- determine the actual human exposure to the impurities under normal use conditions, possibly with — They will present a proposal and timelines and may require further discussions with the Agency before submitting their response
- provide their rationale on the naming terminology
- address concerns regarding safe and effective use of the product
- provide a complete picture of the pharmacokinetics, device aspects of the product, appropriate use of the product, etc.
-

Dr. Harapanhalli referred back to the stability specifications discussion earlier in the meeting. The sponsor indicated that they hoped to have a discussion with the Agency on this issue before submitting their response. The sponsor clarified that they felt they needed two additional meetings with the Agency before they were ready to respond; one to discuss RMP issues, the other to discuss outstanding issues on exposure, stability, etc.

Action Items:

- Additional meetings to clarify other pending issues such as the RMP and CMC, will to be requested by the sponsor as needed.

- The Agency will prepare the official minutes of the meeting and provide the sponsor with a copy.

Minutes prepared by: Kim Compton
Minutes concurred by Chair: Celia Winchell, M.D.

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/s/

Kimberly Compton
10/8/04 07:39:10 PM

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation ODE II

FACSIMILE TRANSMITTAL SHEET

DATE: August 18, 2004

To: Sue Rinne/Kim Gaumer	**From:** Parinda Jani
Company: Alza Corporation	Division of Anesthetic, Critical Care, and Addiction Drug Products
Fax number: (650) 564-2581	**Fax number:** (301) 443-7068
Phone number(650) 564-2520	**Phone number:** (301) 827-7422

Subject: Comments from the Office of Drug Safety for the Risk Management Plan

Total no. of pages including cover:

Comments: Hello Sue and Kim: I am forwarding you these comments provided by the Office of Drug Safety for your proposed Risk Management Plan. Hopefully, this would be helpful to you prior to responding to the action letter and also, prior to meeting with the Agency to discuss the contents of the RMP.

Document to be mailed: • YES ☑ NO

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_ § 552(b)(4) Draft Labeling

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/s/

Parinda Jani
8/18/04 01:33:48 PM
CSO

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-338

DISCIPLENE REVIEW LETTER

ALZA Corporation
1900 Charleston Road
P.O. Box 7210
Mountain View, CA 94039-7210

Attention: Susan P. Rinne
Vice President, Regulatory Affairs

Dear Ms. Rinne:

Please refer to your September 23, 2003, new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Ionsys (fentanyl HCl) system.

The CDRH Office of Compliance has completed the review of the device manufacturing section of your NDA and have identified the following deficiencies.

This combination product should comply with the design controls, purchasing controls and corrective and preventative action portions of 21 CFR part 820 in addition to the requirements of 21 CFR part 211.

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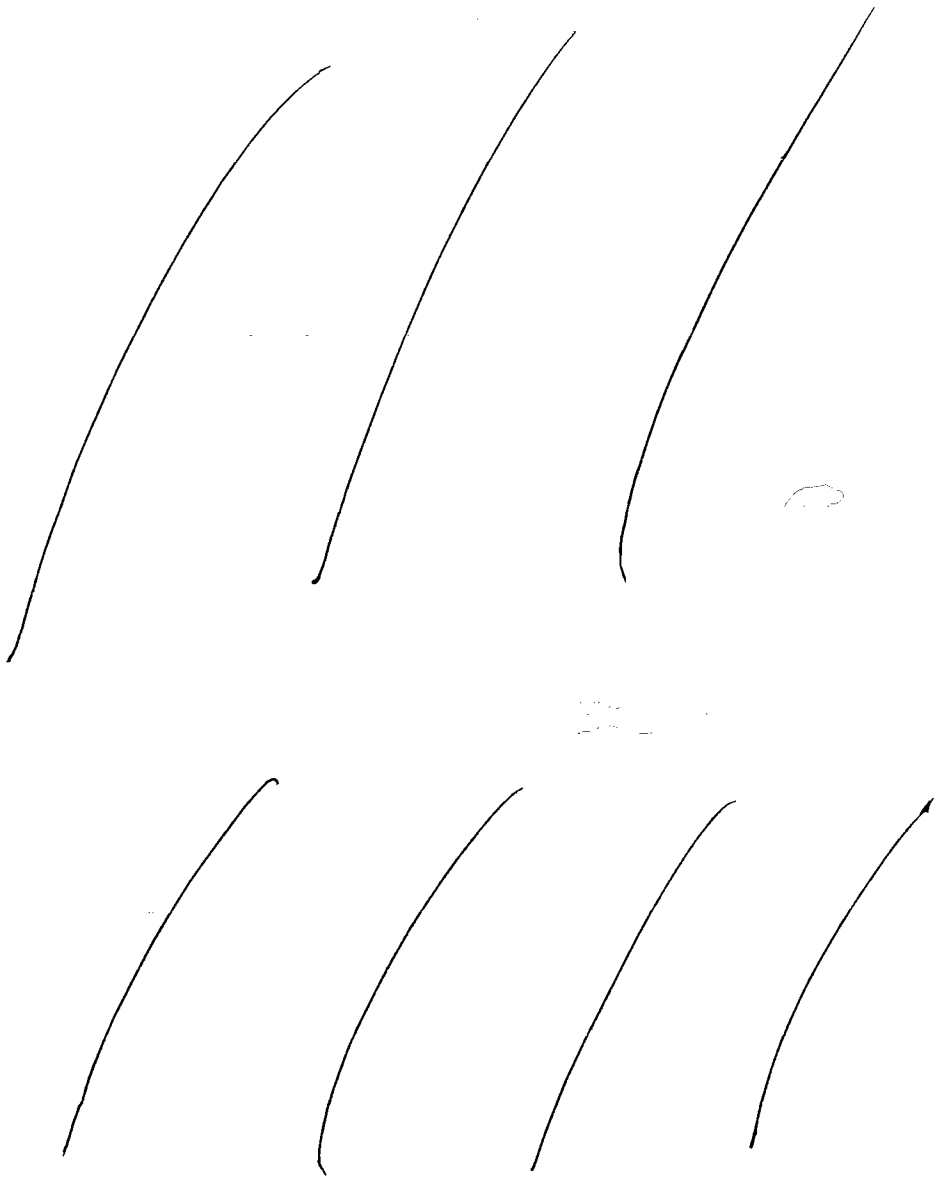
/s/

Parinda Jani
7/23/04 09:17:30 PM

We believe that this combination product should comply with the design controls, purchasing controls and corrective and preventative action portions of 21 CFR part 820 in addition to the requirements of 21 CFR part 211.

OC has reviewed the device manufacturing section of your NDA and believes that it lacks the information necessary to effectively complete a review and determine whether to initiate a QSR inspection. Please provide the following information:



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/s/

Kimberly Compton
7/12/04 03:52:19 PM
CSO
e-copy of CDRH-OC review #1 (list of defs to send to sponsor) rec'd by email 3-16-04. Checking into DFS for ease of future and to complete the record

MEMORANDUM

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

Memo of Clinical Issues - Communicated to Sponsor by fax

DATE: July 9, 2004

TO: Alza Corporation, c/o Jennifer Ekelund (650-564-2581)

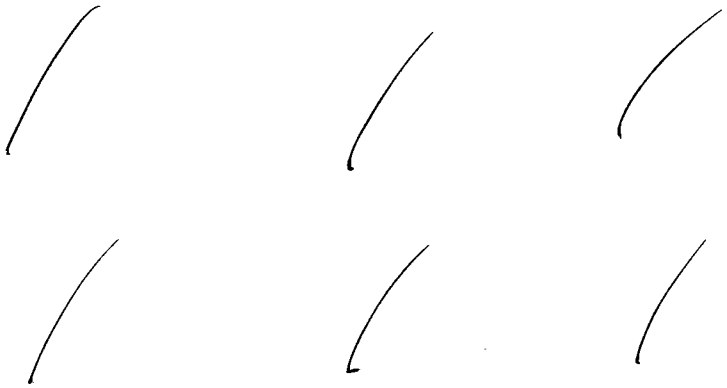
THROUGH : Parinda Jani, CPMS, HFD-170
Ravi Harapanhalli, Ph.D., Chemistry Team Leader, HFD-170
Elizabeth McNeil, M.D., Medical Officer, HFD-170
Bob Rappaport, M.D., Division Director, HFD-170

FROM: Kim Compton (Comptonk@cder.fda.gov, fax # 301-443-7068, phone 301-827-7432)

RE: NDA 21-338, E-trans Fentanyl System CMC Issues

Background:
In a teleconference with the sponsor on June 8, 2004, several CMC issues were outlined that would require additional sponsor follow-up. The issues are provided in this memo for clarity and completeness. *A copy of this memo will be faxed to the sponsor today.*

As discussed during the teleconference on June 8, 2004, provide the following revisions to the specifications.



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/s/

Kimberly Compton
7/9/04 05:47:56 PM
CSO

DATE	June 22, 2004
FROM:	K. Lee, M. D., Medical officer FDA / CDRH / ODE / DGRND / REDB
SUBJECT:	NDA 21338 (fentanyl HCl Patient-Controlled Transdermal System)
TO:	The file

Final Comments by K. Lee
In the last, the following FDA's questions were asked to the sponsor. The sponsor responded to FDA questions The responses from the sponsor were adequate. I don't have any further deficiencies.

1. Explain the mechanism by which the device maintains and regulates voltage. [redacted], and how each component of the device, such as [redacted] integral circuit, etc., work together.

2. Describe how the device maintains the current and voltage for ten minutes and the mechanism by which exactly eighty doses are delivered to the patient.

3. Describe how the [redacted] works to maintain each dose for ten minutes.

4. Describe the [redacted] of each electrode in the device.

5. Specifically describe how the [redacted] mechanism works and comment on its accuracy in the device.

6. Describe how the [redacted] work to maintain the current and voltage for ten minutes in the device.

7. Provide data from [redacted] corrective action lots for the [redacted] problem of the device and explain how design improvements are expected to minimize the incidence of [redacted] seen in the primary stability batches.

8. Provide updated [redacted] long-term stability data in SAS transport files, for the corrective action lots including data on number of non-functional units. Also provide SAS transport files of the stability data at 30°C and 40°C for these lots.

9. [redacted] have been described as the causes for the stability failures seen in the primary stability batches and the corrective action lots. Provide data on the root cause for these design problems. Explain whether [redacted] was a major contributing factor for the stability-related failures.

K. Lee, M.D.
Medical office

The following are the FDA questions and the sponsor's responses.

The questions from the May 28, 2004 Information Request Letter are presented in bold below. The sponsor's responses are provided immediately following each question.

FDA Question

1. Explain the mechanism by which the device maintains and regulates voltage. [redacted] and how each component of the device, such as [redacted] integral circuit, etc., work together.

The Firm stated as the following:
Response:
As described in the NDA overview and the component specification submitted in the April 30, 2004 NDA Amendment, the device consists of the following functional blocks, each with a specific set of components as listed:

5

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CONSULTATION RESPONSE

DIVISION OF MEDICATION ERRORS AND TECHNICAL SUPPORT
OFFICE OF DRUG SAFETY
(DMETS; HFD-420)

DATE RECEIVED:	**DESIRED COMPLETION DATE:**	**ODS CONSULT #:** 04-0131
April 6, 2004	June 8, 2004 **PDUFA DATE:** July 23, 2004	

TO: Bob Rappaport, MD
Director, Division of Anesthetic, Critical Care and Addiction Drug Products
HFD-170

THROUGH: Kim Compton
Project Manager
HFD-170

PRODUCT NAME:	**NDA SPONSOR:** Alza Corporation
Ionsys (Fentanyl Hydrochloride Patient-Controlled Transdermal Analgesic) 40 micrograms per dose **NDA#:** 21-338	

SAFETY EVALUATOR: Kimberly Culley, RPh

RECOMMENDATIONS:

1. DMETS has no objections to the use of the proprietary name, Ionsys. This is considered a tentative decision and the firm should be notified that this name with its associated labels and labeling must be re-evaluated approximately 90 days prior to the expected approval of the NDA. A re-review of the name prior to NDA approval will rule out any objections based upon approvals of other proprietary or established names from the signature date of this document.

2. DMETS recommends implementation of the label and labeling revisions outlined in section III of this review to minimize potential errors with the use of this product.

3. DDMAC finds the proprietary name of Ionsys acceptable from a promotional perspective.

Carol Holquist, RPh
Director, Division of Medication Errors and Technical Support
Office of Drug Safety
Phone: (301) 827-3242
Fax: (301) 443-9664

Division of Medication Errors and Technical Support (DMETS)
Office of Drug Safety
HFD-420; PKLN Rm. 6-34
Center for Drug Evaluation and Research

PROPRIETARY NAME REVIEW

DATE OF REVIEW: May 03, 2004

NDA# 21-338

NAME OF DRUG: Ionsys (Fentanyl Hydrochloride) Patient-Controlled Transdermal Analgesic 40 micrograms per dose

NDA HOLDER: Alza Corporation

I. INTRODUCTION:

This consult was written in response to a request from the Division of Anesthetic, Critical Care and Addiction Drug Products (HFD-170), for proprietary name assessment of Ionsys regarding potential name confusion with other proprietary or established drug names. Container, carton and insert labeling were provided for review and comment.

Because of the potential for serious side effects for patients taking Ionsys, a risk management plan has been proposed by the sponsor. This plan was the subject of an internal meeting between members of the review division and the Office of Drug Safety. DMETS reviewed the risk management plan from a medication safety perspective and provided comments to be incorporated into a coordinated response from the Office of Drug Safety.

PRODUCT INFORMATION

Ionsys is a patient-controlled iontophoretic transdermal system to deliver fentanyl to adult patients for the management of acute pain. This product is to be used only in medically supervised settings. Fentanyl is an opioid analgesic. This medication interacts predominantly with the opioid μ-receptor. These sites are discretely distributed in the human brain, spinal cord, and other tissues. The primary actions of fentanyl are analgesia and sedation. Fentanyl may also cause altered mood, euphoria, dysphoria and drowsiness. Fentanyl depresses the respiratory centers and the cough reflex, and constricts the pupils.

The Ionsys device delivers 40 micrograms of fentanyl over a ten minute period. The device is activated by a pressing the recessed button twice within three seconds. The start of each dose is indicated by an audio tone with a red light illuminates continuously throughout administration. The device is applied to the upper outer arm or chest and delivers a maximum of six 40 microgram doses per hour. The maximum amount of fentanyl that can be administered over twenty-four hours is 3.2 milligram (80-40 microgram doses). Each device operates for twenty-four hours or until eight doses have been administered, whichever comes first.

II. RISK ASSESSMENT:

The medication error staff of DMETS conducted a search of several standard published drug product reference texts[1,2] as well as several FDA databases[3] for existing drug names which sound-alike or look-alike to Ionsys, to a degree where potential confusion between drug names could occur under the usual clinical practice settings. A search of the electronic online version of the U.S. Patent and Trademark Office's Text and Image Database was also conducted[4]. An expert panel discussion was conducted to review all findings from the searches. In addition, DMETS conducted three prescription analysis studies consisting of two written prescription studies (inpatient and outpatient) and one verbal prescription study, involving health care practitioners within FDA. This exercise was conducted to simulate the prescription ordering process in order to evaluate potential errors in handwriting and verbal communication of the name.

A. EXPERT PANEL DISCUSSION (EPD)

An Expert Panel discussion was held by DMETS to gather professional opinions on the safety of the proprietary name, Ionsys. Potential concerns regarding drug marketing and promotion related to the proposed name were also discussed. This group is composed of DMETS Medication Errors Prevention Staff and representation from the Division of Drug Marketing, Advertising, and Communications (DDMAC). The group relies on their clinical expertise, professional experiences and a number of standard references when making a decision on the acceptability of a proprietary name.

1. DDMAC finds the proprietary name Ionsys acceptable from a promotional perspective.

2. The Expert Panel identified one proprietary name that was thought to have the potential for confusion with Ionsys. This product with dosage forms available and usual dosage. is listed in table 1 (see below).

Table 1: Potential Sound-Alike/Look-Alike Names Identified by DMETS Expert Panel

Product Name	Established name, Available dosages, Dosage form	Usual adult dose*	Other**
Ionsys	Fentanyl Hydrochloride, Patient-Controlled Transdermal Analgesic System, Delivers 40 mcg Over Ten Minutes	Patient-Controlled Analgesia. Up to 80 doses of 40 mcg.	
Unasyn	Ampicillin Sodium and Sulbactam Sodium, 1.5 gram (1 gram ampicillin and 0.5 gram sulbactam sodium), 3 grams (2 grams ampicillin sodium/1 gram sulbactam sodium), 15 grams (10 gram ampicillin sodium/5 gram sulbactam sodium), Powder for Injection	1.5 to 3 grams every six hours.	LA
*Frequently used, not all-inclusive. **L/A (look-alike), S/A (sound-alike)			

[1] MICROMEDEX Integrated Index, 2004, MICROMEDEX, Inc., 6200 South Syracuse Way, Suite 300, Englewood, Colorado 80111-4740, which includes all products/databases within ChemKnowledge, DrugKnowledge, and RegsKnowledge Systems.
[2] Facts and Comparisons, online version, Facts and Comparisons, St. Louis, MO.
[3] AMF Decision Support System [DSS], the Division of Medication Errors and Technical Support [DMETS] database of Proprietary name consultation requests, New Drug Approvals 98-04, and the electronic online version of the FDA Orange Book.
[4] WWW location http://tess2.uspto.gov/bin/gate.exe?f=tess&state=2fmprd.1.1

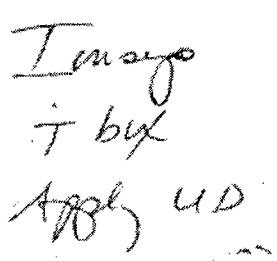
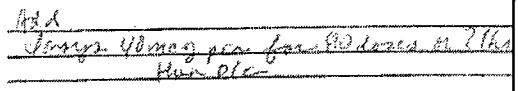
B. PHONETIC and ORTHOGRAPHIC COMPUTER ANALYSIS (POCA)

As part of the name similarity assessment, proposed names are evaluated via a phonetic/orthographic algorithm. The proposed proprietary name is converted into its phonemic representation before it runs through the phonetic algorithm. The phonetic search module returns a numeric score to the search engine based on the phonetic similarity to the input text. Likewise, an orthographic algorithm exists which operates in a similar fashion. All names considered to have significant phonetic or orthographic similarities to Ionsys were discussed by the Expert Panel (EPD).

C. PRESCRIPTION ANALYSIS STUDIES

1. Methodology:

Three separate studies were conducted within the Centers of the FDA for the proposed proprietary name to determine the degree of confusion of Ionsys with marketed U.S. drug names (proprietary and established) due to similarity in visual appearance with handwritten prescriptions or verbal pronunciation of the drug name. These studies employed a total of 124 health care professionals (pharmacists, physicians, and nurses). This exercise was conducted in an attempt to simulate the prescription ordering process. An inpatient order and outpatient prescriptions were written, each consisting of a combination of marketed and unapproved drug products and a prescription for Ionsys (see page 5). These prescriptions were optically scanned and one prescription was delivered to a random sample of the participating health professionals via e-mail. In addition, the outpatient orders were recorded on voice mail and sent to a random sample of the participating health professionals for their interpretations and review. After receiving either the written or verbal prescription orders, the participants sent their interpretation of the orders via e-mail to the medication error staff.

HANDWRITTEN PRESCRIPTION	VERBAL PRESCRIPTION
Outpatient RX: 	Ionsys One Box Use as Directed
Inpatient RX: 	

2. Results:

   None of the interpretations of the proposed name overlap, sound similar or look similar to any currently marketed U.S. product. See appendix A for the complete listing of interpretations from the verbal and written studies.

D. SAFETY EVALUATOR RISK ASSESSMENT

In reviewing the proprietary name Ionsys, the primary concerns related to look-alike confusion with Unasyn. Additionally, DMETS conducted prescription studies to simulate the prescription ordering process. In this case, there was no confirmation that the proposed name could be confused with any of the aforementioned names. The majority of misinterpretations were misspelled/phonetic variations of the proposed name, Ionsys. However, negative findings are not predicative as to what may occur once the drug is widely prescribed, as these studies have limitations primarily due to a small sample size.

Unasyn may look like Ionsys when scripted. Unasyn contains ampicillin sodium and sulbactam sodium for the treatment of infection caused by beta-lactamase producing strains of bacteria. This drug product can treat skin infections caused by beta-lactamase producing strains of Staphylococcus aureus, Escherichia coli, Klebsiella, Proteus mirabilis, Bacteroides fragilis, Enterobacter and Acinetobacter calcoaceticus. It is also used in the treatment of intra-abdominal infections caused by beta-lactamase producing strains of Escherichia coli, Klebsiella, Bacteroides, Enterobacter species and gynecological infections caused by beta-lactamase producing strains of Escherichia coli and Bacteroides species. Unasyn is available as powder for injection in the following strengths: 1.5 grams (1 gram ampicillin sodium and 0.5 gram sulbactam sodium), 3 grams (2 grams ampicillin sodium and 1 gram sulbactam sodium), and 15 grams (10 grams ampicillin sodium and 5 grams sulbactam sodium). Dosing is 1.5 to 3 grams every six hours. The primary visual similarity results from the shared, centrally located "sy" and the resemblance of "U" and "I" when scripted. In addition, the concluding "n" and "s" can look similar when scripted, especially since these are located at the end of the name where letters tend to be tapered and obscured (see page 6).

However, the products have no overlapping characteristics. They differ in strength (1.5 grams, 3 grams and 15 grams compared to 40 micrograms), dosing intervals (every six hours compared to patient controlled dosing), indications (infection versus compared to management), pharmacological-therapeutic category (antibiotic compared to opioid analgesic), dosage forms (injectable compared to iontophorectic transdermal system), and storage (regular pharmacy compared to controlled II substance locked storage). The likelihood for confusion is minimal given these differences.

III. LABELING, PACKAGING, AND SAFETY RELATED ISSUES:

[5]WWW location http://www.ismp.org/MSAarticles/specialissuetable.html

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IV. RECOMMENDATIONS:

A. DMETS has no objections to the use of the proprietary name Ionsys. This is considered a tentative decision and the firm should be notified that this name with its associated labels and labeling must be re-evaluated approximately 90 days prior to the expected approval of the NDA. A re-review of the name prior to NDA approval will rule out any objections based upon approvals of other proprietary and established names from the signature date of this document.

B. DMETS recommends implementation of the label and labeling revisions outlined in section III of his review that might lead to safer use of the product. We would be willing to revisit these issues if the Division receives another draft of the labeling from the manufacturer.

C. DDMAC finds the proprietary name Ionsys acceptable from a promotional perspective.

DMETS would appreciate feedback of the final outcome of this consult. We would be willing to meet with the Division for further discussion, if needed. If you have further questions or need clarifications, please contact Sammie Beam, project manager, at 301-827-2102.

Kimberly Culley, RPh
Safety Evaluator
Division of Medication Errors and Technical Support
Office of Drug Safety

Concur:

Alina Mahmud, RPh
Team Leader
Division of Medication Errors and Technical Support
Office of Drug Safety

Appendix A: DMETS Prescription Study Results

Inpatient	Outpatient	Voice
Ionsys	Ionsyo	Ionosis
Ponsys	Imsys	Ayoncis
Ionsys	Iomsep	Ionses
Ionsys	Imsego	Ionsys
Ionsys	Ionsys	Ionsis
Ionsys	Imsep	Iyonsis
Lovsyx	Imsys	Ionsis
Ionsys	Imsego	Ayatsis
Ionsys	Ionsys	Ionsys
Ionsys	Ionsep or Ionsys	Ayonsis
Ionsys	Imsep	Ionsys
Ionsys	Ionsig	Ionsys
Ionsys	Insep	Ioxis
Ionsys	Ionsep	Ionsis
Iosyn	Insep	Ionsis
Ionsys	Insigo	Ionsis
Ionsys	Insys	Ionsis
Ionsys	Ionsys	
Ionsys	Imsig	
Ionsys	Imsyp	
	Ionsys	
	Ionsys	

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/s/

Kimberly Culley
6/17/04 02:39:10 PM
DRUG SAFETY OFFICE REVIEWER

Alina Mahmud
6/18/04 11:51:42 AM
DRUG SAFETY OFFICE REVIEWER

Carol Holquist
6/18/04 12:54:41 PM
DRUG SAFETY OFFICE REVIEWER

For Consulting Center Use Only:

Date Received: _____
Assigned to: _____
Date Assigned: _____
Assigned by: _____

Completed date: _____
Reviewer Initials: _____
Supervisory Concurrence: _____

Intercenter Request for Consultative or Collaborative Review Form

To (Consulting Center):
Center: CDRH
Division: DGRND
Mail Code: HFZ- 410
Consulting Center Contact: Pauline Fogarty**
Building/Room #: CORP, Rm 350E
Phone #: 301-594-1184
Fax #: 301-594-2358
Email Address: PXF@CDRH.fda.gov
RPM/CSO Name and Mail Code: Pauline Fogarty (PXF@CDRH.fda.gov), HFZ-410, 301-594-1184

From (Originating Center):
Center: CDER
Division: DACCADP
Mail Code: HFD-170
Requesting Reviewer Name: Ravi Harapanhalli, Ph.D.
Building/Room #: PKLN 9B-45
Phone#: 301-827-7410
Fax #: 301-443-7068
Email Address: harapanhalli@cder.fda.gov
RPM/CSO Name: Kim Compton (comptonk@cder.fda.gov)
Requesting Reviewer's Concurring Supervisor's Name: Eric Duffy, Ph.D.

Receiving Division: If you have received this request in error, you must contact the request originator by phone immediately to alert the request originator to the error.

Date of Request: 6-18-04

Requested Completion Date: 6-22-04

Submission/Application Number:21-338
(Not Barcode Number)

Submission Type: NDA
(510(k), PMA, NDA, BLA, IND, IDE, etc.)

Submission Receipt Date: 6-11-04 (Amendment of NDA in response to questions raised by CDRH reviewer

Official Submission Due Date: 7/23/04

Name of Product: E-TRANS Fentanyl Delivery System

Name of Firm: Alza Corporation

Intended Use: [redacted]

Brief Description of Documents Being Provided (e.g., clinical data -- include submission dates if appropriate):
(This NDA Submission is entirely electronic except for vol. #1 which contains necessary forms and some summary information.)

A copy of Vol. #1 was delivered with our original "Filing Consult"for your benefit.

The entire submission (including the most recent submission, which is a response by the sponsor to questions raised in the CDRH review that were conveyed to the sponsor by the CDER review Division) can be accessed in the CDER Electronic Document Room (EDR). We understand that you currently have access to this system. ***The sponsor's responses to the questions posed by the CDRH review are the main topic of this consult.***

Documents to be returned to Requesting Reviewer? □ Yes ■ No

Complete description of the request. Include history and specific issues, (e.g., risks, concerns), if any, and specific question(s) to be answered by the consulted reviewer. The consulted reviewer should contact the request originator if questions/concerns are not clear. Attach extra sheet(s) if necessary:

This product makes extensive use of device technology (it is an iontophoretic delivery system) for its drug delivery function and therefore device aspects will play a key role in the review of the product for approval. Also, CDRH was involved in meetings with the sponsor during the development of the product and gave some advice to the sponsor from a device perspective.

CDER requests that CDRH review the materials recently submitted in response to questions generated by the CDRH reviewer and conveyed to the sponsor by the CDER review division. A response is needed as quickly as possible since we are near the end of the review cycle.

***CDRH PM/Supervisor: Please advise CDER Division requesting review of assigned reviewer as soon as possible so they may be invited to scheduled meetings and included in any correspondence.*

Type of Request: **X** Consultative Review □ Collabortive Review

APPEARS THIS WAY
ON ORIGINAL

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

DATE: **June 18, 2004**

TO: Bob Rappaport, M.D., Director
Division of Anesthetic, Critical Care, and Addiction Drug Products, HFD-170

FROM: Mark Avigan, M.D., Director
Division of Drug Risk Evaluation, HFD-430

Carol Holquist, RPh., Director
Division of Medication Error and Technical Support, HFD-420

Gerald DalPan, M.D., Director
Division of Surveillance, Research and Communication Support, HFD-410

DRUG: Ionsys™ system [formerly E-Trans fentanyl HCL)] Patient Controlled Transdermal System

NDA #: 21-338

APPLICANT: Alza Corporation

SUBJECT: Review of Proposed Risk Management Plan (submitted 4/2/04)

PID #: D040253

EXECUTIVE SUMMARY

Division of Drug Risk Evaluation (DDRE); Division of Surveillance, Research and Communication Support (DSRCS); and Division of Medication Errors and Technical Support (DMETS) have reviewed the Risk Management Plan for the Ionsys™ system submitted by Alza Corporation as part of its new drug application.

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/s/

Mary Dempsey
6/18/04 11:09:21 AM
DRUG SAFETY OFFICE REVIEWER

Mark Avigan
6/18/04 12:17:40 PM
DRUG SAFETY OFFICE REVIEWER

Carol Holquist
6/18/04 01:03:26 PM
DRUG SAFETY OFFICE REVIEWER

Gerald DalPan
6/18/04 04:45:59 PM
MEDICAL OFFICER

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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-338

INFORMATION REQUEST LETTER

ALZA Corporation
1900 Charleston Road
P.O. Box 7210
Mountain View, CA 94039-7210

Attention: Susan P. Rinne
Vice President, Regulatory Affairs

Dear Ms. Rinne:

Please refer to your September 23, 2003, new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for E-Trans (fentanyl HCl) system.

We are reviewing the chemistry and device sections of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

1. Explain the mechanism by which the device maintains and regulates voltage, — and how each component of the device, such as — , integral circuit, etc., work together.

2. Describe how the device maintains the current and voltage for ten minutes and the mechanism by which exactly eighty doses are delivered to the patient.

3. Describe how the — works to maintain each dose for ten minutes.

4. Describe the — of each electrode in the device.

5. Specifically describe how the — mechanism works and comment on its accuracy in the device.

6. Describe how the — work to maintain the current and voltage for ten minutes in the device.

7. Provide data from — corrective action lots for the — problem of the device and explain how design improvements are expected to minimize the incidences of — seen in the primary stability batches.

8. Provide updated [redacted] long-term stability data in SAS transport files, for the corrective action lots including data on number of non-functional units. Also provide SAS transport files of the stability data at 30^0C and 40^0C for these lots.

9. [redacted] have been described as the causes for the stability failures seen in the primary stability batches and the corrective action lots. Provide data on the root cause for these design problems. Explain whether [redacted] was a major contributing factor for the stability-related failures.

If you have any questions, call Kimberly Compton, Regulatory Project Manager, at (301) 827-7432.

Sincerely,

{See appended electronic signature page}

Ravi Harapnhalli, Ph.D.
Chemistry Team Leader
Division of Anesthetic, Critical Care, and
Addiction Drug Products
DNDC II, Office of New Drug Chemistry
Center for Drug Evaluation and Research

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/s/

Ravi Harapanhalli
5/28/04 02:45:49 PM
IR letter

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-338

INFORMATION REQUEST LETTER

ALZA Corporation
1900 Charleston Road
P.O. Box 7210
Mountain View, CA 94039-7210

Attention: Susan P. Rinne
Vice President, Regulatory Affairs

Dear Ms. Rinne:

Please refer to your September 23, 2003, new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for E-Trans (fentanyl HCl) system.

We are reviewing the clinical section of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

1. Review of the submitted data suggests that it would be useful to reanalyze the secondary efficacy endpoint, pain intensity, in study C-2000-008 using the hour 4 VAS scores as the baseline for 1) comparison of the Hour 24 scores and 2) comparison of the last observation VAS. Provide this reanalysis.

2. EFFILE, the efficacy analysis file, included only two variables: PI0 and PILAST for pain intensity at hour 0 and last pain intensity assessment at 24 hours, respectively. Provide a new dataset including variables for pain intensity at hour 0.5, 1, 2, 3, 4, 6, 8, 12, 16, 20 and 24 in addition to PI0 and PILAST for studies C-2001-011, C-2000-008, C-95-016, and C-2000-007.

If you have any questions, call Kimberly Compton, Regulatory Project Manager, at (301) 827-7432.

Sincerely,

{See appended electronic signature page}

Parinda Jani
Chief, Project Management Staff
Division of Anesthetic, Critical Care, and
Addiction Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

Parinda Jani
4/22/04 09:31:11 AM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-338

INFORMATION REQUEST LETTER

ALZA Corporation
1900 Charleston Road
P.O. Box 7210
Mountain View, CA 94039-7210

Attention: Susan P. Rinne
Vice President, Regulatory Affairs

Dear Ms. Rinne:

Please refer to your September 23, 2003, new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for E-Trans (fentanyl HCl) system.

We are reviewing the chemistry section of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

1. Provide the CMC information on the following noncompendial components of E-TRANS. Perform the USP physicochemical (USP <661>) and biological tests (USP <87>, <88>) for plastics.

   a.) —

   b.) Cathode electrode

   c.) — PIB adhesive

   d.) Red- bottom housing

   e.) Polacrilin —

   f.) Polyvinyl alcohol —

   g.) Siliconized — film

2. Provide a specification for the *in vitro* adhesion test for release and product shelf life.

3. Provide a specification for the — in anode and cathode hydrogel at release and through product shelf life.

4. The manufacturing process description indicates that

5. The manufacturing process indicates that

6. Provide the details of the

7. For batch-to-batch consistency, provide the

8.

9. Provide a clear description of the acceptance testing of the top housing assembly (top housing and and the IC being performed at Alza. Provide a representative COA for the top housing assembly obtained from

10. Provide justification for

If you have any questions, call Kimberly Compton, Regulatory Project Manager, at (301) 827-7432.

Sincerely,

{See appended electronic signature page}

Ravi Harapnhalli, Ph.D.
Chemistry Team Leader
Division of Anesthetic, Critical Care, and
Addiction Drug Products
DNDC II, Office of New Drug Chemistry
Center for Drug Evaluation and Research

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/s/

Ravi Harapanhalli
4/22/04 05:39:41 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-338

INFORMATION REQUEST LETTER

ALZA Corporation
1900 Charleston Road
P.O. Box 7210
Mountain View, CA 94039-7210

Attention: Susan P. Rinne
Vice President, Regulatory Affairs

Dear Ms. Rinne:

Please refer to your September 23, 2003, new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for E-Trans (fentanyl HCl) system.

We are reviewing the clinical section of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

1. The following comments pertain to your application in general.

   a. At your January 18, 2001, pre-NDA meeting with the Division, you agreed to provide data on the safety of maximal exposure to the 40 mcg dose. In your May 21, 2001, briefing package you agreed to plan a pharmacokinetic (PK) study of the effect of using the maximal number (N=80) of 40 mcg activations in the minimal amount of time (13.3 hours).

      Data from a PK study of the effect of administering 80 on-demand doses of 40 mcg of fentanyl within 13.3 hours is needed to complete the safety information for the label. Indicate where this information can be found in the NDA submission.

   b. Submit a full risk management plan as soon as possible for review by this Division as well as the Controlled Substances Staff (CSS). We remind you that the RMP must

   c. Six studies were stopped due to [redacted] leading to premature system shutdown. This problem was not the cause of technical failure in the subsequent studies. Provide a detailed description of what changes were made to eliminate the possibility of [redacted] leading to premature system shutdown.

2. Provide the demographics for Studies 95-050-01, 95-053, and 96-003.

3. For Study 95-050-01, your synopsis states that 25 patients enrolled but only 24 completed. Clarify what happened to the other patient.

4. In Study 96-003, 49/51 patients were assessed. Clarify what happened to the other 2 patients.

5. Provide a method of following participants from study 93-023 to study 93-043, using patient ID numbers.

6. The following comments pertain to Study 2000-006.

   a. At the time of withdrawal of consent, patient 827 rated pain as 99/100 and assessed efficacy as poor. This patient should have been classified as withdrawal due to inadequate analgesia.

   b. Patient 803 was estimated to have received 113 doses of fentanyl and had somnolence reported as a SAE. Clarify why the device continued to administer on-demand doses of fentanyl after reaching the stated maximum of 80 doses.

7. For Study 2000-009, clarify the apparent discrepancy between the diagram (p.55-Figure B patient disposition) in the study report and the data in Table11.2.2-1.b. The number of patients who withdrew consent and the number who discontinued for "other reasons" do not match when one compares the information in the table with that in the diagram.

8. The following comments pertain to Study C-95-016.

   a. In light of you protocol amendment #5, dated April 30 1997, subsequent to study initiation, were the concomitant medications CRFs reviewed for mistaken inclusion of rescue medication doses?

   b. Your protocol amendment #6 excluded patients with known hypersensitivity to nickel or metal jewelry due to [redacted] his exclusion does not appear to be present in the proposed labeling. Provide the rationale for the omission.

If you have any questions, call Kimberly Compton, Regulatory Project Manager, at (301) 827-7432.

Sincerely,

{See appended electronic signature page}

Parinda Jani
Chief, Project Management Staff
Division of Anesthetic, Critical Care, and
Addiction Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

Parinda Jani
2/12/04 09:26:30 AM

For Consulting Center Use Only:

Date Received: 1/23/04
Assigned to: Kevin Lee
Date Assigned: 1/23/04
Assigned by: Ted Stevens

Completed date: 4/13/04
Reviewer Initials: KLL
Supervisory Concurrence: TLS 4/14/04

Intercenter Request for Consultative or Collaborative Review Form

To (Consulting Center):
Center: CDRH
Division: DGRND
Mail Code: HFZ- 410
Consulting Center Contact: Pauline Fogarty**
Building/Room #: CORP, Rm 350E
Phone #: 301-594-1184
Fax #: 301-594-2358
Email Address: PXF@CDRH.fda.gov
RPM/CSO Name and Mail Code: ~~Pauline Fogarty~~ (PXF@CDRH.fda.gov), HFZ-410, 301-594-1184

From (Originating Center):
Center: CDER
Division: DACCADP
Mail Code: HFD-170
Requesting Reviewer Name: Ravi Harapanhalli, Ph.D.
Building/Room #: PKLN 9B-45
Phone#: 301-827-7410
Fax #: 301-443-7068
Email Address: harapanhalli@cder.fda.gov
RPM/CSO Name: Kim Compton (comptonk@cder.fda.gov)
Requesting Reviewer's Concurring Supervisor's Name: Eric Duffy, Ph.D.

Receiving Division: If you have received this request in error, you must contact the request originator by phone immediately to alert the request originator to the error.

Date of Request: 12-9-03

Requested Completion Date: May 1, 2004

Submission/Application Number:21-338
(Not Barcode Number)

Submission Type: NDA
(510(k), PMA, NDA, BLA, IND, IDE, etc.)

Submission Receipt Date: 9/24/03

Official Submission Due Date: 7/23/04

Name of Product: E-TRANS Fentanyl Delivery System

Name of Firm: Alza Corporation

Intended Use:

Brief Description of Documents Being Provided (e.g., clinical data -- include submission dates if appropriate):
This NDA Submission is entirely electronic except for vol. #1 which contains necessary forms and some summary information.

A copy of Vol. #1 was delivered with our "Filing Consult"for your benefit. If additional copies are required, please notify the consulting project manager so they can be requested from the sponsor.

The entire submission can be accessed in the CDER Electronic Document Room (EDR). We understand that you currently have access to this system.

Documents to be returned to Requesting Reviewer? □ Yes ■ No

Complete description of the request. Include history and specific issues, (e.g., risks, concerns), if any, and specific question(s) to be answered by the consulted reviewer. The consulted reviewer should contact the request originator if questions/concerns are not clear. Attach extra sheet(s) if necessary:

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NO FILING ISSUES IDENTIFIED

NDA 21-338

ALZA Corporation
1900 Charleston Road
P.O. Box 7210
Mountain View, CA 94039-7210

Attention: Susan P. Rinne
Vice President, Regulatory Affairs

Dear Ms. Rinne:

Please refer to your September 23, 2003, new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for E-Trans (fentanyl HCl) system.

We also refer to your submissions dated November 12 and 14, 2003.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, this application has been filed under section 505(b) of the Act on November 23, 2003 in accordance with 21 CFR 314.101(a).

At this time, we have not identified any potential filing review issues. Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review.

If you have any questions, call Kim Compton, Regulatory Project Manager, at (301) 827-7432.

Sincerely,

{See appended electronic signature page}

Parinda Jani
Chief, Project Management Staff
Division of Anesthetic, Critical Care, and
Addiction Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

Parinda Jani
12/5/03 02:45:41 PM

August 28, 2003

U.S. Food and Drug Administration (360909)
Mellon Client Service Center, Rm. 670
500 Ross Street
Pittsburgh, PA 15262-0001

RE: FDA User Fee for E-TRANS® (fentanyl HCl) System
New Drug Application

NDA No. 21-338 (N021338)
User Fee ID No. 4315

To Whom It May Concern:

Enclosed please find a check in the amount of $533,400 to cover the Prescription Drug User Fee for Fiscal Year 2003 for a new drug application requiring clinical data for approval, as published in the Federal Register (Vol. 67, No. 149 / Friday, August 2, 2002), for E-TRANS® (fentanyl HCl) System (NDA No. 21-338). A copy of the signed User Fee Cover Sheet (Form FDA 3397) for NDA 21-338 is also enclosed.

The User Fee Identification Number is 4315.

If you have any questions, please contact me by telephone at 650-564-2523 or by facsimile at 650-564-2581.

Sincerely,

Susan P. Rinne
Vice President, Regulatory Affairs
ALZA Corporation

Enclosures:
Check No. 4218543
Copy of Form FDA 3397 (User Fee Cover Sheet)

Invoice No	Date	Vcher	Att	Gross Amt	Discount	Net Amount	CHECK NUMBER	4218543
				NDA21-338 FEE4315 /VERBO-MALLAX				
Q6601886	082103	K01886	Y	533,400.00		533,400.00		

VISIT OUR WEBSITE AT WWW.AP.JNJ.COM
FOR INVOICING ON THE WEB,
ELECTRONIC PAYMENTS, AND PAYMENT HISTORY.
YOUR SUPPLIER NUMBER IS 026449523

Query? Call 877-557-4487 or write ALZA CORPORATION , Box 16538, NEW BRUNSWICK NJ 08906
SUPPLIER#: 026449523 SUPPLIER: US FOOD & DRUG ADMIN TOTAL: 533,400.00
Please Validate Tax Id # ==> EIN 53-0196965

DETACH HERE DETACH HERE

THE FACE OF THIS DOCUMENT HAS A MULTICOLORED BACKGROUND - NOT A WHITE BACKGROUND

ALZA CORPORATION

Johnson & Johnson SERVICES, INC.
AS PAYING AGENT

THE CHASE MANHATTAN BANK, N.A.
SYRACUSE, NEW YORK

CHECK NO: 4218543

50-937
213

**********533,400.00

PAYABLES CHECK

DATE	CHECK AMOUNT
08/25/03	*$****533,400.00

PAY EXACTLY: FIVE HUNDRED THIRTY THREE THOUSAND *** FOUR HUNDRED AND NO/100 DOLLARS ******

TO THE ORDER OF: US FOOD & DRUG ADMIN (360909)
MELLON CLIENT SERV CTR
500 ROSS STREET RM 670
PITTSBURGH PA 15260-0001

John H Kapp

Johnson & Johnson

THE BACK OF THIS DOCUMENT CONTAINS AN ARTIFICIAL WATERMARK - HOLD AT AN ANGLE TO VIEW

⑈4218543⑈ ⑆021309379⑆ 601⑈2⑈21252⑈

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

IND 41,574

ALZA Corporation
1900 Charleston Road
P.O. Box 7210
Mountain View, California 94039-7210

Attention: Kimberley Gaumer
Associate Director, Regulatory Affairs

Dear Ms. Gaumer:

Please refer to the meeting between representatives of your firm and FDA on June 6, 2001. The purpose of the meeting was to obtain concurrence from the Agency on the current E-TRANS system design and to obtain agreement on the

The official minutes of that meeting are enclosed. You are responsible for notifying us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at (301) 827-7440.

Sincerely,

{See appended electronic signature page}

Judit Milstein
Regulatory Project Manager
Division of Anesthetic, Critical Care, and
Addiction Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure: Minutes of the meeting

Minutes of the Meeting

INDUSTRY MEETING Date: June 6, 2001 Time:1:30 p.m. Location: Conference Room B

DRUG: E-TRANS (fentanyl hydrochloride) delivery system IND 41,574

INDICATION: ———

SPONSOR: ALZA Corp.

TYPE of MEETING: guidance

INDUSTRY PARTICIPANTS:
Linda Atkinson, PhD, Director, Clinical Operations
Kimberley Gaumer, Associate Director, Regulatory Affairs
Suneel Gupta, PhD, Vice President, Clinical Pharmacology
Martin O'Connell, PhD, Senior Director, Data Management and Statistics
Edward Schnipper, M.D., Vice President, Clinical Research
Janne Wissel, Senior Vice President, Operations

FDA PARTICIPANTS:
Cynthia McCormick, M.D., Division Director
Bob Rappaport, M.D., Deputy Division Director
Hal Blatt, D.D.S., Medical Officer
Albert Chen, Ph.D., Biopharmaceutics Reviewer
Gerald DalPan, M.D., Medical Officer
Judit Milstein, Regulatory Project Manager

MEETING OBJECTIVES:

To obtain concurrence from the Agency on the current E-TRANS system design and to obtain agreement ———

BACKGROUND

In response to the minutes of the pre-NDA meeting conducted on January 18, 2001 (FDA's minutes issued on March 21, 2001), and a subsequent teleconference on February 23, 2001, Alza Corp. submitted a Type A meeting request on April 16, 2001. Included in the meeting request were a draft list of specific questions in reference to:

A. /

B. The current E-TRANS system design (Question #2) and

A. — ———

In a letter dated May 5, 2001, the Division informed Alza Corp. that a type A meeting would be granted to address Question #1, and a Type C meeting would be granted to address Questions #2-4.

These minutes reflect the discussions and agreements reached in the Type C meeting.

DISCUSSION

Following the introduction of the participants, a general discussion on the clinical development plan for E-TRANS was held. Highlights of this discussion are summarized below.

1. The Division indicated that the major obstacles to Alza's current development plan for E-Trans are and the need for safety data on the higher and maximum number of activations with the 40 µg dose.

2. Alza indicated that in Patient Controlled Activation (PCA) systems, the safety is the sum of the safety of the delivery system, the drug delivered, and the patient experience of pain. The E-TRANS development plan has a built-in program to determine the accuracy of the delivery of drug. In addition, Alza's current safety database (approximately 1700 patients, 1400 of them in Phase 3 trials) indicates that the number of subjects using the higher(>70) or maximum (80) number of activations represent only 5% of the total population investigated.

3. In light of the information provided above, and in order to achieve a sufficient number of subjects to provide an adequate safety database in the cohort of patients treated with the higher or maximum number of activations, the E-TRANS system would have to be studied in 10,000-15,000 subjects. Alza proposed studying the safety of using the higher and maximum number of activations as a Post-Marketing Commitment.

1. Alza indicated that their intention is to launch the 40 µg dose . The Division also encouraged Alza to provide in their submission a rationale for the safety of the E-TRANS system, including the history of safety of PCA morphine and PCA fentanyl.

5.

6. A Risk Management Program has to be implemented at the time of the NDA approval. It should include

7. It is likely that an Advisory Committee will have to be convened to evaluate the safety profile of the E-TRANS product.

8.

9.

10.

Judit Milstein, Regulatory Project Manager, 6-14-01

Bob Rappaport, Deputy Division Director concurrence 7-3-01

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/s/

Judit Milstein
7/3/01 04:49:24 PM

Bob Rappaport
7/3/01 05:02:05 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

IND 41,574

ALZA Corporation
1900 Charleston Road
P.O. Box 7210
Mountain View, California 94039-7210

Attention: Kimberley Gaumer
Associate Director, Regulatory Affairs

Dear Ms. Gaumer:

Please refer to the meeting between representatives of your firm and FDA on January 18, 2001. The purpose of the meeting was to discuss the submission of the NDA for E-TRANS (fentanyl hydrochloride) delivery system.

The official minutes of that meeting are enclosed. You are responsible for notifying us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at (301) 827-7440.

Sincerely,

{See appended electronic signature page}

Judit Milstein
Regulatory Project Manager
Division of Anesthetic, Critical Care, and
Addiction Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure: Minutes of the meeting

Minutes of the Meeting

INDUSTRY MEETING Date: January 18, 2001 Time:10:30 a.m. Location: Potomac Room

DRUG: E-TRANS (fentanyl hydrochloride) delivery system IND 41,574

INDICATION: ——

SPONSOR: ALZA Corp.

TYPE of MEETING: pre-NDA

FDA PARTICIPANTS:

Cynthia McCormick, M.D.	Division Director
Bob Rappaport, M.D.	Deputy Division Director
Hal Blatt, D.D.S.	Medical Officer 1-22-01
Kathleen Haberny, Ph.D.	Pharm-Tox Reviewer 1-22-01
Tom Papoian, Ph.D.	Supervisory Pharmacologist
Mike Theodorakis, Ph.D.	Chemistry Reviewer
Dale Koble, Ph.D.	Acting Chemistry Team Leader
Albert Chen, Ph.D.	Biopharmaceutics Reviewer
Suresh Doddapaneni, Ph.D.	Biopharmaceutics Team Leader
George Liao,	Regulatory Health Information Specialist
Stella Grosser, Ph.D.	Biostatistics Reviewer
Tom Permutt, Ph.D.	Biostatistics Team Leader
Sharon Hertz, M.D.	Medical Officer
Gerald DalPan M.D.	Medical Officer
John Jenkins, M.D.	Director, Office of Drug Evaluation II
Kevin Lee, Ph.D.	Medical Officer, CDRH
Judit Milstein	Regulatory Project Manager

INDUSTRY PARTICIPANTS:

Linda Atkinson, PhD, Director, Clinical Operations
Anne Chester, PhD, DABT, Director, Toxicology
Kimberley Gaumer, Associate Director, Regulatory Affairs
Suneel Gupta, PhD, Vice President, Clinical Pharmacology
Rebecca Mock, Manager, Technical Regulatory Affairs
Martin O'Connell, PhD, Senior Director, Data Management and Statistics
Bradley Phipps, PhD, Vice President, Transdermal Technologies
Edward Schnipper, PhD, Vice President, Clinical Operations
Janne Wissel, Senior Vice President, Operations

MEETING OBJECTIVES:

Discuss the questions posted by the sponsor in the briefing package submitted on December 15, 2000.

After introductions, the questions posted by the sponsor were addressed as follows:

QUESTIONS:

1. General/NDA Format

1.a Does the Division concur with the content of the NDA in support of E-TRANS® (fentanyl HCl) Electrotransport System ***[see tab: "NDA Table of Contents"]***

Each discipline addressed this question in their presentation.

1.b ALZA plans to format the NDA as outlined in 21 CFR 314, with the exception of the CMC section, which we plan to format using the ICH M-4 Common Technical Document guideline. Is this acceptable to FDA?

Using the ICH M-4 Common Technical Document guideline is acceptable.

1.c *Archival Copy of NDA:*

Electronic Archival Records:
ALZA plans to submit electronic archival copies (pdf files on CD-ROMs) for the following sections of the NDA, based on FDA's Guidance for Industry: "Providing Regulatory Submissions in Electronic Format - NDAs" and "Providing Regulatory Submissions in Electronic Format - General Considerations"

Form 356h Section:
Section 2: Labeling
Section 3: Summary
Section 4: CMC & Device
Section 5: Nonclinical
Section 6: Human Pharmacokinetics
Sections 8 & 10: Clinical/Statistical
Section 11: Case Report Tabulations (CRTs)
Section 12: Case Report Forms (CRFs)

Paper Archival Records:
We propose to provide a paper archival copy of documents that contain a signature (financial disclosure forms, patent certification, debarment statement). Does the Division concur that a primarily electronic NDA (with only the above referenced documents provided on paper) is acceptable? Is the proposed format and organization of the electronic submission (extent of hypertext links, bookmarks, fonts) acceptable? ***[see tab: "Electronic NDA Scope and Format"].***

The Division concurs with ALZA on the electronic and archival record's proposal. Please, also note the following comments provided by Mr. George Liao, Regulatory Health Information Specialist.

1. Include fonts in PDF files.

2. Avoid SCANNED images.

3. Suggest Electronic Study Reports from Contract Laboratories.

4. Use a Unique ID number in all studies.

5. Use Define.pdf to define all data variable names.

6. Avoid merging multiple variables into a single column.

7. Use Bookmarks or Hyperlinks to link

   a. Tables
   b. Appendices
   c. Figures
   d. References
   e. Individual Narratives

1.d *Review Copy of Technical Sections of NDA:*
We propose to submit electronic review copies (no paper) of all of the above electronic archival sections (Form 356h sections 4: CMC & Device, 5: Nonclinical, 6: Human Pharmacokinetics, 8: Clinical, 10: Statistical, 11: CRTs and 12: CRFs. Paper review copies would be provided for Section 2 (Labeling), Section 3 (Summaries) as well as all documents that are provided in paper archival form as noted in 1.b above. Is this proposal acceptable to FDA?

Provide 6 paper copies of the 1.1 volume including the index and table of context as well as Word version of the annotated, non-annotated ("clean"), and highlighted labeling.

2. Preclinical

2.a *ALZA has performed several skin irritation and delayed contact sensitization studies with E-TRANS® (fentanyl HCl) Electrotransport Systems, as well as skin irritation, sensitization and biocompatibility studies with many of the individual system components. In addition, ALZA plans to include in the NDA a letter allowing right of reference to non-clinical data on fentanyl from Janssen Research Foundation.*

- *Does the Division concur that the completed E-TRANS® (fentanyl HCl) non-clinical studies are adequate to support the intended use of the E-TRANS® (fentanyl HCl) Electrotransport System* ***[see tab: "Pharmacology/Toxicology" for list of studies to be submitted in the NDA]***

The Division concurs with ALZA in the adequacy of the non-clinical studies to support the use of E-TRANS

2.b *Due to the well-established pharmacological and toxicological actions of fentanyl, we propose to include hypertext links to all non-clinical fentanyl references cited in the NDA pre-clinical summary and to have available upon request references listed in each individual E-TRANS® (fentanyl HCl) toxicology report. Does the Division concur that this is an acceptable approach for this NDA?*

The Division concurs with ALZA that this is an acceptable approach for this NDA.

3. Clinical/Statistical

3.a *The outline for the Integrated Summary of Safety (ISS) is presented in the briefing package. Does the Division concur that the proposal, including sub-analyses and pooling plan, is adequate?* ***[see tab: "ISS Outline/Pooling Plan"]***

The plan appears to be generally adequate. However, data collected from all patients on all levels of <95% O_2 saturation are needed. These data should be categorized into groups of two or three percentage points (not just O_2 saturation levels below 90% or 88%) in the "Outline of Pooling Plan" section under "Methods for Data Collection and Adverse event Categorization" [p.105/159, 105/162].

3.b *Are the mock data tables (primary efficacy/safety) presented in the briefing package acceptable to the medical/statistical/PK reviewers?* ***[see tabs: "Draft Tables in ISS" and "Mock Safety and Efficacy Tables"***

Mock data tables presented in the briefing package are generally acceptable. However, changes or additions may become necessary at the time of filing and/or review.

3.c *In the "Clinstat" folder, we propose to include all the study reports as outlined in Section 8 of the NDA Table of Contents (to be provided with briefing package). In addition, we plan to include statistical methodology, and SAS data sets for 3 controlled clinical trials (2 placebo-controlled studies, C-95-016 and C-2000-008, and 1 active comparator [IV PCA morphine] trial, C-2000-007) and the ISS. Data sets will be bookmarked in the "Clinstat" table of contents to the appropriate data definition file (define.pdf). Is this proposed content for the electronic submission of Section 8/10 acceptable to FDA? Are the proposed fonts to be used in tables (letter gothic and SAS monospace) acceptable?*

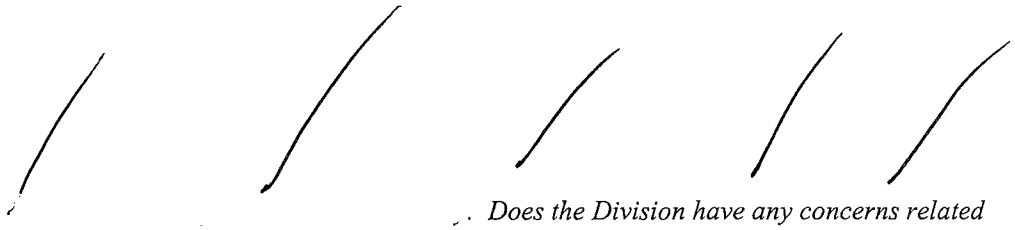
a. Clarification was requested on the meaning of the term "statistical methodology." Alza indicated that the term was meant broadly and could include the program utilized in their analysis. ALZA also indicated that the term "SAS data sets" refer to SAS transport files. The statistical reviewer indicated that on a primary basis, the SAS transport files and a detailed summary of the analysis are needed. The Division will request the program if needed during the review process.

b. While the usage of the proposed fonts (letter gothic and SAS monospace) is understandable, we request minimal use of them in the electronic submissions. Utilization of these fonts in their True Type versions is acceptable

3.d *In Sections 6 (PK) and 8 (clinical), we propose to include all publications from clinical and pharmacokinetic investigations performed with the E-TRANS® (fentanyl HCl) Electrotransport*

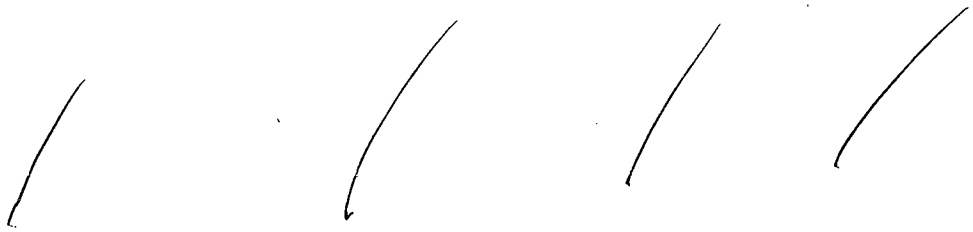
System developed for the management of acute pain requiring opioid analgesia. In addition, we plan to include references from a literature search on the clinical use of IV PCA fentanyl for the management of acute pain. Does the Division concur with this proposal?

The Division concurs with the proposal to include all publications from clinical and pharmacokinetic investigations performed with E-TRANS, as well as a literature search on the clinical use of IV PCA fentanyl.

3.e 

. Does the Division have any concerns related to the planned waiver request for children < 6 years of age? ***[see tab: "Pediatric Data"].***

The Division has no concerns related to the planned waiver request for children < 6 years of age.



3.f For all key Phase 1 and Phase 3 study reports in the NDA, we plan to include ICH appendices per the ICH E3 guideline, "Structure and Content of Clinical Study Reports". As the majority of the early Phase 1 feasibility and Phase 2 reports were written prior to the issuance of the E3 guideline, we propose to not include ICH appendix documents for these studies. Does the Division concur with this proposal?

a. The division concurs with your proposal regarding ICH appendices per the ICH E3 guidance as long as all critical studies follow the guideline and 21 CFR 314. However, there may be loss of useful safety data if you do not have the appendices for the non-key studies.

b. Any significant data from the earlier studies should be submitted in a clear, concise, and well-organized manner.

4. CMC/Device

4.a We plan to submit — real-time stability data on finished product lots — in the NDA. Additionally, — of data will be provided on used in the Phase 3 studies. The — data on the Phase 3 lots will be submitted during the NDA review period. The —primary registration lots contain the intended commercial anode (fentanyl-containing) and cathode hydrogel formulation. The top housing material (which holds the electronics) for the

commercial lots has been improved to assure the product meets the finished product specification throughout the proposed shelf life. A full description of the proposed primary registration lots compared to commercial product is presented in the briefing package. Does the Division agree that these lots, in conjunction with supportive data from the Phase 3 clinical lots, will support a expiry for E-TRANS® (fentanyl HCl) Electrotransport System? ***[see tabs: "Formulation in Phase 3 vs. Commercial" and "Stability"]***

The Division indicated that the used in Phase 3 studies (which are the to- be-commercialized device and manufactured at the proposed commercial site of Vaccaville) constitute the primary stability data. The lots manufactured at Palo Alto are supportive. Because of the close similarities in the device and the transfer of the manufacturing equipment from Palo Alto to Vaccaville, the NDA may be filed with the proposed stability data. However, this is at Alza's risk if any relevant questions arise concerning the similarities between the two sets of stability data.

In addition, the following issues have to be addressed at the time of NDA submission.

1. Data to demonstrate that the device remains reliable throughout its shelf life are needed. For instance

   a. Does the device shut off properly after administration of a single dose, after administration of six doses in one hour, and after administration of 80 doses?

   b. Are the LED function, beeper, and switch button reliable?

   c. Do the adhesion characteristics of the device remain unchanged throughout the shelf-life?

   d. Is there any impact on functionality due to

   e. Is still a problem for the electromechanical subassembly?

2. The drug product must have a 0% failure rate for the critical performance parameters (e.g., delivery of the correct amount of fentanyl). Provide the information characterizing the failure rate of the drug product and the controls that will ensure a 0% failure rate for the commercial drug product.

3. Provide a Drug Release Testing method and acceptance criteria for the drug product. The Division is aware of the difficulties of the methodology. However, it is essential to have a procedure to routinely test the release of drug from the device. In this context, it will also be appropriate to test with all the stability lots, with emphasis on conditions of low and high humidity. Frequency of the testing may be discussed further, once the data on the first lots have been evaluated.

4. Impurities have to be qualified per ICH guidelines.

5. Provide justification for all specifications (e.g.,

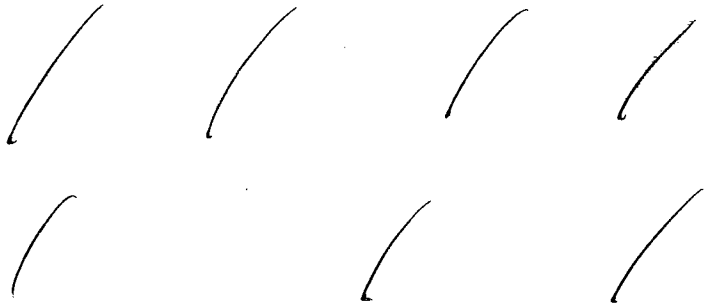
4.b Since E-TRANS® (fentanyl HCl) Electrotransport System contains device components, it has been agreed that CDRH will provide consultation on the pertinent device aspects of the application.

ALZA's initial proposal for a stand-alone device dossier for CDRH review was discussed at an August 1998 CDER/CDRH teleconference. Our proposed device dossier content has been revised based on that input. Are the sections of the submission that we propose to supply to CDRH adequate for their review? ***[see tabs: Key FDA Meeting Minutes, #6 "Device-related: CDER & CDRH" and "NDA Table of Contents", pages iii–vii of table of contents]***

The following information is needed for CDRH's review of the NDA:

1. Intended use of the device.
2. Full description of the device, and its components.
3. The specification and function of printed circuit and circuitry components.
4. Integrated circuit.

5. Current density and voltage, with its error limit.
6. Stability test including
7. The of the device during shelf life.
8. Size, material, and current density of active and disperse electrodes.
9. Skin irritation studies with electrode wearing.
10.
11.



4.c

4.d *Does the Division agree to waive the submission of the methods validation package with the original NDA submission? ALZA will provide those items upon request.*

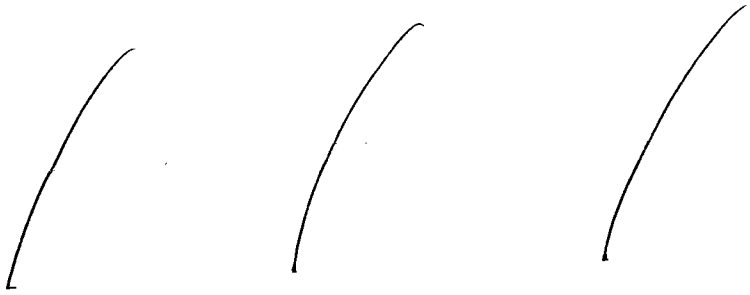
A method validation package must be included at the time of the NDA submission.

4.e *We propose to submit the CMC section of the NDA following the ICH M-4 guideline "Organization of the Common Technical Document for Registration of Pharmaceuticals for Human Use". Is this acceptable to FDA?* ***[see tab: "NDA Table of Contents", pages iii–vii of table of contents]***

Refer to item 1.b

Items 5. and 6. were not addressed at the meeting due to time constraints. However, included in this minutes are the Division's comments.

5. Planned Submissions during NDA Review Period



6. Advisory Committee Meeting
The product design, proposed clinical development plan, and potential risks and benefits of the E-TRANS® (fentanyl HCl) Electrotransport System were discussed at a closed session of the Life Support and Anesthetics Advisory Committee in April 1996. [see tab: Key FDA Meeting Minutes, #2, "Advisory Committee Meeting 4/30/96"]. The proposed clinical development plan was considered adequate to establish the efficacy and safety of the product. ALZA is evaluating a risk management program for the product, and plans to present this plan to FDA at a future date. Can the Division comment on the likelihood of an external consult via an Advisory Committee for the E-TRANS® (fentanyl HCl) Electrotransport System?

Review of the data submitted in the NDA will determine the necessity of an Advisory Committee.

7. Communication with FDA
We propose to establish an encrypted e-mail link with the Division to facilitate communication during the NDA review clock. Is this proposal acceptable to the Division? Is the Project Manager the appropriate FDA contact for setting up the e-mail link?

The Division concurs with your proposal to set up an encrypted e-mail link between Alza and the Division's Project Manager.

The following issues not included as specific questions in the briefing package were also addressed:

2. The Division wasn't able to identify in the development plan, any PK or safety data on the maximal exposure (on the 40µg dose to support its use. If patients would be able to administer up to a maximum of 80 doses in as proposed in the label, safety and PK data to support this dosing regimen are needed.

3.

4. Justification (e.g., batch data results and stability batch results) of drug product acceptance criteria is needed at the time of the NDA submission.

5. In addition to collecting and evaluating all failed device units, collect "non-failed" device units after patient use for performance evaluation.

6. Submit for review, as soon as it is available, a comprehensive risk management plan. The plan should address

7. Provide under Human Pharmacokinetics and Bioavailability section, summary tables for:

   a. Batches and formulation(s) used including electric currents.

   b. Assay method(s) and validation result(s) for plasma and/or urinary drug and/or metabolite levels.

8. Submission dated August 30, 1999, containing the protocol entitled "In-vivo/in vitro (IVIC) correlation of fentanyl drug delivery with electrical current" is still under review.

9.

Judit Milstein, Regulatory Project Manager

Bob Rappaport, Deputy Division Director concurrence

/s/

Bob Rappaport
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