DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 50-467/S-064/S-067
NDA 50-629/S-010/S-013

Pharmacia & Upjohn Company
Unit 0633-298-113
7000 Portage Road
Kalamazoo, MI 49001

Attention: Gregory A. Brier
Senior Regulatory Manager

Dear Mr. Brier:

Please refer to your supplemental new drug applications dated August 3, 2000 and October 25, 2001(S-064 and S-010) and (S-067 and S-013), received August 8, 2000 and October 29, 2001 respectively, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for ADRIAMYCIN RDF® (doxorubicin hydrochloride injection) and ADRIAMYCIN PFS® (doxorubicin hydrochloride injection).

The "Changes Being Effected" supplemental new drug applications S-064 and S-010 are superseded by "Prior Approval" supplemental new drug applications S-067 and S-013 submitted October 25, 2001. Therefore, these documents will be retained in our files.

The "Prior Approval" supplemental new drug applications (S-067 and S-013) were submitted in response to our July 11, 2001 request to "update the boxed **WARNING** section of your labeling to include leukemia risk after doxorubicin therapy in the adjuvant setting as soon as possible."

We have completed the review of these applications, as amended, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the October 25, 2001 labeling text and with the agreed upon editorial revisions listed below.

1. Our February 20, 2002 facsimile requested and you agreed in your March 27, 2002, letter to incorporate FDA recommendations for the black box **WARNING** section for myocardial toxicity, previously communicated to you in June 1999. The current wording in the black box WARNING section of the package insert (PI) for myocardial toxicity states

   "Myocardial toxicity manifested in its most severe form by potentially fatal congestive heart failure may occur either during therapy or months to years after termination of therapy. The probability of developing impaired myocardial function based on a combined index of signs, symptoms and decline in left ventricular ejection fraction (LVEF) is estimated to be 1 to 2%

at a total cumulative dose of 300 mg/m^2 of doxorubicin, 3 to 5% at a dose of 400 mg/m^2, 5 to 8% at 450 mg/m^2 and 6 to 20% at 500 mg/m^2.* The risk of developing CHF increases rapidly with increasing total cumulative doses of doxorubicin in excess of 450 mg/m^2. (b)----------
(b)---------- ---------- ----------
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are at increased risk for developing delayed cardiotoxicity."

The FDA recommended that the above second to last sentence ("(b)----------
(b)---…") should be replaced with the following:

"Risks factors (active or dormant cardiovascular disease, prior or concomitant radiotherapy to the mediastinal/pericardial area, previous therapy with other anthracyclines or anthracenediones, concomitant use of other cardiotoxic drugs) may increase the risk of cardiac toxicity. Cardiac toxicity with doxorubicin may occur at lower cumulative doses whether or not cardiac risk factors are present."

2. The following should be added under **REFERENCES**:

   ONS Clinical Practice Committee. Cancer Chemotherapy Guidelines and Recommendations for Practice Pittsburgh, Pa: Oncology Nursing Society; 1999:32-41.

   The footnote number should be changed from "1-7" to "1-8" under the **Handling and Disposal** section at the end of the sentence that states "Several guidelines on this subject have been published.[1-7]" of the PI.

Accordingly, the supplemental applications S-067 and S-013 are approved effective on the date of this letter.

In addition to the above comments, the following items should be addressed in subsequent supplemental new drug applications.

1. We remind you of our February 13, 1998 and January 11, 2000 requests that you submit additional labeling supplements to these applications at your earliest convenience, to include in appropriate sections of the labeling the evidence regarding decreased response rates of Zinecard plus cyclophosphamide, ADRIAMYCIN, and fluorouracil (CAF) compared to CAF alone in the initial treatment of breast cancer. Since the initial request was made over 4 years ago, please provide a timeline as to when this request will be fulfilled.

2. Our February 20, 2002 facsimile requested that you submit a supplement with updated leukemia risks based on analysis of data on file at Pharmacia & Upjohn (P&U) similar to the analysis performed for epirubicin and that you consider requesting information from the NSABP and the CALGB. Your March 27, 2002 response stated that "P&U will update the leukemia risk text of the Black Box Warning based upon results from the NSABP trial as appropriate. The Company has already contacted the NSABP and is reviewing draft results from the NSABP, but it may take a few months before NSABP information is finalized and available for reference. It is understood that the larger trials from NSABP and (b)----------

should be relied upon as the basis for the leukemia risk text. The CALGB trial, since it has a smaller number of patients then the larger trials from NSABP and (b)---------- should not be relied upon for the leukemia risk text."

3. Please submit "Prior Approval" Geriatric Labeling supplements incorporating a "Geriatric Use" subsection under the **PRECAUTIONS** section of the Package Insert [21 CFR 201.57 (f)(10)]. According to the October 2001 guidance document "Content and Format for Geriatric Labeling", a supplement should have been submitted by August 28, 2000 for NDA 50-629 (originally approved December 23, 1987) and by August 27, 2002 for NDA 50-467 (originally approved August 7, 1974).

The final printed labeling (FPL) must be identical to the submitted proposed package insert dated October 25, 2000 (enclosed) with the editorial revisions indicated above. These revisions are terms of the approval of these applications.

Please submit the copies of final printed labeling (FPL) electronically to each application 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, these submissions should be designated "FPL for approved supplement NDA 50-467/S-067 and NDA 50-629/S-013." Approval of these submissions by FDA is not required before the labeling is used.

Please submit 20 paper copies of the FPL as soon as it is available, in no case more than 30 days after it is printed to each application. Please mount individually ten of the copies on heavy-weight paper or similar material. Alternatively, you may submit the FPL electronically according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format – NDAs* (January 1999). For administrative purposes, these submissions should be designated "FPL for approved supplements NDA 50-467/S-067 and NDA 50-629/S-013. Approval of these submissions by FDA is not required before the labeling is used.

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 Brenda Atkins, Consumer Safety Officer, at 301 594-5767.

Sincerely,

{See appended electronic signature page}
Richard Pazdur, M.D.
Director
Division of Oncology Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Enclosure – Proposed Package Insert Revised October 2000 (6 pages)
Copy Code 817 336 305

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

/s/

Richard Pazdur

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