

LAW OFFICES
WILLIAMS & CONNOLLY

725 TWELFTH STREET, N.W.

WASHINGTON, D. C. 20005

(202) 434-5000

FAX (202) 434-5029

EDWARD BENNETT WILLIAMS (1920-1988)
PAUL R. CONNOLLY (1922-1978)

VINCENT J FULLER
RAYMOND W BERGAN
JEREMIAH C COLLINS
ROBERT L WEINBERG
DAVID POVICH
STEVEN M UMIN
JOHN W VARDAMAN
PAUL MARTIN WOLFF
J ALAN GALBRAITH
JOHN G KESTER
WILLIAM E MCDANIELS
BRENDAN V SULLIVAN, JR
AUBREY M. DANIEL, III
RICHARD M COOPER
GERALD A FEFFER
ROBERT P. WATKINS
JERRY L SHULMAN
LAWRENCE LUCCHINO
LEWIS H FERGUSON, III
ROBERT B. BARNETT

DAVID E KENDALL
GREGORY B CRAIG
JOHN J BUCKLEY, JR
TERRENCE O'DONNELL
DOUGLAS R. MARVIN
JOHN K VILLA
BARRY S. SIMON
KEVIN T BAINE
STEPHEN L URBANCZYK
PHILIP J WARD
FREDERICK WHITTEN PETERS
PETER J KAHN
JUDITH A MILLER
LON S BABBY
SCOTT BLAKE HARRIS
MICHAEL S SUNDERMEYER
JAMES T. FULLER, III
DAVID D. AUFHAUSER
BRUCE R. GENDERSON
CAROLYN H WILLIAMS

F LANE HEARD III
STEVEN R KUNEY
ROBERT S LITT
GERSON A ZWEIFACH
SARAH HELENE DUGGIN
PAUL MOGIN
DANIELA WINKLER
HOWARD W GUTMAN
NANCY F PREISS
RICHARD S HOFFMAN
PAULA MICHELE ELLISON
STEVEN A. STEINBACH
MARK S LEVINSTEIN
MARY G CLARK
VICTORIA L RADD
DANIEL F KATZ
NICOLE K. SELIGMAN
ROBERT M KRASNE
KATHLEEN L BEGGS
SVEN ERIK HOLMES

April 22, 1993

APR 23 AM 8:05
DOCKETS MANAGEMENT BRANCH

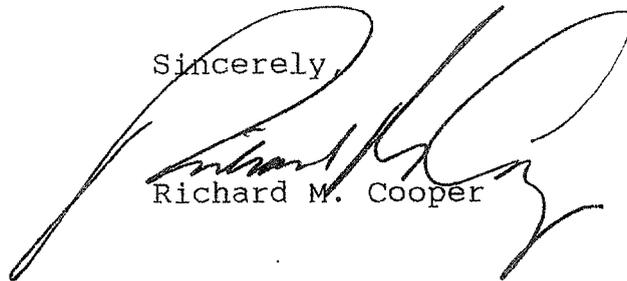
Dockets Management Branch
Food and Drug Administration
Department of Health and
Human Services
Room 1-23
12420 Parklawn Drive
Rockville, Maryland 20857

Dear Sir/Madam:

Enclosed are four copies of our reply comments in FDA docket #93P-0115/PSA1. Please stamp one copy to be returned by our messenger, and file the others as appropriate.

Thank you.

Sincerely,



Richard M. Cooper

RMC:amj
Enclosures

93P-0115

RCI

April 22, 1993

Dockets Management Branch
Food and Drug Administration
Department of Health
and Human Services
Room 1-23
12420 Parklawn Drive
Rockville, MD 20857

REPLY COMMENTS IN SUPPORT
OF PETITION FOR STAY OF ACTION
IN DOCKET NO. 93P-0115/PSA1

These comments, submitted on behalf of Pfizer, Inc. ("Pfizer"), respond to the opposition comments submitted by Elan Pharmaceutical Research Corp. ("Elan") on April 13, 1993 ("Elan's Opp.").

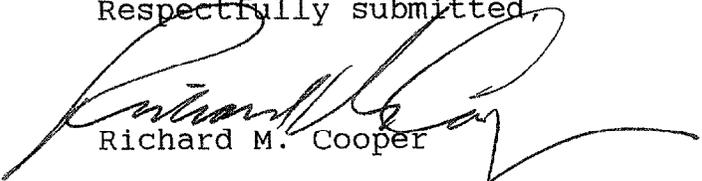
1. This reply is short, to avoid diversion of resources from consideration of the merits of Elan's application for approval of its extended-release nifedipine product ("Elan's NDA") and the merits, related thereto, of Pfizer's Citizen Petition, Dkt. No. 93P-0115/CP 1 ("Pfizer's Cit. Pet.").

2. The Agency has advised Pfizer that its petition is under consideration. That is appropriate because the issue raised by the petition relates to the lawfulness of an approval of Elan's NDA; and, before granting any such approval, the Agency should be satisfied that it would be lawful. Although there is substantial public interest in prompt approvals of NDAs, that interest is outweighed by the public interest in compliance with the legal requirement for adequate scientific support of NDAs.

3. Elan's Opp. is, essentially, an attack on Pfizer's good faith in filing Pfizer's Cit. Pet. and the accompanying petition for stay of action. Elan's attack is without merit. Pfizer acted in good faith, even to the extent of pointing out, specifically and in detail, readily identifiable possible circumstances in which the petition could be summarily denied. Pfizer's Cit. Pet. 3-4. Elan's Opp. does not allege that any of those circumstances is present. Indeed, by stating that it intends to submit comments in opposition to Pfizer's Cit. Pet., Elan's Opp. 2, Elan acknowledges that the issue it raises is substantial. Moreover, contrary to Elan's assertions, Pfizer did raise with FDA in 1990 concerns substantially similar to those presented in Pfizer's Cit. Pet. See Letter from Marvin Frank to Gerald F. Meyer (June 5, 1990)(copy attached).

4. The issue is whether Elan's NDA contains (or lawfully refers to) data adequate to make an approval of the NDA lawful. Agency officials have a responsibility to resolve that issue before acting on Elan's application. Fairness to both Elan and Pfizer, and to the public, requires prompt resolution of that issue. Even Elan is not urging the Agency to ignore it.

Respectfully submitted,



Richard M. Cooper

Williams & Connolly
725 Twelfth Street, N.W.
Washington, D.C. 20005

(202) 434-5466

Counsel for Pfizer, Inc.



PFIZER INC., 235 EAST 42nd STREET, NEW YORK, N. Y. 10017

MARVIN R. FRANK, Pharm. D., J.D.
Assistant General Counsel
and Assistant Secretary
(212) 573 7733

June 5, 1990

Mr. Gerald F. Meyer
Deputy Director
Center for Drug Evaluation and Research
Food and Drug Administration
Parklawn Bldg., Room 13B-45
5600 Fishers Lane
Rockville, Maryland 20857-1706

Dear Mr. Meyer:

We are writing this letter to obtain clarification of the Food and Drug Administration's policy on two issues of importance to pharmaceutical companies engaged in the research and development of innovative drug therapies. The first issue concerns the fairness of FDA's procedures for reviewing product approval requests from pharmaceutical companies seeking to market copies or slight variations of already-marketed drugs through the submission of full rather than abbreviated new drug applications. The second issue, also one of fairness, concerns the amount of data such applications are required to contain to be considered full, as opposed to paper or abbreviated, new drug applications.

Certain information has come to our attention that makes it prudent for us to seek reassurance from the Center that it is applying the drug approval provisions of the Federal Food, Drug, and Cosmetic Act evenhandedly and in accord with the 1984 amendments. Because we anticipate that our concerns will be met by a clarification of existing policy and procedures, we do not believe that a more formal and time-consuming approach to FDA, as by a citizen petition, is necessary.

1. Our first question concerns the procedures for handling full new drug applications seeking approval of generic copies of already-approved drugs. Under the 1984 amendments,

approval of generic copies of marketed drugs may be obtained by filing an abbreviated new drug application, provided certain conditions are met. Those conditions include the provision of a certification regarding any applicable patent and the giving of notice to NDA holders and patent owners in the event the validity or applicability of a patent is challenged. Furthermore, an ANDA cannot be approved or made effective until after the expiration of any period of market exclusivity to which an already approved NDA is entitled. The same conditions and restrictions apply to so-called "paper NDAs," i.e., applications filed pursuant to section 505(b)(2) of the Act.

If a firm wants to market a generic copy of an approved drug without being subject to the limitations imposed on abbreviated applications, it is legally free under the Act to file a "full" new drug application. That is, it may file an application pursuant to section 505(b)(1), which governs the procedures and substantive requirements for applications that contain the results of original, proprietary research establishing the safety and effectiveness of drug products. Although that provision of the Act is generally used to obtain approval of new chemical entities and other pharmaceutical innovations, it is available to any company willing to meet its stringent standards, even for a generic copy (subject, of course, to applicable patent rights enforced outside the NDA approval framework).

FDA's procedures for handling abbreviated generic drug approval applications have been the subject of scrutiny and debate over the past several years. FDA has concluded that to eliminate the potential for real or apparent unfairness in the processing of applications for competing versions of the same drug product, it intends to impose a strict "first in-first reviewed" policy, subject to limited exceptions and close monitoring. Division of Generic Drugs Policy and Procedure Guides 15-90 (January 18, 1990) and 16-90 (March 7, 1990). Under this policy, the schedule for review of a generic drug approval application cannot be adjusted to advantage or disadvantage that application in relation to other applications unless there are sound scientific, technical, or administrative reasons for doing so, and those reasons are recognized in official, written policy or explained to supervisory management. The purpose of this policy is to assure that generic drug approval applications are handled in due course, and are not affected, positively or negatively, by extraneous factors.

The same policy must apply to the review of full applications for generic copies of approved drugs. Given the time and expense involved in duplicating the originator's NDA,

there will be far fewer full applications than abbreviated applications for generic copies of approved drugs. Nevertheless, it is no less imperative as a legal and policy matter that such applications be managed with the same impartiality whose importance is recognized in the context of abbreviated applications. Applicants and the public generally are entitled to assume that all drug approval applications will be processed without reference to irrelevant factors that may prejudice the rights of competitors, patients, third-party payors, and others with a stake in the fair and equitable treatment of marketing applications.

We assume that the Center for Drug Evaluation and Research agrees that fairness is a paramount objective in the management of competing drug approval applications, whether full, "paper," or abbreviated, and that reliance by those responsible for reviewing such applications on considerations that are irrelevant from a legal, scientific, or public health perspective in order to expedite or retard the approval process is antithetical to achieving that objective. We therefore seek your confirmation that a recent account in the Pink Sheet is either erroneous or that it reflects the views of lower level Center employees and not that of senior management and that management will advise all Center employees that the statements in the Pink Sheet article do not reflect Center policy.

The report, a copy of which is attached, concerns remarks made by Robert Cawthorn of Rhone-Poulenc Rorer (RPR) at a meeting of securities analysts in New York City on May 10. According to Mr. Cawthorn, RPR expects to avoid the ten-year exclusivity period applicable to Marion's Cardizem by obtaining approval of a full new drug application for diltiazem. The Pink Sheet paraphrases Mr. Cawthorn as predicting that his company's product "will get the jump on generic diltiazem ANDA approvals by reaching the market before the expiration of Marion's Cardizem exclusivity in November 1992," by the "second quarter of 1992."

Ordinarily, a company that had submitted a full NDA in April of 1990 would be in no position one month later to predict with confidence that approval would occur at any specific time in the future, much less a time merely two years away. But Mr. Cawthorn's certainty and optimism were based, he said, on statements by employees of the FDA (not identified in the Pink Sheet article):

[W]e know, from talking to FDA, that they are quite interested in seeing somebody else come with a diltiazem product on the market ... it may not be FDA's official mandate to encourage competition and try to reduce health care costs ... it is certainly an unofficial one.

Apparently on the basis of FDA's alleged interest in bringing competition to the diltiazem marketplace, RPR was "led to believe that we will get very capable and prompt review."

A policy of expediting the review of applications for generic drugs based on the private, unofficial views of Center employees about what is best for the competitive environment is clearly at odds with the Center's recent initiative to regularize procedures for the management of the generic drug evaluation process. That effort is intended to preclude the consideration in the processing of generic drug approval applications of exactly the sort of legally irrelevant factor RPR was allegedly told by Center employees would enter into the scheduling of its application for diltiazem.

We would appreciate your clarification of the Center's policy regarding the processing of full NDA's for generic drugs and your assurance that applications for generic drugs will be subject to equitable, evenhanded management irrespective of whether they are filed as full, "paper," or abbreviated applications.

2. The second question we have relates to FDA's policy on what constitutes a full, as opposed to a "paper," NDA. It has come to our attention that a pharmaceutical firm may recently have submitted an NDA under section 505(b)(1) that is properly subject to review only under section 505(b)(2), thereby sidestepping the procedural protections afforded innovator pharmaceutical firms against generic competition that potentially compromises the innovator company's patent rights. Such an occurrence raises a broader issue that to our knowledge has not been addressed by FDA.

That issue concerns the extent to which an applicant seeking a second or subsequent approval for a drug product under section 505(b)(1) is required to meet the same data requirements that were imposed on the first successful applicant. The question is important for two reasons. First, all applicants should be treated fairly. Therefore, a second applicant should not be excused from requirements imposed on the first applicant. In addition, in the case of section 505(b), if an application is not required to contain the same data as a previous, full application, the reason why must be that the second applicant is relying explicitly or implicitly on studies performed by or for someone other than the applicant -- studies that either generate "paper" contained in the second application or that are relied on more generally by the applicant and FDA reviewers to conclude that a particular scientific or medical question has been answered sufficiently to dispense with the need for relevant evidence in the

application, despite the fact that the first applicant was required to submit evidence to answer the question. In that case, the second application is properly considered under section 505(b)(2), so that the applicant under section 505(b)(1) receives the benefit of the patent notification and exclusivity provisions applicable to paper NDAs.

We are not aware that FDA has issued either formal or informal guidance to its staff or to the public regarding the required content of a second or subsequent NDA under section 505(b)(1). We therefore seek your assurance that FDA will require that such an NDA contain all of the safety and effectiveness information that the first applicant was required to submit to obtain approval of its NDA.

This request specifically includes the situation in which the second applicant contends that a particular data requirement is no longer applicable because the proposition for which data had been required of the first applicant has become in some sense sufficiently "accepted" in the scientific community that its validity need no longer be shown by specific scientific procedures. Such a contention is squarely in conflict with the 1984 amendments, which enacted the principle that any application that lacks investigations required of the innovator applicant under section 505(b)(1) is by definition a "paper NDA" that must be filed and reviewed under section 505(b)(2) (or, of course, section 505(j)). That result is required for two reasons.

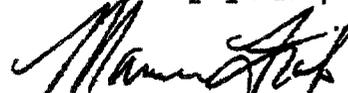
First, if a subsequent applicant is excused from submitting an original investigation to answer a question deemed relevant by Center reviewers for the first applicant, the subsequent applicant is necessarily relying on investigations that were not conducted by or for that applicant. That reliance occurs despite the fact that the investigations that answered the question -- or even the need for them -- may have become obscured by the passage of time. We believe that reliance on such investigations, although indirect or tacit, is functionally equivalent to direct reliance on published studies in the form of a traditional "paper NDA" and should give rise to the same result, i.e., submission and review under section 505(b)(2).

The second reason why an NDA lacking the same investigations that were required in a pioneer NDA must be reviewed under section 505(b)(2) is that failure to do so implicates the constitutional and statutory rights of holders of pioneer NDAs. These rights are protected by requiring a subsequent applicant for approval to market a drug approved under section 505(b)(1) to adhere to the special procedures for

the submission and review of any approval application that is not a "full" application. To define a "full" application as anything less than an application containing all the investigations in the first application makes the distinction between sections 505(b)(1) and (b)(2) administratively unmanageable and, ultimately, meaningless.

As explained in the beginning of this letter, the issues we are raising are important enough for us to seek the Center's response. Nevertheless, because we do not anticipate a serious divergence between our view and what we expect is the Center's position, it is satisfactory to us that the response be informal. If we should utilize another procedure, however, please let us know. We would be happy to meet with you to discuss these issues if you believe that would be useful.

Sincerely yours,


Marvin Frank