DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 12-892/S-015, S-016

Roberts Pharmaceutical Corporation
Meridian Center III
6 Industrial Way West
Eatontown, NJ 07724

MAY 6 1999

Attention: Richard Raffa
Associate Director, Regulatory Affairs

Dear Mr. Raffa:

Please refer to your supplemental new drug applications dated January 19, 1982, received January 22, 1982 (S-015), and February 20, 1986, received February 28, 1986 (S-016) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Uracil Mustard Capsules, USP.

We acknowledge receipt of your submissions dated March 23, 1987 and January 29, 1988. We note that the latter submission included draft labeling which incorporated the revisions from both supplements.

Supplement S-016 was submitted as "Special Supplement - Changes Being Effected" under 21 CFR 314.70(c) and provides for the addition of information regarding the handling and disposal of cancer drugs. We have completed our review of this supplement, and it is approved, effective on the date of this letter.

S-015 provides for revisions in format to comply with 21 CFR 201.57 as well as updates throughout the labeling. We have completed the review of this supplemental application as submitted with draft labeling, and it is approvable. Before this supplemental application may be approved, however, it will be necessary for you to address the following:

1. All labeling and labels must be changed to reflect Roberts' ownership.

2. Under WARNINGS, Carcinogenesis, mutagenesis, impairment of fertility, the following should replace the existing wording:

> In humans, alkylating agent therapy has been associated with the occurrence of acute nonlymphocytic leukemia and acute myeloblastic leukemia. Long-term carcinogenicity studies of uracil mustard have not been conducted. Administration of uracil mustard to mice weekly, thrice weekly, or every 3 weeks i.p. for up to 26 weeks at doses of 1/6 to 1/3 of the recommended human dose on a body surface area basis caused an increased incidence of lung, liver, and ovarian carcinomas and lymphomas. In rats, thrice weekly i.p. administration of uracil mustard for 8-26 weeks at 1/3 to 1/2 the recommended human dose on a body surface area basis resulted in a significant

incidence of peritoneal sarcomas, lymphomas, and pancreatic, ovarian and mammary carcinomas.

3. Under WARNINGS, Pregnancy Category D, existing wording should be replaced by:

Uracil mustard may cause fetal harm when administered to a pregnant woman. In rats dosed on day 12 of pregnancy with 0.3 or 0.6 mg/kg uracil mustard (1/3 to 1/2 the recommended human dose on a body surface area basis), malformations included exencephaly, retarded and clubbed appendages, and deformed paws and tails. There are no adequate and well-controlled studies in pregnant women. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus. Women of child bearing potential should be advised to avoid becoming pregnant.

4. Delete the ANIMAL PHARMACOLOGY AND TOXICITY section.

5. Additionally, it is the current policy for oncology drug labeling to include only references pertaining to safe handling of oncologic drugs (see list attached). All other references should be deleted from the package insert.

We understand that this product is no longer being marketed. Should you decide to remarket this product, you will need to submit a complete update of any changes which have occurred in the manufacturing of this product since it was last marketed, including the change of ownership of the NDA, as well as updated labeling which includes the above revisions to the January 29, 1988 draft labeling.

Within 10 days after the date of this letter, you are required to amend these applications, 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 such action FDA may take action to withdraw these applications.

If you have any questions, contact Amy Chapman, Regulatory Project Manager, at (301) 594-5771.

Sincerely,

Robert L. Justice, M.D. 5/6/99

Robert L. Justice, M.D.
Acting Director
Division of Oncology Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Enclosure

REFERENCES

1. Recommendations for the Safe Handling of Parenteral Antineoplastic Drugs, NIH Publication No. 83-2621. For sale by the Superintendent of Documents, U.S. Government Printing office, Washington, DC 20402.

2. AMA Council Report, Guidelines for Handling Parenteral Antineoplastics. JAMA, 1985; 2.53(11):1590-1592.

3. National Study Commission on Cytotoxic Exposure - Recommendations for Handling Cytotoxic Agents. Available from Louis P. Jeffrey, ScD., Chairman, National Study Commission on Cytotoxic Exposure, Massachusetts College of Pharmacy and Allied Health Sciences, 179 Longwood Avenue, Boston, Massachusetts 02115.

4. Clinical Oncological Society of Australia, Guidelines and Recommendations for Safe Handling of Antineoplastic Agents. Med J Australia, 1983; 1:426-428.

5. Jones RB, et al: Safe Handling Of Chemotherapeutic Agents: A Report from the Mount Sinai Medical Center. CA - A Cancer Journal for Clinicians, 1983; (Sept/Oct) 258-263.

6. American Society of Hospital Pharmacists Technical Assistance Bulletin on Handling Cytotoxic and Hazardous Drugs. Am J. Hosp Pharm, 1990; 47:1033-1049.

7. Controlling Occupational Exposure to Hazardous Drugs. (OSHA Work-Practice Guidelines), Am J Health-Syst Pharm, 1996; 53:1669-1685.

cc: Archival NDA 12-892
HFD-150/Div. Files
HFD-735 (with labeling)
HF-2/MedWatch (with labeling - this product is not currently marketed)
HFD-002/ORM (with labeling)
HFD-613/OGD (with labeling)
HFD-102/ADRA (with labeling)
HFD-40/DDMAC (with labeling)
HFD-820/DNDC Division Director
DISTRICT OFFICE
HFD-150/AChapman
HFD-150/WSchmidt
HFD-150/PAndrews

Drafted by: dwp/4-28-99/f/t dwp 5-3-99 dwp sent 5-3-99
Initialed by: AChapman 4-29-99
WSchmidt 4-29-99
PAndrews 4-29-99
JJohnson 4-30-99

S-016 APPROVED (AP)
S-015 APPROVABLE (AE)