CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20931

CORRESPONDENCE

V Wallace

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-931

DEC 5 1997

Pfizer, Inc.
Attention: William R. Murphy, Ph.D.
Eastern Point Road
Groton, CT 06340

Dear Dr. Murphy:

We have received your pre-submission of certain chemistry and other partial information for the following:

Name of Drug Product: dofetilide, 0.125 mg, 0.25 mg, and 0.5 mg

Date of Application: November 25, 1997

Date of Receipt: November 25, 1997

Our Reference Number: NDA 20-931

We will review this early submission as resources permit. We will not, however, consider it subject to a review clock or to a filing decision by FDA. If you have any questions regarding this information, please contact:

Ms. Diana Willard
Regulatory Health Project Manager
(301) 594-5311

Our willingness to accept your pre-submission is based upon the condition that the full application will be submitted no sooner than 90 days nor later than 120 days from the date of your submission.

Please cite the NDA number assigned to this application at the top of the first page of every communication concerning this application.

Sincerely yours,

Natalia A. Morgenstern
Chief, Project Management Staff
Division of Cardio-Renal Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

D. Willard

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

NDA 20-931

Food and Drug Administration
Rockville MD 20857

Pfizer Pharmaceuticals Production Corporation Limited
Ringaskiddy
County Cork, Ireland

MAR 19 1998

Dear Sir or Madam

We acknowledge receipt of your March 4, 1998 correspondence notifying the Food and Drug Administration of the change of ownership of the following new drug application (NDA):

Name of Drug: Tikosyn (dofetilide) Capsules

NDA Number: 20-931

Date of Submission: March 4, 1998

Date of Receipt: March 11, 1998

Name of New Owner: Pfizer Pharmaceuticals Production Corporation Limited

Name of Previous Owner: Pfizer Inc.

Under 21 CFR 314.72, the following information is required to complete the change of ownership procedure:

A new Form FDA 356h signed by an authorized agent or official of the company.

If you have any questions, please contact:

Ms. Diana Willard
Regulatory Health Project Manager
(301) 594-5311

Sincerely yours,

Natalia A. Morgenstern
Chief, Project Management Staff
Division of Cardio-Renal Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

cc: Pfizer Inc.
Attn: William R. Murphy, Ph.D.
Eastern Point Road
Groton, CT 06340-5146

DEPARTMENT OF HEALTH & HUMAN SERVICES

D. Willard
Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-931

JUN 5 1998

Pfizer Pharmaceutical Production Corporation Limited
Ringaskiddy
County Cork, Ireland

Dear Sir or Madam:

I have reviewed your request for priority designation of NDA 20-931 for Tikosyn (dofetilide) Capsules for treatment of supraventricular arrhythmias. You believe it merits priority designation principally because of dofetilide's safety in patients with underlying structural heart disease, distinguishing it from other drugs indicated for the management of supraventricular arrhythmias (letter of April 28, 1998). You also believe (letter to Dr. Raymond Lipicky of January 22, 1998) that there is evidence that dofetilide shows increased effectiveness in treating supraventricular arrhythmias, eliminates or reduces treatment-limiting drug reactions, and shows documented enhancement of patient compliance. You contrast these properties with those of the only two other drugs indicated for maintaining normal sinus rhythm, quinidine and flecainide (propafenone is also indicated for this use).

Dofetilide may indeed prove, on full review, to have some of these advantages but at this stage of examination it does not appear that these claims will be supported by available data.

1. *Evidence of increased effectiveness:*
The comparative studies in the NDA are limited but do not appear to show an advantage over other therapy. There were 3 such studies, two with only 40-50 patients per group comparing dofetilide to sotalol, propafenone, or quinidine. The results do not support a superiority claim for dofetilide. In one study, dofetilide .25 mg bid was not more effective than quinidine 300 mg bid in preventing the recurrence of paroxysmal atrial fibrillation/flutter. Dofetilide at a higher dose (.50 mg bid) was also indistinguishable from propafenone (150 mg tid) in the prevention of symptomatic attacks of paroxysmal supraventricular tachycardia. Although a study of dofetilide versus sotalol showed that patients who were treated with dofetilide .50 mg bid may be at somewhat lower risk for recurrence of atrial arrhythmias, sotalol is generally not recommended for use in this patient population.

2. *Elimination/reduction of limiting drug reaction:*
Dofetilide may be better tolerated than some other drugs for prevention of recurrent supraventricular arrhythmias with respect to non-serious experiences, but may have a greater potential for life threatening adverse reactions. We are concerned about the proarrhythmic effect of dofetilide and its

potential adverse impact on mortality. Despite a seemingly neutral effect on survival in the DIAMOND study, certainly encouraging, we are not convinced that dofetilide is safer than other agents approved for similar indications:

a. There is no doubt that dofetilide causes QTc prolongation and Torsade de Pointes-type VT. This proarrhythmic effect appears to be dose-dependent, has led to termination of the 0.75 mg bid dose group in clinical trials and resulted in a narrow therapeutic window (doses below 0.5 mg bid were not effective).

b. In the pooled placebo controlled trials in supraventricular arrhythmias, there were twice as many deaths in the dofetilide treated patients as in the placebo group. Although this imbalance could be attributed to differences in follow-up duration (placebo patients were withdrawn earlier due to treatment failure), the support for this conclusion will need to be examined closely (ideally, patients should have been followed for mortality even if they reverted). With the current information, a five fold increase in mortality risk in users of dofetilide cannot be excluded. The unadjusted hazard ratio and its 95% confidence interval (from Dr. Pritchett's analyses) is 1.4 (0.4-5.1). Although dofetilide may be less negatively inotropic than some drugs and less pro-arrhythmic in some settings, Torsade de Pointes type arrhythmias may be more common in patients with underlying heart disease, which could mitigate any advantage.

   Oral verapamil is also approved for prophylaxis of PSVT; at the recommended dosages, it is not known to cause proarrhythmias or excessive deaths in the indicated population.

c. Deaths and serious adverse events appear to increase with dose (14 of the 66 patients who received >1.0 mg total daily dose oral dofetilide died on or within 7 days of stopping the drug), but about half (or more, because downward titration was allowed) of the patients in the controlled studies were treated with possibly subtherapeutic dosages (i.e., <1.0 mg/day). Thus, the relative risk of 1.4 could be underestimated.

d. This possibility that risk is underestimated because of inadequate dose also applies to the results of the DIAMOND studies, in which the dofetilide dosages were mostly lower than 1 mg/day. We are also concerned by an increased incidence of serious, life threatening arrhythmias (VF/VT and torsade) in the dofetilide treated group (5.0% vs 1.7% for placebo, from Table 7.5.1 of NDA) in the DIAMOND studies (MI and CHF arms combined).

e. With respect to a direct comparison of the safety of dofetilide to other agents, the active controlled studies appeared to be too small to provide adequate exposure.

3. *Enhancement of patient compliance:*
We have not seen evidence that this issue has been evaluated in the dofetilide NDA nor are we aware of direct comparisons of compliance with alternative drugs.

4. *Indication in a new subpopulation:*
We agree that for patients with structural heart diseases or left ventricular dysfunction, treatment options for supraventricular arrhythmias are somewhat limited (e.g., flecainide or propafenone are approved only for patients *without* structural heart diseases). Quinidine, however, is not so limited in its scope. If it can be shown that dofetilide has a much more favorable benefit/risk ratio than quinidine in this subpopulation, a priority status may be justifiable. The only study directly comparing dofetilide and quinidine in the NDA, however, is a small study of 105 patients (only about half of whom had ischemic or other forms of heart disease) treated for 6 months. This study does not appear adequate to draw any meaningful conclusion about the relative advantages of dofetilide. Note also that dofetilide and quinidine share the ability to create new arrhythmias, especially Torsade de Pointes-type ventricular tachycardia. Whether dofetilide has an advantage at the recommended dose remains to be seen.

If you have any questions, please contact:

Ms. Diana Willard
Regulatory Health Project Manager
(301) 594-5311

Sincerely yours,

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

cc: Pfizer Inc.
Attention: William R. Murphy, Ph.D.
Eastern Point Road
Groton, CT 06340

D. Roeder

NOV 17 1998

NDA 20-931

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

Dear Sir or Madam:

Please refer to your new drug application (NDA) for Tikosyn (dofetilide) Capsules.

In reviewing your submission of March 9, 1998, our Statistician has raised a number of questions that require your attention. Our comments on your submission are detailed as part of this correspondence

Sincerely yours,

Natalia A. Morgenstern
Chief, Project Management Staff
Division of Cardio-Renal Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Enclosure

cc:
Original NDA
HFD-110
HFD-110/DRoeder
Initialed by:
Final:
File Name: 20931gc981117

GENERAL CORRESPONDENCE

ROEDER

NOV 12 1998

NDA 20-931

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

Dear Sir or Madam:

Please refer to your new drug application (NDA) for Tikosyn (dofetilide) Capsules.

In reviewing your submission of March 9, 1998, our Medical Officer has raised a number of questions that require your attention. Our comments on your submission are detailed as part of this correspondence

Sincerely yours,

Natalia A. Morgenstern
Chief, Project Management Staff
Division of Cardio-Renal Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Enclosure

cc:
Original NDA
HFD-110
HFD-110/DRoeder
Initialed by:
Final:
File Name: 20931gc981112

GENERAL CORRESPONDENCE

D. Roeder

NOV - 5 1998

NDA 20-931

Pfizer Pharmaceutical Production Corporation Limited
Ringaskiddy
County Cork, Ireland

Dear Sir or Madam:

Please refer to your new drug application (NDA) for Tikosyn (dofetilide) Capsules.

In reviewing your submission of March 9, 1998, our Medical Officer and Clinical Pharmacologist have raised a number of questions that require your attention. Our comments on your submission are detailed as part of this correspondence

Sincerely yours,

Natalia A. Morgenstern
Chief, Project Management Staff
Division of Cardio-Renal Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Enclosure

cc: Pfizer Inc.
Attention: William R. Murphy, Ph.D.
Eastern Point Road
Groton, CT 06340

cc:
Original NDA
HFD-110
HFD-110/DRoeder
Initialed by: G Buehler for Nmorgenstern/11/5/98
Final:sb/11/5/98
File Name: 20931gc981105

GENERAL CORRESPONDENCE

DEPARTMENT OF HEALTH & HUMAN SERVICES

D. Roeder

Food and Drug Administration
Rockville MD 20857

OCT 28 1998

NDA 20-931

Pfizer Pharmaceutical Production Corporation Limited
Ringaskiddy
County Cork, Ireland

Dear Sir or Madam:

Please refer to your pending March 9, 1998 new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Tikosyn (dofetilide) Capsules.

Refer also to your August 20, 1998 meeting with our Division in which we requested that you supply us with a sample of dofetilide for the purpose of conducting a study to determine whether dofetilide is a P-glygoprotein substrate. The protocol that we intend to follow is included in the enclosed publication. We are requesting 50 mg of dofetilide.

If you have any questions, please contact:

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

Sincerely yours,

Raymond J. Lipicky, M.D.
Director
Division of Cardio-Renal Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Enclosure

cc: Pfizer Inc.
Attention: William R. Murphy, Ph.D.
Eastern Point Road
Groton, CT 06340

11

Estimation of Drug Resistance by Flow Cytometry

Adorjan Aszalos and James L. Weaver

1. Introduction

Drug resistance is a subject that covers two areas. In one case it refers to the bility of microbes to defeat antibiotics. In a different setting it refers to the bility of cancer cells to resist chemotherapy. In the first case, the drug resistance is evaluated on the basis of the percentage of viable cells after treatment with a given drug concentration. This is then simply an application of viability testing, the reader interested in this specific area is referred to Chapter 7.

The second area, multidrug resistance in cancer includes several different mechanisms by which tumor cells are able to evade or defeat the effects of chemotherapeutic drugs. Several types of resistance have been characterized. This includes MDR1 (P-glycoprotein/P170) and MRP *(1,2)* as well as mechanisms that increase the production of a drug target and elevate drug metabolism *(3)*. This list is not intended to be comprehensive and it is nearly certain that additional mechanisms of drug resistance remain to be described.

There are several efflux pumps, two of which have been reasonably well characterized, MDR1 and MRP. These are both members of a larger family of proteins that include a number of bacterial transport proteins and the CFTR chloride channel *(2)*. MDR1 and MRP both have the ability to move neutral molecules from the cytoplasm to the exterior of the cell and require ATP for this activity *(4)* but differ in that MDR1 can also move positively charged molecules *(5)*, whereas MRP appears to be able to move negatively charged substrates *(6)*. They also differ in the tissues in which they are normally expressed and in their comparative substrate and blocker specificities. For example, probenecid is a blocker for MRP *(7)*, but has no effect on MDR1 activities *(5)*. However there is significant overlap in the molecules that can be transported

From: *Methods in Molecular Biology, Vol. 91: Flow Cytometry Protocols*
Edited by: M. J. Jaroszeski and R. Heller

by these two proteins. A more recently described efflux pump, LRP, is able to affect intracellular doxorubicin levels and can be blocked by brefeldin-A *(8)*, but is otherwise still in the process of being characterized.

Flow cytometry has been widely used in the characterization of the activity of efflux pumps, but is not currently the method of choice for characterizing other mechanisms of drug resistance such as increased levels of glutathione. In the case of efflux pumps, the standard strategy is to incubate cells with an inherently fluorescent efflux pump substrate such as daunorubicin or rhodamine 123 (R123). Expression of efflux proteins can also be measured using standard antibody-labeling methods *(9)*.

2. Materials

1. Probenecid: 30 mg/mL in DMSO (Sigma, St. Louis, MO).
2. Verapamil: 10 m*M* in DMSO (Sigma).
3. Genistein: 20 m*M* in DMSO (Sigma).
4. Daunorubicin: 100 μg/mL in DMSO (Sigma).
5. Calcein-AM: 50 μ*M* in DMSO (Molecular Probes, Eugene, OR).
6. Rhodamine 123: 2.6 m*M* (1 μg/mL) in ethanol (Sigma).
7. Cyclosporin A: 1 mg/mL in DMSO (Sigma).
8. Flunarazine: 10 mg/mL in DMSO (Sigma).
9. MRK-16, a mouse monoclonal antibody to MDR1 (Signet Labs, Dedham, MA).
10. Anti-Mouse-IgG-FITC (Sigma).
11. MRPPr1, a rat monoclonal antibody to MRP (Signet).
12. Anti-rat-IgG-FITC (Sigma).
13. FACS Permeabilizing Solution: 10% (v/v) in PBS (Becton Dickinson, San Jose, CA).

3. Methods

3.1. Evaluation of Potential Blockers of MRP Pumping Activity

1. For this purpose, parental and MRP-expressing cells are collected (with or without trypsinization) and are resuspended in phenol red-free medium at 0.5×10^6 cells/mL (*see* **Note 1**). After equilibration for 2–5 min, both parental and MRP cells are treated with potential blockers, solvents, positive controls, or no treatment. As positive controls for blocking MRP activity, any of the following compounds could be used: probenecid (100–300 μg/mL), verapamil (10 μg/mL), or genistein (200 μ*M*).
2. Cells are incubated with test compounds or controls for 10–20 min. If genistein is used, the incubation period before addition of substrate should be at least 1 h since this agent acts by blocking the phosphorylation needed for MRP activity.
3. Next the substrate is added, recommended substrates are daunorubicin (0.3 μg/mL) or calcein-AM (250 n*M*). Incubation with the substrate is for 1 h at either 22 or 37°C in the dark. This time has been shown to be sufficient to allow maximal accumulation of substrates in parental and MRP cell lines.
4. After incubation, cells are collected by centrifugation and kept as a pellet without supernatant until flow cytometry (*see* **Note 2**). Pellets keep their intensity for

>1 h if kept in the dark (*see* **Note 3**). One-parameter histograms are collected for the substrate (calcein: 525–535 nm [FL1]; daunorubicin: 565–605 nm [FL2]). Data are collected for 3000–10,000 cells.

5. Evaluation of the blocking ability of a specific compound is done by comparing the relative percent fluorescence of untreated parental vs MRP cells to the drug treated pair. Correct evaluation of a given drug should include two experiments on different days as well as dose response studies.

3.2. Evaluation of Potential Blockers of MDR1 Pumping Activity

Testing for MDR1 activity is similar to that for MRP, since MDR1 has different substrate preferences, the substrates and blockers are different from those used for the MRP method.

1. Parental and MDR1-expressing cells are collected (with or without trypsinization) and are resuspended in phenol red-free medium at 0.5×10^6 cells/mL (*see* **Note 1**). After equilibration for 2–5 min, both parental and MDR1 cells are treated with potential blockers, solvents, positive controls, or no treatment. As positive controls for blocking MDR1 activity, the following compounds could be used: cyclosporin A (1 μg/mL), or flunarazine (5 μ*M*).
2. Cells are incubated with test compounds or controls for 10 min.
3. Next the substrate is added, recommended substrate is R123 (5.2 μ*M*). Incubation with the substrate is for 20 min at 37°C in the dark.
4. After incubation, cells are collected by centrifugation and kept as a pellet without supernatant until flow cytometry (*see* **Note 2**). Pellets keep their intensity for >1 h if kept in the dark (*see* **Note 3**). One parameter histograms are collected for 10,000 cells in the FITC channel.
5. Evaluation of the blocking ability of a specific compound is done by comparing the relative percent fluorescence of untreated parental vs MDR1 cells to the drug-treated pair. Correct evaluation of a given drug should include two experiments on different days as well as dose response studies.

An example of the results of this type of experiment is shown in **Fig. 1**. Here L5178Y cells from parental and MDR1–transfected cell lines were exposed to no treatment or 1 μ*M* cyclosporin A (CsA). The inhibition of MDR1 by CsA prevents the efflux of R123 and results in a large increase in R123 fluorescence. In contrast, CsA has almost no effect on R123 fluorescence in the MDR1–negative parental cells. The mean fluorescence values are: parental: 30.0, parental/CsA: 26.4, MDR: 0.329, MDR/CsA: 22.2.

3.3. Testing for Expression of MDR1 (P-Glycoprotein)

Testing for MDR1 gene expression on MDR1-positive and MDR1-negative cells can be needed to differentiate between cells expressing MDR1, MRP, or both. This is very important in evaluation of potential blockers since interpretation can be very complex if cells express both proteins. Expression of MDR1

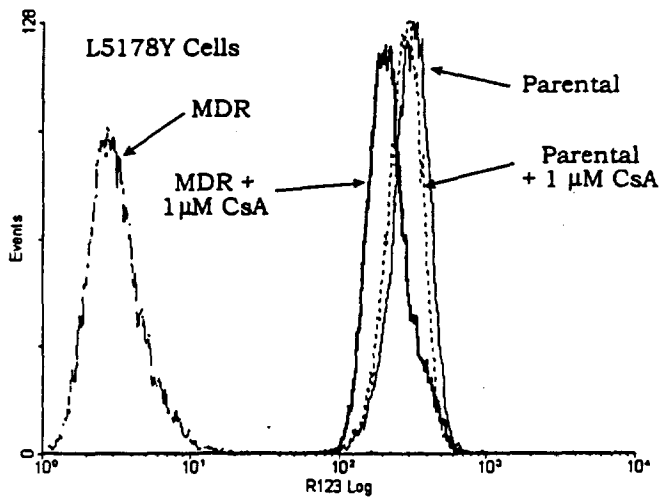

Fig. 1. The effect of cyclosporin A on rhodamine 123 fluorescence in parental and MDR1–transfected mouse L5178Y lymphoma cells. Thin solid line: parental, dashed line: parental with 1 μM CsA, interrupted line: MDR, strong solid line: MDR with 1 μM CsA.

can be evaluated using the monoclonal antibodies such as MRK-16 or 4E3.16, which bind to a extracellular epitopes of MDR1. Other antibodies are available to internal epitopes, but these require fixation and permeabilization to allow the MAb access to the epitope. Any of these antibodies can be used either as a direct-fluorochrome conjugate or with a secondary labeled antibody.

1. Collect at least 10^5 cells/tube by centrifugation and resuspend in 100 μL of PBS. Inclusion of controls including isotype control for the primary, is recommended. For MDR1 expression, add 2 μL of: MRK-16 from a stock of 0.5 mg/mL, or an equivalent amount of MRK-16-FITC. Mix and incubate on ice for 20–30 min.
2. If unlabeled primary antibody is used, add 1 mL of ice-cold PBS, spin, and resuspend in 100 μL of cold PBS. Add 5 μL of antimouse IgG-FITC, mix and incubate on ice for 20–30 min. If labeled primary antibody is used, proceed directly to **step 3**.
3. After all antibody labeling steps are completed, wash the cells 2X in PBS and resuspend in 0.5 mL PBS. Single parameter histograms are collected on 10,000 cells. Labeling is evaluated as increase in fluorescence as compared to isotype controls (*see* **Note 4**).

An example of the results of this type of experiment is shown in **Fig. 2**. Here, transfected NIH3T3MDR cells were exposed to either directly labeled MRK-16-FITC or unlabeled MRK-16 followed by antimouse-IgG-FITC. Note the significant nonspecific binding of the antimouse-IgG-FITC.

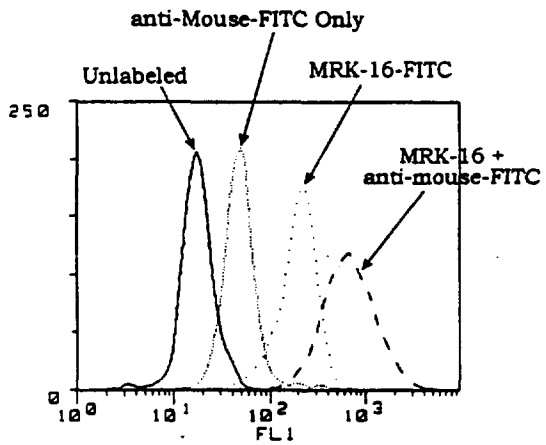

Fig. 2. Binding of FITC-labeled or unlabeled MRK-16 to NIH3T3MDR cells. Cells were treated with MRK-16-FITC, MRK-16 followed by antimouse-IgG-FITC, or antimouse-IgG-FITC only.

3.4. Testing for Expression of MRP

The antibody to MRP detects an intracellular epitope, therefore the cells must be permeabilized to allow the antibody access to its target.

1. Collect 0.5 × 10^6 cells by centrifugation and resuspend in 1 mL of FACS-permeabilizing stock, incubate for 10 min at room temperature.
2. Add 1.5 µg of MRPPr1 and incubate 60 min at room temperature.
3. Wash cells 1X, resuspend in 1 mL PBS, add 10 µL of antirat-IgG-FITC, and incubate for 30 min.
4. Wash 2X and resuspend in 0.5 mL PBS. Single parameter histograms are collected on 10,000 cells. Labeling is evaluated as increase in fluorescence as compared to isotype controls (*see* **Note 4**).

4. Notes

1. We have suggested the use of cell-culture medium for incubations for efflux experiments since both MDR1 and MRP require good levels of ATP for proper function. Extended incubations in nonglucose-containing solutions such as PBS may result in loss of efflux activity.
2. In some cell lines, it is necessary to allow the cells an efflux period between exposure to the fluorescent substrate and evaluation by flow cytometry. Typically, after the incubation with the substrate, cells would be washed 1X and resuspended in phenol red-free medium, and incubated for an additional time period that can range between 20 and 60 min. If no change in fluorescence is seen after 60 min, efflux activity is probably not biologically significant.

3. Note that many fluorescent substrates have a significant "spontaneous" leak rate. Be sure to use controls with either non-MDR/MRP expressing cells or cells treated with strong blockers to differentiate between efflux and leakage.
4. Levels of expression of these efflux pumps varies significantly among various cell lines. For example, four different MDR transfected cell lines showed expression varying from 8000–55,000 antibody binding sites/cell *(9)*.

References

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D. Roeder

JUN 15 1999

NDA 20-931

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) for Tikosyn (dofetilide) Capsules.

In reviewing your submissions of April 29 and May 3, 1999, our Office Director has raised a number of questions that require your attention. Our concerns with your submission are detailed as part of this correspondence. We have enclosed a copy of the review.

If you have any questions, please contact:

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

Sincerely yours,

Natalia A. Morgenstern
Chief, Project Management Staff
Division of Cardio-Renal Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

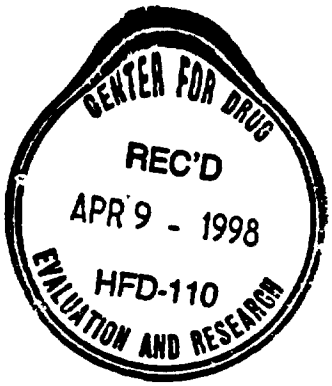
Enclosure
Dr. Temple's Memorandum
cc:
Archival NDA 20-931
HFD-110/Div. Files
HFD-110/D.Roeder

Drafted by: dlr/June 15, 1999
Initialed by: Z McDonald for N Morgenstern
final:sb/6/15/99
filename: 20931gc990615.doc

GENERAL CORRESPONDENCE

Pfizer Inc
Eastern Point Road
Groton, CT 06340
Tel 860 441 4100

DESK COPY



Central Research

Department of Clinical Research

April 8, 1998

Raymond J. Lipicky, M.D., Director
Division of Cardio-Renal Drug Products
Center for Drug Evaluation and Research HFD #110
ATTN: Document Control Room #16B-30
1451 Rockville Pike
Rockville, MD 20852

Dear Doctor Lipicky:

RE: NDA-20-931 - TIKOSYN™ (dofetilide) Capsules

GENERAL CORRESPONDENCE

Reference is made to a telephone conversation with Ms. Diana Willard, Regulatory Health Project Manager, Division of Cardio-Renal Drug Products on March 24, 1998. Ms. Willard informed Pfizer that the debarment statement included in the cover letter to NDA-20-931, Tikosyn™ (dofetilide) capsules, submitted on March 9, 1998 was not adequate. Ms. Willard requested that Pfizer submit a new debarment statement to NDA-20-931.

By means of this letter Pfizer is providing a revised debarment statement for NDA-20-931. The revised debarment statement is as follows: In accordance with the requirements of the Generic Drug Enforcement Act of 1992, and in connection with this Application, Pfizer Inc did not use in any capacity the services of any person debarred under Section 306 of the Federal Food, Drug, and Cosmetic Act.

Please include this information in the file for NDA-20-391. Please feel free to contact me at 860-441-4290 if you have any questions concerning this submission.

Sincerely,

William R. Murphy, Ph.D.
Senior Associate Director
Regulatory Affairs Department

WRM/aed
Desk copy: Ms. Diana Willard
NDA Submission No. 005