DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 16-798/S-050
NDA 17-516/S-020

Pfizer Inc.
Attention: Gil Granados
Regulatory Affairs
235 E 42nd Street
New York, NY 10017

Dear Mr. Granados:

We acknowledge receipt of your supplemental new drug applications dated May 15, 2003, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Sinequan (doxepin HCl) 10 mg, 25 mg, 50 mg, 75 mg, 100 mg, and 150 mg capsules (NDA 16-798) & 10 mg/ml Oral Concentrate (NDA 17-516).

Reference is also made to telephone conversations between Mr. Paul David, of this Agency, and yourself dated September 11, and 25, 2003, agreeing to labeling revisions to your proposed labeling.

These "Changes Being Effected" supplemental new drug applications propose revisions to the **PRECAUTIONS-Drug Interactions**, **OVERDOSAGE**, and **HOW SUPPLIED** sections.

As referenced above, we note your agreement to revise the **PRECAUTIONS-Drug Interactions** section as follows:

> [Strike through font denotes deletions to your proposed labeling, and double underline font denotes additions to your proposed labeling.]
>
> Doxepin~~, like other tricyclic antidepressants (TCAs),~~ is primarily metabolized by CYP2D6 (with CYP1A2 & CYP3A4 as minor pathways). Inhibitors or substrates of CYP2D6 (i.e., quinidine, selective serotonin reuptake inhibitors [SSRIs]) may increase the plasma concentration of doxepin ~~TCAs~~ when administered concomitantly. The extent of interaction depends on the variability of effect on CYP2D6 ~~and the therapeutic index of the TCA~~. The clinical significance of this interaction with doxepin has not been systematically evaluated.

We have completed the review of these supplemental applications, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in agreed upon labeling. Accordingly, these applications are approved effective on the date of this letter.

The final printed labeling (FPL) must be identical to the labeling (text for the package insert) submitted on May 15, 2003 except for the revisions agreed upon above. Marketing the product with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

Please submit the copies of final printed labeling (FPL) electronically according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDA* (January 1999). Alternatively, you may submit 20 paper copies of the FPL as soon as it is available but no more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, this submission should be designated "FPL for approved NDAs 16-798/S-050 and 17-516/S-020." Approval of this submission by FDA is not required before the labeling is used.

Additionally, we note that the current label lacks a "**CLINICAL PHARMACOLOGY**" section. We request you to revise the Sinequan product labeling to incorporate a new **CLINICAL PHARMACOLOGY** section and incorporate relevant information from literature and/or other available sources. Relevant information includes, but not limited to, the following: pharmacodynamics, mechanism of action, pharmacokinetics (absorption, distribution, metabolism, and elimination), and intrinsic and extrinsic factors (such as gender, age, race, renal or hepatic impairment, food, drug-drug interactions) that could affect the pharmacokinetics of doxepin.

These revisions to the product labeling should be submitted as draft labeling in the form of a "Prior Approval" labeling supplement. Please incorporate all previous revisions as reflected in the most recently approved package insert. To facilitate review of your submission, provide a highlighted or marked-up copy that shows the changes that are being made.

If a letter communicating important information about this drug product (i.e., a "Dear Health Care Practitioner" letter) is issued to physicians and others responsible for patient care, we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH, HF-2
FDA
5600 Fishers Lane
Rockville, MD 20857

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, call Mr. Paul David, R.Ph., Senior Regulatory Project Manager, at (301) 594-5530.

Sincerely,

{See appended electronic signature page}

Russell Katz, M.D.
Director
Division of Neuropharmacological Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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

/s/

Russell Katz
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