CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-338

CHEMISTRY REVIEW(S)

NDA 21-338

IONSYS (fentanyl iontophoretic transdermal system)
40 mcg/activation
Patient -activated

ALZA Corporation

Rajiv Agarwal, Ph.D

DIVISION OF PRE-MARKETING DRUG QUALITY ASSESSMENT
(Division II, Branch III)

For the

Division of Anesthesia, Analgesia, and Rheumatology Products
(HFD-170)

Table of Contents

Chemistry Review Data Sheet

1. NDA # 21-338

2. REVIEW #: 2

3. REVIEW DATE: 19-MAY-2006

4. REVIEWER: Rajiv Agarwal

5. PREVIOUS DOCUMENTS: None

Submission(s) Reviewed	Document Date
Original	23-SEP-2003
Amendment	25-MAR-2003
Amendment	02-APR-2004
Amendment	16-APR-2004
Amendment	13-MAY-2004
Amendment	04-JUN-2004
Amendment	11-JUN-2004

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Amendment	17-JUL-2004
Amendment	21-NOV-2005
Amendment	06-JAN-2006
Amendment	14-MAR-2006
Amendment	10-MAY-2006
Amendment	11-MAY-2006
Amendment	17-MAY-2006
Amendment	18-MAY-2006

7. NAME & ADDRESS OF APPLICANT:

Name: ALZA Corporation

Address: 1900 Charleston Road, P.O. Box 7210, Mountain View, CA 94039-7210

Chemistry Review Data Sheet

Representative: Ms. Susan P. Rinne

Telephone: (650) 564-2523

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: IONSYS
b) Non-Proprietary Name (USAN): Fentanyl Hydrochloride
c) Code Name/# (ONDQA only): None
d) Chem. Type/Submission Priority (ONDQA only):

- Chem. Type: 3
- Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: 505 (b)(1)

10. PHARMACOL. CATEGORY:

Acute pain requiring opioid analgesia. For use in medically supervised settings only.

11. DOSAGE FORM: (fentanyl iontophoretic transdermal system)
Patient-Activated

12. STRENGTH/POTENCY: 40 mcg/activation

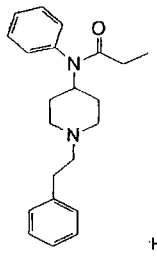
13. ROUTE OF ADMINISTRATION: Transdermal

14. Rx/OTC DISPENSED: _x__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:



Chemical name: Propanamide, N-phenyl-N-[1-(2-phenylethyl)-4-piperidinyl] monohydrochloride.
Molecular Formula: $C_{22}H_{29}N_2OCl$
Molecular Weight: 372.92

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	EVALUATIONS
—	II	/	Fentanyl Hydrochloride	1	Adequate	18-MAY-2006	Rajiv Agarwal

[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 "Evaluations")

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

B. Other Documents:

20-MAR-2001: Pre-NDA meeting (under IND 41,574)
09-APR-2004: Risk management Plan
22-APR-2004: CMC IR Letter # 1
28-MAY-2004: CMC IR Letter # 2
09-JUL-2004: CMC IR letter # 3
19-JUL-2004: CMC review # 1

23-JUL-2004: Approvable letter
10-SEP-2004: Post approval CMC meeting minutes
10-FEB-2005: Post approval CMC meeting minutes

18. STATUS:

ONDQA:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
EES	Acceptable	21-FEB-2006	Ms. Janine D. Ambrogio
Methods Validation	Samples will be submitted to FDA labs*.		Rajiv Agarwal
DMETS	Acceptable	19-APR-2006	Ms. Alina Mahmud
CDRH	Acceptable	24-APR-2006	Ms. T. Bourke

* Updated SFTA method validation package is provided via an amendment dated 19-MAY-2006.

This reviewer, Dr. Harapanhalli, Dr. Poochikian, Ms. Yana Mille (OPS), and Dr. Chi-Wan Chen, discussed the issue about the established name in detail. There have been several proposals and counter-proposals for the established name and a final resolution is reached. See the labeling section for details.

APPEARS THIS WAY ON ORIGINAL

The Chemistry Review for NDA 21-338

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The application may be approved from the CMC stand point. An expiration dating period of 6 months, as requested by the applicant, may be granted from the date of manufacture.

The following reminder should be included in the action letter:

"We remind you of your agreement to submit a prior approval supplement to support the use of dose current and dose duration as surrogates for drug release assay following accrual of data on at least twenty commercial batches of Ionsys."

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

None

II. Summary of Chemistry Assessments

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

The drug product, IONSYS (fentanyl iontophoretic transdermal syatem), 40 µg/activation, patient activated, is an electrically-assisted transdermal delivery system which provides on demand, a systemic delivery of fentanyl by electric current over 10 minutes. The drug is delivered through the skin by electromigration (iontophoresis). This product is recommended for use
As with other patient controlled analgesic (PCA) systems, patients are titrated to an acceptable level of analgesia before using IONSYS.

The transdermal system consists of a top housing assembly (**device component**) and a bottom housing assemble (**drug component**). The top housing assembly (THA) houses and protects the printed circuit board assembly (PCBA). The bottom housing assembly (BHA) consists of a red plastic with two hydrogel cavities. One cavity is filled with the anode hydrogel formulation, which contains fentanyl hydrochloride (10.8 mg) in combination with inactive ingredients. The second cavity is filled with the inactive cathode hydrogel formulation . These cavities also house anode and cathode electrodes. A anode electrode is made of an polyisobutylene adhesive The cathode electrode, however, is made of

and polyisobutylene adhesive).

The plastic top and bottom housing assemblies are

A release liner, which the patient removes before application, protects the hydrogels. The IONSYS transdermal system is packaged in a luminum foil pouch.

To initiate the drug administration, the patient must press the recessed button located on the THA twice within 3 seconds. An audio beep indicates the start of delivery of each dose and a red light from a light emitting diode (LED) remains on throughout the 10 minute dosing period. During operation.

PK data indicate passive delivery occurs at clinically insignificant levels (190 µg over 80 doses).

The average amount of fentanyl delivered at 170 µA (the product output current) per dose is about 40 µg over 10 minutes. Dosing may be completed up to 6 times per hour, with a maximum of 80 doses available from each system. Each system is designed to operate for 24 hours or until the 80 doses have been administered. Each system is capable of delivering 3.2 mg of fentanyl (as a free base) over 24 hours.

IVIVC, for the system, was examined using in vivo data from two PK studies and from in-vitro data. In these studies, the in vivo amount absorbed was estimated 23 hours after treatment was initiated, following the delivery of the 47th and 48th doses. The amount absorbed in-vivo during the last hour of application of the system was compared to the amount delivered in-vitro at the same dose number. The regression analysis (R^2=0.99) demonstrated a good IVIVC.

The drug product is controlled by the quality attributes o

The labeling comments and issues related to reducing the amounts of potential genotoxic impurities in drug substance were communicated to both drug substance and drug product manufacturers via IR letters and approvable letter, respectively. The

applicant satisfactorily addressed the concerns via amendments dated 21-NOV-2005 and 14-MAR-2006.

The to-be-marketed product (Proof of Concept lots) differs from the clinical product only in the changes made to the device component. The applicant is using a

Originally the applicant proposed of expiration dating period. The primary stability batches (registration lots) had a particularly high rate of out-of-box failures (~ which was also attributed to
Therefore, corrective action lots (CAL) were manufactured having a
Even after this change systems either failed to deliver the required dose or skipped doses. A total of systems failed to pass electronic function test (Push button test) when stored at all three storage conditions. Stability data up to months is provided on CAL lots, and the applicant requests a of expiry from the date of manufacture. After analysis of the provided data, only a expiration date is justified for CAL batches.

After the analysis of non-initiating systems in the current submission, the applicant made ***Proof of Concept (POC)*** batches incorporating the

. It was concluded from the stability studies, that the POC batches performed better at accelerated storage conditions than CAL batches, but at room temperature both CAL and POC lots demonstrated the same failure rates . Based on the analysis of the provided data, 6 month expiration date is justified for POC batches.

manufactures the drug substance, fentanyl hydrochloride. Fentanyl HCl is soluble in water (25 mg/ml) over the pH range of 3 to 6 and has a pKa of 8.4.

. Chemistry, Manufacturing and Controls information of the drug substance is located in DMF and is adequate.

In 2004, CDER and CDRH agreed that the combination product should comply with the Design Controls, Purchasing Controls, and CAPA portions of 21 CFR Part 820 in addition to the requirements of 21 CFR Part 211. CDRH/ODE reviewed the device design and bench testing aspects of the NDA and found the information adequate to support the NDA from device evaluation perspective. Additionally, CDRH/OC reviewed the manufacturing section of the NDA, sent deficiencies to the firm, and reviewed the firm's responses to all communicated deficiencies. CDRH/OC finds that overall, those Part 820 requirements have been sufficiently addressed. Although there

are minor issues remaining, it is recommended that they be addressed during a post market inspection (if one can be done per CDER regulations), as pre market inspections of the manufacturing facilities have already occurred.

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

Once applied to the patient's skin, IONSYS, is activated by firmly pressing the recessed button located on the top of the system **twice within 3 seconds.** The start of each dose delivery is indicated by an audio tone; a red light illuminates continuously throughout each dose administration (a period of 10 minutes). The patient cannot initiate the next dose until the previous dose cycle is completed (i.e. if the patient attempts to activate a dose during the 10-minute dose delivery period, the system will not respond).

Whenever a dose is not being delivered, the system will indicate the approximate number of doses given by red light flashes (1 flash for each 5 doses). This is followed by a 2-second pause, and the series of flashes repeats the dose count. For example, if the system flashes 1 time, followed by a 2-second pause, the patient has received 1 to 5 doses since application. If the system flashes 2 times, followed by a 2-second pause, the patient has received 6 to 10 doses since application, and so on. If the patient presses the button to activate a dose during a dose count (i.e. when the red light is flashing), the system will terminate the dose count and the red light will illuminate continuously for 10 minutes.

During drug delivery the approximate dose count can be obtained by pressing the button once. In this case since the red light is already on, the system will flash off once for each 5 doses delivered. After the dose count, the red light remains on throughout dose administration. For example, if the patient is receiving a dose (with the light on continuously) and the patient presses the button once, the light will flash off and on 3 times if the patient has received 11 to 15 doses since application, 4 times for 16 to 20 doses, etc.

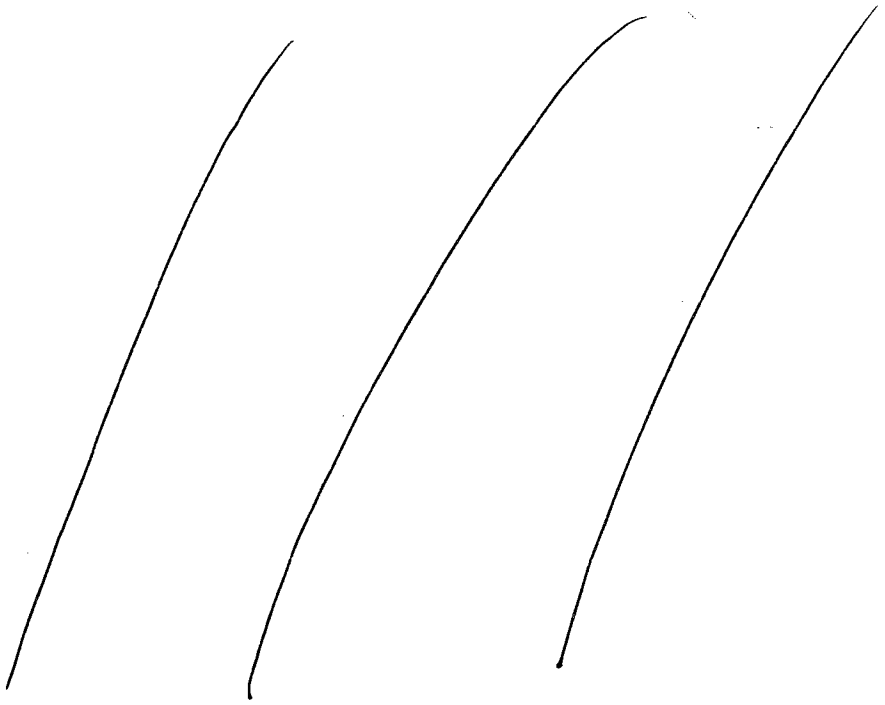
IONSYS will operate for 24 hours following completion of the first dose or for 80 doses, whichever comes first, and then becomes inoperative. If the patient attempts to initiate a dose after 80 doses or 24 hours from the first dose, the system will not respond (i.e. no red light, no beeps).

Safety features:

- If the switch should fail to operate, doses are not delivered or if the switch is in the "ON" position (electric contact closed), the system does not respond with a dose initiation.
- System must do close/open and close/open **(twice within 3 seconds)** operation to start a dose.
- If patients hold the switch for many seconds, the system does not respond with a dose initiation.

- If the patient presses the button while a dose being delivered, the system does not start another dose.
- Because the button is recessed, a patient rolling over the system will not initiate the dose delivery.

"IONSYS Testing Instructions" for the Pharmacist or Other Health Care Professional (To be Performed Prior to Dispensing)



C. Basis for Approvability or Not-Approval Recommendation

- Outstanding issues from Chemistry Review # 1 (IR letter dated 23-JUL-2004) have been satisfactorily resolved.
- The final recommendation from the Office of Compliance for the Manufacturing, Testing and Control sites is **Acceptable** (see **Appendix-1**).
- CDRH/ODE deemed that the application is acceptable from Device Evaluation perspective during the first cycle review.
- CDRH/OC finds that overall, those Part 820 requirements have been sufficiently addressed. (see **Appendix-2**)

III. Administrative

A. Reviewer's Signature **Rajiv Agarwal, Ph.D**

Electronically captured in DFS

B. Endorsement Block

Chemist's Name:	**Rajiv Agarwal, Ph.D**
Chemistry Branch Chief:	**Ravi Harapanhalli, Ph.D**
Project Manager	**Kimberly Compton, HFD-170**

55 Page(s) Withheld

✓ § 552(b)(4) Trade Secret / Confidential

_ § 552(b)(5) Deliberative Process

_ § 552(b)(4) Draft Labeling

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

/s/

Rajiv Agarwal
5/19/2006 01:30:20 PM
CHEMIST

Ravi Harapanhalli
5/19/2006 02:56:27 PM
CHEMIST

REVIEW MEMORANDUM

DATE: April 24, 2006

TO: The Record

THRU: William MacFarland, Chief, Orthopedic, Physical Medicine and Anesthesiology Devices Branch, DOEB, OC, CDRH

WCM 4-25-2006
initials date

FROM: Tracey Bourke, CSO, OPMADB, DOEB, OC, CDRH, HFZ-343

SUBJECT: NDA – Combination Product
NDA 21-338
CDER Consult Request
ALZA response to March 22, 2006 letter

Applicant: ALZA Corporation
1900 Charleston Rd
P.O. Box 7210
Mountain View, CA 94039-07210

FEI: 1000123587
CFN: 2950681

Mfg Site: ALZA Corporation
700 Eubanks Drive
Vacaville, CA
FEI & CFN: 2938701

DEVICE: IONSYS (previously E-TRANS System) – combination

device/drug product

OC RECOMMENDATION: Information Adequate from a CDRH/OC QS/GMP perspective. However, OC did **not** review and does not approve the , design and process changes planned for the commercial product.
Approve NDA; post-market follow-up inspection recommended.

INTENDED USE:
To manage acute pain in patients requiring opioid analgesia.

DEVICE DESCRIPTION:
The device is an electrically-assisted, transdermal delivery system that is patient-activated and provides on-demand systemic delivery of fentanyl by means of a small electric current. A top housing assembly (THA) consists of housing and a printed circuit board, which supplies electric energy through two electrodes. The bottom housing assembly (BHA) consists of housing with two hydrogel cavities, each of which has an electrode and hydrogel. The anode electrode and hydrogel deliver the fentanyl through the skin and the cathode electrode and hydrogel close the electrical circuit.

INSPECTION HISTORY:
ALZA Corporation
1900 Charleston Road
Mountain View, CA 94043
FEI: 3003732939
6/7-13/05: NAI
12/16 – 18/02: NAI

ALZA Corporation
700 Eubanks Drive
Vacaville, CA
FEI & CFN: 2938701
01/06/03: Referred to Center

FEI:
5/3 – 4/04: NAI. Initial inspection,

FIRM CONTACT (US ADDRESS ONLY):
Susan P. Rinne
Vice President, Regulatory Affairs
ALZA Corporation

1900 Charleston Road
P.O. Box 7210
Mountain View, CA 94039
650-564-2523 (phone)
650-564-2581 (fax)

BACKGROUND:
CDRH OC sent a deficiency letter dated March 22, 2006 subsequent to reviewing the sponsor's November 22, 2005 submission. On March 30, 2006, FDA had a teleconference with the firm to discuss the deficiencies in the letter. This submission is the written response to the deficiencies. It also serves as the closeout memo.

REVIEW:
The following are the deficiencies and the review of the responses:

10 Page(s) Withheld

✓ § 552(b)(4) Trade Secret / Confidential

_ § 552(b)(5) Deliberative Process

_ § 552(b)(4) Draft Labeling

Prepared:TBourke:4/17/06
Reviewed:
Final: TBourke: 4/25/06

cc:

HFZ-343	Branch Firm File
HFZ-340	Division Chron File
HFZ-402	ODE/POS
HFZ-306	OC/FPB/PMA Program Coordinator
HFZ-343	Bourke
HFZ-224	

OC Doc. No.: 120652

NDA 21-338

IONSYS
(fentanyl HCl patient-controlled transdermal analgesic)

ALZA Corporation

Rajiv Agarwal, Ph.D @ HFD-580
Division of Anesthetic, Critical Care and Addiction
(HFD-170)

Table of Contents

Chemistry Review Data Sheet

1. NDA # 21-338

2. REVIEW #: 1

3. REVIEW DATE: 19-JUL-2004

4. REVIEWER: Rajiv Agarwal, Ph.D

5. PREVIOUS DOCUMENTS: None

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original	23-SEP-2003
Amendment	25-MAR-2003
Amendment	02-APR-2004
Amendment	16-APR-2004
Amendment	13-MAY-2004
Amendment	04-JUN-2004
Amendment	11-JUN-2004

SUBMISSION NOT REVIEWED:

Submission(s) Reviewed	Document Date
Amendment	17-JUL-2004

7. NAME & ADDRESS OF APPLICANT

Name:	ALZA Corporation
Address:	1900 Charleston Road, P.O. Box 7210, Mountain View, CA 94039-7210
Representative:	Ms. Susan P. Rinne
Telephone	(650) 564-2523

8. DRUG PRODUCT NAME/CODE/TYPE

a) Proprietary Name: IONSYS
b) Non-Proprietary Name (USAN): Fentanyl Hydrochloride
c) Code Name/# (ONDC only): None
d) Chem. Type/Submission Priority (ONDC only):

- Chem. Type: 3
- Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: 505 (b)(1)

10. PHARMACOL. CATEGORY:

Acute pain requiring opioid analgesia. For use in medically supervised settings only.

11. DOSAGE FORM: Iontophoretic drug delivery system

12. STRENGTH/POTENCY: 40 µg/dose

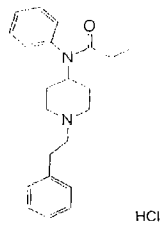
13. ROUTE OF ADMINISTRATION: Transdermal

14. Rx/OTC DISPENSED: _x__ 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:



Chemical name: Propanamide, N-phenyl-N-[1-(2-phenylethyl)-4-piperidinyl] monohydrochloride.

Molecular Formula: $C_{22}H_{29}N_2OCl$
Molecular Weight: 372.92

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	EVALUATIONS
—	II	/	Fentanyl Hydrochloride	1	Deficient	16-JUL-2004	Rajiv Agarwal
—	III	/	/	1	Adequate	16-JUL-2004	Rajiv Agarwal
—	III	/	/	1	Adequate	16-JUL-2004	Rajiv Agarwal
—	II	/	/	4	N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)		

[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 "Evaluations")

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

B. Other Documents:

20-MAR-2001: Pre-NDA meeting (under IND 41,574)
09-APR-2004: Risk management Plan
12-APR-2004: Information Request letter by CDRH (reviewed by Ms Carol Arras on 12-JUL-2004).
22-APR-2004: CMC IR Letter # 1

28-MAY-2004: CMC IR Letter # 2
09-JUL-2004: CMC IR letter # 3

18. STATUS:

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
CDRH	Acceptable	13-JUL-2004	Dr. K. Lee
CDRH (Office of Compliance)	**Not Adequate**	**12-JUL-2004**	**Ms. Carol Arras**
EES	Acceptable	26-MAY-2004	Ms. Janine D. Ambrogio
Stability	Completed	28-JUN-2004	Dr. Joan Buenconsejo
LNC	Final resolution pending*		
Methods Validation	Samples will be submitted to FDA labs.		
DMETS	Acceptable	06-JUN-2004	Ms. Kimberly Culley
Micro	Acceptable	27-APR-2004	Dr. John Metcalfe
Biopharmaceutics	Acceptable	09-JUL-2004	Dr. Srikanth Nallani
Pharmacology and Toxicology	**Approvable**	**16-JUL-2004**	**Dr. Mamata De**
EA	Granted		See page 104 of this review

**This reviewer, Dr. Harapanhalli, Dr. Poochikian, Ms. Yana Mille, Dr. Chiwan Chen, Mr. Bill Hess, Mr. Don Hare, Ms. Mary Ann Holovac, and Mr. Mike Jones discussed the issue of established name in detail. There have been several proposals and counter-proposals for the established name and final resolution is awaited. See the labeling section for details.*

APPEARS THIS WAY ON ORIGINAL

Description of various amendments submitted by the applicant during the course of this review cycle:

Chemistry Review Data Sheet

25-MAR-2004: Trade name and established names are provided to the NDA via this amendment.
02-APR-2004: Risk management plan is provided.
16-APR-2004: The following updates are provided to this NDA via this amendment:

- Revised labeling to include instructions for testing of system by pharmacist.
- Name and address of a new contract testing facility.
- Revised —— specification.
- Revised justification for identity tests specification.
- Updated shelf life recommendation
- Primary container closure change protocol.
- Manufacturing change protocols

30-APR-2004: Responses to the Information Request Letter sent by CDRH (dated 12-APR-2004).
13-MAY-2004: Responses to the Information Request Letter # 1.
04-JUN-2004: Additional —— (long term) of stability data on Corrective Action Lots (CALs).
11-JUN-2004: Responses to the Information Request Letter # 2 and results of No beep/No LED testing on CALs.
17-JUL-2004: Not reviewed. (received on 19-JUL-2004 by this reviewer)

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL

The Chemistry Review for NDA 21-338

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The application is **approvable** pending resolution of all deficiencies delineated in the action letter and listed at the end of this review.

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

None

II. Summary of Chemistry Assessments

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

The drug product, IONSYS (fentanyl HCl patient-controlled transdermal analgesic), 40 µg, is an electrically-assisted transdermal delivery system which provide on-demand, a systemic delivery of fentanyl by electric current over 10 minutes. The drug is delivered through the skin by electromigration (iontophoresis). This product is recommended for use in a medically supervised setting. As with other patient-controlled analgesic (PCA) systems, patients are titrated to an acceptable level of analgesia before using IONSYS.

The transdermal system consists of a top housing assembly (**device component**) and a bottom housing assemble (**drug component**). The top housing assembly (THA) houses and protects the printed circuit board assembly (PCBA). The bottom housing assembly (BHA) consists of a red [redacted] plastic with two hydrogel cavities [redacted]. One cavity is filled with the anode hydrogel formulation, which contains fentanyl hydrochloride (10.8 mg) in combination with inactive ingredients. The second cavity is filled with the inactive cathode hydrogel formulation [redacted]. These cavities also house anode and cathode electrodes. A [redacted] anode electrode is made of [redacted] layer of polyisobutylene adhesive [redacted]. The cathode electrode, however, is made of [redacted] and polyisobutylene adhesive). [redacted]

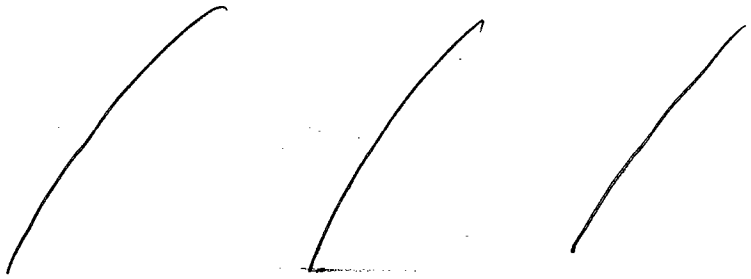
The plastic top and bottom housing assemblies are [redacted] A release liner, which the patient removes before application, protects the hydrogels. The IONSYS transdermal system is packaged in a [redacted] *aluminum foil* [redacted] pouch.

To initiate the drug administration, the patient must press the recessed button located on the THA twice within 3 seconds. An audio beep indicates the start of delivery of each dose and a red light from a light emitting diode (LED) remains on throughout the 10 minute dosing period. During operation,

PK data indicate passive delivery occurs at clinically insignificant levels (190 µg over 80 doses).

The average amount of fentanyl delivered at (the product output current) per dose is about 40 µg over 10 minutes. Dosing may be completed up to 6 times per hour, with a maximum of 80 doses available from each system. Each system is designed to operate for 24 hours or until the 80 doses have been administered. One system is capable of delivering 3.2 mg of fentanyl (as a free base) over 24 hours.

IVIVC, for the system, was examined using in vivo data from two PK studies and from in-vitro data. In these studies, the in vivo amount absorbed was estimated 23 hours after treatment was initiated, following the delivery of the 47th and 48th doses. The amount absorbed in-vivo during the last hour of application of the system was compared to the amount delivered in-vitro at the same dose number. The regression analysis (R^2=0.99) demonstrated a good IVIVC.



The drug product is controlled by the quality attributes of

To further provide an assurance that the quality of the drug product will be maintained over the shelf life, tests for are recommended. In-process tests at the critical steps are provided. The o ensure that the process is controlled is recommended. To further control the quality of the drug product product, ALZA is asked to perform testing of the critical raw materials upon their receipt.

are recommended to control the quality of the drug product if ALZA changes the vendors. The applicant addressed the recommendations in an amendment dated 17-JUL-2004 that was received on 19-

JUL-2004. Owing to the paucity of time (action date is 23-JUL-2004), this amendment was not reviewed in this cycle.

The manufacturer of the drug product is ALZA at Vacaville, CA. The Office of Compliance on 26-MAY-2004 has recommended the drug substance and drug product manufacturing/testing sites for **approval.**

The to-be-marketed product (corrective action lots) differs from the clinical product only in the changes made to the device component. The applicant is using a

Originally the applicant proposed of expiration date. The primary stability batches (registration lots) had a particularly high rate of out-of-box failures ( ) which was also attributed to Therefore, ***corrective action lots (to-be-marketed batches)*** were manufactured but systems failed to deliver the required dose, or skipped doses. A total of systems failed to pass electronic function test (Push button test). Stability data up to is provided on corrective action lots, and the applicant requests a of expiry from the date of manufacture. ***Analysis of the provided data only justify a expiration date from the date of manufacture.***

The Office of Compliance (CDRH) concluded that ALZA has not completed its proposed commercial scale-up Design Validation and Design Transfer Activities and it does not appear that ALZA has a final product design that will meet specifications for stability. The Office of Compliance (CDRH) recommends scheduling another inspection, once ALZA submits adequate documentation of its commercial manufacturing scale up and its Design Control Activities. The final recommendation of the Office of Compliance (CDRH) is " Not adequate".

Several comparability protocols are submitted in the NDA for potential post-approval changes in the drug substance and the drug product. The protocols **are not acceptable** in their present form as they lack clarity and adequate justification. The proposed changes include:

In view of the criticality of this unique combination product of fentanyl drug delivery, several of these proposed changes are not appropriate for regulatory relief through comparability protocols. Specifically, are deemed not appropriate for the comparability protocols and therefore should be submitted as prior-approval supplements. These changes include the following:

For some other changes proposed in the comparability protocol, additional clarification and supporting data from the pharmaceutical development are needed before an assessment can be made on their appropriateness. Such changes include:

The changes acceptable "as is" include:

Statements of subjective interpretation such as '
' should be deleted from the comparability protocols. The comparability protocols should also state clearly the changes that are likely made

nanufactures the drug substance, fentanyl hydrochloride. Fentanyl HCl is soluble in water (25 mg/ml) over the pH range of 3 to 6 and has a pKa of 8.4.

Chemistry, Manufacturing and Controls information of the drug substance is located in DMF and deficiencies are conveyed to the DMF holder.

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

Once applied to the patient's skin, IONSYS, is activated by firmly pressing the recessed button located on the top of the system **twice within 3 seconds.** The start of each dose delivery is indicated by an audio tone; a red light illuminates continuously throughout each dose administration (a period of 10 minutes). The patient cannot initiate the next dose until the previous dose cycle is completed (i.e. if the patient attempts to activate a dose during the 10-minute dose delivery period, the system will not respond).

Whenever a dose is not being delivered, the system will indicate the approximate number of doses given by red light flashes (1 flash for each 5 doses). This is followed by a 2-second pause, and the series of flashes repeats the dose count. For example, if the system flashes 1 time, followed by a 2-second pause, the patient has received 1 to 5 doses since application. If

the system flashes 2 times, followed by a 2-second pause, the patient has received 6 to 10 doses since application, and so on. If the patient presses the button to activate a dose during a dose count (i.e. when the red light is flashing), the system will terminate the dose count and the red light will illuminate continuously for 10 minutes.

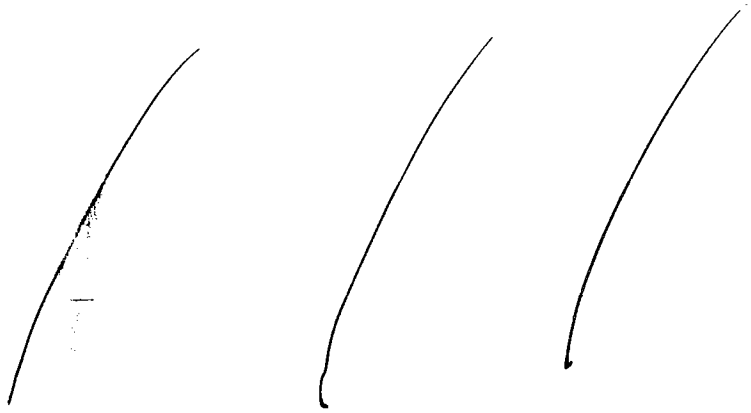
During drug delivery the approximate dose count can be obtained by pressing the button once. In this case since the red light is already on, the system will flash off once for each 5 doses delivered. After the dose count, the red light remains on throughout dose administration. For example, if the patient is receiving a dose (with the light on continuously) and the patient presses the button once, the light will flash off and on 3 times if the patient has received 11 to 15 doses since application, 4 times for 16 to 20 doses, etc.

IONSYS will operate for 24 hours following completion of the first dose or for 80 doses, whichever comes first, and then becomes inoperative. If the patient attempts to initiate a dose after 80 doses or 24 hours from the first dose, the system will not respond (i.e. no red light, no beeps).

Safety features:

- If the switch should fail to operate, doses are not delivered or if the switch is in the "ON" position (electric contact closed), the system does not respond with a dose initiation.
- System must do close/open and close/open (**twice within 3 seconds)** operation to start a dose.
- If patients hold the switch for many seconds, the system does not respond with a dose initiation.
- If the patient presses the button while a dose being delivered, the system does not start another dose.
- Rolling over the system and recessing button will not initiate the dose delivery.

"IONSYS Testing Instructions" for the Pharmacist or Other Health Care Professional (To be Performed Prior to Dispensing)



C. **Basis for Approvability or Not-Approval Recommendation**

- The NDA is **approvable** pending satisfactory response to the Information Request presented at the end of the review.
- Since test are recommended.
- To further provide an assurance that the quality of the drug product will be maintained over the shelf life, tests for are recommended.
- The to ensure that the process is controlled is recommended.
- To further control the quality of the drug product, ALZA is asked to . The applicant did not address the recommendations.
- Based on the stability provided, it is recommended that only of expiry be granted from the date of manufacture.
- **The established name should be revised to " (fentanyl iontophoretic transdermal system)".**
- In order to make sure that pharmacist performs the "BEEP/LED push button" test, testing information should be printed on the back of the pouch. There should also be a box under the instruction where the pharmacist should initial/date after testing the system. This will prove to be an important check point.

III. Administrative

A. **Reviewer's Signature** **Rajiv Agarwal, Ph.D**

Electronically captured in DFS

B. **Endorsement Block**

Chemist Name:	**Rajiv Agarwal, Ph.D, HFD-580**
Chemistry Team Leader:	**Ravi Harapanhalli, Ph.D, HFD-170**
Project Manager	**Kimberly Compton, HFD-170**

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_ § 552(b)(4) Draft Labeling

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/s/

Rajiv Agarwal
7/19/04 05:28:24 PM
CHEMIST

Ravi Harapanhalli
7/19/04 06:03:47 PM
CHEMIST
AE

Memo to file
NDA 21338: IonSys (fentanyl iontophoretic transdermal system)
Ravi S. Harapanhalli, Ph.D.
Team Leader, CMC, HFD-170
July 23, 2004

The following is the list of all outstanding CMC deficiencies and labeling comments to be included in the action letter for this NDA. From CMC perspective, the NDA is approvable pending resolution of these issues.

There are several comments from CDRH/OC on the design controls, CAPA, and design validation. These issues were discussed in a teleconference today among me, Rajiv Agarwal, Dr. Bob Rappaport, Parinda Jani, Dr. Patricia Love, and Mark Chan (SF-DO). Mark stated that his investigations of the firm indicated that they had all the essential elements of the documentations in conformance with the 820 regulations and that he did not quite go into the level of detail described by the CDRH/OC. He agreed that there is ample of room for refining the documentation as raised by the CDRH/OC and that these issues may still be considered within the "VAI" category. Dr. Love stated that the CDRH deficiencies may not constitute real deficiencies in the true sense but should be included in the action letter to indicate that the firm should address them from the point of product safety and to be in full compliance with the 820 regulations.

CMC List of deficiencies and comments to NDA 21338:

The following deficiencies pertain to the specifications for the impurities in the drug substance and the drug product.

1. [redacted] are structural alerts for mutagenicity. Therefore provide a time line to achieve a limit of NMT [redacted] each for these impurities in the drug substance. Alternatively support the proposed levels by demonstration that these [redacted] are human metabolites, or by two genotoxicology studies; one an in vitro mutation assay such as Ames bacterial mutagenicity assay and the other an in vitro cytogenetic assay. Studies should achieve the limit doses for these assays with the isolated impurities. If the impurities are mutagenic, provide a limit of [redacted] or provide an assessment of carcinogenic potential in a standard 2-year model or an appropriate alternative model. Consultation with the Agency in the design of these studies is encouraged.

2. Provide a revised limit of NMT [redacted] for the [redacted] in the drug substance.

The following deficiencies pertain to the drug product specifications.

3. Revise the acceptance criterion of "Number of doses" from [redacted] doses per system to [redacted].

4. Revise the specification for electronic function test (double-press push button test) in the drug product as follows:

5. Provide a statement that the adhesion strength will be tested during stability studies.

The following comments pertain to the drug product stability and the post-approval stability protocol.

6. Based on the analysis of the stability data on the corrective action lots presented in the NDA, an expiration dating period of , is granted for the product packaged in . Provide a statement that a prior-approval supplement will be submitted for the extension of expiration dating beyond months.

7. Revise the postapproval stability commitment by deleting the rom section *B*.

The comparability protocols (CPs) for potential post-approval changes in the drug substance and the drug product are either not appropriate or not adequate in their present form as they lack clarity and adequate justification.

8. Revise the following CPs stating that prior-approval supplements would be submitted for the listed changes

The following CPs need additional clarity and justification

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_ § 552(b)(4) Draft Labeling

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/s/

Ravi Harapanhalli
7/23/04 02:14:50 PM
CHEMIST
AE

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_ § 552(b)(5) Deliberative Process

_ § 552(b)(4) Draft Labeling

ESTABLISHMENT EVALUATION REQUEST

DETAIL REPORT

Application:	NDA 21338/000	Action Goal:	
:	24-SEP-2003	District Goal:	25-MAY-2004
Regulatory Due:	22-MAY-2006	Brand Name:	FENTANYL
Applicant:	ALZA CORPORATION	Estab. Name:	
	2190 PKY LAKE DR	Generic Name:	FENTANYL
	BIRMINGHAM, AL 35244		
Priority:	3S	Dosage Form:	(TRANSDERMAL SYSTEM)
Org Code:	170	Strength:	40 MCG/APPLICATION

Application Comment: THE DRUG PRODUCT IS E-TRANS FENTANYL FOR [redacted]. THIS IS A TRANSDERMAL IONTOPHORETIC PATCH. USING IONTOPHORESIS (BATTERY-OPERATED ELECTRIC CURRENT) THE SYSTEM DELIVERS FENTANYL TRANSDERMALLY. BOTH THE ELECTRIC CIRCUITRY INCLUDING THE BATTERY AND THE DRUG ARE PART OF THE PATCH. THE TOP HOUSING CONTAINS THE RED PRINTED CIRCUIT BOARD ASSEMBLY INCLUDING THE BATTER SOUCE. THE BOTTOM HOUSING INCLUDES THE [redacted], THE ANODE AND CATHODE HYDROGELS CONTAINING THE DRUG, THE SKIN ADHESIVE LAYER AND THE RELEASE LINER. THE PRIMARY JURISDICTIONS FOR THIS NDA ARE WITH CDER AS THE PRIMARY MODE OF ACTION IS FROM THE DRUG. THE OFFICE OF COMPLIANCE SHOULD DETERMINE WHETHER THEY WILL INSPECT THE ENTIRE SYSTEM UNDER 21 CFR 210/211 OR CONSULT OUT THE DEVICE PART OF THE PATCH TO CDRH TO BE INSPECTED UNDER 21 CFR 820. IN VIEW OF THE TECHNICAL COMPLEXITY OF THE DRUG PRODUCT, THIS REVIEWER (RAVI S. HARAPANHALLI) WOULD LIKE TO ACCOMPANY THE INVESTIGATOR IN A PAI. (on 07-NOV-2003 by R. HARAPANHALLI () 301-796-1676)

FDA Contacts:	K. COMPTON	301-796-2280	, Project Manager
	R. HARAPANHALLI	301-796-1676	, Review Chemist
	E. DUFFY	301-796-1666	, Team Leader

Overall Recommendation: ACCEPTABLE on 22-FEB-2006by J. D AMBROGIO(HFD-322)301-827-9049

WITHHOLD on 13-DEC-2005by J. D AMBROGIO(HFD-322)301-827-9049

ACCEPTABLE on 26-MAY-2004by J. D AMBROGIO(HFD-322)301-827-9049

Establishment: CFN FEI

DMF No: AADA:

Responsibilities:

Profile: CTL OAI Status: NONE

Estab. Comment:

ESTABLISHMENT EVALUATION REQUEST

DETAIL REPORT

HARAPANHALLI () 301-796-1676)

Milestone Name	Date	Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	07-NOV-2003				HARAPANHALL
OC RECOMMENDATION	10-NOV-2003			ACCEPTABLE BASED ON PROFILE	DAMBROGIOJ
SUBMITTED TO OC	07-DEC-2005				AGARWALR
OC RECOMMENDATION	08-DEC-2005			ACCEPTABLE BASED ON PROFILE	FERGUSONS

Establishment: CFN 2938701 FEI 2938701

ALZA CORP

700 EUBANKS DR

VACAVILLE, CA 956889470

DMF No: AADA:

Responsibilities: FINISHED DOSAGE MANUFACTURER

FINISHED DOSAGE RELEASE TESTER

FINISHED DOSAGE STABILITY TESTER

Profile: TDP OAI Status: NONE

Estab. Comment: MANUFACTURER OF THE DRUG PRODUCT, IN-PROCESS MATERIALS, PACKAGER, AND LABELER. TESTING SITE FOR BULK DRUG SUBSTANCE, COMPONENTS, INTERMEDIATES, CONTAINER CLOSURE SYSTEMS, AND FINISHED PRODUCT INCLUDING STABILITY TESTING. (on 07-NOV-2003 by R. HARAPANHALLI () 301-796-1676)

Milestone Name	Date	Type	Insp. Date	Decision & Reason	Creator
ıITTED TO OC	07-NOV-2003				HARAPANHALL
SUBMITTED TO DO	10-NOV-2003	10D			DAMBROGIOJ

ASSIGNED INSPECTION T 26-NOV-2003 PS RYOUNG

INSPECTION PERFORMED 12-MAY-2004 12-MAY-2004 RYOUNG

ADDITIONAL PARTICIPANTS: MARK CHAN AND RAVI HARAPANHALLI (CDER, NDA TEAM LEADER) APPROVED

INSPECTION PERFORMED 14-MAY-2004 14-MAY-2004 JEFFREY.WAT

A product specific and GMP inspection of this drug substance manufacturer, drug component and device component final product manufacturer, stability and release tester for E-TRANS? (fentanyl HCL), 40 ?g/Dose System, NDA 21-338, was requested by CDRH, HFD-170, and CDER's Investigations and Compliance Branch, HFD-324, and was performed under Compliance Program 7346.832, NDA/ANDA Pre-Approval Inspections/Investigations, CP 7356.002, Drug Manufacturing Inspections, and CP 7382.845, Inspection of Medical Device Manufacturers. The assignment was dated 9/24/03.

This was a pre-announced team inspection conducted by:

Jeffrey M. Watson (JMW), Investigator/ORA/SAN-DO

ESTABLISHMENT EVALUATION REQUEST

DETAIL REPORT

APPEARS THIS WAY ON ORIGINAL

Mark E. Chan (MEC), Investigator/ORA/SAN-DO

Ravi S. Harapanhalli (RSH), Chemist/NDA Team Leader/CDER

Investigators Watson and Chan were present all days of the inspection. Chemist Harapanhalli was present 5/03-07/04 and called in for the close out meeting on 5/14/04.

The scope of the inspection covered manufacturing and laboratory operations including equipment, calibrations, maintenance, validations, and SOP's; batch record review, raw data review, QC test records, release tests, stability, product design and functionality, laboratory notebooks, and facilities. The Vacaville and Menlo Park, CA facilities were visited for the PAI. The Menlo Park facility houses the , and all other operations are at the Vacaville facility. The Mt. View, CA facility was not visited, this facility is where the for the system occurs. Since the submission of NDA 21-338, , has been no longer required by the firm due to the product showing

Lot # 0327192, Exp. 10/05, (cont. in Endorsement Text)

INSPECTION SCHEDULED	20-MAY-2004			RYOUNG
DO RECOMMENDATION	26-MAY-2004		ACCEPTABLE INSPECTION	RYOUNG
OC RECOMMENDATION	26-MAY-2004		ACCEPTABLE DISTRICT RECOMMENDATION	DAMBROGIOJ
SUBMITTED TO OC	07-DEC-2005			AGARWALR
SUBMITTED TO DO	08-DEC-2005	10D		FERGUSONS
DO RECOMMENDATION	12-DEC-2005		ACCEPTABLE BASED ON FILE REVIEW	DALMOGEL

THIS APPLICATION WAS PREVIOUSLY INSPECTED AND RECOMMENDED FOR APPROVAL AND THERE ARE NO CHANGE IN COMPLIANCE STATUS OF THIS FIRM

RECOMMENDATION	13-DEC-2005		ACCEPTABLE DISTRICT RECOMMENDATION	DAMBROGIOJ

Establishment: CFN 2939776 FEI 2939776

ALZA CORP

1050 HAMILTON CT

MENLO PARK, CA 940251423

DMF No: AADA:

Responsibilities: DRUG SUBSTANCE RELEASE TESTER

Profile: CTL OAI Status: NONE

Estab. Comment: ALTERNATE TEST SITE FOR RAW MATERIALS TESTING AS NEEDED. (on 07-NOV-2003 by R. HARAPANHALLI () 301-796-1676)

Milestone Name	Date	Type	Insp. Date	Decision & Reason	Creator

APPEARS THIS WAY
ON ORIGINAL

ESTABLISHMENT EVALUATION REQUEST

DETAIL REPORT

SUBMITTED TO OC	07-NOV-2003			HARAPANHALL
SUBMITTED TO DO	10-NOV-2003	GMP		DAMBROGIOJ
ASSIGNED INSPECTION T	26-NOV-2003	PS		RYOUNG
INSPECTION PERFORMED	12-MAY-2004		12-MAY-2004	RYOUNG

ADDITIONAL PARTICIPANTS MARK CHAN AND RAVI HARAPANHALLI (CDER, NDA TEAM LEADER) APPROVED

INSPECTION PERFORMED	14-MAY-2004	14-MAY-2004	JEFFREY.WAT

A product specific and GMP inspection of this drug substance manufacturer, drug component and device component final product manufacturer, stability and release tester for E-TRANS? (fentanyl HCL), 40 ?g/Dose System, NDA 21-338, was requested by CDRH, HFD-170, and CDER's Investigations and Compliance Branch, HFD-324, and was performed under Compliance Program 7346.832, NDA/ANDA Pre-Approval Inspections/Investigations, CP 7356.002, Drug Manufacturing Inspections, and CP 7382.845, Inspection of Medical Device Manufacturers. The assignment was dated 9/24/03.

This was a pre-announced team inspection conducted by:
Jeffrey M. Watson (JMW), Investigator/ORA/SAN-DO
Mark E. Chan (MEC), Investigator/ORA/SAN-DO
Ravi S. Harapanhalli (RSH), Chemist/NDA Team Leader/CDER
Investigators Watson and Chan were present all days of the inspection. Chemist Harapanhalli was present 5/03-07/04 and called in for the close out meeting on 5/14/04.

The scope of the inspection covered manufacturing and laboratory operations including equipment, calibrations, maintenance, validations, and SOP's; batch record review, raw data review, QC test records, release tests, stability, product design and functionality, laboratory notebooks, and facilities. The Vacaville and Menlo Park, CA facilities were visited for the PAI. The Menlo Park facility houses the [redacted] and all other operations are at the Vacaville facility. The Mt. View, CA facility was not visited, this facility is where the [redacted] for the system occurs. Since the submission of NDA 21-338, [redacted] has been no longer required by the firm due [redacted] he product [redacted]

INSPECTION SCHEDULED	20-MAY-2004		RYOUNG
DO RECOMMENDATION	26-MAY-2004	ACCEPTABLE	RYOUNG
		INSPECTION	
ECOMMENDATION	26-MAY-2004	ACCEPTABLE	DAMBROGIOJ
		DISTRICT RECOMMENDATION	
SUBMITTED TO OC	07-DEC-2005		AGARWALR
OC RECOMMENDATION	08-DEC-2005	ACCEPTABLE	FERGUSONS
		BASED ON PROFILE	

Establishment: CFN 2950681 FEI 1000123587

ALZA CORP

1015 JOAQUIN ST

APPEARS THIS WAY
ON ORIGINAL

ESTABLISHMENT EVALUATION REQUEST

DETAIL REPORT

MOUNTAIN VIEW, CA 94043

DMF No: AADA:

Responsibilities: DRUG SUBSTANCE RELEASE TESTER

Profile: CTL OAI Status: NONE

Estab. Comment: NOTE THAT UNDER THE SAME DRUG ESTABLISHMENT NUMBER (2950681) ALZA LISTS THE ADDRESS AS: 1058B HUFF AVENUE, MOUNTAIN VIEW, CA 94043. THIS FACILITY IS AN ALTERNATE TEST SITE FOR RAW MATERIALS TESTING AS NEEDED. UNDER A NEW DRUG ESTABLISHMENT REGISTRATION NUMBER 295068, ALZA LISTS ANOTHER FACILITY THAT IS NOT TO BE FOUND IN THE EES. THE FACILITY IS: ALZA CORPORATION, 1900 CHARLESTON ROAD, MOUNTAIN VIEW, CA 94043. THIS FACILITY IS STATED TO BE THE TESTING SITE FOR BULK DRUG SUBSTANCE, COMPONENTS, INTERMEDIATES, CONTAINER CLOSURE SYSTEMS, AND FINISHED PRODUCT INCLUDING STABILITY TESTING. (on 07-NOV-2003 by R. HARAPANHALLI () 301-796-1676)

Milestone Name	Date	Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	07-NOV-2003				HARAPANHALL
SUBMITTED TO DO	10-NOV-2003	GMP			DAMBROGIOJ
ASSIGNED INSPECTION T	26-NOV-2003	PS			RYOUNG
INSPECTION PERFORMED	12-MAY-2004		12-MAY-2004		RYOUNG
ADDITIONAL PARTICIPANTS MARK CHAN AND RAVI HARAPANHALLI (CDER, NDA TEAM LEADER)					APPROVED
INSPECTION SCHEDULED	20-MAY-2004				RYOUNG
DO RECOMMENDATION	26-MAY-2004			ACCEPTABLE INSPECTION	RYOUNG
OC RECOMMENDATION	26-MAY-2004			ACCEPTABLE DISTRICT RECOMMENDATION	DAMBROGIOJ
SUBMITTED TO OC	07-DEC-2005				AGARWALR
OC RECOMMENDATION	08-DEC-2005			ACCEPTABLE BASED ON PROFILE	FERGUSONS

Establishment: CFN [redacted] FEI [redacted]

DMF No: AADA:

Responsibilities: [redacted]

Profile: CTL OAI Status: NONE

Estab. Comment: [redacted]

[redacted] (on 07-NOV-2003 by R. HARAPANHALLI () 301-796-1676)

Milestone Name	Date	Type	Insp. Date	Decision & Reason	Creator

APPEARS THIS WAY
ON ORIGINAL

ESTABLISHMENT EVALUATION REQUEST

DETAIL REPORT

SUBMITTED TO OC	07-NOV-2003		HARAPANHALL
OC RECOMMENDATION	10-NOV-2003	ACCEPTABLE	DAMBROGIOJ
		BASED ON PROFILE	
SUBMITTED TO OC	07-DEC-2005		AGARWALR
OC RECOMMENDATION	08-DEC-2005	ACCEPTABLE	FERGUSONS
		BASED ON PROFILE	

Establishment: CFN — FEI —

DMF No: AADA:

nsibilities: —

Profile: CTL OAI Status: NONE

Estab. Comment:

() 301-796-1322)

Milestone Name	Date	Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	11-MAY-2004				AGARWALR
OC RECOMMENDATION	11-MAY-2004			ACCEPTABLE	DAMBROGIOJ
				BASED ON PROFILE	
SUBMITTED TO OC	07-DEC-2005				AGARWALR
OC RECOMMENDATION	08-DEC-2005			ACCEPTABLE	FERGUSONS
				BASED ON PROFILE	

Establishment: CFN — FEI —

DMF No: — AADA:

asibilities: —

Profile: CSN OAI Status: NONE

EMilestone Name	Date	Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	07-NOV-2003				HARAPANHALL
OC RECOMMENDATION	10-NOV-2003			ACCEPTABLE BASED ON PROFILE	DAMBROGIOJ
SUBMITTED TO OC	07-DEC-2005				AGARWALR
OC RECOMMENDATION	08-DEC-2005			ACCEPTABLE	FERGUSONS

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL

ESTABLISHMENT EVALUATION REQUEST

DETAIL REPORT

APPEARS THIS WAY
ON ORIGINAL

BASED ON PROFILE

Establishment: CFN [redacted] FEI [redacted]

DMF No: AADA:

Responsibilities: [redacted]

Profile: CTL OAI Status: NONE

Comment:

Milestone Name	Date	Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	07-NOV-2003				HARAPANHALL
OC RECOMMENDATION	10-NOV-2003			ACCEPTABLE BASED ON PROFILE	DAMBROGIOJ
SUBMITTED TO OC	07-DEC-2005				AGARWALR
OC RECOMMENDATION	08-DEC-2005			ACCEPTABLE BASED ON PROFILE	FERGUSONS

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_ § 552(b)(4) Draft Labeling

DATE April 13, 2004
FROM: K. Lee, M. D., Medical officer
FDA / CDRH / ODE / DGRND / REDB
SUBJECT: N21-338 E-TRANS® (fentanyl HCl) System Alza Corporation
TO: The file

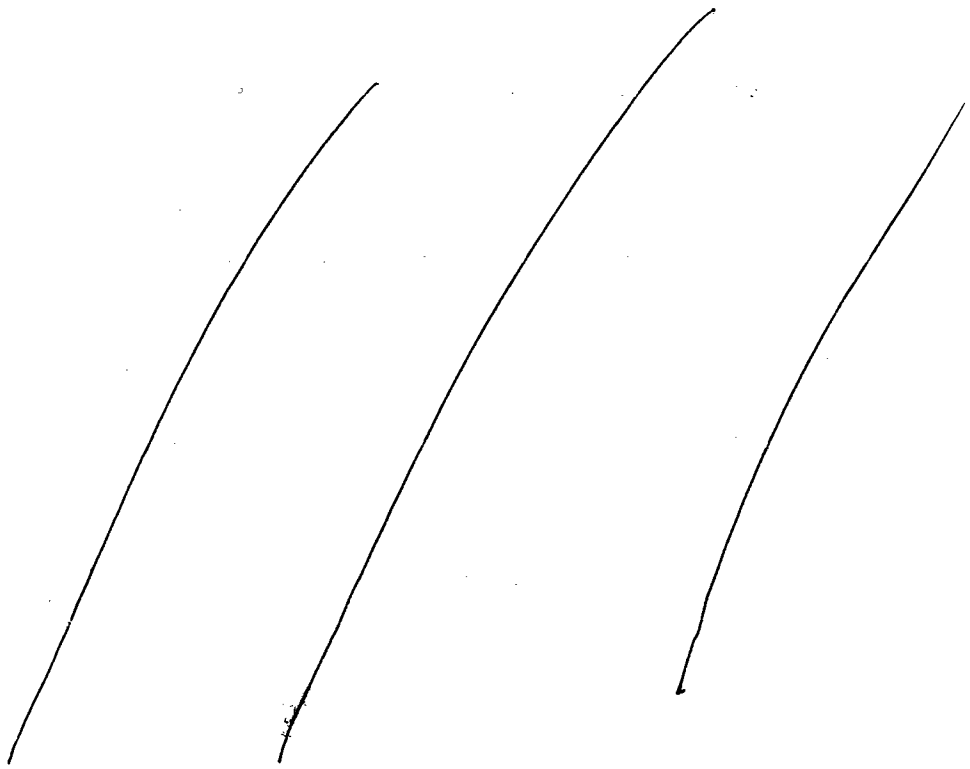
4/14/03

I reviewed the device aspect of this NDA, which is a combination product of drug and device

Final comments by K. Lee
First of all, I don't have any safety issue. The sponsor provided the device component description and device testing in this NDA. The sponsor did not describe the detailed and exact mechanism in which each component of the device is working in the device. The sponsor should describe how each component of device works. I have deficiencies in the end of this final comment. In the stability test of the device, — of devices for — failed to work properly and seems too high.

The E-TRANS (fentanyl HCl) System is an electrically-assisted transdermal delivery system designed for the management of acute pain in patients requiring opioid analgesia. This product is recommended for use in —— — The system is patient-activated and provides on-demand systemic delivery of fentanyl by means of a small electric current (a technology known as iontophoresis or electrotransport). Electrotransport technology uses an electrical potential to provide noninvasive delivery of therapeutic substances across intact skin for local and systemic applications. The — skin contact area is 2.8cm^{-2}. —— —— The specifications are as the following:
The pHs of anode and cathode are — respectively. The current density is — µA/ cm^{-2} (- —— µA/ cm^{-2}). Mean interdose current is set for — and number of dose of the device is — doses.

The following table is "Functional Parameters for the Top Housing Assembly (0012204)".
The Top Housing Assembly (THA) consists of a — that conforms to the inside of a top housing component. The — has electrical and mechanical components ——



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The sponsor also stated as the following:
— corrective action lots have been manufactured and placed on accelerated stability. Data from these lots will be submitted for review when available to verify successful resolution of the ——— problem.

As to the risk analysis, the sponsor stated as the following:
There are risk of overdose, which seems unlikely since the device is shown to fail safely (non function). Intentional abuse of the product is another risk, which is not relevant to intended use of this device. The sponsor stated that stability data for these lots will be provided in the update to this NDA. Once the stability data is updated, the stability data will be reviewed. The non function device was — for — months for —system from 25°C, and — for — months from — from 40°C. The failed devices were all not functioning. <u>There is no safety issue.</u>
The sponsor also described "Post-Approval Stability Protocol and Stability Commitment, for the quality assurance of the device, which seems appropriate.
— <u>% of devices for — months failed to work properly and seems too high.</u>

The sponsor did not describe the detailed and exact mechanism in which each component of the device is working in the sponsor's device. The sponsor should describe how each component of device works.

I found the following deficiencies, based on the review.
Deficiencies
1. **Please explain the mechanism your device maintains and regulates current, voltage, — , and how each component of your device, such as — integral circuit, etc, is working altogether in your device.**
2. **Please describe how your device maintains the current and voltage for 10 minutes and the mechanism how 80 doses are exactly delivered to the patients in your device.**
3. **Please describe the mechanism how — is working to maintain each dose for 10 minutes in your device.**
4. **Please describe the leakage current of each electrode, e.g., cathode and anode, in your device.**
5. **Please describe the mechanism how the — is working and its accuracy in your device.**
6. **Please describe how the — working to maintain the current and voltage for 10 minutes in your device.**
7. **Please provide data from — corrective action lots for the — problem of the device when these are available.**

Kyung Nam Lee
K. Lee, M.D.
Medical officer

The following is the summary of the sponsor's NDA submission

The E-TRANS (fentanyl HCl) System is a novel electrically-assisted transdermal delivery system designed for the management of acute pain in patients requiring opioid analgesia. This product is recommended for use in a —
— . The system is patient-activated and provides on-demand systemic delivery of fentanyl by means of a small electric current (a technology known as iontophoresis or electrotransport). Electrotransport technology uses an electrical potential to provide noninvasive delivery of therapeutic substances across intact skin for local and systemic applications.

The E-TRANS® (fentanyl HCl) System consists of a device portion (the top housing assembly) and a drug portion (the bottom housing assembly and drug-containing hydrogels) (Figure 3.2.P.9.1-A)

The top housing assembly (THA) consists of the top housing, an ——— plastic component that protects the electronics. and a ———

Design verification testing included testing of the full system, the completed THA, and specific testing on the — The THA has been tested thoroughly on the bench to ensure the design meets the specified performance requirements. During testing, two versions of the E-TRANS® (fentanyl HCl) System were used, a 25 µg system and a 40 µg system. The similarities in design between these two systems allow the use of both sets of test data to support the proposed commercial release of the 40 µg system specifications of the 40 µg system were tested on the 40 µg system (Section 3.2.P.9.4.2).

The design verification testing demonstrated that the components and finished product all met the design and performance requirements. The device portion of the E-TRANS® (fentanyl HCl) System performs consistently to deliver the specified current and operates with the proper controls and safety features so that, even in the event of a failure, the device fails safely.

Throughout development, ALZA has established quality processes for continually assessing and improving the device portion of the system. ALZA evaluated the design, materials, and quality of the device portion and made changes needed to optimize the system. As is typical with device development, components were changed to reduce costs, improve reliability, or ease manufacturing. These changes were made following procedures for testing and evaluating the change and ensuring proper documentation in accordance with written procedures. Decisions were made consistent with typical approaches to managing development of a medical device wherever the device portion of the system was concerned.

During stability testing of the primary stability lots (RSLs), some systems failed to turn on when the systems were tested for functionality during stability testing (Section 3.2.P.8, Stability). This out-of-box failure, i.e., nonfunctioning systems, was a safe failure and was identifiable immediately when the dose initiation button was pressed. All systems that experienced failures, failed safely (no output delivery of fentanyl), demonstrating proper performance of the device under failure conditions. The primary cause of nonfunctioning systems was identified as
Based on extensive investigation and confirmatory data, corrective action lots (CALs) were manufactured incorporating changes to improve system reliability (see Section 3.2.P.9.4.2.5). Each CAL was packaged in an resulting in stability studies. Data from these lots will be submitted for review, when available, to verify successful resolution of the . The process of testing, analyzing, investigating, correcting, and retesting is expected to continue for the E-TRANS (fentanyl HCl) System, as is common for all combination products incorporating medical devices.

Analysis of suspected technical failures (Clinical Reliability Section 3.2.P.9.4.4) from Phase 3 clinical studies identified failure modes that were also observed in the primary stability studies; with the most common mode being nonfunctioning systems caused by Failures due to human interaction with the system were few in number and primarily due to cosmetic and skin adhesion issues. No serious failure modes were seen in the clinical studies. All systems failed safely and no adverse events resulted from any failure.

3.2.P.9.1 Device Characteristics

The E-TRANS (fentanyl HCl) System consists of a top housing assembly, considered the device portion, and a bottom housing assembly, considered the drug portion of the system (Figure 3.2.P.9.1-A). The top housing assembly consists of the top housing, an plastic component that protects the electronics, and a contains the electronic circuitry, including an integrated circuit (IC) th
The bottom housing assembly consists of a thermoformed bottom housing with two hydrogel cavities: each cavity has an electrode and is filled with a hydrogel formulation.

The skin adhesive covers most of the bottom side of the system and attaching the system to the skin. A protective liner covers the skin adhesive and both hydrogel formulations. The E-TRANS (fentanyl HCl) System is packaged in a foil pouch.

The system is prepared for use by removing the protective liner and pressing the adhesive side of the system to the selected skin site. The skin-contacting portions of the system have been fully tested for biocompatibility as required by ISO 10995 and FDA Blue Book Memorandum #G95-1 (Section 3.2.P.9.3).

The E-TRANS (fentanyl HCl) System provides a nominal 40 µg dose of fentanyl (base equivalent) per activation, which is delivered over a 10-minute period with a current of 170 A. To initiate administration of a fentanyl dose, the patient must press the recessed button on the top of the system firmly twice within 3 seconds. An audio tone (beep) indicates the start of delivery of each dose, and a red light from a light emitting diode (LED) remains on throughout the 10-minute dosing period. A maximum of six 40 µg doses per hour can be administered by the E-TRANS (fentanyl HCl) System. **Each system operates for 24 hours, or until 80 doses have been administered, whichever occurs first. The system becomes inoperable after this period. The maximum nominal amount of fentanyl that can be administered from a single system over 24 hours is 3.2 mg (80 individual 40 µg doses). The system will terminate delivery if error conditions are detected.**

A discussion of the physicochemical and biological properties affecting fentanyl delivery can be found in Section 3.2.P.2.2.3. A complete list of the ingredients used in the hydrogels and the components of the system is provided in Section 3.2.P.1. A rationale for selection of each ingredient and component of the bottom housing assembly is provided in Section 3.2.P.2.1. This section will focus on the device portion of the system, referred to as the top housing assembly (THA).

3.2.P.9.1.1 Description of Top Housing Assembly and Function

3.2.P.9.1.1 Description of Top Housing Assembly and Function Top Housing

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_ § 552(b)(5) Deliberative Process

_ § 552(b)(4) Draft Labeling

In accordance with good risk management methods, the risk assessment will be reviewed and updated as appropriate when new information is received or changes are made that could impact the risk assessment. Copies of risk assessment documents are maintained on file for inspectional review.

3.2.P.9.4.4 Clinical Studies and Conclusions

During the development of the E-TRANS® (fentanyl HCl) System, a number of clinical studies were conducted to evaluate the safety and effectiveness of the system for its intended use. The E-TRANS® (fentanyl HCl) System is a patient controlled transdermal system for the management of acute pain in adult patients requiring opioid analgesia. The system delivers 40 μg of fentanyl through the patient's skin using iontophoresis, and is a noninvasive, preprogrammed drug device combination product for patient-controlled analgesia (PCA). Patient controlled analgesia is a method of analgesic administration that is the standard of care in many facilities for the management of postoperative and other acute pain. In three placebo-controlled clinical trials (C-2001-011, C-2000-008, and C-95-016), a total of 475 patients received the E-TRANS® (fentanyl HCl) System for postoperative analgesia following major surgery (i.e., abdominal, orthopedic, and thoracic). E-TRANS® (fentanyl HCl) System was effective in the management of moderate to severe pain as shown by the following comparisons to placebo:

- Fewer patients withdrew because of inadequate pain relief
- A higher percentage of patients reported good to excellent pain management
- Patients rated their pain at the end of treatment as significantly lower

In the multicenter, active-controlled trial (C-2000-007), pain management with the E-TRANS® (fentanyl HCl) System was compared to patient-controlled intravenous (IV) infusion of morphine from a pump. E-TRANS® (fentanyl HCl) System provided therapeutically equivalent analgesia as judged by patient and investigator global assessments, patient withdrawals, and assessments of pain intensity. For greater detail on the clinical efficacy results, refer to the Integrated Summary of Efficacy. During the clinical trials, information regarding adverse effects and device performance was collected. Adverse drug experiences are reported in the

Integrated Summary of Safety.

No clinically relevant respiratory depression was observed in any patient treated with E-TRANS® (fentanyl HCl) System. Most adverse events were typical of opioids (e.g., nausea, vomiting, and pruritis). **Five of the 1142 patients who used the E-TRANS® (fentanyl HCl) System had serious adverse events judged related to study medication: confusion (1), nausea and vomiting (1), and ileus (3).**

In the Phase 3 trials, any system suspected of a technical failure was removed and a new system was either applied to a different location to complete the 24-hour treatment period or the patient was withdrawn from the trial. Suspect systems were returned to ALZA for evaluation.

In addition to the analysis of suspected technical failures, the FDA requested that a sample of systems used by patients from one clinical study (C-2000-007) be returned to ALZA for analysis. The purpose of this investigation was to confirm that systems presumed to have operated normally in clinical use did, in fact, meet established functional requirements.

Analysis results for the suspected technical failures (Clinical Reliability) and the systems used by patients are presented in this section. **The analysis shows that the majority of failure modes seen in the clinical study were the same as those identified during stability testing. New failure modes were observed as a result of human interactions with the system. All systems that malfunctioned did so in a safe manner as designed, and no adverse events resulted from any malfunction. In addition, analysis of systems that operated normally on patients demonstrated that the systems functioned as intended.**

1.0 Clinical Reliability

During development of the E-TRANS (fentanyl HCl) System, modifications were made to improve clinical performance. Specific details on the changes made during development can be found in Section 3.2.P.2.2. **As new system configurations were used in clinical studies, knowledge was gathered of how the systems functioned in the hands of physicians and their staff**. In many cases, this information guided system modifications to improve system performance. **In early clinical studies, system performance was relatively poor. In most cases, systems were nonfunctional when removed from the primary package (foil pouch). In some cases, systems failed prematurely while in use. As the device design was optimized, clinical performance improved.**

Each system believed to have not functioned properly by the clinical investigator or their staff, referred to as a .suspected technical failure,. was documented and returned to ALZA for analysis. Table 3.2.P.9.4.4-A provides a summary of the number of systems returned from key clinical trials. The number and percent of suspected technical failures observed in each study are noted in the last two columns. **A total of 2956 systems were used on patients in these trials and about 6% (183) were returned for analysis.**

The results from the analysis of the suspected technical failures can be separated into two categories:

1) failure modes due to device components (e.g., [redacted], and

2) failure modes that resulted from use by the patient or caregiver (e.g., adhesion). The majority of systems returned were the result of electrical component failures, with [redacted] being the most common component to fail.

The specific types of failure modes observed in clinical studies C-2000-005, C-2001-011, and C-2002-027 are presented in Figure 3.2.P.9.4.4-A. The systems used in these studies were from the most recently fabricated clinical lots, which were also used in two primary stability studies (SS3422 and SS3432). As is clearly evident from this figure, the largest cause of failures for systems returned from these clinical studies was [redacted] (67% of all systems returned). This was also the most common cause of failure identified in the primary stability studies. A summary of the investigation leading to specific corrective action for the [redacted] failure mode is provided in Section 3.2.P.9.4.2.5, Device Shelf Life (this failure mode has been addressed by [redacted]

TABLE 3.2.P.9.4.4-A
Number of Suspected Technical Failures Occurring During Clinical Use

Clinical Protocol Number	Dosage (µg)	Systems Used Number	Systems Used Percent	Suspected Failures Number	Suspected Failures Percent
C-94-067	25	87		5	5.8
C-95-016	40	77		0	0
	0	25		3	2.9
C-2000-005	25	120		3	2.5
		68		3	4.4
	40	50		2	4.0
		3		0	0.0
		10		2	20.0
C-2000-006	25	163		9	5.5
C-2000-007	40	590		22[a]	3.9
C-2000-008	40	164		6	3.7
	0	55		4	7.3
C-2000-009	25	755		51	6.8
C-2000-009	40	87		5	5.8
C-2000-011	40	259		17[b]	6.6
	0	277		42[a]	15.2
C-2000-027	40	166		8	4.8
TOTAL		2956		183	6.2

a Value excludes 1 system not used on a patient, but returned to ALZA.
b Value excludes 3 systems not used on a patient, but returned to ALZA.

The next most common cause for systems returned from the clinic was "No Problem Found" (13% of all systems returned). These systems were returned from the clinic but were found to be functioning normally when analyzed. A thorough examination of each component of these systems was unable to identify any defect.

The third most common reason for return (9% of all systems returned) was related to weak or absent audio output from the system. [redacted] was the root cause. Modifications to the design [redacted] have been made to improve audio performance.

Partial adhesion of the system to the patient was the fourth most common reason for return (6% of all systems returned). This is a typical problem for transdermal products due to the variety of skin conditions in the patient population. Since it is not possible to develop an adhesive that will function acceptably for all skin types under all conditions, this problem is typically resolved by the caregiver applying adhesive tape over the system or by replacing the system. In the placebo-controlled studies, approximately 95% of patients experienced adequate adhesion (i.e., at least 75% of system surface area adhered to the skin). Of the 854 systems applied, 20 (2.3%) required taping to ensure adhesion and 7 (0.8%) fell off the patient.

The fifth most common reason for returning a system (3% of all returned systems) was for cosmetic blemishes noted in the hydrogel (e.g., voids) or shrinkage of the hydrogel. The investigational sites identified these as suspected technical failure; these systems, however, operated normally upon analysis. Visual inspection procedures to identify cosmetic defects are used during the manufacturing process (see Section 3.2.P.3).

One returned system had a defective light emitting diode (LED) and another system was returned after being exposed to a magnetic resonance imaging (MRI) procedure. This system was found to be inoperable. Product labeling has been modified to specify that the system should be removed before MRI exposure. The patient was uninjured by the exposure.

2.0 Comparative Performance: IV PCA and E-TRANS® (fentanyl HCl) System

The dosing pattern of E-TRANS® (fentanyl HCl) System use was similar to that observed with the IV PCA morphine treatment with respect to frequency of dosing over time and the proportion of total available doses activated. The mean total amounts of fentanyl and morphine administered to all patients were within ranges commonly reported in the literature.

In the active-controlled trial (C-2000-007), system replacement due to suspected technical failures included 5.2% of the IV PCA pumps activated (17 of 330 pumps) and 3.7% of the E-TRANS® (fentanyl HCl) Systems activated (22 of 590 systems). In addition, among 185 lines used for IV PCA morphine patients, 36 lines (19.5%) required removal, primarily for infiltration and nonpatency.

3.0 Used System Analysis

In addition to the systems returned due to possible malfunction, 60 systems that were perceived to have functioned correctly in clinical study C-2000-007 were also analyzed per agreement with the Agency. This analysis included functionality testing of the and chemical analysis of the drug-containing anode hydrogels. The fentanyl content was determined and found to be correlated with the clinical information indicating the number of doses administered. All 60 systems were found to be free of defects and had normal function, confirming the perception of normal function.

4.0 Conclusions

The E-TRANS® (fentanyl HCl) System was effective in the management of moderate to severe pain as shown by comparison to placebo systems. In addition, pain management was found to be therapeutically equivalent to patient-controlled IV infusion of morphine from a pump.

Analysis of suspected technical failures (Clinical Reliability) from Phase 3 clinical studies identified failure modes that were also observed in the primary stability studies, with the most common mode being nonfunctioning systems caused by Failures due to human interaction with the system were few in number and primarily due to cosmetic and skin adhesion issues. No serious failure modes were seen in the clinical studies. All systems failed safely, and no adverse events resulted from any failure. In addition, analysis of systems that functioned normally during clinical use confirmed the clinicians. and patients' perception of normal system function.

Comment by K. Lee

The E-TRANS (fentanyl HCl) System is an electrically-assisted transdermal delivery system designed for the management of acute pain in patients requiring opioid analgesia. This product is recommended for use

The system is patient-activated and provides on-demand systemic delivery of fentanyl by means of a small electric current (a technology known as iontophoresis or electrotransport). Electrotransport technology uses an electrical potential to provide noninvasive delivery of therapeutic substances across intact skin for local and systemic applications. The Hydrogen skin contact area is 2.8cm^{-2}.

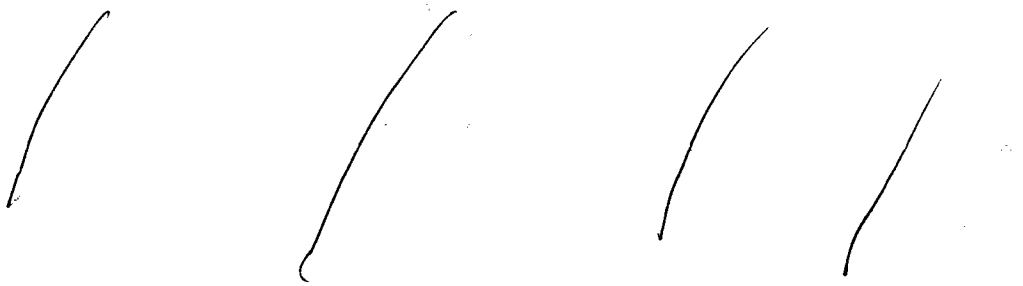
The specifications are as the following:

The pHs of anode and cathode are respectively. The current density is μA/ cm^{-2} (= μA/ cm^{-2}). Mean interdose current is set for and number of dose of the device is doses.

The following table is "Functional Parameters for the Top Housing Assembly (0012204)"

The Top Housing Assembly (THA) consists of a nat conforms to the inside of a top housing component.

P



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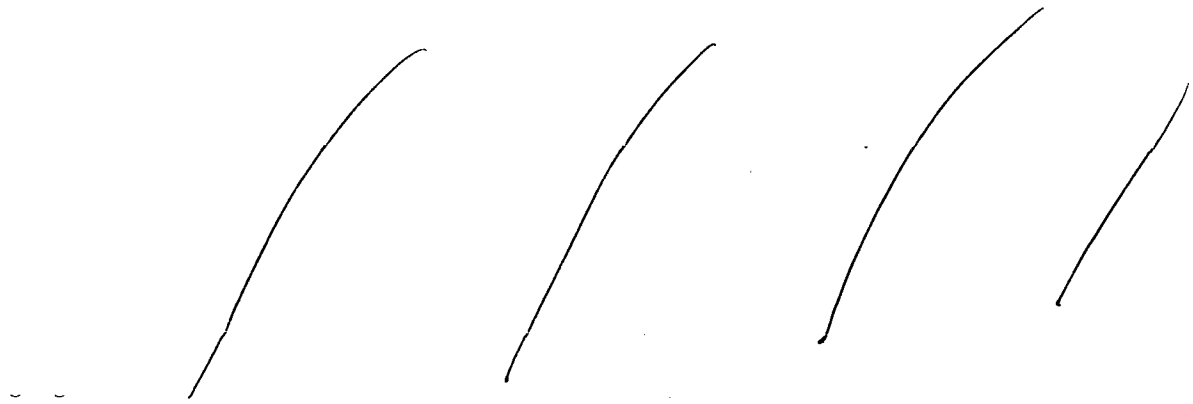

As to "Shelf Life Results for E-TRANS® (fentanyl HCl) Systems" , the sponsor stated as the following:
"The shelf life for the E-TRANS (fentanyl HCl) System is based on stability results from three primary stability lots (referred to as registration stability lots [RSLs]) and supporting data from clinical lots and qualification lots.

A total of systems from 25°C storage were tested through . Of these, s) were found to be nonfunctional, the majority (210) caused by . A total of systems from 40°C storage were tested through . Of these, systems) were found to be nonfunctional, the majority caused by Some of the systems functioned properly after failing the initial button-push test, and no problem was identified in these systems."

The sponsor also stated as the following:
corrective action lots have been manufactured and placed on accelerated stability. Data from these lots will be submitted for review when available to verify successful resolution of the problem.

As to the risk analysis, the sponsor stated as the following:
There are risk of overdose, which seems unlikely since the device is shown to fail safely(non function). Intentional abuse of the product is another risk, which is not relevant to intended use of this device. The sponsor stated that stability data for these lots will be provided in the update to this NDA. Once the stability data is updated, the stability data will be reviewed. The non function device was for for system from 25°C, and for from from 40°C. The failed devices were all not functioning. There is no safety issue.
The sponsor also described " Post-Approval Stability Protocol and Stability Commitment, for the quality assurance of the device, which seems appropriate. % of devices for months failed to work properly and seems too high.

The sponsor did not describe the detailed and exact mechanism in which each component of the device is working.
The sponsor should describe how each component of device works.

I found the following deficiencies, based on the review.
Deficiencies

1. Please explain the mechanism your device maintains and regulates current, voltage , and how each component of your device, such as integral circuit, etc, is working altogether in your device.
2. Please describe how your device maintains the current and voltage for 10 minutes and the mechanism how 80 doses are exactly delivered to the patients in your device.
3. Please describe the mechanism how is working to maintain each dose for 10 minutes in your device.
4. Please describe the leakage current of each electrode, e.g., cathode and anode in your device.
5. Please describe the mechanism how the is working and its accuracy in your device.
6. Please describe how the working to maintain the current and voltage for 10 minutes in your device.
7. Please provide data from corrective action lots for the problem of the device when these are available.

K. Lee, M.D.
Medical officer

T. Stevens
Chief, REOB