CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-338

APPROVABLE LETTER(S)

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) dated September 23, 2003, received September 24, 2003, submitted under to section 505(b) of the Federal Food, Drug, and Cosmetic Act for Ionsys (fentanyl HCl) system.

We acknowledge receipt of your submissions dated November 12, 14, and December 3, 2003, and January 20 and 21, March 15 (2), 25 and 26, April 2, 16 and 30(2), May 13, June 4 , 11, and 18, and July 1, 2004.

We also acknowledge receipt of your submissions dated July 13 and 16, 2004. These submissions were not reviewed for this action. You may incorporate this submission by specific reference as part of your response to the deficiencies cited in this letter.

We have completed our review of this application, as amended, and it is approvable. Before the application may be approved, however, it will be necessary for you to address the following:

1. You have not provided adequate clinical data to support the safe use of your product. Before we can approve this product, provide the following:

   a. Clinical data supporting the safe use of the Patient and Health-Care Provider product instructions for use and the instructions for product performance testing; and

   b. Clinical data evaluating conversion from and adjunctive therapy with other opioid analgesics during the early treatment phase with Ionsys system.

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

   a. [redacted] contain [redacted] and are structural alerts for mutagenicity. Therefore, provide a time line to achieve a limit of NMT [redacted] each

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

b. Provide a revised limit of NMT — for the — in the drug substance.

3. The following deficiencies pertain to the drug product specifications.

a. Revise the acceptance criterion of "Number of doses" from —

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

(1) At product release —
(2) Stability — . Not more than — do not illuminate and do not beep (fail)

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

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

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

b. Revise the —

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

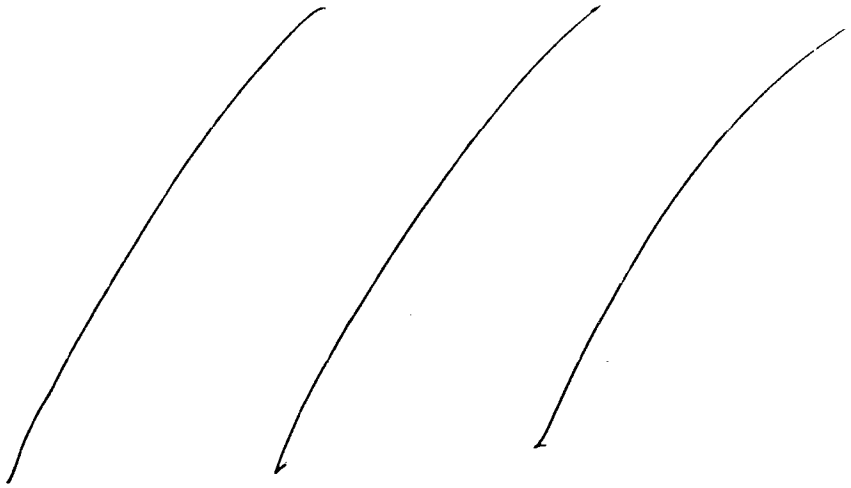
a. Revise the following CPs stating that prior-approval supplements would be submitted for the listed changes —

1 Page(s) Withheld

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

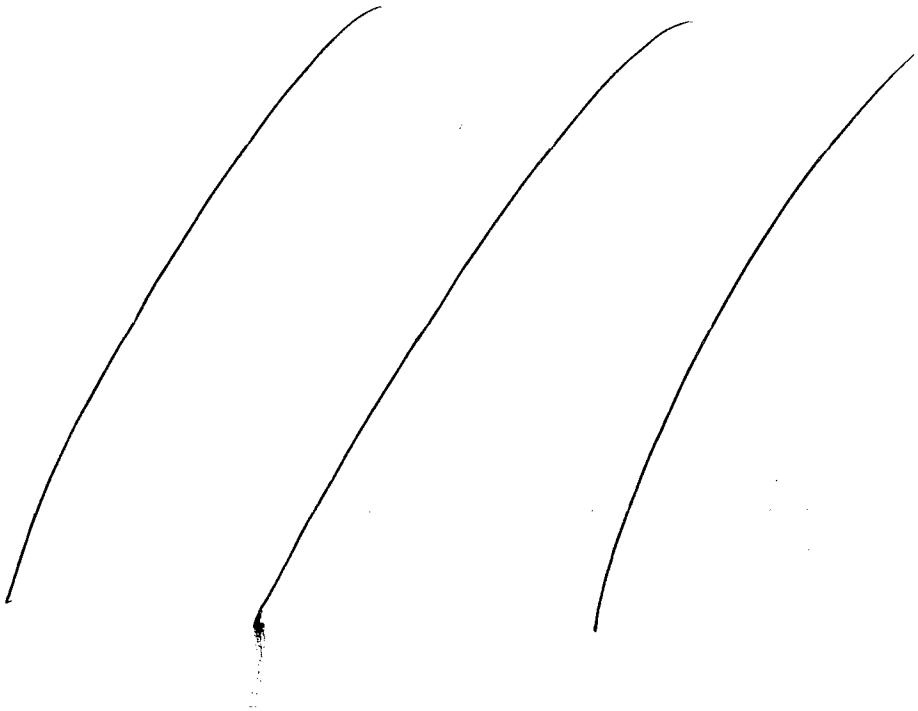
§ 552(b)(5) Deliberative Process

§ 552(b)(4) Draft Labeling



In addition, it will be necessary for you to submit a draft package insert, system and immediate carton, and container labels modified to reflect the following comments, and the revisions noted in the attached draft label. Further labeling comments will be provided once the aforementioned deficiencies are adequately addressed.

6. The following comments pertain to the labels and labeling.



If additional information relating to the safety or effectiveness of this drug becomes available, revision of the labeling may be required.

When you respond to the above deficiencies, include a safety update as described at 21 CFR 314.50(d)(5)(vi)(b). The safety update should include data from all non-clinical and clinical studies of the drug under consideration regardless of indication, dosage form, or dose level.

1. Describe in detail any significant changes or findings in the safety profile.

2. When assembling the sections describing discontinuations due to adverse events, serious adverse events, and common adverse events, incorporate new safety data as follows:

   - Present new safety data from the studies for the proposed indication using the same format as the original NDA submission.
   - Present tabulations of the new safety data combined with the original NDA data.
   - Include tables that compare frequencies of adverse events in the original NDA with the retabulated frequencies described in the bullet above.
   - For indications other than the proposed indication, provide separate tables for the frequencies of adverse events occurring in clinical trials.

3. Present a retabulation of the reasons for premature study discontinuation by incorporating the drop-outs from the newly completed studies. Describe any new trends or patterns identified.

4. Provide case report forms and narrative summaries for each patient who died during a clinical study or who did not complete a study because of an adverse event. In addition, provide narrative summaries for serious adverse events.

5. Describe any information that suggests a substantial change in the incidence of common, but less serious, adverse events between the new data and the original NDA data.

6. Provide a summary of worldwide experience on the safety of this drug. Include an updated estimate of use for drug marketed in other countries.

7. Provide English translations of current approved foreign labeling not previously submitted.

In addition, we have the following comments.

1. Please address issues related to the safe manufacturing of the device described in the DISCIPLINE REVIEW LETTER dated July 23, 2004.

2. You have agreed to implement a risk management plan (RMP) to ensure the safe use of the product post-approval. We would like to have further discussions with you regarding your proposed RMP.

Within 10 days after the date of this letter, you are required to amend this application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. If you do not follow one of these options, we will consider your lack of response a request to withdraw the application under 21 CFR 314.65. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

Under 21 CFR 314.102(d), you may request an informal meeting or telephone conference with this Division to discuss what steps need to be taken before the application may be approved.

The drug product may not be legally marketed until you have been notified in writing that the application is approved.

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

Sincerely,

{See appended electronic signature page}

Bob Rappaport, M.D.
Director
Division of Anesthetic, Critical Care and
Addiction Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure

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

/s/

Bob Rappaport
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