

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER: 20-687

APPROVABLE LETTER

IS/

NDA 20-687

SEP 18 1996

The Population Council
Attention: Ann Robbins, Ph.D.
Scientist
1230 York Avenue
New York, NY 10021

Dear Dr. Robbins:

Please refer to your new drug application dated March 14, 1996, received March 18, 1996, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Mifepristone Tablets, 200 mg.

We acknowledge receipt of your amendments dated April 19, June 20, July 25, August 15, and September 16 (telefacsimile), 1996.

We have completed the review of this application as submitted with draft labeling, and it is approvable. Before this application may be approved, however, it will be necessary for you to submit the following information:

Clinical

Please submit a comprehensive description of the proposed distribution system.

Chemistry, Manufacturing, and Controls

Drug Substance:

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[Redacted]

[Redacted]

Drug Product:

[Redacted]

Biopharmaceutics

To support the rationale for using the stated dissolution medium and volume plus the selected [Redacted] for the proposed dissolution method, please provide the following information:

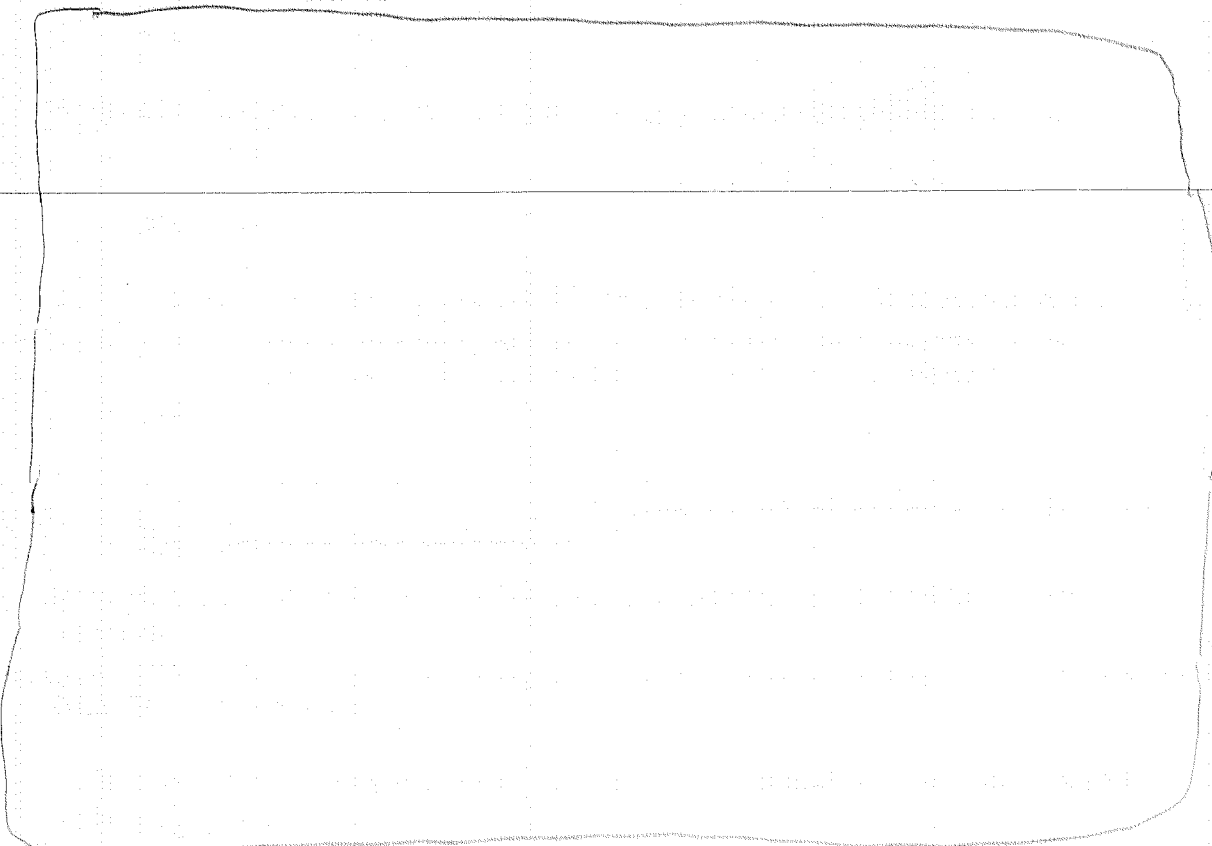
1. pH solubility data for mifepristone;
2. [Redacted] condition information at [Redacted] for various media;
3. Tablet dissolution profiles (including raw data and mean data) in various media (i.e., simulated gastric fluid and simulated intestinal fluid, at a range of pH's representative of physiological conditions) that provide adequate [Redacted] conditions with appropriate sampling times to characterize the profile; and
4. Raw data and profiles at different [Redacted] in the dissolution media cited above.

Physician Labeling

General Comments

1. Please excerpt and incorporate sections from the approved labeling for misoprostol that are relevant for single-dose use of misoprostol as provided for in this labeling.
2. Since mifepristone is not an established name as described under section 502(e)(3) of the Federal Food, Drug, and Cosmetic Act, you should apply to the USAN Council for adoption of a name that will comply with that section of the act. They can be reached at the following address:

United States Adopted Names (USAN) Council
American Medical Association
535 North Dearborn Street
Chicago, IL 60610



3 Page(s) Redacted

Draft

Labeling

Phase 4 Commitments

We remind you of your commitments dated September 16, 1996, to perform the following Phase 4 studies:

1. To monitor the adequacy of the distribution and credentialing system.
2. To follow-up on the outcome of a representative sample of mifepristone-treated women who have surgical abortion because of method failure.
3. To assess the long-term effects of multiple use of the regimen.

4. To ascertain the frequency with which women follow the complete treatment regimen and the outcome of those who do not.
5. To study the safety and efficacy of the regimen in women (1) under 18 years of age, (2) over age 35, and (3) who smoke.
6. To ascertain the effect of the regimen on children born after treatment failure.

Under 21 CFR 314.50(d)(5)(vi)(b), we request that you update your NDA by submitting all safety information you now have regarding your new drug. Please provide updated information as listed below:

1. Retabulate all safety data including results of trials that were still ongoing at the time of NDA submission. The tabulation can take the same form as in your initial submission. Tables comparing adverse reactions at the time the NDA was submitted versus now will facilitate review.
2. Retabulate drop-outs with new drop-outs identified. Discuss, if appropriate.
3. Provide details of any significant changes or findings, if any.
4. Summarize worldwide experience on the safety of this drug product.
5. Submit case report forms for each patient who died during a clinical study or who did not complete a study because of an adverse event.

Please also update the new drug application with respect to reports of relevant safety information, including all deaths and any adverse events that led to discontinuation of the drug, and any information suggesting a substantial difference in the rate of occurrence of common but less serious adverse events. The update should cover all studies and uses of the drug including: (1) those involving indications not being sought in the present submission, (2) other dosage forms, (3) other dose levels, etc.

In addition, we have the following requests for information that should be addressed:

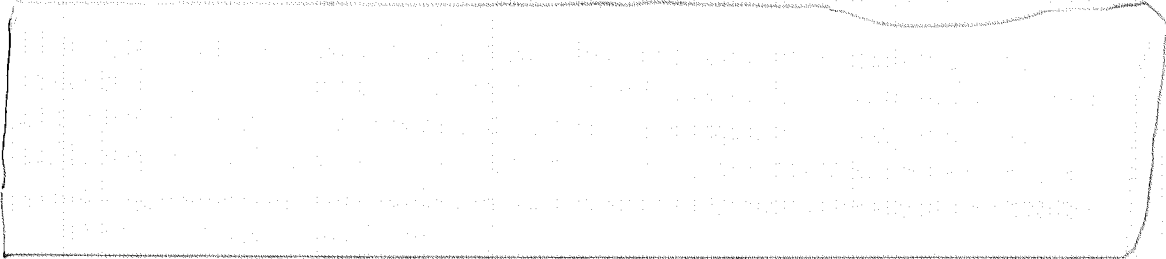
Clinical:

We remind you of your commitment to submit full study reports of the U.S. trials promptly after their completion. We anticipate that you will revise your labeling to incorporate U.S. data at that time.

Drug Substance:



Drug Product:



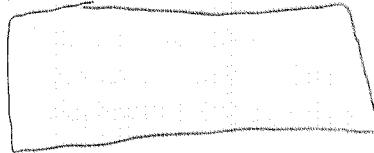
In addition, please submit three copies of the introductory promotional material that you propose to use for this product. All proposed materials should be submitted in draft or mock-up form, not final print. Please submit one copy to the Division of Reproductive and Urologic Drug Products, and two copies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

Food and Drug Administration
Division of Drug Marketing, Advertising, and Communications, HFD _____
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 such action FDA may take action to withdraw the application.

The drug product may not be legally marketed until you have been notified in writing that the application is approved.

Should you have any questions, please contact:



Sincerely yours,

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7/18/96