CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20931

APPROVABLE LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-931

MAR -- 5 1999

Pfizer Pharmaceutical Production Corporation Limited
c/o Pfizer Inc.
Attention: William R. Murphy, Ph.D.
Eastern Point Road
Groton, CT 06340

Dear Dr. Murphy:

Please refer to your new drug application (NDA) dated March 9, 1998, received March 9, 1998, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Tikosyn (dofetilide) Capsules, 0.125 mg (125 mcg), 0.25 mg (250 mcg) and 0.5 mg (500 mcg).

We acknowledge receipt of your submissions dated November 25, 1997; March 4 (two), April 8, 9, 10, 28 and 30, May 5, 8, 13, 20 and 22, June 3, 4, 9, 16, 22 and 25, July 1, 10, 21, 24, 28 and 31, August 7, 18 and 20, September 2, 9 and 28, October 9 (two), 13, 16, 19, 27 and 29, November 6, 12, 13(two), 17, 20, 23, 24 (two) and 25, and December 3, 7, 8, 10, 14 (two), 21 and 24, 1998; and January 7, 8, 11, 12, 13, 21, 22, 25 and 27 (two), and February 3, 9, 10, 12, 22 and 24, and March 1, 3, and 4, 1999.

We have completed the review of this application, as amended, and it is approvable. We have provided draft labeling that differs in many respects from the labeling you submitted. Imbedded in the text are a number of requests for new paragraphs or support for the proposed language. We expect further discussions or meetings will be needed before you can submit final printed labeling reflecting the attached draft and subsequent mutually agreed to revisions.

Although a patient package insert will be necessary, we believe that it is important first to come to an agreement on the content of the professional package insert. We will then be able to discuss with you the content of the patient package insert.

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

Please note that we have determined the approvable interim dissolution method, medium and specification to be: USP Apparatus I (basket) at 100 rpm in 0.001 M hydrochloric acid; Q at 30 minutes. In order to develop a dissolution method that will be reflective of the *in vivo* performance of dofetilide capsule formulations, please submit (after NDA approval) additional dissolution data in three media (water, acid and buffer) with and without an enzyme (pepsin in water and pH $\leq$ 6.8 or pancreatin in pH $\geq$ 6.8). The "cross-linked" capsule formulation with low dissolution (mean % dissolved at 45 minutes) and the capsules with isolated hydrophobic effect (mean % dissolved at 45 minutes) as well as stability samples that show evidence of "cross-linking" should be used to develop the optimum dissolution conditions.

We also note that you have agreed to meet with us prior to approval to continue our discussions and come to a decision regarding your proposed marketing and distribution plan.

In addition, please submit three copies of the introductory promotional materials that you propose to use for this product. All proposed materials should be submitted in draft or mock-up form, not final print. Please send one copy to the Division of Cardio-Renal Drug Products and two copies of both the promotional materials and the package insert directly to:

Division of Drug Marketing, Advertising, and Communications, HFD-40
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

Within 10 days after the date of this letter, you are required to amend the application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. In the absence of any such action FDA may proceed to withdraw the application. 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.

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, please contact:

Mr. David Roeder
Regulatory Health Project Manager
(301) 594-5313

Sincerely yours,

Robert Temple, M.D.
Director
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Enclosure