redacted]

B. Description of How the Drug Product is Intended to be Used

Physicians should individualize treatment using a progressive plan of pain management. Healthcare professionals should follow appropriate pain management principles of careful assessment and ongoing monitoring (see BOXED WARNING and Dose Titration). Patients should be instructed not to open the blister until ready to administer. Separate one of the blister units from the blister card by tearing apart at the perforations. Bend the blister unit along the line where indicated. Peel the blister backing to expose the tablet. Patients should NOT attempt to push the tablet through the blister because this could damage the tablet. The tablet should not be stored once removed from the blister package as the tablet integrity may be compromised and a risk of accidental exposure to a tablet can occur.

Patients should remove the tablet from the blister unit and immediately place the entire TRADE NAME tablet in the buccal cavity (above a rear molar between the upper cheek and gum). Patients should not attempt to split the tablet.

The TRADE NAME tablet should not be sucked, chewed or swallowed, as this will result in lower plasma concentrations than when taken as directed.

The TRADE NAME tablet should be left between the cheek and gum until disintegrated, which usually takes approximately 14-25 minutes.

After 30 minutes, if remnants from the TRADE NAME tablet remain, they may be swallowed with a glass of water.

Dwell time (defined as the length of time that the tablet takes to fully disintegrate following buccal administration), does not appear to affect early systemic exposure to fentanyl.

Dose Titration

Patients should be titrated to a dose of TRADE NAME that provides adequate analgesia with minimal side effects. The initial dose of TRADE NAME should be 100 mcg. For patients switching from oral transmucosal fentanyl citrate to *TRADE NAME*, the starting dose of *TRADE NAME* should be initiated as shown below:

Current OTFC Dose (mcg)	Initial *TRADE NAME* Dose (mcg)
200	100
400	100
600	—
800	200

1200 400

Re-dosing Patients Within a Single Episode: Dosing may be repeated once during a single episode of breakthrough pain if pain is not adequately relieved by one *TRADE NAME* dose. Re-dosing may occur 30 minutes after the start of administration of *TRADE NAME* and the same dosage strength should be used.

Increasing the Dose: From an initial dose, patients should be closely followed and the dosage strength changed until the patient reaches a dose that provides adequate analgesia with *strike* *and substitute "tolerable"* side effects using a single *TRADE NAME* tablet. Patients should record their use of *TRADE NAME* over several episodes of breakthrough pain and discuss their experience with their physician to determine if a dosage adjustment is warranted. Available dosage strengths of *TRADE NAME* are 100mcg, 200mcg, 400mcg, 600mcg, and 800mcg.

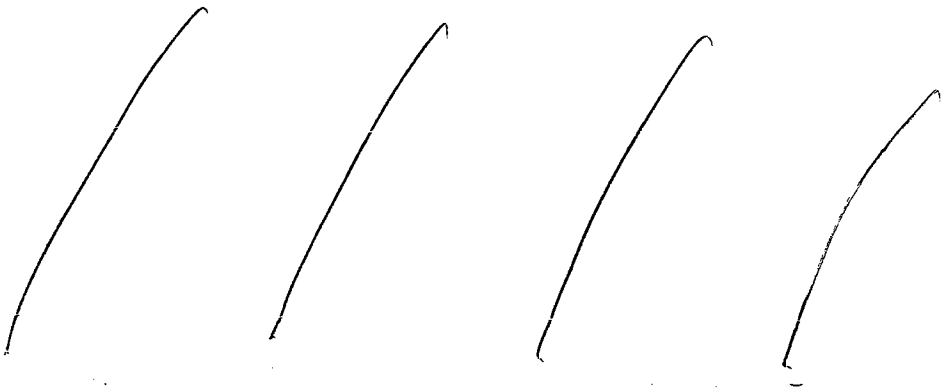
SAFETY AND HANDLING
TRADE NAME is supplied in individually sealed child-resistant blister packages. The amount of fentanyl contained in TRADE NAME can be fatal to a child. Patients and their caregivers must be instructed to keep TRADE NAME out of the reach of children (see BOX WARNING, WARNINGS, PRECAUTIONS, and MEDICATION GUIDE).

Store at 20-25°C (68-77°F) with excursions permitted between 15° and 30°C (59° to 86°F) until ready to use. (See USP Controlled Room Temperature.)

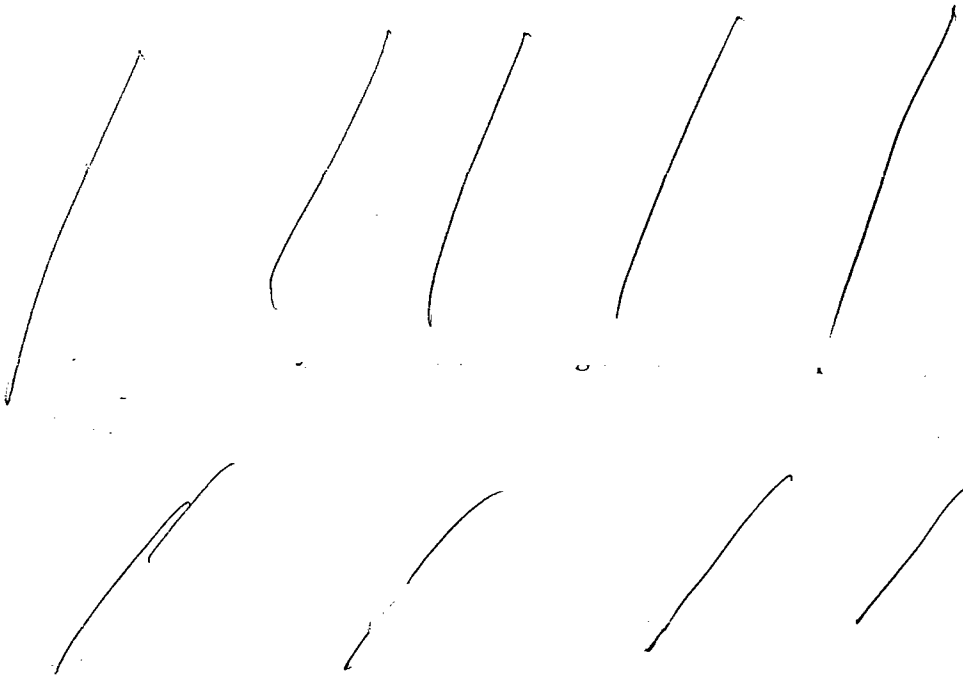
TRADE NAME should be protected from freezing and moisture. Do not use if the blister package has been tampered with.

C. Basis for Approvability or Not-Approval Recommendation

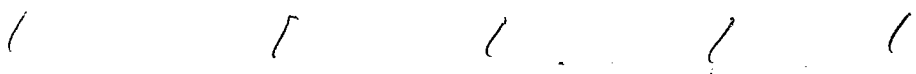
The pharmaceutical development was replete with the information and data on the product and process design and development. Critical quality attributes of the low-dose effervescent formulation were addressed. Compatibility of the drug substance and excipients of the formulation were studied in Adequate justification for the choice of the final excipients of the formulation was provided. The



Physicochemical properties of the tablets that affect the product performance and transmucosal bioavailabilty of the dosage form were discussed in the pharmaceutical development report.



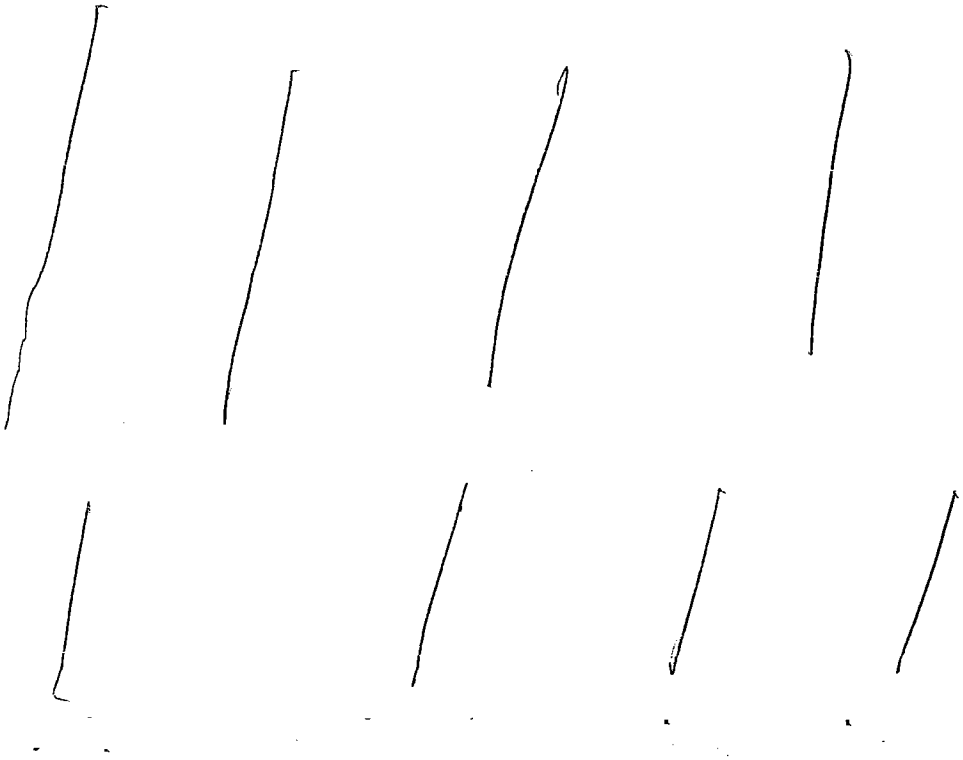
A comparison of dissolution of the drug product at various time points as a function of pH for a representative batch of 800 µg tablet was performed. The dissolution profile data showed rapid dissolution of this product across the entire pH range of 1.0 to 7.5, even at the 3-minute time point. Adequate dissolution specification for this product is Q= —of LC in 10 minutes



Eden Prairie and Salt Lake City were identified as commercial manufacturing sites. The commercial batch size translates to a theoretical yield of for the 1/4 inch tablets and tablets for the 5/16 inch tablets. Fentanyl is a highly potent drug with narrow therapeutic range in a given individual and is formulated at very low % active w/w free base). The manufacturing process consists of

Adequate in-process controls have been established for assuring the tablet content uniformity and potency.

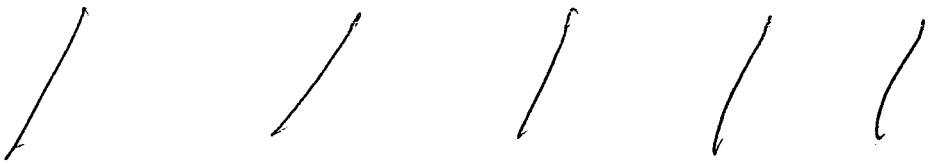
The proposed drug product specification include a second ID tests, a single point dissolution specification, disintegration [NMT n=6) or NMT , drug related degradation products

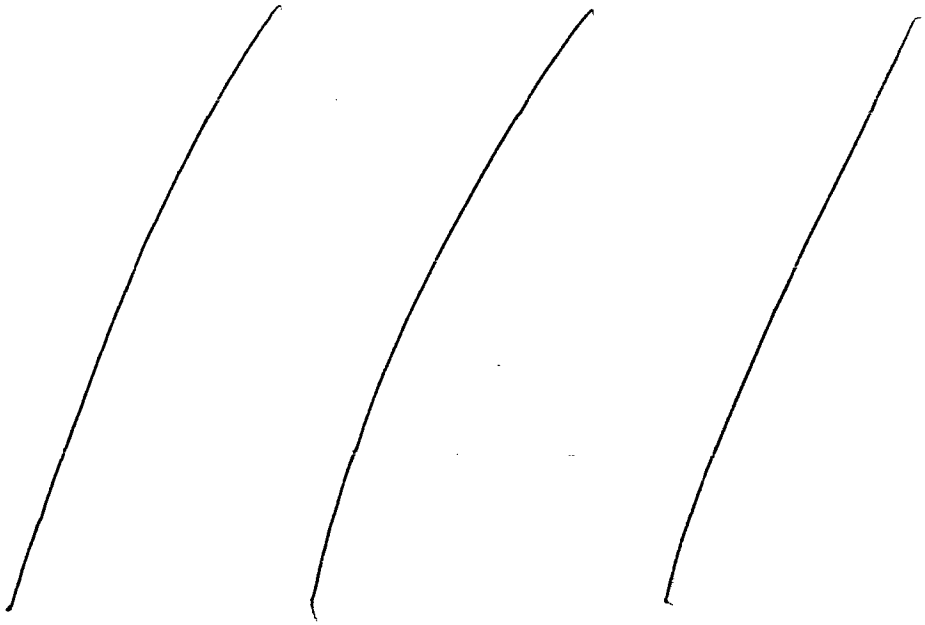


Drug product is packaged in child-resistant (CR), moisture-resistant, foil/foil blister packages. were determined using samples of each foil laminate. testing results demonstrated that the container closure system protects product's performance and that the pH of the tablet does not change over shelf-life stability of the product.

The proposed expiration dating for the drug product is 24 months, whereas long-term stability data are provided for 18 months for registration batches manufactured at at pilot scale. The 12 months of long term stability data for registration batches manufactured at pilot and commercial scale at Eden Prairie and Salt Lake City sites were requested and were provided in an amendment. In consultation with the statistical reviewer, it was concluded that the stability results support extrapolation of the shelf-life to 24 months. Thus a product shelf life of 24 months when packaged in the blisters described in the NDA and stored at 25°C/60%RH may be granted.

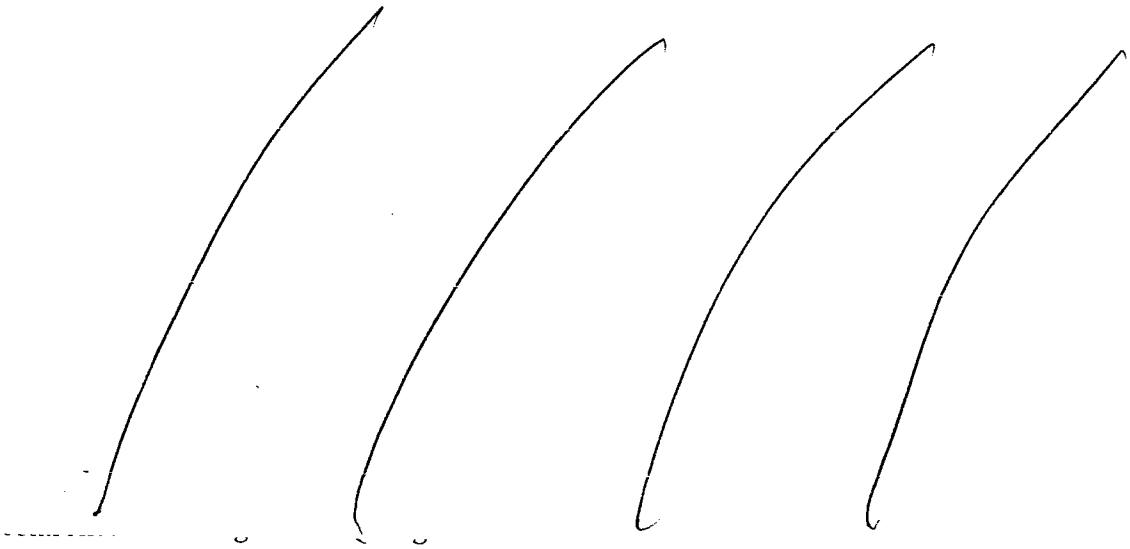
The 100 microgram and the 200 microgram tablets were both initially white. The composition of the 100 µg tablet strength was slightly modified to include





Comparability between the debossed proposed commercial tablets and the non-debossed tablets from validation / registration batches was established adequately. Quality of the product from the three manufacturing sites were comparable through specifications of the three representative batches of the 800 microgram tablets that were manufactured at each of the three sites. The NDA registration batches are not debossed whereas the commercial tablets will be debossed. Case C dissolution was performed to assess the effect of both tablet debossing and site of manufacture. The 800 µg strength tablet was selected for evaluation in these studies, as it contained the highest fentanyl citrate concentration and represented the worst case in terms of dissolution. Tablet dissolution was studied in multiple dissolution media across a range of pH values. One of the batches selected was manufactured with _____ to represent the proposed debossed market image for the 800 mcg strength. It was confirmed that the _____ The dissolution data in multiple media submitted in support of site change as well as debossing showed comparable dissolution among these three representative batches.

Critical quality attributes of fentanyl citrate were identified and controlled appropriately for this formulation _____



Safety qualification and genetic toxicology screens with the isolated structural alert impurities i.e., were proved to be negative for induction of mutations in Salmonella typhimurium and Escherichia coli with and without metabolic activation and did not induce structural or numerical chromosome aberrations in human peripheral blood lymphocytes in the presence or absence of metabolic activation. Since the level of these three impurities in any batches of fentanyl citrate manufactured to date have been found to be at or below the level of detection of , these impurities are therefore controlled at , by the individual unspecified limits.

. Currently, the drug substance is labeled by the manufacturer for retest after of storage. The drug substance may be stored at controlled room temperature (see USP).

In summary, all critical quality attributes of the drug substance and the drug product and the critical process parameters of the manufacture of the drug product have been identified and controlled adequately to assure tablet content uniformity and potency. All critical CMC issues identified during the earlier meetings were addressed adequately. An overall "acceptable" recommendation was entered into the EES by the Office of Compliance on May 26, 2006. The NDA is recommended for approval from CMC perspective. An expiration dating period of 24 months may be granted.

III. Administrative

A. Reviewer's Signature

B. Endorsement Block

CMC Reviewer Name/Date: BoalJ/ June 16, 2006
CMC Branch Chief Name /Date: HarapanhalliR/
Project Manager Name/Date: ComptonK

C. CC Block

197 Page(s) Withheld

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_____ Draft Labeling

_____ Deliberative Process

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

/s/

Ravi Harapanhalli
6/16/2006 05:28:12 PM
CHEMIST

Placing Jila BOals review in DFS following my corrections.
She is on sick leave.