

SECTION 16: DEBARMENT CERTIFICATION

ALZA Corporation hereby certifies that it did not and will not use in any capacity the services of any person(s) or firm debarred under section 306 of the Federal Food, Drug, and Cosmetic Act, as amended, in connection with this application.



Janne Wissel
Senior Vice President
Operations

19 May 03

Date

NDA/EFFICACY SUPPLEMENT ACTION PACKAGE CHECKLIST

NDA 21-338	Efficacy Supplement Type SE-	Supplement Number
Drug: IONSYS (fentanyl iontophoretic transdermal system)		Applicant: Alza Corporation
RPM: Kim Compton		HFD-170 Phone # 301-796-1191
<p>Application Type: <input checked="" type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) (This can be determined by consulting page 1 of the NDA Regulatory Filing Review for this application or Appendix A to this Action Package Checklist.)</p> <p>If this is a 505(b)(2) application, please review and confirm the information previously provided in Appendix B to the NDA Regulatory Filing Review. Please update any information (including patent certification information) that is no longer correct.</p> <p><input type="checkbox"/> Confirmed and/or corrected</p>		Listed drug(s) referred to in 505(b)(2) application (NDA #(s), Drug name(s)):
❖ Application Classifications:		
• Review priority		<input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority
• Chem class (NDAs only)		4S
• Other (e.g., orphan, OTC)		
❖ User Fee Goal Dates		
		5-22-06
❖ Special programs (indicate all that apply)		
		<input checked="" type="checkbox"/> None <input type="checkbox"/> Subpart H <input type="checkbox"/> 21 CFR 314.510 (accelerated approval) <input type="checkbox"/> 21 CFR 314.520 (restricted distribution) <input type="checkbox"/> Fast Track <input type="checkbox"/> Rolling Review <input type="checkbox"/> CMA Pilot 1 <input type="checkbox"/> CMA Pilot 2
❖ User Fee Information		
• User Fee		<input checked="" type="checkbox"/> Paid UF ID number 4315
• User Fee waiver		<input type="checkbox"/> Small business <input type="checkbox"/> Public health <input type="checkbox"/> Barrier-to-Innovation <input type="checkbox"/> Other (specify)
• User Fee exception		<input type="checkbox"/> Orphan designation <input type="checkbox"/> No-fee 505(b)(2) (see NDA Regulatory Filing Review for instructions) <input type="checkbox"/> Other (specify)
❖ Application Integrity Policy (AIP)		
• Applicant is on the AIP		<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
• This application is on the AIP		<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
• Exception for review (Center Director's memo)		

<ul style="list-style-type: none"> • OC clearance for approval 	
<ul style="list-style-type: none"> ❖ Debarment certification: verified that qualifying language (e.g., willingly, knowingly) was not used in certification & certifications from foreign applicants are cosigned by US agent. 	(X) Verified
<ul style="list-style-type: none"> ❖ Patent 	
<ul style="list-style-type: none"> • Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought. 	(X) Verified
<ul style="list-style-type: none"> • Patent certification [505(b)(2) applications]: Verify that a certification was submitted for each patent for the listed drug(s) in the Orange Book and identify the type of certification submitted for each patent. 	21 CFR 314.50(i)(1)(i)(A) () Verified 21 CFR 314.50(i)(1) () (ii) () (iii)
<ul style="list-style-type: none"> • [505(b)(2) applications] If the application includes a paragraph III certification, it cannot be approved until the date that the patent to which the certification pertains expires (but may be tentatively approved if it is otherwise ready for approval). 	
<ul style="list-style-type: none"> • [505(b)(2) applications] For each paragraph IV certification, verify that the applicant notified the NDA holder and patent owner(s) of its certification that the patent(s) is invalid, unenforceable, or will not be infringed (review documentation of notification by applicant and documentation of receipt of notice by patent owner and NDA holder). <i>(If the application does not include any paragraph IV certifications, mark "N/A" and skip to the next box below (Exclusivity)).</i> • [505(b)(2) applications] For each paragraph IV certification, based on the questions below, determine whether a 30-month stay of approval is in effect due to patent infringement litigation. <p>Answer the following questions for each paragraph IV certification:</p>	() N/A (no paragraph IV certification) () Verified
<p>(1) Have 45 days passed since the patent owner's receipt of the applicant's notice of certification?</p> <p>(Note: The date that the patent owner received the applicant's notice of certification can be determined by checking the application. The applicant is required to amend its 505(b)(2) application to include documentation of this date (e.g., copy of return receipt or letter from recipient acknowledging its receipt of the notice) (see 21 CFR 314.52(e)).</p>	() Yes () No
<p><i>If "Yes," skip to question (4) below. If "No," continue with question (2).</i></p> <p>(2) Has the patent owner (or NDA holder, if it is an exclusive patent licensee) submitted a written waiver of its right to file a legal action for patent infringement after receiving the applicant's notice of certification, as provided for by 21 CFR 314.107(f)(3)?</p> <p><i>If "Yes," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next box below (Exclusivity).</i></p> <p><i>If "No," continue with question (3).</i></p>	() Yes () No
<p>(3) Has the patent owner, its representative, or the exclusive patent licensee filed a lawsuit for patent infringement against the applicant?</p> <p>(Note: This can be determined by confirming whether the Division has received a written notice from the applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of</p>	() Yes () No

receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)).

If "No," the patent owner (or NDA holder, if it is an exclusive patent licensee) has until the expiration of the 45-day period described in question (1) to waive its right to bring a patent infringement action or to bring such an action. After the 45-day period expires, continue with question (4) below.

- (4) Did the patent owner (or NDA holder, if it is an exclusive patent licensee) submit a written waiver of its right to file a legal action for patent infringement within the 45-day period described in question (1), as provided for by 21 CFR 314.107(f)(3)? () Yes () No

If "Yes," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next box below (Exclusivity).

If "No," continue with question (5).

- (5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification? () Yes () No

(Note: This can be determined by confirming whether the Division has received a written notice from the applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced within the 45-day period).

If "No," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next box below (Exclusivity).

If "Yes," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007) and attach a summary of the response.

❖ Exclusivity (approvals only)	
<ul style="list-style-type: none"> • Exclusivity summary • Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? (Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.) 	Summary is attached (signed 5-22-06).
<ul style="list-style-type: none"> • Is there existing orphan drug exclusivity protection for the "same drug" for the proposed indication(s)? Refer to 21 CFR 316.3(b)(13) for the definition of "same drug" for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification. 	() Yes, Application # _____ (X) No
❖ Administrative Reviews (Project Manager, ADRA) (indicate date of each review)	N/A

❖ Actions	
• Proposed action	(X) AP () TA () AE () NA
• Previous actions (specify type and date for each action taken)	AE—7-23-04
• Status of advertising (approvals only)	(X) Materials requested in AP letter () Reviewed for Subpart H
❖ Public communications	
• Press Office notified of action (approval only)	(X) Yes () Not applicable
• Indicate what types (if any) of information dissemination are anticipated	(X) None () Press Release () Talk Paper () Dear Health Care Professional Letter
❖ Labeling (package insert, patient package insert (if applicable), MedGuide (if applicable))	
• Division's proposed labeling (only if generated after latest applicant submission of labeling)	X (see AP letter)
• Most recent applicant-proposed labeling	X (2 nd Cycle original)
• Original applicant-proposed labeling	X (1 st Cycle original)
• Labeling reviews (including DDMAC, DMETS, DSRCS) and minutes of labeling meetings (<i>indicate dates of reviews and meetings</i>)	DDMAC—4/13/06 DSRCS—3/15/06 and 4/13/06 DMETS—6/18/04 (cycle 1), 4/14/06 and 4/20/06
• Other relevant labeling (e.g., most recent 3 in class, class labeling)	
❖ Labels (immediate container & carton labels)	
• Division proposed (only if generated after latest applicant submission)	X (agreed on 5/18/06)
• Applicant proposed	
• Reviews	(Information incorporated into labeling reviews listed above)
❖ Post-marketing commitments	
• Agency request for post-marketing commitments	N/A
• Documentation of discussions and/or agreements relating to post-marketing commitments	
❖ Outgoing correspondence (i.e., letters, E-mails, faxes)	X
❖ Memoranda and Telecons	
❖ Minutes of Meetings	
• EOP2 meeting (indicate date)	2/18/99
• Pre-NDA meeting (indicate date)	1/18/01
• Pre-Approval Safety Conference (indicate date; approvals only)	N/A
• Other	Type C—6/6/01 Post-Action (cycle 1) #1—9-10-04 Post-Action (cycle 1) #2—11-23-04 Post-Action (cycle 1) #3—2/10/05 Post-Action (cycle 1) #4—4/22/05
❖ Advisory Committee Meeting	
• Date of Meeting	N/A
• 48-hour alert	N/A

❖ Federal Register Notices, DESI documents, NAS/NRC reports (if applicable)	N/A
❖ Summary Reviews (e.g., Office Director, Division Director, Medical Team Leader) (indicate date for each review)	X (TL memo-cycle 1)—7/15/04 X (Div Dir AE memo)—7/23/04 X (Div Dir AP memo)—5/22/06
❖ Clinical review(s) (indicate date for each review)	X (cycle 1)—7/23/04 X (cycle 2)—5/19/06
❖ Microbiology (efficacy) review(s) (indicate date for each review)	N/A
❖ Safety Update review(s) (indicate date or location if incorporated in another review)	See Clinical Rvw
❖ Risk Management Plan review(s) (indicate date/location if incorporated in another rev)	X (ODS-cycle 1) – 6/18/04 X (ODS-cycle 2, Rvw #1) – 4/4/06 X (ODS-cycle 2, Rvw #2) – 4/27/06 (plus CSS rvws listed below)
❖ Pediatric Page(separate page for each indication addressing status of all age groups)	X (5/22/06)
❖ Demographic Worksheet (NME approvals only)	N/A
❖ Statistical review(s) (indicate date for each review)	X (cycle 1) – 6/21/04
❖ Biopharmaceutical review(s) (indicate date for each review)	X (cycle 1) – 7/9/04
❖ Controlled Substance Staff review(s) and recommendation for scheduling (indicate date for each review)	X (cycle 1) – 6/3/04 X (cycle 2) – 5/8/06
❖ Clinical Inspection Review Summary (DSI)	
• Clinical studies	N/A
• Bioequivalence studies	N/A
❖ CMC review(s) (indicate date for each review)	X (cycle 1) – 7/19/04 X (cycle 2) – 5/19/06
❖ Environmental Assessment	
• Categorical Exclusion (indicate review date)	X (7/19/04)
• Review & FONSI (indicate date of review)	
• Review & Environmental Impact Statement (indicate date of each review)	
❖ Microbiology (validation of sterilization & product sterility) review(s) (indicate date for each review)	X (cycle1) – 4/27/04
❖ Facilities inspection (provide EER report)	Date completed: (X) Acceptable () Withhold recommendation
❖ Methods validation	() Completed (X) Requested () Not yet requested
❖ Pharm/tox review(s), including referenced IND reviews (indicate date for each review)	X (cycle 1) – 7/23/04 X (cycle 2) – 5/19/06
❖ Nonclinical inspection review summary	
❖ Statistical review(s) of carcinogenicity studies (indicate date for each review)	
❖ CAC/ECAC report	



NDA 21-338

DISCIPLINE 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 patient-activated transdermal system.)

We also refer to your submissions dated November 21, 2005 and March 21, 2006.

The Office of Drug Safety (ODS) and the Controlled Substances Staff (CSS) reviews of your RiskMAP are complete, and we have identified the following deficiencies:

[Redacted content]

A

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

§ 552(b)(5) Deliberative Process

§ 552(b)(4) Draft Labeling

We are providing these comments to you before we complete our review of the entire application to give you preliminary notice of issues that we have identified. In conformance with the prescription drug user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and subject to change as we finalize our review of your application. In addition, we may identify other information that must be provided before we can approve this application. If you respond to these issues during this review cycle, depending on the timing of your response, and in conformance with the user fee reauthorization agreements, we may not be able to consider your response before we take an action on your application during this review cycle.

If you have any questions, call Kimberly Compton, Regulatory Project Manager, at (301) 796-1191.

Sincerely,

{See appended electronic signature page}

Sara E. Stradley, M.S.
Chief, Project Management Staff
Division of Anesthesia, Analgesia and
Rheumatology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

Parinda Jani
5/12/2006 04:16:22 PM
for Sara Stradley



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 Ionsys (fentanyl HCl patient-activated transdermal system.)

We also refer to your submissions dated November 21, 2005.

We have reviewed your proposed carton and container labeling and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

B

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§ 552(b)(4) Draft Labeling

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/s/

Sara Stradley
5/5/2006 06:50:30 PM

MEMORANDUM
DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
CONTROLLED SUBSTANCE STAFF

Date: April 24, 2006

To: Robert Rappaport, M.D., Director
Division of Anesthesia, Analgesia, and Rheumatology Products
(HFD-170)

Through: Deborah Leiderman, M.D., Director
Sylvia Calderon, Ph.D., Team Leader
Controlled Substances Staff (HFD-009)

From: Patricia Beaston, M.D., Ph.D., Medical Officer

Consult: The Division of Anesthesia, Analgesia, and Rheumatology Products consulted the Controlled Substance Staff (CSS) for comments on the RMP for the Ionsys (fentanyl HCL) Patient Activated Transdermal System. (NDA 21-388)

Company: ALZA Corporation

Materials received: A copy of the Risk Management Program (RMP) proposed by the Company (submitted to the NDA March 21, 2006, Volume No. 33).

Materials reviewed: The RMP proposed by ALZA; meeting minutes and reviews found in DFS for NDA 21-338; the initial CSS consult for abuse potential provided to the Division of Anesthetic, Critical Care, and Addiction Products in June 3, 2004; and discussions with the Office of Drug Safety (ODS) review team.

C

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§ 552(b)(5) Deliberative Process

§ 552(b)(4) Draft Labeling

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/s/

Patricia Beaston
4/28/2006 10:30:06 AM
MEDICAL OFFICER

Silvia Calderon
5/1/2006 11:03:07 AM
CHEMIST

Deborah Leiderman
5/8/2006 05:42:06 PM
MEDICAL OFFICER

Office of Drug Safety

MEMO

To: Bob Rappaport, MD
Director, Division of Anesthesia, Analgesia, and Rheumatology Products, HFD-170

From: Todd Bridges, RPh, Safety Evaluator
Division of Medication Errors and Technical Support, WO22, Mailstop 4447

Through: Linda Y. Kim-Jung, PharmD, Team Leader
Denise P. Toyer, PharmD, Deputy Director
Carol Holquist, RPh, Director
Division of Medication Errors and Technical Support (DMETS), WO22, Mailstop 4447

Date: April 13, 2006

Re: ODS Consult 04-0131-2; Ionsys (Fentanyl Hydrochloride Patient-Activated Transdermal System) 40 micrograms per dose; NDA 21-338

This memorandum is in response to a March 9, 2006 request from your Division for a re-review of the proprietary name, Ionsys. The proposed proprietary name, Ionsys, was previously found acceptable by the Division of Medication Errors and Technical Support (DMETS) in ODS Consult 04-0131 dated June 17, 2004. Since the completion of our initial consult, DMETS has not identified any additional proprietary or established drug names which have the potential for confusion with Ionsys. Additionally, label and labeling are being reviewed in a separate consult (ODS Consult 04-0131-1).

In summary, DMETS has no objections to the use of the proprietary name, Ionsys. DMETS recommends implementation of the label and labeling revisions in ODS Consult 04-0131-1 which will be sent under separate cover. Additionally, DMETS recommends consulting Guiragos Poochikian of the CDER Labeling and Nomenclature Committee (LNC) on the proper designation of the established name of this product. Furthermore, DDMAC has no objections to the name from a promotional perspective. DMETS consider this a final review. However, if the approval of the NDA is delayed beyond 90 days from the date of this review, the name must be re-evaluated. A re-review of the name before NDA approval will rule out any objections based upon approvals of other proprietary and/or established names from the signature date of this document. If you have any questions or need clarification, please contact Diane Smith, Project Manager, at 301-796-0538.

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/s/

Todd Bridges
4/14/2006 02:09:31 PM
DRUG SAFETY OFFICE REVIEWER

Linda Kim-Jung
4/14/2006 02:10:42 PM
DRUG SAFETY OFFICE REVIEWER

Denise Toyer
4/14/2006 02:31:13 PM
DRUG SAFETY OFFICE REVIEWER
Also signing for Carol Holquist, DMETS Director, in her
absence

D

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§ 552(b)(5) Deliberative Process

§ 552(b)(4) Draft Labeling

MEMORANDUM

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

DATE: April 13, 2006

TO: Bob Rappaport, M.D., Director
Division of Anesthetic, Analgesia, and Rheumatology Products

VIA: Kim Compton, Regulatory Health Project Manager
Division of Anesthetic, Analgesia, and Rheumatology Products

FROM: Jeanine Best, M.S.N., R.N., P.N.P.
Patient Product Information Specialist
Division of Surveillance, Research, and Communication Support

THROUGH: Toni Piazza-Hepp, Pharm.D., Acting Director
Division of Surveillance, Research, and Communication Support

SUBJECT: DSRCs Review # 2 of Patient Labeling for Ionsys (fentanyl HCL patient-activated transdermal system), NDA 21-338

Background and Summary

The sponsor submitted revised patient labeling on April 4, 2006, for Ionsys (fentanyl HCL patient-activated transdermal system), NDA 21-338, in response to an Agency Information Request letter sent March 26, 2006.

The sponsor agreed to re-title the patient labeling as "Patient Bedside Sheet" and accepted most of the Agency's other requested revisions. We have reviewed the sponsor's April 4, 2006, submission and have shortened sentence length, simplified words, and deleted abbreviations in order to enhance comprehensibility for patients (see attached).

We can provide marked-up and clean copies of the revised document in Word if requested by the review division. Please let us know if you have any questions.

E

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/s/

Jeanine Best
4/13/2006 12:54:54 PM
DRUG SAFETY OFFICE REVIEWER

Laura Governale
4/13/2006 01:04:13 PM
DRUG SAFETY OFFICE REVIEWER
signed for Toni Piazza-Hepp, Acting Director

Stradley, Sara

From: Stradley, Sara
Sent: Tuesday, April 11, 2006 8:29 AM
To: 'Narayan, Sujatha [ALZUS]'; 'Gaumer, Kim [ALZUS]'
Cc: Compton, Kimberly; Stradley, Sara
Subject: IONSYS info request

Sujatha and Kim

We note that on page 61 of your submission, figure 4 shows all of the proposed educational materials grouped by different target groups. Please provide the following as soon as possible:

...



Thanks

Sara E. Stradley, MS
Chief, Project Management Staff
Division of Anesthesia, Analgesia and Rheumatology Products
Office of Drug Evaluation II
Office of New Drugs
Center for Drug Evaluation and Research
phone # 301-796-1298
email: Sara.Stradley@fda.hhs.gov

MEMORANDUM

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

DATE: March 15, 2006

TO: Bob Rappaport, M.D., Director
Division of Anesthetic, Analgesia, and Rheumatology Products

VIA: Kim Compton, Regulatory Health Project Manager
Division of Anesthetic, Analgesia, and Rheumatology Products

FROM: Jeanine Best, M.S.N., R.N., P.N.P.
Patient Product Information Specialist
Division of Surveillance, Research, and Communication Support

THROUGH: Toni Piazza-Hepp, Pharm.D., Acting Director
Division of Surveillance, Research, and Communication Support

SUBJECT: DSRCS Review of Patient Labeling for Ionsys (fentanyl HCL patient-activated transdermal system), NDA 21-338

Background and Summary

The sponsor submitted a complete response on November 21, 2005, in response to the July 23, 2004, Approvable Action for Ionsys (fentanyl HCL patient-activated transdermal system), NDA 21-338. The complete response submission included patient labeling, titled: _____

See the attached patient labeling that contain our recommended revisions.



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/s/

Jeanine Best
3/15/2006 02:27:47 PM
DRUG SAFETY OFFICE REVIEWER

Toni Piazza Hepp
3/15/2006 05:00:03 PM
DRUG SAFETY OFFICE REVIEWER

MEMORANDUM

**Division of Medication Errors and Technical Support
Office of Drug Safety
HFD-420; WO22, Mail Stop 4447
Center for Drug Evaluation and Research**

To: Bob Rappaport, MD
Director, Division of Anesthesia, Analgesia, and Rheumatology Products, HFD-170

Through: Denise Toyer, PharmD, Deputy Director
Carol Holquist, RPh, Director
Division of Medication Errors and Technical Support, HFD-420

From: Alina R. Mahmud, RPh, MS, Team Leader
Division of Medication Errors and Technical Support, HFD-420

Date: March 8, 2006

Re: ODS Consult #04-0131-1 Ionsys (Fentanyl HCl Patient-Activated Transdermal System)
40 mcg/dose; NDA 21-338

This memorandum is in response to the February 10, 2006 request from your Division for a review of the device label, pouch, carton and insert labeling as well as the Patient Information Sheet of Ionsys. Additionally, DMETS was requested to review the revised Risk Management Plan. At this time, DMETS will only provide comments pertaining to the device label, pouch, carton and insert labeling. Comments concerning the revised RMP will be forwarded from the Office of Drug Safety (ODS) Risk Management group in a separate consult. The Division of Surveillance, Research and Communication Support (DSRCS) will provide their revisions to the Patient Information Sheet in a separate consult.

In the review of the labels and labeling, DMETS has attempted to focus on safety issues relating to possible medication errors. DMETS has identified the following areas of possible improvement, which might minimize potential user error.



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/s/

Alina Mahmud
4/19/2006 02:12:37 PM
DRUG SAFETY OFFICE REVIEWER

Denise Toyer
4/20/2006 04:17:06 PM
DRUG SAFETY OFFICE REVIEWER
Also signing for Carol Holquist, Director, DMETS



MEMORANDUM

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

DATE: April 4, 2006

TO: Bob Rappaport, MD, Director
Division of Anesthesia, Analgesia, and Rheumatology Products
(DAARP)

THROUGH: Jonca Bull, MD, Acting Deputy Director
Office of Drug Safety (ODS)

FROM: Ionsys™ Risk Minimization Action Plan (RiskMAP) Team

DRUG: Ionsys™ (fentanyl HCL Patient Activated Transdermal System)

NDA: 21-338

SPONSOR: Alza Corporation, Mountain View, CA

SUBJECT: Interim Review of Revised RiskMAP submitted March 22, 2006

PID: D060006

The Office of Drug Safety reviewed the Ionsys™ (fentanyl HCL Patient Activated Transdermal System) Revised RiskMAP stamp dated March 22, 2006.

ODS offers the following comments to share with the sponsor:

H

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/s/

Mary Dempsey
4/4/2006 11:55:13 AM
DRUG SAFETY OFFICE REVIEWER

Jonca Bull
4/4/2006 05:31:10 PM
MEDICAL OFFICER



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 Ionsys (fentanyl HCl patient-activated transdermal system.)

We also refer to your submission dated November 21, 2005.

The Division of Surveillance, Research and Communication Support (DSRCS) has reviewed your _____ and has the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

N 21-338

Page 2

If you have any questions, call Kimberly Compton, Regulatory Project Manager, at (301) 796-1191.

Sincerely,

{See appended electronic signature page}

Sara E. Stradley, M.S.
Chief, Project Management Staff
Division of Anesthesia, Analgesia and
Rheumatology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure
Patient Bedside Information Sheet

I

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/s/

Bob Rappaport
3/26/2006 04:48:08 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

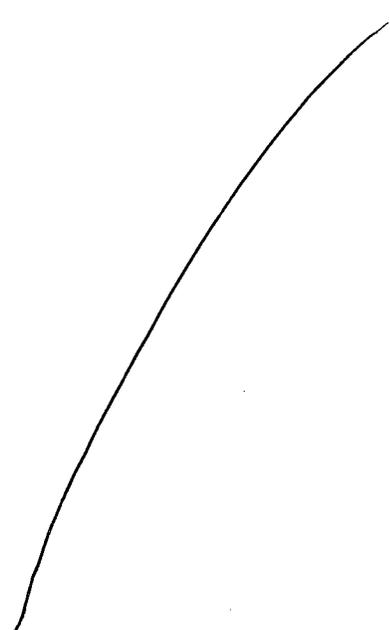
Attention: Susan P. Rinne
Vice President, Regulatory Affairs

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 Ionsys (fentanyl HCl) system.

We also refer to your submission dated November 21, 2005.

The Center for Devices and Radiologic Health (CDRH) is reviewing the device aspects of your submission and has the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.



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/s/

Sara Stradley
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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

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 New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Ionsys (fentanyl HCl) system.

We also refer to your April 22, 2005, correspondence, received April 25, 2005, requesting a meeting to discuss your proposed responses to the ODS comments on your RiskMAP and your proposed revisions to the RiskMAP for your product. We have considered your request and concluded that the meeting is unnecessary. However, in order to assist you in your preparation for NDA resubmission, we are providing the following information in response to questions included in your meeting request.

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§ 552(b)(4) Draft Labeling

N 21-338
Page 10

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

Sincerely,

{See appended electronic signature page}

Bob Rappaport, M.D.
Director
Division of Division of Anesthesia,
Analgesia and Rheumatology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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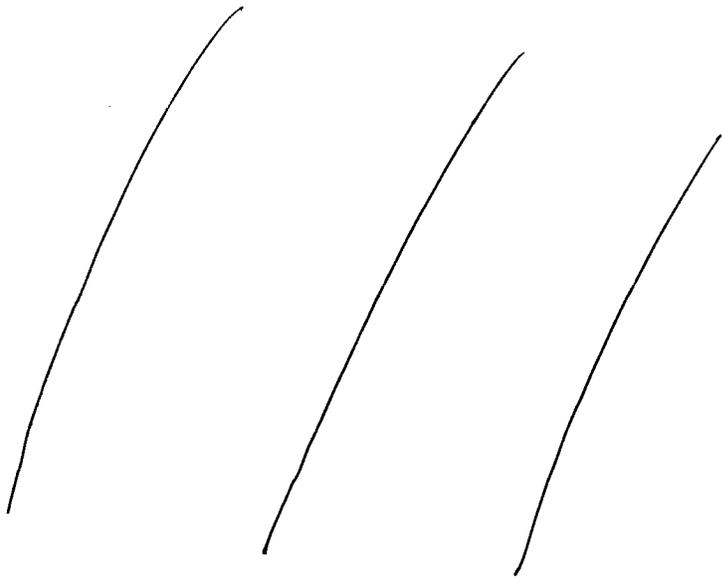
/s/

Rigoberto Roca
7/29/05 05:38:33 PM
for Bob Rappaport, M.D.

MEMORANDUM

Subject: Minutes of April 1, 2005 teleconference
Date: May 13, 2005
To: The file
Through: Bill MacFarland, Chief, OPMAD
From: Tracey Bourke, CSO, OPMAD

Teleconference held on April 1, 2005 to discuss Device-related issues for the E-TRANS as they relate to the planned resubmission of the NDA. Issues were provided to the sponsor via email prior to the teleconference.



ALZA planned to submit an informal, written response and inquired if there will be another such teleconference prior to the official response. Office of Compliance (OC) stated that since an in depth review of the current submission was done, the submission of responses to these issues should be complete given today's discussion. Therefore, OC declined to recommend informal resubmission of the responses and instead proposed to do another in depth review of the official NDA resubmission, including action items and responses to all of the deficiencies, when that official document is submitted.

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/s/

Kimberly Compton
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CSO



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

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 New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Ionsys (fentanyl HCl) system.

We also refer to your April 22, 2005, correspondence, received April 25, 2005, requesting a meeting to discuss your proposed responses to the ODS comments on your RiskMAP and your proposed revisions to the RiskMAP for your product. We have considered your request and concluded that the meeting is unnecessary. However, in order to assist you in your drug development program, we will be providing you with written comments in response to questions included in your meeting request.

If you have any questions me (301) 827-7432.

Sincerely,

{See appended electronic signature page}

Kimberly Compton, R.Ph.
Regulatory Project Manager
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/

Kimberly Compton
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NDA 21-338

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

Attention: Kimberley Gaumer
Senior Director, Regulatory Affairs

Dear Ms. Gaumer:

Please refer to your post-action meeting request dated December 20, 2004 for your Ionsys (Fentanyl HCl) product. You requested a meeting to obtain clarification on issues related to the Chemistry Manufacturing and Control (CMC) and device aspects of your product.

On February 8, 2005, we forwarded our *preliminary* responses to your questions to you. After you reviewing our responses you decided that further clarification was needed on several items, so a teleconference was held on February 10, 2005, in lieu of the originally scheduled face-to-face meeting of that date.

We are now enclosing a copy of our responses and the minutes of our teleconference discussions as the *final* minutes of our interactions on this issue.

If you have any questions, call me at 301-827-7432.

Sincerely,

{See appended electronic signature page}

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

Enclosure

INDUSTRY TELECONFERENCE MINUTES

Meeting Date: February 10, 2005

Sponsor: Alza Corporation.

NDA: 21-338

Drug Name: Ionsys (Fentanyl HCl)

Type of Meeting: Type A, post-action meeting (CMC-CDRH)

Industry	
Alza Corporation	
Representatives	
Susan Rinne	Vice President, Regulatory Affairs
Kim Gaumer	Senior Director, Regulatory Affairs
Orlando Reyes, Ph.D.	Vice President, Development
Aliza Peterson	Product Development Director
Steven Fields, Ph.D.	Research Fellow, E-Trans
Brad Phipps, Ph.D.	Vice President, E-TRANS Research & Development
Terri Jollymour	Compound Development Team Leader
Andrea Maciale	Regulatory Affairs, Johnson and Johnson Liaison Office
FDA	Title
Rigoberto Roca, M.D.	Deputy Division Director, DACCADP
Rajiv Agarwal, Ph.D.	Chemist
Ravi Harapanhalli, Ph.D.	Chemistry Team Leader
Mamata De, Ph.D.	Pharmacology/Toxicology Reviewer
Dan Mellon, Ph.D.	Supervisory Pharmacologist
Kim Compton	Regulatory Project Manager
Eric Duffy, Ph.D.	Director, Division of New Drug Chemistry II
Patricia Love, M.D.	Office of Combination Products
Carol Arras, M.S.	Consumer Safety Officer, Center for Devices and Radiologic Health/ Office of Compliance (CDRH/OC)
Tracey Bourke	CDRH/OC
William MacFarland	CDRH/OC

Meeting Objective:

To provide clarification on issues related to outstanding CMC and device aspects of the E-trans product.

General Discussion:

The sponsor's questions are listed in *Italics* with the FDA responses presented at the meeting following. Pertinent discussion that took place at the meeting regarding a specific question will follow the question and FDA response.

The sponsor was provided with FDA's responses prior to the meeting. Since the sponsor only required further clarification on questions 1, 2, 4, and 8, they requested a change in format from

a face-to-face meeting to a teleconference. The questions are therefore presented below in that order, with the remainder of the questions and Agency responses included after those discussed at the teleconference.

Question 1

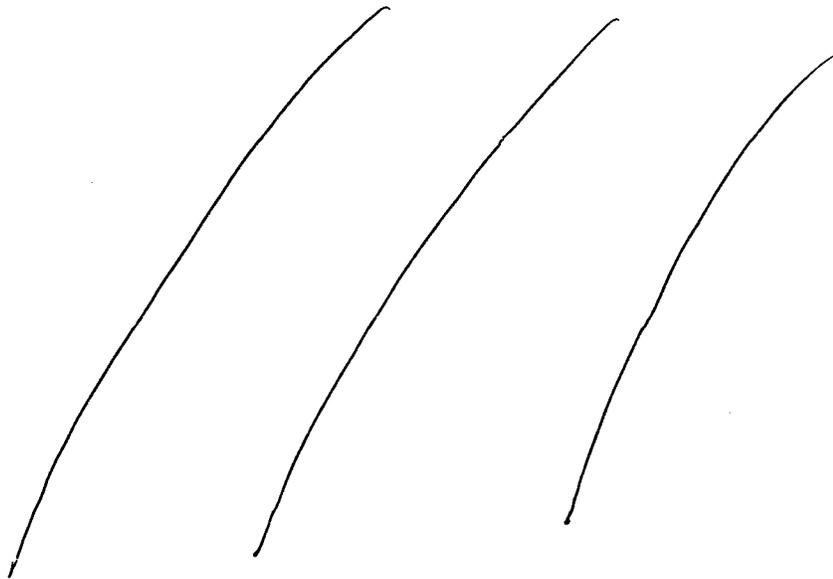
Does the Agency agree that the information provided regarding the response to the CDRH Discipline Review letter is adequate and will address the Centers' concerns around CAPA, design control, and purchasing controls?

FDA Response

CDRH has determined that the information is administratively sufficient to permit an in-depth review

Discussion of Question 1

CDRH representatives stated that they conducted an overview of the submission and checked it to ensure that it provided thorough responses to the items outlined in the Discipline Review letter of July 23, 2004. They stated that the items appeared to have been fully addressed in the response. An in-depth review and determination of whether it addresses all of the concerns will be made during the formal review of the submission. CDRH's review is ongoing and a more detailed list of questions is to follow.



Question 2

Does the Agency agree that the proposed stability data (pending review of actual data) for the NDA resubmission will support 6-month expiry dating and a defect level of — at 6 months (product will be labeled for storage at 25°C)?

FDA Response

- Real time stability data for three lots is needed to evaluate the request for a 6-month expiry dating. Calculation of defect levels will be based on the analysis of the data set.
- Stability testing of the three proof-of-concept lots should include all test attributes in addition to the push button test listed for two lots.
- Statistical analysis of the stability data for the CAL lots as well as for the proof-of-concept lots should be provided.

Disussion of Question 2

The sponsor indicated that there is a typographical error in Table 2 of the briefing document regarding lots 2 and 3, noting that they do have the data and plan a time testing period.

The sponsor stated that the stability batches are 1/2 the size of the proof-of-concept (POC) lots and that the process validation lot will be a truly representative lot.

Dr. Harapanhalli stated that the Agency would consider the POC lots as true primary stability lots for NDA registration batches. Dr. Duffy reiterated that the defect rate is to be based on the analysis of that data set.

Dr. Harapanhalli stated that the CAL lot will be considered only as supporting data due to the changes made to it. Dr. Duffy clarified that those lots are NOT to be included in the data analysis; the sponsor should use only the post-change lots for the analysis.

Question 4

Does the agency agree with a limit of NMT for in the drug substance, as proposed by the sponsor in the July 16, 2004, response?

FDA Response

As counter-proposed by the Agency in the September 10, 2004 meeting, you could propose a specification based on the amount of the impurity the body is actually exposed to at the end of the 80th dose. In the absence of this information, the Agency would assume 100% exposure and would require the default specification of as indicated in approvable letter.

Disussion of Question 4

Dr. Mellon stated that if the specification for exceeds ICH limits, the sponsor should provide adequate qualification of the impurity that includes a minimal genetic toxicology screen. He noted that if the sponsor can provide scientific rationale that the maximum amount of impurity that actually could be absorbed by the patient under clinical conditions is below the ICH thresholds for qualification, the requirement for further qualification may be revised. From the toxicological perspective, the total daily exposure, expressed as mcg/day, should be provided for this assessment.

The sponsor stated that it is their intent to use the to establish the exposure to approach. Dr. Duffy stated that the proposed approach is acceptable.

Question 8

Until such a specification can be established for _____ as outlined in Question 4 above, dose the Agency agree with a NMT _____ limit for _____ in the drug product?

FDA Response

As proposed by the Agency in the September 10, 2004 meeting, you could propose a specification based on the amount of the impurity the body is actually exposed to at the end of the 80th dose for ten samples each at product release and at the end of six months. In the absence of this information, the Agency would assume 100% exposure and would require the default specification of _____ as an interim specification until April 2006 (see rationale in Q 3).

Disussion of Question 8

Dr. Harapanhalli observed that since the _____, the sponsor will need to assess the _____ of the impurity _____. The sponsor agreed to submit the data they had available on this issue.

The sponsor stated that they were still developing an approach with the _____ to test for impurities. They feel they can be more conclusive with the _____ and also have an estimate of *in vitro/in vivo* correlation.

The sponsor stated that _____ is the only known degradant for the product and they felt they would have the requested final data on the impurity in April 2006. They plan to propose an interim specification for the impurity in their resubmission.

The sponsor stated that they plan to resubmit their application by early fourth quarter 2005. They plan to have all of their validation completed by March 2005.

The sponsor stated that they will choose a single method to determine exposure to _____ and provide a justification for that choice in their resubmission and will study the _____.

The sponsor explained that the *European Pharmacopeia* (EP) considered the substance qualified, but stated that they did not have access to the EP's data on the substance. Dr. Mellon stated that the Agency needed data on the substance and simply being listed as "qualified" without any data was not acceptable. He requested that the sponsor provide the Agency with a total exposure to _____ in clinical use.

The sponsor stated that the maximum exposure to _____ will be based on the active delivery rate. The sponsor will estimate what the active and passive exposure to the impurities will be. Dr. Mellon stated that the Agency was hesitant to agree to any interim specification without data on exposure to the substances, but agreed that the sponsor's approach seemed acceptable at this time. He requested that the sponsor express the exposure in terms of both the total daily exposure (mcg/day) and percent exposure _____.

The sponsor summarized their understanding of the items discussed as follows:

- The sponsor will submit _____ and establish a dialogue with CDRH reviewers through the CDER project manager.
- Three POC lots are acceptable to submit for 6 months expiration dating. The sponsor will provide additional data as needed in this regard.
- The CAL data will only be considered supportive and will be submitted only if the sponsor feels additional chemical aspects of the product need the support.
- The Agency will require data on _____ and _____

Dr. Duffy stated that the safety qualification requirements for _____ will be based on the total amount of _____ present in the product unless the sponsor provides data demonstrating that the actual exposure is below ICH thresholds. For _____, the sponsor's proposal to determine the actual exposure based on the _____ appears reasonable. The Agency is willing to consider an interim specification for _____ and await additional data, expected in April 2006, pending an analysis of existing exposure data at the time of submission.

The following questions and responses were not discussed at the teleconference (the slides containing the Agency's responses were sent to the sponsor in advance of the meeting) **and are included here for completion of the administrative record of the responses to the meeting questions.**

Question 3

At the September 10, 2004 FDA meeting, it was agreed that the proposed drug substance specification of NMT _____ for each of the three structural alert impurities was acceptable on an interim basis, until it was feasible to establish a lower limit of _____. Does the agency agree with the timeline and list of activities planned to achieve a NMT _____ specification limit for _____ in the drug substance?

FDA Response

The Agency concurs with the proposal to update specifications to _____ level by April 2006 [unless additional mutagenicity data become available.]

Question 5

In the original NDA submission, section 3.2.P.5.5, we provided the scientific rationale to show that _____ is not a degradation product. An expanded discussion of the data is presented in this briefing package. Does the Agency agree with this rationale and conclusion?

FDA Response

The Agency agrees with this rationale: The specification for this impurity in the drug product will not be necessary as long as it is specified and monitored in the drug substance.

Question 6

The sponsor believes the same is true for [redacted] but additional work will be conducted to ensure that it is not a degradation product at the proposed limits. Does the Agency agree with the experimental approach provided?

FDA Response

You are proposing to use a more sensitive method for the testing of a retained drug substance sample and long term stability samples of drug product (at least [redacted] to demonstrate that [redacted] is not a degradation product. You should also test the long term and accelerated stability samples of drug substance. In general, the proposed experimental approach is acceptable to the Division.

Question 7

Does the Agency agree with the experimental approach to determine an appropriate specification limit for [redacted] in the drug product?

FDA Response

You are working on an experimental approach to determine the actual *in vivo* exposure to propose an appropriate specification limit for [redacted], by April 2006. The Agency concurs with the proposal.

Question 9

Does the Agency agree with the rationale presented that the potential for passive delivery of [redacted] does not warrant further investigation and assessment?

FDA Response

Experimental data is required to rule out the possibility of the passive delivery of [redacted]. You are advised to implement the experimental plan outlined in Q 7.

Minutes prepared by : Kimberly Compton, Regulatory Project Manager
Concurred by Meeting Chair : Rigoberto Roca, M.D., Deputy Division Director

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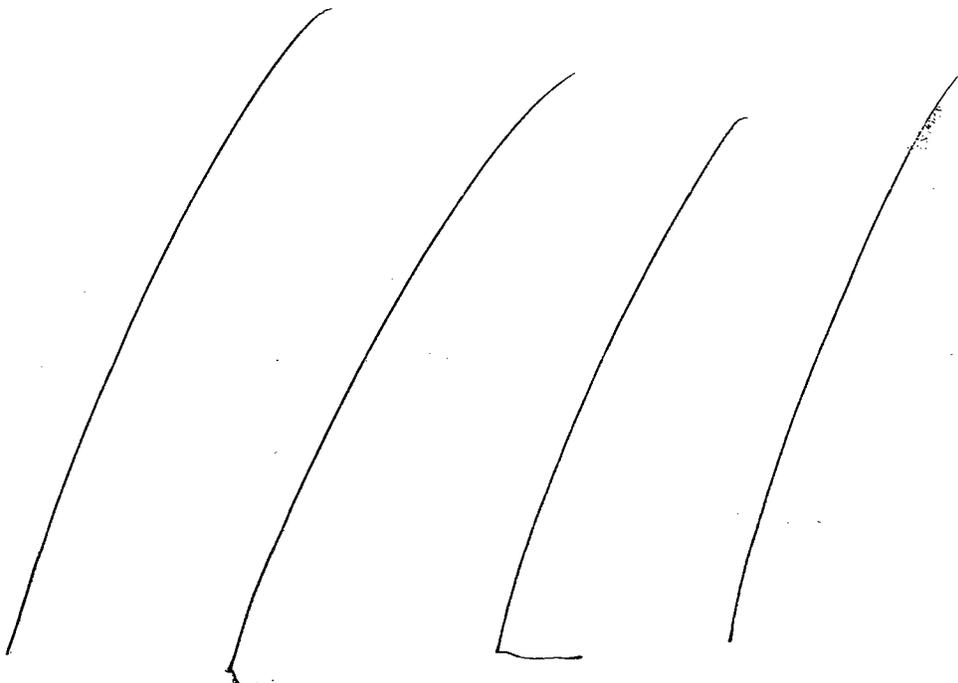
/s/

Kimberly Compton
3/7/05 04:37:55 PM

Inspectional Guidance

To:	The Record
Facility:	Applicant: ALZA Corporation 1900 Charleston Road Mountain View, CA 94043 FEI: 3003732939 ALZA Corporation 700 Eubanks Drive Vacaville, CA FEI & CFN: 2938701
Device:	IONSYS (previously E-TRANS System) – combination device/drug product
Document:	NDA 21-338
Reviewer:	Tracey Bourke, CDRH/OC/DOE-B, HFZ-343, 240-276-0357 <i>TCB</i>

During the CDRH review of the applicable QS/GMP sections of the NDA for the above combination product, we identified areas that require further scrutiny. As the inspection has already taken place, please do the following during the post-market follow-up inspection of ALZA Corporation's manufacturing site:



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MEMORANDUM

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

Memo of Device Issues - Communicated to Sponsor by email

DATE: March 31, 2005

TO: Alza Corporation, Kim Gaumer (KGAUMER@alzus.jnj.com)

THROUGH : Parinda Jani, CPMS, HFD-170
Ravi Harapanhalli, Ph.D., Chemistry Team Leader, HFD-170
Eric Duffy, Ph.D., Director, DNDC II
Bob Rappaport, M.D., Division Director, HFD-170
Patricia Love, M.D., Office of Combination Products, HFG-3
Tracey Bourke, D. V. M, CDRH/ OPMADB
William MacFarland, Chief, CDRH/OPMADB

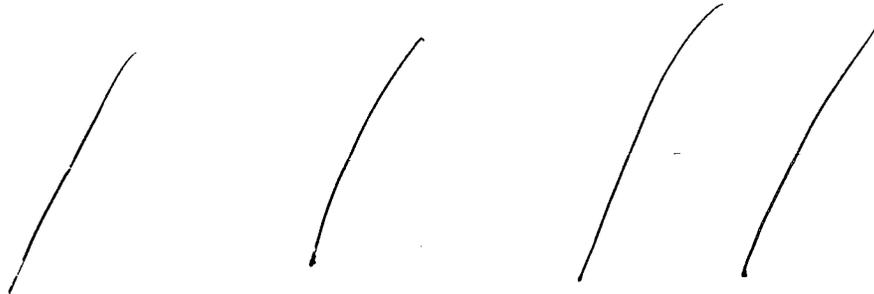
FROM: Kim Compton (Comptonk@cder.fda.gov, fax # 301-443-7068,
phone 301-827-7432)

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

Background:

A teleconference with the sponsor is scheduled for April 1, 2005 to discuss the Device related issues for the product listed below as they relate to the planned resubmission of the NDA.

These issues are being provided to the sponsor by email to facilitate discussion of them at the teleconference.



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/s/

Kimberly Compton
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CSO



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-338

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

Attention: Kimberley Gaumer
Senior Director, Regulatory Affairs

Dear Ms. Gaumer:

Please refer to your post-action meeting request dated October 29, 2004 for your Ionsys (Fentanyl HCl) product. You requested a meeting to obtain clarification on issues surrounding further studies that might be required with your product. This issue was first discussed at our previous post-action meeting that took place September 10, 2004.

On November 23, 2004, we forwarded our *preliminary* responses to your questions to you. After you reviewed our responses you decided your questions had been addressed and that a face-to-face meeting was no longer needed.

Therefore, for archiving and tracking purposes, and since no further recommendations or exchanges on this issue took place, we are now enclosing a copy of our responses as the *final* minutes of our interactions on this issue.

If you have any questions, call me at 301-827-7432.

Sincerely,

{See appended electronic signature page}

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

Enclosure

MEMORANDUM OF MEETING MINUTES

MEETING DATE: Originally scheduled for December 2, 2004, but face-to-face discussion did not occur following issuance on November 23, 2004, of Agency responses to sponsors questions in meeting package.

APPLICATION: N 21-338

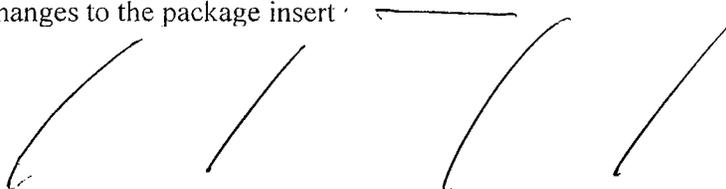
DRUG NAME: **Ionsys (Fentanyl HCl)**

TYPE OF MEETING: Type-A, Post-Action Meeting

AGENCY RESPONSES (FINAL): (Originally issued and forwarded to sponsor November 23, 2004)

As regards your post-action meeting request dated October 29, 2004, for your Ionsys (Fentanyl HCl) product, you requested a meeting to obtain clarification on issues surrounding further studies that might be required with your product. This issue was first discussed at our previous post-action meeting that took place September 10, 2004. We have received your briefing package for the Type A meeting, currently scheduled for December 2 2004, and have the following comments.

We note the proposed changes to the package insert



We are willing to accept, as a complete response to our action letter, a submission containing data from the completed studies, CAPSS 319 and CAPSS 320, along with a focused and in-depth discussion of the in-use safety and actual use of rescue medication across the safety database, in lieu of the "actual-use" study suggested at the meeting of September 10 2004. However, approval of your product will hinge on the adequacy of this data.

We are aware that CAPSS 319 and CAPSS 320 are ongoing so complete study reports are not yet available. Upon review of the interim data provided in your briefing package, we note the following issues:

- Clarify whether the survey data (briefing package p.16) comes from pharmacy directors or the front-line pharmacists. As we stated during the meeting, we are interested in the opinions of the *dispensing* pharmacists.
- Of the 38 pharmacists surveyed, 95% felt that the instructions on testing of the system were clear and easy to understand (table 1, p. 17) but 21% had difficulty in performing the test (table 3, p.17). We would be interested in knowing more about the perceived difficulty in performance of the test.

- We note that 10-11% of the 110 patients surveyed did not read the instructions for use of IONSYS. We would be interested in knowing why they did not do so.
- We note that under 75% of the patients were “extremely confident” about the use of IONSYS after having been provided education in the form of a video and written instructions as well as verbal instructions from a member of the study staff (table 2, p.19)
- We note that 20% of the patients found the educational materials provided less than extremely helpful in understanding the meaning of the IONSYS red light, the meaning of the IONSYS beeps and the IONSYS safety information (table 3, p.20). We note however that 99-100% of the patients found the instructions given by a nurse were helpful in understanding proper product usage (table 8, p.22).
- While we note that 100% of the patients understood that IONSYS was to be applied and removed by a nurse, 5-11% did not understand the importance of not touching the squares on the underside. This remains a safety concern.

In order to address the issues stated above, you should submit a risk management plan (RMP) and a detailed plan for post marketing surveillance to assess the safety of this product that

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/s/

Kimberly Compton
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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-338

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

Attention: Susan P. Rinne, M.S.
Vice President, Regulatory Affairs

Dear Ms. Rinne:

Please refer to the post-action meeting between representatives of your firm and FDA on September 10, 2004. The purpose of the meeting was to provide clarification on several issues raised in our July 23, 2004 approvable and discipline review letters for your Ionsys (Fentanyl HCl) product.

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 301-827-7432.

Sincerely,

{See appended electronic signature page}

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

Enclosure

INDUSTRY MEETING MINUTES

Meeting Date: September 10, 2004

Location: Parklawn Building, Chesapeake Conference Room

Sponsor: Alza Corporation.

NDA: 21-338

Drug Name: Ionsys (Fentanyl HCl)

Type of Meeting: Type A, post-action meeting

Meeting Chair: Celia Winchell, M.D.
Division of Anesthetic, Critical Care, and Addiction Drug Products

Minutes Recorder: Kimberly Compton, Regulatory Project Manager

Industry	
Alza Corporation Representatives	
Jennifer Ekelund	Director, Regulatory Affairs
Kim Gaumer	Senior Director, Regulatory Affairs
Bonnie Goldmann, MD	Senior Vice President, Global Regulatory Affairs
Suneel Gupta, PhD	Senior Vice President Pharmacology and Clinical Research
Juergen Haeussler, MD	Senior Director, Clinical R&D
David Hewitt, MD	Director, Medical Affairs
Drew Jones, MD	Director, Clinical Research
David Pass	Executive Director, J&J Pharmaceutical Group Strategic Marketing
Aliza Peterson	Product Development Director
Gayatri Sathyan, PhD	Director, Clinical Pharmacology
Steven Fields, PhD	Senior Director, E-Trans Product Development
Toni Marie Nearing	Director of Regulatory Affairs, FDA Liaison
FDA	Title
Bob Rappaport, M.D.	Division Director
Rigoberto Roca, M.D.	Deputy Division Director
Elizabeth McNeil, M.D.	Medical Officer
Celia Winchell, M.D.	Medical Team Leader
Rajiv Agarwal, Ph.D.	Chemist
Ravi Harapanhalli, Ph.D.	Chemistry Team Leader
Eric Duffy, Ph.D.	DNDC II, Director
Mamata De, Ph.D.	Pharmacology/Toxicology Reviewer
Dan Mellon, Ph.D.	Supervisory Pharmacologist
Srikanth Nallani, Ph.D.	Biopharmaceutical Reviewer
Milton Fan, Ph.D.	Statistician
Tom Permutt, Ph.D.	Statistics Team Leader

Patricia Love, M.D.	Office of Combination Products
Sandra Birdsong	Project Manager, ODS
Tracey Bourke	CDRH/OC (by phone)
William MacFarland	CDRH/OC (by phone)
Kim Compton	Regulatory Project Manager

Meeting Objective: To provide the sponsor with feedback on issues raised in the July 23, 2004 action and discipline review letters.

General Discussion:

The sponsor's questions are listed in *Italics* with the FDA responses presented at the meeting following. Pertinent discussion that took place at the meeting regarding a specific question will follow the question and FDA response.

Opening Discussion

In their opening remarks, the sponsor stated that they plan to address all the issues raised by the Agency in the July 23, 2004 action letter in their complete response submission. They would like to focus this meeting to discuss the issues raised by the Center for Devices and Radiological Health (CDRH), and some of the Chemistry, Manufacturing, and Controls (CMC) issues raised by the Center for Drug Evaluation and Research (CDER). Risk Management Plan (RMP) and possibly issues surrounding the ongoing investigation into stability of the product will be discussed in a separate meeting.

Question 6

Is it acceptable to submit the response to the CDRH Discipline Review letter and the Agency comments on the proposed Risk Management Plan (received 8/18/04) separately from the complete response to the action letter?

FDA Response

CDRH DR letter:

- A separate response to the DR letter is not required.
- But, the information in the DR letter should be considered and incorporated into your response to the action letter deficiencies for safety, chemistry and manufacturing.
- Also, these must be resolved before the pre-approval inspection update.

Risk Management Comments:

- These responses need to be part of the complete response to the action letter.

Discussion of Question 6

Since there are extensive comments from CDRH, the sponsor requested clarification that their product was still considered a "drug" with CDER assigned the primary review responsibility. Dr. Love noted that Ionsys is a combination product. Good manufacturing practice for a device may be developed under the CGMPs, but focusing on the issues from a device perspective [i.e., from the device consult Discipline Review letter] will facilitate resolution of any questions affecting the overall manufacture. Dr. Rappaport stated that the critical issue is that the product, i.e., drug and device perform together as predicted.

Question 4a

We would like to confirm that the request to limit the three specified impurities in item 2a above to NMT — applies to the drug substance (fentanyl HCl) and not the drug product. Does the Agency concur?

FDA Response

- Yes, the specification of — , applies to the drug substance (Fentanyl HCl).
- Specifications for these impurities in the drug product will not be necessary if data is provided to confirm that the impurities are not enriched in the drug product via degradation.

Discussion of Question 4a

Dr. Duffy stated that the sponsor should follow the ICH Q3A and Q3B guidance documents, which stated that if a process impurity is present, there needs to be a limit and a test for it only in the drug substance, but if a degradation product is present, there must be a limit and a test for it in both the drug substance and drug product.

Question 4b

In the NDA Amendment dated July 16, 2004, at the request of the Agency, ALZA committed to drug substance specifications of NMT — for each of the three impurities mentioned in item 2a of the approvable letter. There are substantial technical hurdles to achieving the specified impurity levels in the drug substance with the current vendor — However, we commit to instituting a specification of NMT — in the drug substance —



Does the Agency concur with this proposal?

FDA Response:

- From the toxicological perspective, the primary safety concern is with the uncharacterized risks associated with the maximum possible daily exposure to these impurities.
- For the three — , an assessment of their — is therefore needed. Provide the base line levels before patch activation and at the end of 80th dose for ten samples each at product release and at the end of six months.
- You may provide for review a data-based scientific rationale justifying alternative specifications based on risk associated with the potential exposure to the drug impurities.
 - Such a rationale should include characterization of the levels of impurities that could be transferred from the patch and known toxicological data.

- If available, provide the levels of these impurities in the batches used for the key preclinical toxicology studies already completed with fentanyl.

Discussion of Question 4b

Dr. Mellon stated that, if the sponsor can provide data to demonstrate exactly what and how much of each of these impurities are actually absorbed, the specifications for these impurities may be revised. The burden is on the sponsor to demonstrate how much of the impurities are being delivered. Dr. Mellon stated that _____ might be one way to determine the potential exposure to the impurities, but noted that the sponsor should explore different methods to determine the actual exposure to the impurity.

The sponsor observed that other transdermal products have broader specifications for these structural alert impurities and asked whether the iontophoretic nature of drug delivery posed any specific concerns about these structural alerts from a safety perspective. Dr. Harapanhalli stated that this issue is common to all dosage forms and would be addressed with those products as well. He further stated that the structural alert for fentanyl was just recently discovered and the _____s. He also stated that, since the three structural alerts are the _____, they are likely to be electrotransported _____ effectively as fentanyl. Therefore, it is important to demonstrate their relative electromigration potential, determine their exposure levels and limit them appropriately in the drug substance and, if needed, in the drug product.

The sponsor stated that they have not been informed of a consistent specification for genotoxic or potentially genotoxic impurities and that there is no specification in the ICH guidances to address this issue. They noted that they are getting conflicting answers from both European regulatory authorities and different Divisions within FDA. Dr. Mellon noted that this is an evolving issue and that the FDA was actively evaluating the draft European guidance document _____. However, he also reminded the sponsor that the scientific community as a whole has not come to an agreement on what would be an acceptable level for a genotoxic impurity, therefore, the recommendations provided may be amended in the future.

The sponsor inquired about the timing required to implement such tight specifications, noting that most recommendations they have received, even for orally dosed products, have not limited the levels to the extent currently being requested. The sponsor also pointed out that their product was an acute use product. The sponsor stated that they are committed to reducing the levels of all potential genotoxic impurities to as low as possible.

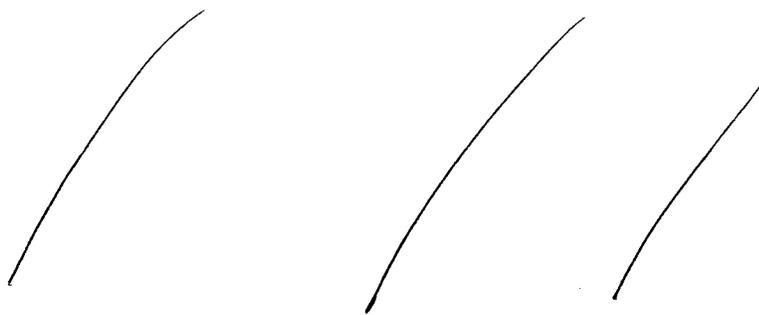
Dr. Harapanhalli indicated that the Division would work with the sponsor on the timing related to this issue and that limiting them to NMT _____ as currently proposed would be considered acceptable on an interim basis.

Dr. Mellon stated that the European guidelines were still under discussion with the genotoxicity group so this was a difficult issue to address. He outlined a three-pronged approach which the Division recommends the sponsor pursue in parallel:

1. attempt to reduce the levels of any potentially genotoxic impurity to as low as technically possible.
2. characterize the potential genetic toxicity of the impurities via a minimum genotoxic screen (two *in vitro* studies), and

- As part of premarketing risk analysis and minimization, medication error prevention analysis (MEPA) on the established name seems to support this name.
- Iontophoretic describes the "active" transdermal delivery versus the passive delivery from Alza's related product Duragesic (Fentanyl transdermal system).
- Transdermal system indicates that the dose is administered through the dermal layer of the skin to the systemic circulation by diffusion as defined in the current CDER Data Standards Manual and the USP.

Discussion of Question 7a



Dr. Harapanhalli stated that the issue of stability failures and the expiration dating was listed in the original post-action meeting request but was not part of the detailed meeting package and therefore this issue will not be discussed during this meeting. The sponsor agreed and stated that they have gathered additional data on stability and the root cause analysis of product failures and would request a separate meeting with the Agency.

Question 7b



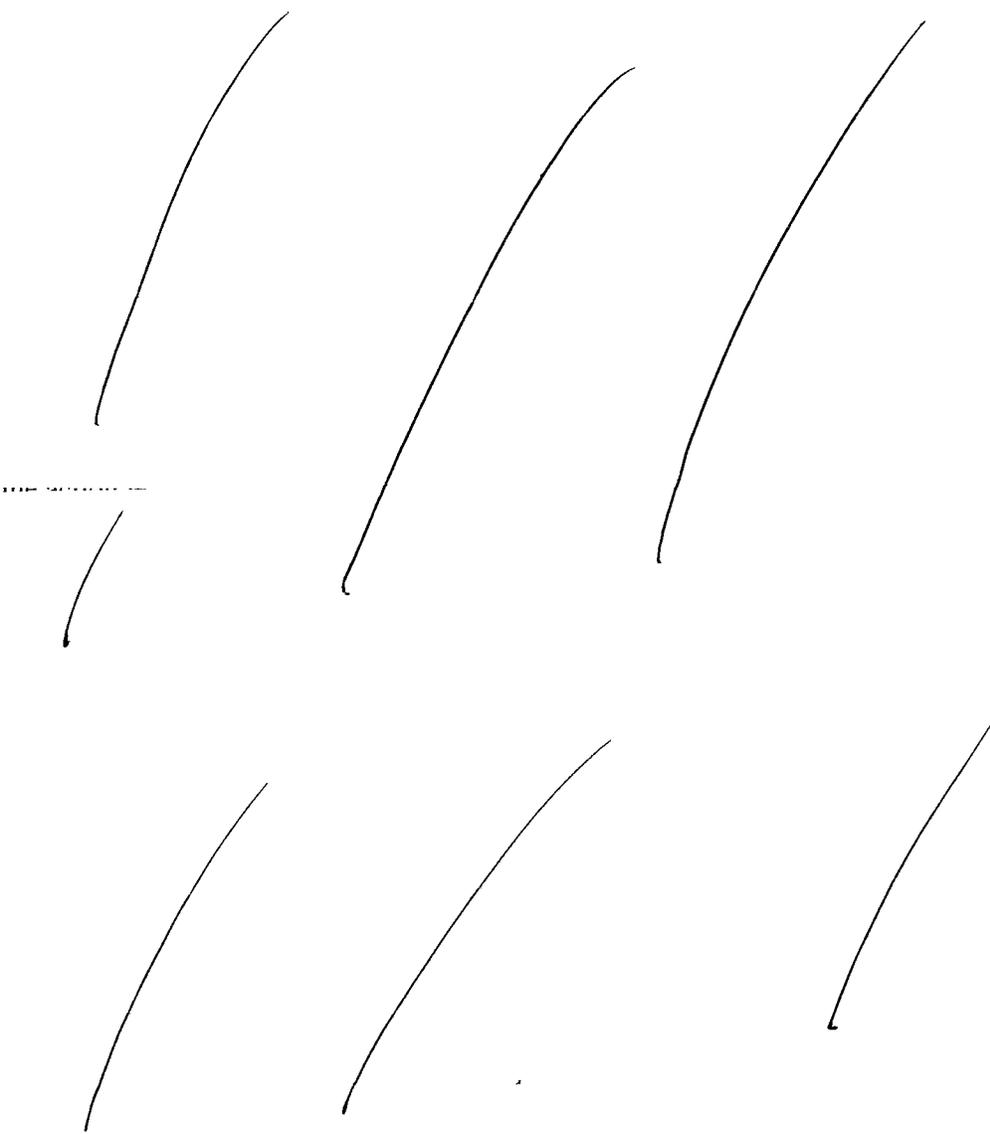
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§ 552(b)(4) Trade Secret / Confidential

§ 552(b)(5) Deliberative Process

§ 552(b)(4) Draft Labeling



Question 2

All patients in the NDA safety database received routine pre-operative and postoperative medications following major surgery, and were titrated to comfort using IV opioids for at least 30 minutes before being administered IONSYS™ for pain management. Further, all patients were allowed access to supplemental IV opioid (fentanyl in the placebo-controlled trials, fentanyl or morphine in the active comparator trial) during the first three hours of IONSYS™ use. Therefore, we are unclear about what additional clinical information the Agency is referring to in the request to provide clinical data on “adjunctive therapy with other opioid analgesics during the early treatment phase.” Please clarify.

FDA Response

- We are in agreement that for the first 3 hours of treatment supplemental analgesia ~~will probably be required~~ should be available (verbally edited at the meeting).
- The information presented thus far has not convinced us that it is the duration of contact with the skin rather than the number of activations that allows IONSYS to provide 40 mcg/dose.
- We need clinical documentation that a system which has not been activated but has been in contact with skin for 3 hours will provide 40mcg at that first activation e.g. at minute 181.

Discussion of Question 2

Dr. Nallani explained that the proposed usage of the product was different compared to how the product was used in the clinical efficacy trials. While the product was used with the availability of IV rescue medication in the clinical trials, the

Hence, the Division is interested in knowing whether 40 mcg of drug is delivered with the first activation following 3 hours of application, even if the unit had not been previously activated. The sponsor explained that the frequency of activations makes no difference in the dose delivered by the unit. However, they also stated that the device cannot, in fact, provide 40 mcg at the first activation after 3 hours in contact with the skin, but this was regarded as immaterial since this limitation was also present in the clinical trials where efficacy was demonstrated. In addition, the sponsor stated that

Dr. Rappaport stated that the sponsor should include the safety data with the PK data and device issues to demonstrate how the product actually works and is used. Dr. McNeil stated that this information would be necessary to draft the most appropriate labeling.

Question 3

Please clarify what specific data FDA is seeking in the request to provide "clinical data evaluating conversion from...other opioid analgesics during the early treatment phase with Ionsys system".

FDA Response

We would like a range (in morphine equivalents) of opioid doses that may be converted safely and appropriately to IONSYS 40 mcg use. You may use your existing data to create that table if you provide us with links to the original data sets.

Discussion of Question 3

The sponsor stated that patient comfort level was not related to the dose of medication, but to the level of pain. They felt they might provide better specificity of what range of pain scores could be used to identify appropriate patients for IONSYS. The sponsor indicated they would

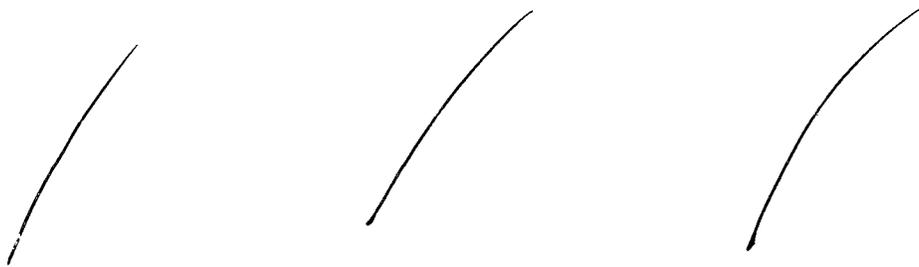
Question 5a

Is it acceptable to provide with the complete response, a comprehensive safety update that encompasses any new nonclinical or clinical studies performed with IONSYS™ (included integration of the safety data into the NDA ISS)?

FDA Response

It is acceptable to provide with the complete response, a comprehensive safety update that encompasses any new nonclinical or clinical studies performed with IONSYS (including integration of the safety data in to the NDA ISS).

Question 5b



Question 5c

Does the Agency agree to waive the requirement to submit CRFs for patients who died, discontinued due to an adverse event, or had a related serious event? (These would be available upon request).

FDA Response

- The Agency does not agree to waive the requirement for submit CRFs for patients who died, discontinued due to an adverse event, or had a related serious event.
- You are not required to duplicate the CRFs submitted as part of the original NDA. However, we will expect submissions of CRFs from new deaths, new SAEs and new discontinuations due to AEs.

Discussion of Question 5c

Dr. McNeil clarified that only CRFs for new deaths, discontinuations and SAEs should be submitted with the response.

Closing Discussion

The sponsor summarized their understanding of the meeting:

In the process of responding to the Division's action letter, they will:

- address all of the device issues prior to any pre-approval inspections and incorporate the appropriate information
- respond to the RMP issues (to be discussed at a separate meeting with the Division)