CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

202788Orig1s000

<u>CHEMISTRY REVIEW(S)</u>

NDA 202788

Subsys™ (Fentanyl)
Sublingual Spray

Insys Therapuetics, Inc

Julia C. Pinto, Ph.D.
Office of New Drug Quality Assessment, Division III

Division of Anesthesia, Analgesia and Addiction Products

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Chemistry Review Data Sheet

Chemistry Review Sheet

1. NDA 202788

2. REVIEW #: 2

3. REVIEW DATE: Dec 28, 2011

4. REVIEWER: Julia C. Pinto, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
Original	March 4, 2011
Amendement	April 5, 2011
Amendement	April 15, 2011
Amendement	April 29, 2011
Amendement	May 18, 2011
Amendement	May 20, 2011
Amendement	May 27, 2011
Amendement	June 3, 2011
Amendement	June 29, 2011
Amendement	July 7, 2011
Amendement	July 11, 2011

6. SUBMISSIONS BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original	March 4, 2011
Amendement	April 5, 2011
Amendement	April 15, 2011
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Amendement	May 18, 2011
Amendement	May 20, 2011
Amendement	May 27, 2011
Amendement	June 3, 2011
Amendement	June 29, 2011
Amendement	July 7, 2011
Amendement	July 11, 2011
Amendment	Dec. 21, 2011

7. NAME AND ADDRESS OF APPLICANT:

Name: Insys Therapuetics, Inc
Address: 10220 South 51st Street
Suite 2
Phoenix, AZ 85044

Reference ID: 3064639

8. Product Drug Code and Name:
   a) Proprietary Name: None
   b) Non-Proprietary Name (USAN): Fentanyl
   c) Code name/#(ONDQA only):
   d) Chem. Type/Submission Priority (ONDQA only):
      - Chem. Type: Type 3
      - Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: FD&C ACT 505(b)(2)

10. PHARMACOLOGICAL CATEGORY:
Treatment of break through pain in patients with malignancies who are already receiving and who are tolerant to around-the-clock opioid therapy for their underlying persistent cancer pain.

11. DOSAGE FORM: Sublingual Spray

12. STRENGTH/POTENCY: 100, 200, 400, 600 and 800mcg in (b) (4) of solution

13. ROUTE OF ADMINSITRATION: Sublingual

14. Rx/OTC DISPENSED: __√__Rx ___OTC

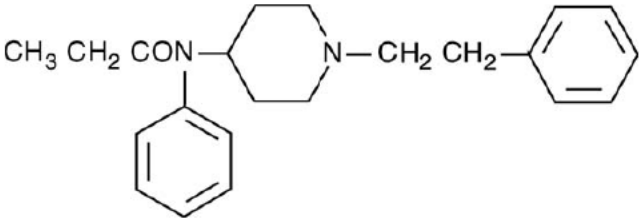
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):
_____SPOTS product – Form Completed

__x___Not a SPOTS product

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

INN Name: Fentanyl
USAN name: Fentanyl [p
IUPAC name: *N*-phenyl-*N*-[1-(2-phenylethyl)piperidin-4-yl] propanamide

Molecular formula: $C_{22}H_{28}N_2O$
Relative molecular weight 336.47 (base):



Reference ID: 3064639

17. RELATED/SUPPORTED DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	Code[1]	Status	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	IV		(b) (4)	3	Adequate	June 2009 Oct 2011	P. Maturu J. Pinto
	III			3	adequate	Nov 2010	P. Baucom
	III			3	adequate	Nov 2009	E. Jao
	III			4			
	III			3	Adequate	June 2011	J. Lee
	III			4			
	III			4			
	III			4			
	III			4			

[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)

Reference ID: 3064639

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	72411	Fentanyl Sublingual Spray

18. Status

ONDQA:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	Adequate	May 2011	Bryan Riley, Ph.D.
EES	Adequate	April 18, 2011	Office of Compliance
Pharm/Tox	Adequate	Rev #1	E. Bolan, Ph.D.
Biopharm	NA		
LNC	NA		
Methods Validation	NA		
DMET/DDMAC	Adequate		LaToya Toombs
EA	Categorical exclusion satisfactory	March 4, 2011	J. Pinto

Reference ID: 3064639

The Chemistry Review for NDA 202788

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

Sufficient CMC information, to assure the identity, strength, purity, and quality of the drug product, is provided in this NDA submission. The drug substance manufacture and product attributes are referenced to DMF (b) (4) and has been reviewed as Adequate (P. Maturu, Rev #4 June 2009 and J. Pinto, Rev #5, Oct 2011). The Office of Compliance has issued an "Acceptable" overall recommendation for all facilities involved in production of the product. All DMFs are adequate. All outstanding deficiencies in the drug product stability protocol and stability specifications have been adequately addressed. From a quality perspective, this NDA is recommended for approval

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

No Post Approval commitments are required.

II. Summary of Chemistry Assessment

A. Description of Drug Substance and Drug Product:

The drug substance, fentanyl base, is a narcotic analgesic and a Schedule II controlled substance that binds to opioid receptors. The Chemistry, Manufacturing, and Control (CMC) information for Fentanyl base is provided in DMF (b) (4) (held by (b) (4). The API is made by (b) (4) at their (b) (4) facility, (b) (4) which is recommend as adequate by OC (report attached in the appendix). The API will be stored and shipped (b) (4) and has a retest period of (b) (4). The DMF has been reviewed and found to be adequate (P. Maturu, Rev #4 June 2009 and J. Pinto, Rev #5, Oct 2011).

The drug product is fentanyl formulated in a sublingual, single dose, spray in concentrations of 1mg/ml, 2mg/ml, 4mg/ml, 6mg/ml and 8mg/ml. The total fill per vial is (b) (4). The solution components consist of the active substance, in dehydrated alcohol, propylene glycol, water, xylitol and menthol. The solution is intended for sublingual administration for mucosal absorption. The spray is a single-dose vial, stored in a carton that contains a disposal bottle (b) (4) and disposal bags, for the used vials, (b) (4) bottles containing unused doses. The DP is made by (b) (4) at their (b) (4) facility which as been recommended as adequate by OC (OC report attached in the appendix. The clinical batches were made on a (b) (4) scale. The proposed commercial scale is (b) (4)

The manufacturing process is (b) (4)

Reference ID: 3064639

The pump consists of an actuator, insert, spray pin, needle, stopper, glass vial and vial holder and assembled by (b) (4) (b) (4) . The filled spray device is co-packaged with a (b) (4) bottle to be used for disposal of any unused vials.

Extraction studies of the (b) (4) bottle, holding 28 units of the maximum strength drug product were conducted to evaluate the amount of recoverable fentanyl. The results show that there is some recovery of fentanyl with extraction using acetone, alcohols (dehydrated, isopropanol), ethyl acetate and 6N HCl. The most fentanyl recovered was (b) (4) µg using dehydrated ethanol which is equivalent to about 1.3%. Heat, shaking, and pH adjustments, did not afford any additional fentanyl to be extracted.

The recommended storage temperature is 25° C (77° F) with excursions permitted from 15° to 30°C (59°-86°F) and an expiry of 36 months is supported.

B. Description of How the drug is intended to be used:

Subsys™ (name under review by DMEPA) is an opioid analgesic indicated only for the management of breakthrough cancer pain in patients who are already receiving and who are tolerant to regular opioid therapy. Each dose is administered as a single spray under the tongue. Each spray delivers (b) (4) of solution containing either 100 mcg, 200 mcg, 400 mcg, 600 mcg or 800 mcg of fentanyl base. There is no recoverable residual in the vial, after dose delivery. Off the (b) (4) fill volume, (b) (4) is delivered and the remaining (b) (4) is retained by the pump assembly parts. Since this is a controlled substance, the applicant provides a (b) (4) bottle into which excess drug is to be sprayed and disposed of in the trash.

C. Basis for Approvability Recommendation

Sufficient CMC information, to assure the identity, strength, purity, and quality of the drug product, is provided in this NDA submission.

III. Administrative

A. Reviewer's Signature

B. Endorsement Block

Chemistry Reviewer: Julia Pinto, Ph.D.
Pharmaceutical Assessment Leader: Danae Christodoulou, Ph.D.
Project Manager: Kathleen Davies
Branch Chief: Prasad Peri, Ph.D.

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Reference ID: 3064639

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

/s/

JULIA C PINTO
12/28/2011

PRASAD PERI
12/28/2011
I concur

NDA 202788

Subsys™ (Fentanyl)
Sublingual Spray

Insys Therapuetics, Inc

Julia C. Pinto, Ph.D.
Office of New Drug Quality Assessment, Division III

Division of Anesthesia, Analgesia and Addiction Products

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Chemistry Review Data Sheet

Chemistry Review Sheet

1. NDA 202788

2. REVIEW #: 1

3. REVIEW DATE: Nov 16, 2011

4. REVIEWER: Julia C. Pinto, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
Original	March 4, 2011
Amendement	April 5, 2011
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Amendement	May 27, 2011
Amendement	June 3, 2011
Amendement	June 29, 2011
Amendement	July 7, 2011
Amendement	July 11, 2011

7. NAME AND ADDRESS OF APPLICANT:

Name: Insys Therapuetics, Inc
Address: 10220 South 51st Street
Suite 2
Phoenix, AZ 85044

Reference ID: 3047930

8. Product Drug Code and Name:
   a) Proprietary Name: None
   b) Non-Proprietary Name (USAN): Fentanyl
   c) Code name/#(ONDQA only):
   d) Chem. Type/Submission Priority (ONDQA only):
      - Chem. Type: Type 3
      - Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: FD&C ACT 505(b)(2)

10. PHARMACOLOGICAL CATEGORY:
Treatment of break through pain in patients with malignancies who are already receiving and who are tolerant to around-the-clock opioid therapy for their underlying persistent cancer pain.

11. DOSAGE FORM: Sublingual Spray

12. STRENGTH/POTENCY: 100, 200, 400, 600 and 800mcg in (b) (4) of solution

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14. Rx/OTC DISPENSED: __√__Rx ___OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM:
_____SPOTS product – Form Completed

__x___Not a SPOTS product

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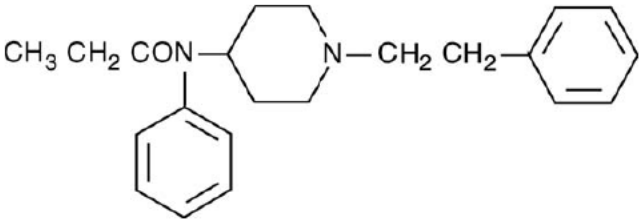
USAN name: Fentanyl [p
IUPAC name: *N*-phenyl-*N*-[1-(2-phenylethyl)piperidin-4-yl] propanamide

Molecular formula: $C_{22}H_{28}N_2O$
Relative molecular weight 336.47 (base):



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LNC	NA		
Methods Validation	NA		
DMET/DDMAC	Adequate		LaToya Toombs
EA	Categorical exclusion satisfactory	March 4, 2011	J. Pinto

The Chemistry Review for NDA 202788

The Executive Summary

I. Recommendations

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

No Post Approval commitments are required.

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Reference ID: 3047930

The manufacturing process is [redacted] (b) (4) The pump consists of an actuator, insert, spray pin, needle, stopper, glass vial and vial holder and assembled by [redacted] (b) (4)). [redacted] (b) (4). The filled spray device is co-packaged with a [redacted] (b) (4) bottle to be used for disposal of any unused vials.

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C. Basis for Approvability Recommendation

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III. Administrative

A. Reviewer's Signature

B. Endorsement Block

Chemistry Reviewer: Julia Pinto, Ph.D.
Pharmaceutical Assessment Leader: Danae Christodoulou, Ph.D.
Project Manager: Kathleen Davies
Branch Chief: Prasad Peri, Ph.D.

55 Page(s) has been Withheld in Full as B4 (CCI/TS) immediately following this page

Reference ID: 3047930

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

/s/

JULIA C PINTO
11/21/2011

PRASAD PERI
11/21/2011
I concur