1. INTRODUCTION

Mifepristone is a synthetic steroid currently used for medical abortion in France, Sweden, United Kingdom and China. It acts as a competitive blocker of progesterone and cortisol through binding to their receptors. Because of its antiprogesterone activity, mifepristone has been developed primarily as a medical abortifacient. When used alone in different regimens with total doses ranging from 140 to 1600 mg administered over one to ten days, the success rate of abortion in women with amenorrhea of less than 50 days duration usually varied between 64-85%[1].

Subsequent studies demonstrated that when mifepristone (600 mg) was followed two days later by a prostaglandin analog administered either by the intramuscular route (sulprostone, a prostaglandin E_2 analog), or as a vaginal pessary (gemeprost, a prostaglandin E_1 analog), the efficacy rate for complete abortion increased to 95% and above. Based on these observations, mifepristone has been marketed in France since September 1989 as a medical alternative to surgical abortion for the termination of pregnancies in women with amenorrhea of 49 days or less. Recently, this mifepristone-prostaglandin regimen was approved in the United Kingdom, and in Sweden. In the latter two countries, this combination is used in women with amenorrhea of up to 63 days.

In Europe there is now an accumulated experience with over 150,000 subjects who have received mifepristone together with various prostaglandins. Clinical trials have been conducted in several countries and have confirmed the initial experience. Unlike treatment with mifepristone alone where the success rate decreased with advancing duration of amenorrhea, the combination was effective up to 63 days of amenorrhea and in various published studies, the incidence of abortion induction ranged from 92.7% to 99%[1].

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The most comprehensive study published to date comprises 16,369 subjects from over 450 clinics[2]. In this study 0.8% of the cases experienced uterine bleeding significant enough to necessitate vacuum aspiration or dilatation and curettage and in 0.07% (11 women), a blood transfusion was required. Significant cardiovascular side effects were reported in four cases following sulprostone administration. In three of these subjects, there was severe hypotension necessitating infusion of macromolecular solutes and in the final subject, a 38 year-old smoker, there was an acute myocardial infarction. In these four subjects, symptoms commenced within one hour of sulprostone administration and all recovered uneventfully. However, in general use, there was a fatal myocardial infarction in one woman, who was a 31-year-old heavy smoker, following sulprostone[3]. No cardiovascular complications have been reported following gemeprost, but this may be related to the fact that this analog has been used less often than sulprostone. Sulprostone is rapidly absorbed into the circulation following intramuscular injection, therefore, it is not unreasonable to assume that this prostaglandin carries a higher risk of cardiovascular problems than preparations that are administered orally or vaginally and are absorbed more gradually. Moreover, gemeprost, unlike sulprostone, is an E_1 analog.

As a consequence, parenteral prostaglandins should be used cautiously in women with heart disease, those over 35 years of age or in heavy smokers. The French health authorities have in fact withdrawn sulprostone as one of the prostaglandin preparations which can be given with mifepristone.

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Because of the cardiovascular side effects reported with sulprostone as well as the inconvenience of both sulprostone and gemeprost which both require refrigeration, alternate prostaglandin preparations are now being used. Misoprostol, (methyl 11α, 16-dihydroxy-16-methyl-9-oxoprost-13 E-en-1-oate) is a prostaglandin E_1 analog that has been safely used for the prevention of nonsteroidal anti-inflammatory drug-induced gastric ulcers in patients at high risk for complications from gastric ulcers for many years; for this indication, it is given in an oral dose of 200 μg four times daily. Its effects on uterine tone are similar to those of other prostaglandins. Misoprostol is inexpensive, orally active and stable. In a recent published French study in women with amenorrhea of 49 days or less, one group comprising 505 women received 400 μg misoprostol 48 hours after mifepristone; the success rate for termination of pregnancy was 96.9%[4]. A second group of 390 women initially followed the same protocol, but

In this second group, the overall success rate was 98.7%. These results indicate that the combination of mifepristone and misoprostol is of equal or greater effectiveness than the combination of mifepristone and parenteral or vaginal prostaglandin for the termination of early pregnancy.[4] No serious cardiovascular side effects have been observed. Other side effects were neither more frequent nor more severe than after parenteral or vaginal prostaglandin preparations[4].

A study from Britain reported complete abortion in 92 out of 99 women with amenorrhea of less than 57 days who were given 200 mg mifepristone followed 48 hours later by 600 μg misoprostol. There were three on-going pregnancies and four incomplete abortions. Vomiting was exhibited in 24% and diarrhea in 7% of the women. No analgesia was needed in 62% of the women[5].

In the two studies reported above, approximately 60-80% of women aborted during the four hours following prostaglandin administration. A number of side effects have been observed during this four hour period. These include: uterine pain, nausea, vomiting and diarrhea. In one of these studies the incidence of nausea, vomiting and diarrhea were 43%, ~~17%~~ and 14% respectively[4].

In Europe, there is now an accumulated experience with over 52,000 women who have received mifepristone followed 48 hours later by misoprostol and the results have been similar.

2. SUMMARY OF STUDY

The aim of the study is to determine the safety, efficacy, acceptability and feasibility of mifepristone plus misoprostol in inducing abortion, within the U.S. health care system setting, when administered to women exhibiting amenorrhea of varying duration (up to 63 days). **The duration of amenorrhea will be defined throughout this document as the number of days from the first day of the last menstrual period.** In addition to the large pivotal studies, a small initial pilot study will be conducted to enable the investigators to gain first hand experience with the proposed dosing regimen.

A total of 1,050 pregnant subjects will be enrolled in this and an identical sister protocol, to be conducted simultaneously. Thus a total of 2,100 subjects will be enrolled in the two trials. Three groups of subjects will be examined:

Group 1: Amenorrhea of $\leq$ 49 days
Group 2: Amenorrhea of 50 through 56 days
Group 3: Amenorrhea of 57 through 63 days

Analysis will also be conducted on safety, efficacy and acceptability of all subjects taken as a single group, regardless of the duration of amenorrhea. This will be a multicenter trial utilizing a minimum of six centers in each of the two studies. The centers will all perform pregnancy interruption on a regular basis. The centers will have access to facilities for blood transfusion and routine emergency resuscitation techniques. In all the trial centers, the recruitment of subjects will be such that, as close as possible, equal numbers of subjects will be enrolled into each of the three groups defined above.

Subjects shall visit the study center three times. At the initial visit (Day 1), a full history and physical examination will be performed and the duration of amenorrhea will be determined and the reasons for selecting a medical abortion will all be recorded. At this visit, 600 mg of mifepristone (three 200 mg tablets) will be administered. The subject will return to the study center for the second visit on Day 3 to receive oral misoprostol (400 μg as two 200 μg tablets). The subject will be monitored at the center for at least four hours post the administration of the prostaglandin. The third visit will occur on Day 15. At this visit the completeness of the medical pregnancy termination will be assessed. In the event that the pregnancy is on-going at this time, or if the abortion has been incomplete, either vacuum aspiration or dilation and curettage will be performed. Subjects who undergo a surgical abortion at any time during their enrollment in the study will return to the center two weeks post the surgical procedure for a follow-up assessment.

3. OBJECTIVE

The objective of this trial is to evaluate the effectiveness, safety, acceptability and feasibility of mifepristone plus misoprostol in inducing abortion when given to women, who have experienced up to 63 days of amenorrhea, within the U.S. health care system setting. Prior to initiation of the pivotal studies, a pilot study comprising 15 women will be performed at each of the selected study centers. The purpose of this pilot trial is to give the investigators exposure to the proposed dosing regimen so they will have first hand experience prior to the initiation of the pivotal studies. The results of the pilot trial will be included in the safety analysis for the product, but the efficacy data will be treated as a subgroup analysis relative to the pivotal trials.

Investigators selected to conduct the trials will be experienced abortion providers and medical investigators. They should have access to an IRB able to review the protocol, and will have malpractice insurance as well as institutional insurance for the clinic, hospital or office where the study will be performed. The investigators should be able to complete the study in six months at a maximum.

The investigators will operate in an appropriate study center; the study center will:

a) Provide routine emergency resuscitation such as O_2, Ambu bag and will be staffed with personnel trained in routine emergency care.

b) Have access on a 24 hour a day basis to blood transfusion, D & C and more elaborate resuscitation procedures.

c) Have space to conduct the study including a room where a woman can be monitored for at least four hours after the prostaglandin administration.

d) Have the physician responsible for the study on call on a 24 hour a day basis, or his/her delegate of equal qualification.

e) Have adequate and sufficient trained personnel for counselling of subjects and conduct of the study.

f) Have transvaginal ultrasound available and personnel trained in the use of the equipment as well as the interpretation of the sonograms for the assessment of gestational age in relation to the reported duration of amenorrhea.

g) Investigators and staff will answer a provided questionnaire at the completion of the study.

4. PATIENT SELECTION

4.1 Patient Sample:

4.1.1 Number of patients: A total of 1,050 patients per each of the identical trials for a total of 2,100 subjects will be enrolled at multiple centers.

4.1.2 Age range: 18 years or older.

4.2 Inclusion Criteria:

4.2.1 Good general health.

4.2.2 Age 18 years or older.

4.2.3 Request termination of pregnancy.

4.2.4 Agree to undergo surgical pregnancy termination in case of failure of the medical abortion method being evaluated.

4.2.5 Have an intrauterine pregnancy of known duration which is less than or equal to 63 days of amenorrhea period. The final determined estimated duration of pregnancy should be less than 64 days of amenorrhea, and as confirmed by uterine size on vaginal examination and ultrasonographic examination.

4.2.6 Have a positive urine pregnancy test.

4.2.7 Willing and able to participate in the study after its precise nature and duration have been explained.

4.2.8 Able and willing to sign an informed consent form.

4.3 Exclusion Criteria:

4.3.1 Evidence of the presence of any disorder which represents a contraindication to the use of mifepristone (e.g., chronic corticosteroid administration, adrenal disease) or misoprostol (e.g., asthma, glaucoma, mitral stenosis, arterial hypotension, sickle cell anemia, or known allergy to prostaglandin).

4.3.2 History of severe liver, respiratory, or renal disease or repeated thromboembolism.

4.3.3 Cardiovascular disease (e.g., angina, valve disease, arrythmia, cardiac failure).

4.3.4 Hypertension being treated on a chronic basis or untreated patients who present with: a blood pressure of > 140 (systolic) or > 90 (diastolic).

4.3.5 Anemia (hemoglobin level below 10 g/dL) at the Day 1 visit.

4.3.6 A known clotting defect or receiving anticoagulants.

4.3.7 Prior uterine surgery where the myometrium has been cut.

4.3.8 Insulin dependent diabetes mellitus.

4.3.9 More than 63 days of amenorrhea or results of bimanual pelvic examination or vaginal ultrasound which are inconsistent with 63 days or less of amenorrhea.

4.3.10 Breast-feeding.

4.3.11 Adnexal masses or adnexal tenderness on vaginal examination suggesting pelvic inflammatory disease.

4.3.12 Suspicion of ectopic pregnancy or threatened abortion.

4.3.13 Women 35 years of age or older who smoke more than 10 cigarettes per day and have another risk factor for cardiovascular disease (e.g., diabetes mellitus, hyperlipidemia, hypertension or family history of ischemic heart diseases).

4.3.14 Unlikely to understand or comply with the protocol requirements.

4.3.15 Women who live more than two hours drive from the source of emergency medical care that serves the abortion center.

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5. STUDY MEDICATION

5.1 Assignment of Study Medication

This is a multicenter trial evaluating the effectiveness, safety and acceptability of mifepristone plus misoprostol in inducing abortion when given to women in one of three groups depending upon the duration of amenorrhea. The three groups are:

Group 1 - Amenorrhea of $\leq$ 49 days
Group 2 - Amenorrhea of 50 through 56 days
Group 3 - Amenorrhea of 57 through 63 days

As closely as is possible, equal numbers of subjects will be enrolled into each of the three groups. There may be differing numbers of patients enrolled from center to center, but the number per group per center should be approximately one third into each of the groups.

5.2 Dosage and Administration

There will be three visits to the study center. At the initial visit (Day 1), a full history and physical examination will be performed and the duration of amenorrhea will be determined and the reasons for selecting a medical abortion will all be recorded. At this visit, 600 mg of mifepristone (three 200 mg tablets) will be administered. The subject will return to the study center for the second visit on Day 3 to receive oral misoprostol (400 μg as two 200 μg tablets). The subject will be monitored at the center for at least four hours post the administration of the prostaglandin. The third visit will occur on Day 15. At this visit the completeness of the medical pregnancy termination will be assessed and an acceptability questionnaire administered. In the event that the pregnancy is on-going at this time, or if the abortion has been incomplete, either vacuum aspiration or dilation and curettage will be performed. Subjects who undergo a surgical abortion at any time during their enrollment in the study will return to the center two weeks post the surgical procedure for a follow-up assessment.

5.3 Packaging

A) Mifepristone — Mifepristone will be provided as 200 mg tablets of micronized mifepristone in packages of three.

B) Misoprostol — Misoprostol will be provided as 200 μg tablets of commercially available misoprostol in packages of two.

All study supplies will be kept in a locked dry cabinet.

5.4 Labeling

A) Mifepristone — Mifepristone will have a label which will include product identification, expiration date, and drug concentration. In addition the following will be printed on the labels: CAUTION: New drug. Limited by Federal Law to Investigational Use. All medication packets will be labelled with the protocol number, center number and a patient number.

B) Misoprostol — Misoprostol will be purchased commercially, and dispensed from the center pharmacy.

5.5 Concomitant Medications

No salicylates, indomethacin, or any other drug which inhibits prostaglandin synthesis should be taken. If necessary, analgesics belonging to other pharmacologic classes or spasmolytic drugs may be used. Drugs such as trifluoperazine and related phenothiazines (for treatment of nausea and vomiting) that could increase the risk of hypertension should be avoided as should oxytocin and any other prostaglandin preparation.

The use of concomitant medications during the course of this study will be recorded in the Case Report Form, and these data will be analyzed.

6. STUDY PROCEDURES

Each participating study center will record on a daily basis the number of subjects recruited in each of the three groups. All women approached to participate in the study will be recorded in the study data. Those who refuse to participate in the trial will have a special form completed for the database. These data will be communicated to the sponsor on a weekly basis. At each center, the number of subjects recruited into each of the groups will be equal to one-third the total assigned to the center if possible. When any of the groups has been filled, no further recruitment into that particular group will be conducted. Under no circumstances will any member of the study center staff suggest that a subject appearing at the center, with a duration of amenorrhea consistent with a completed group, be deferred in her request for pregnancy termination to allow for enrollment into an open group at a later time.

6.1 VISIT 1 (Admission, Day 1 of Study)

At the time of the subjects enrollment (Day 1), all the following should be done:

- Counseling.
- Medical, obstetrical and gynecological history.
- Medical examination, including: height, weight, blood pressure, and pulse.
- Bimanual pelvic examination.
- Urine pregnancy test.
- Vaginal ultrasound.
- Determination of blood group and Rh status.
- Hemoglobin or hematocrit determination.

Food should be withheld for one hour prior to and one hour post administration of the study drug. At admission to the study, the three tablets of mifepristone (600 mg total) will be swallowed by the subject with 240 mL of water in the presence of a member of the center's study staff who will record the date and time of the administration.

Subjects who smoke will be instructed to refrain from smoking until after the administration of misoprostol at Visit 2, and an appointment will be made for Visit 2.

Subjects will be given written information describing symptoms which require emergency treatment. These include: heavy bleeding, fever, and severe abdominal pain. The subjects will be given the address and 24 hour telephone number of a medical center (including the name of physicians) which receives patients on a 24 hour a day basis.

A diary will be provided to each of the subjects for recording medications and symptoms, such as pain, nausea, vomiting and diarrhea. The diary will also be used to record the occurrence of vaginal bleeding on each day. The subject will be instructed to record the bleeding relative to their normal menstrual flow (e.g., lighter, the same as or heavier than normal). If the expulsion takes place before Visit 2, the date and time should be recorded on the subjects diary.

6.2 VISIT 2 (Prostaglandin Administration, Day 3 of Study)

Visit 2 will be conducted on Day three (3) of the study. The following will be performed:

- Clinical examination.

- If expulsion occurred prior to Visit 2, the date and time will be recorded on the case report form as they were noted in the subjects diary. A vaginal examination will be performed, and if necessary, an ultrasound may be required to confirm that the abortion was complete. If the abortion was complete, the misoprostol will not be administered. If the abortion is incomplete or if there is any uncertainty about the completeness of the abortion, the misoprostol will be administered.

- Brief interview and review of the diary.

- Any adverse events which occurred since Visit 1 will be recorded on the case report form.

- Subject will receive an injection of anti-D globulin (Rhogam) if the subject is Rh negative.

- Food should be withheld for one hour prior to and one hour post the administration of misoprostol. The two tablets of misoprostol (400 μg total) will be swallowed by the subject with 240 mL of water in the presence of a member of the center's study staff who will record the date and time of the administration.

- The subject will be observed at the study center for the four hour period post the administration of misoprostol at a minimum. The facility should be capable of surgical termination of pregnancy (by vacuum aspiration or dilation and curettage), have access to blood transfusion, and emergency resuscitation if necessary.

- During the observation period, the following should be recorded at least hourly:

  - Occurrence of nausea, vomiting, or diarrhea. Intensity should be recorded as:

    0: none
    1: mild
    2: moderate
    3: severe

    Any treatment for these will be recorded as concomitant medications.

  - At the onset of any abdominal pain, the following will be recorded:

    Intensity, recorded as: none, mild, moderate, or severe.

    Duration, documenting any treatment as a concomitant medication.

  - Blood pressure and heart rate at hourly intervals unless more frequent readings are indicated.

  - Time of expulsion, if occurring during the observation period.

  - Any unexpected symptom or clinical finding.

The use of intramuscular sulprostone in combination with mifepristone in previous studies has occasionally precipitated an episode of hypotension usually associated with bradycardia. In extremely rare circumstances this previously utilized treatment regimen has been associated with myocardial infarction and ventricular tachycardia. These complications are very unlikely with the combination of misoprostol and mifepristone. However, any significant fall in blood pressure or significant change in heart rate, however transient, following the administration of misoprostol will be recorded and the subject observed for at least three hours after their blood pressure and heart rate have returned to baseline. In case of chest pain, hypotension or cardiac arrhythmia, an ECG should be performed immediately and if required adequate resuscitation should be undertaken.

The cycle immediately following the administration of mifepristone is ovulatory. Therefore, subjects will be counseled to initiate contraception. Barrier contraception may be initiated within three days of misoprostol administration.

- A gynecological examination will be performed to determine if products of conception remain in the vagina or cervix.

- A very active attempt should be made to contact any subject who fails to appear for the Visit 2 appointment. The administration of misoprostol after Day 3 is strongly discouraged.

Additionally, misoprostol may be administered as soon as 36 - 48 hours post the administration of mifepristone in subjects who need to return early because of severe bleeding or pain, as well as in subjects who cannot return on Day 3.

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6.3 VISIT 3 (Exit Interview, Day 15 of Study)

Visit 3 will be conducted on Day fifteen (15) of the study. At Visit 3 the following will be performed:

- Clinical and gynecological examination.

- Assessment of severity and duration of uterine bleeding.

- Assessment of hemoglobin if indicated.

- Verification of any concomitant medications or other therapeutic measures since Visit 2.

- Assessment of expulsion (history, vaginal examination), as well as date and time of occurrence if appropriate.

- Final evaluation of the treatment outcome through the clinical and gynecological examination. If necessary perform ultrasonography and/or urine pregnancy test.

- In instances where the medical abortion method has failed, either completely or partially, perform the necessary additional surgical procedure. In the subjects for whom a surgical procedure is required, schedule a follow-up visit as per Section 6.6 below.

- Examine the subject's view of her abortion experience including her view of the experience relative to expectations; assessment of discomforts and side effects; timing and place of abortion; satisfaction with the experience; comparison to any previous abortion experience; best and worst features of the method being assessed in the trial; attitude toward self-administration of prostaglandin at home and preference for home or clinic treatment. All responses will be recorded in the case report forms.

- Verify the subjects willingness or unwillingness to be contacted at a later date for either further scientific inquiry and/or public information purposes.

- Assure that the subject's case record forms have been completely, accurately and properly filled in.

- A very active attempt should be made to contact any subject who fails to appear for the Visit 3 appointment.

6.4 UNSCHEDULED VISITS

At Visits 1 and 2, subjects will be advised that they may return to the study center at any time if they experience medical problems associated with the medical abortion or for any other medical problem. At any unscheduled visits the following will be recorded:

- Reason for the visit.

- Use of any concomitant medications since the last visit.

- Information regarding utilization of any other medical resources.

- Pregnancy status at onset of visit.

- Temperature, blood pressure, heart rate, and hemoglobin.

- Any medication administered during visit as well as any medications prescribed.

- Any procedures conducted during the visit.

- Results of any pathology testing.

Subjects who have a surgical abortion at any unscheduled visit will have the exit interview (As defined in Section 6.3 above) prior to departure from the study center on the day of the surgical abortion, and will not return for the scheduled Visit 3. However, subjects undergoing surgical abortion will be scheduled for a follow-up visit as outlined in Section 6.6 below.

6.5 SAFETY ASSESSMENT COMMITTEE

If serious adverse events occur beyond expectation, the decision of whether or not the study should be discontinued or modified will be taken by the Sponsor in consultation with the Safety Assessment Committee.

6.6 FOLLOW-UP

Subjects who are enrolled and receive either or both drugs in the study and undergo surgical abortion at any time during their enrollment will be scheduled for a follow-up visit. This follow-up visit will be scheduled for two weeks post the date of the surgical abortion. At this visit the following will be recorded:

- Brief medical history and clinical examination.

6.7 EARLY WITHDRAWAL FROM THE TRIAL

Withdrawal may be defined as a subject who refuses to ingest misoprostol or refuses a physical examination. Withdrawal also includes subjects lost to follow-up.

Patients may withdraw at their own request. In all cases, the reasons for the subjects withdrawal must be recorded in detail in the case report forms and in the patients medical records.

All efforts will be made to contact subjects who fail to return for the necessary visits (telephone, registered mail). The subject will not be given misoprostol if contacted after Day 6 of the study. A subject may not complete the treatment regimen if severe side effects or symptoms develop after mifepristone administration that, in the opinion of the principal investigator, constitute a threat to the woman's health. Any subjects who do not complete the treatment regimen for any reason will be assessed for the completeness of the abortion, if possible. Any subject who has received mifepristone and has at the time of early termination had an incomplete abortion, as described above, will undergo surgical abortion as described in Section 6.3 above, and will be considered a failure.

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7. ADVERSE EXPERIENCES

7.1 General Aspects

Adverse Reactions

Subjects will be notified of possible adverse reactions they could experience and instructed to immediately report them to the investigator.

Any adverse reaction, noticed by the investigator or reported by the subject, including clinically significant lab abnormalities, will be recorded in the appropriate section of the case report form, regardless of its severity and relationship to study drug.

Serious or unexpected adverse events will be immediately reported by telephone to: [redacted]

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All serious ("any experience that is fatal or life-threatening, is permanently disabling, incapacitating, requires inpatient hospitalization, or causes a congenital anomaly, cancer or is due to overdose") and/or unexpected ("any adverse experience that is not identified in nature, severity or frequency in the current investigator's brochure for the study") adverse reactions must be immediately (within 24 hours) reported by telephone to the Sponsor and a written report must be submitted to the medical monitor within 24 hours.

The initial telephone contact will be followed within 3 days by a detailed report of the event which will include copies of hospital case reports, autopsy reports and other documents, when applicable. The adverse event must be followed through resolution.

The same applies to all subjects who died during the course of the study or within 30 days of completion of treatment irrespective of whether the adverse reaction was judged as related to treatment. In case of a death, copy of the autopsy report should be sent to the sponsor, if performed.

For each adverse reaction, the following information will be entered in the case report form: description of event, onset date, resolution date, severity (1=mild; awareness of sign or symptom, but easily tolerated; 2=moderate, discomfort enough to cause interference with usual activity; 3=severe, incapacitating with inability to do usual activity), drug cause-effect relationship and the outcome of the event. The investigator will also note if any action was taken regarding the test drug (temporarily or permanently discontinued) and if therapy or hospitalization was required.

ETHICAL ASPECTS

A. Informed Consent Form

The purpose of the study, those adverse reactions that are known to occur with the study drug and the subject's right to withdraw from the study at any time without prejudice, must be explained to each subject in a language she understands. The subject is then required to sign in the presence of a witness an approved informed consent form in a language she understands containing all the above-mentioned information and a statement that the subject will permit examination of his/her study case report forms by a third party. Willing subjects may be interviewed by a representative of the sponsor about her understanding of the risks, benefits, procedures, and the experimental nature of the study.

B. Institutional Review Board

This study will not be initiated until the protocol and informed consent form have been reviewed and approved by a duly constituted Institutional Review Board (IRB) as required by U.S. FDA regulations. It is the responsibility of the investigator to submit the study protocol with its attachments to the IRB for review and approval.

The names and professional affiliations of all the members of the board or the IRB general assurance number must be given to the Sponsor of the study prior to study initiation, along with a signed and dated statement that the protocol and informed consent form have been reviewed and approved by the IRB.

The investigator is committed, in compliance with FDA regulations, to inform the IRB of any emergent problems, serious adverse reactions or protocol amendments.

C. Protocol Amendments

Any amendment to the protocol will be with mutual agreement between the investigator and the Sponsor. All amendments to the protocol will be submitted to the FDA and to the Institutional Review Board (IRB) concerned for review and, if necessary, approval prior to implementation of the changes.

D. Study Monitoring

A pre-study visit will be made by the monitor to the investigative site in order to review the protocol and to ascertain that the facility is adequate for satisfactory conduct of the study, as well as to discuss the obligations of both the sponsor and the investigator.

The investigator will permit a representative of the sponsor or his designate and the FDA, if requested, to inspect all case report forms and corresponding portion of the study subjects original office and/or hospital medical records, at regular intervals throughout the study. These inspections are for the purpose of assessing the progress of the study, verifying adherence to the protocol, determining the completeness and exactness of the data being entered on the case report forms and assessing the status of study drug storage and accountability. During site visits, case report forms will be examined by the study monitor(s) and verified by comparison with corresponding source data (such as hospital and/or office records).

ADMINISTRATIVE ASPECTS

A. Curricula Vitae

The investigator will provide the Sponsor with copies of the curricula vitae of himself/herself and the co-investigators listed on the FDA Form 1572.

B. Data Collection in the Case Report Form

A Case Report Form in triplicate will be provided by the sponsor for each subject to be filled in at each visit. Additional forms will be used for screening of the subjects prior to enrollment. In the event of additional visits, extra case report forms for the unscheduled visits will be filled out. At the visit on Day 15, acceptability questions will be asked, and the data recorded.

Acceptability questions will be asked on the day of surgical abortion for those having a surgical abortion.

One copy of the forms will be retained by the clinical study site, the other copies will be retrieved by the study monitor at the monitoring visits. All forms will be filled in legibly in black ball point pen. All entries, corrections and alterations are to be initialed and dated by the investigator, co-investigator, or study coordinator making the correction. Corrections will be made by crossing through the incorrect data with a single line so that the incorrect information remains visible, and putting the correct information next to the incorrect data. A reasonable explanation must be given by the investigator for all missing data.

C. Data Retrieval

At intervals during the study and at the conclusion of the study, the study monitor will retrieve signed and dated case report forms from the study site for data entry and analysis. The original and one copy of each page will be retrieved by the monitor. The investigator will keep a copy of all original case report forms and source documents.

D. Records Retention

Pursuant to applicable federal regulations, the investigator must retain copies of all study records for a period of two (2) years following the date a marketing application is approved for the indication for which the drug is being investigated. If no application is filed or if the application is not approved, the study records must be retained until 2 years after the investigation is discontinued and FDA is notified.

E. Study Termination

Either the investigator or the sponsor may terminate the study at any time for well documented reasons, provided a written notice is submitted at a reasonable time in advance of intended termination.

8. STATISTICAL ANALYSIS

8.1 Population Analyzed

All subjects to whom mifepristone has been administered will be included in the analyses.

A) Efficacy

Efficacy will be determined by each subject's abortion status and history at Visit 3 (Day 15), two weeks post the administration of mifepristone. The pregnancy/abortion status requires a clinical evaluation, including where necessary ultrasonographic and/or urine pregnancy results.

One measure of success will be defined as a pregnancy termination by Visit 3 (Day 15) without the need for surgical or instrumentation procedures except for forceps extraction of ovular tissue fragments extending through the external cervical os. If pregnancy has not been terminated by Visit 3 (Day 15), this will be considered a failure.

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FAILURES

Two categories of failures will be recognized. These will be called medical failures and acceptability failures.

Medical failures are of two types:

i) persisting pregnancy at Visit 3 (Day 15).
ii) medically indicated surgical intervention because of:
    a) incomplete expulsion at Visit 3 (Day 15).
    b) serious adverse advents that warrant early surgical interruption of pregnancy.

Acceptability failures are deemed to have occurred when subjects request surgical interruption of a persisting pregnancy before Visit 3 (Day 15) without medical necessity.

In consequences of this distinction between types of failure, there will be two evaluations of success and failure rates.

The *medical failure rate* (MFR) will be determined by life table analysis on a day to day basis from Visit 1 (Day 1) through Visit 3 (Day 15). Women who request surgical abortions before Visit 3 (acceptability failures) will be considered as censored as of mid-day on the day of the surgical abortion. Persisting pregnancies as of Visit 3 are considered failures. The method success rate is 1-MFR for any day or cumulative analysis. Women with persisting pregnancies of less than two weeks post the administration of mifepristone when last observed (e.g., lost to follow-up) will be treated as censored in mid-day of the last observation in the calculation of gross rates.

The *total failure rate* (TFR) will also be determined by life table techniques using the assumption that some of the subjects with persisting pregnancies are last observed before two weeks post the administration of mifepristone. Daily total failure rates are computed under the assumption that subjects with continuing pregnancies last observed before Visit 3 were last observed in the middle of the day of last observation.

Data will be recorded in the case report forms to allow for the distinction between medical and acceptability failures.

All failures will undergo vacuum aspiration or dilation and curettage. Material will be submitted for histological examination.

B) Safety

Safety will be assessed utilizing the following parameters:

- Duration and severity of uterine bleeding; data obtained from subject diary, determination of hemoglobin, by treatment (e.g., transfusion, surgical procedure) necessary secondary to heavy and prolonged uterine bleeding.

- Occurrence of any adverse event or abnormal clinical finding (e.g., signs of pelvic infection).

- Adverse events linked to drug administration and abortion (e.g., nausea, vomiting, diarrhea, painful uterine contractions).

- Assessment of heart rate and blood pressure during the observation period following the administration of misoprostol.

Safety data will include all safety parameters at all visits both scheduled and unscheduled, as well as data collected in the subject's diary, of all subjects to whom mifepristone has been administered.

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C) Acceptability

Acceptability will be measured by patient interviews at the final discharge visit. The assessments will be made on the basis of answers to questions concerning:

- satisfaction with the information and counseling,
- satisfaction with the procedure,
- comparison to previous abortion experience, where applicable,
- willingness to choose the method again, and,
- willingness to recommend the method to others.

All these variables will be assessed in light of the level of complications, discomforts, and side effects recorded for each patient on both the questionnaire and symptomatology diary.

Acceptability of the regimen will also be determined through a questionnaire for providers.

D) Feasibility of Use in the U.S. Health Care System

Variability is built into the study with regard to: Type of abortion site (hospital clinic, Planned Parenthood clinic, feminist health clinic, private practice, free-standing abortion clinic), ethnicity of patient, socioeconomic status (Medicare, self-pay, insurance, help fund, etc.), and location in inner city, small city, suburb, or rural area. The association of these factors with:

- adherence to the protocol
- complications and side effects
- failure (and type of failure)
- patient satisfaction with medical abortion
- provider comfort with medical abortion

will be analyzed.

8.2 ANALYTIC METHODS

8.2.0. A detailed plan, outlining in advance the statistical evaluation of each baseline, safety and efficacy variable, will be submitted to file prior to statistical examination of the data. Essential features of this plan, as presently anticipated, are described below.

8.2.1. Descriptive Statistics: Characteristics of subjects measured at admission through the administration of mifepristone will be summarized. All variables pertaining to safety, efficacy and acceptability will be summarized.

8.2.2. Lifetable Analysis of Efficacy: Single and multiple decrement failure rates for each type of failure and for the total failure rate will be analyzed for each amenorrhea duration, and all durations. Failure rates, by duration of amenorrhea, for age, ethnic group, payment status, and service delivery groups will be determined.

8.2.3. Efficacy Analysis: Multinomial logistic models will be employed to evaluate efficacy. Successful abortion, incomplete expulsion, early surgical interruption due to medical necessity and early surgical interruption at the patient's request (no medical necessity) will serve as the outcome categories used to form response vectors for the models. In one model, the response vector will be comprised of the cumulative log odds over the three types of failure (i.e., incomplete expulsion, medical interruption and requested interruption). In another model, the response vector will be the log odds of these individual types of failure *per se*. In all models, the independent vector will be amenorrhea duration ($\leq$ 49 days, 50-56 days and 57-63 days).

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The models will be used to test the overall (omnibus) effect of amenorrhea status. Additionally, pairwise contrasts among the amenorrhea groups will be evaluated. Both the overall effect and pairwise effects will be examined using traditional hypothesis tests to assess the *complete response vector* (i.e. all failure categories considered simultaneously). However, *individual response categories* will be examined in two ways. First, a traditional hypothesis test will be used to conduct a test of the overall affect of amenorrhea. Second, the examination of pairwise amenorrhea group contrasts will take the form of an equivalency test.

All traditional tests will be evaluated using a type I error rate of 0.05. Equivalence tests will be performed using 90% confidence intervals (which mathematically correspond to a type I error rate of 0.05) and an equivalence interval of $\pm$ 5 percentage points.

Single and or multiple decrement life table techniques, as appropriate, will be used to display failure rate probabilities by time, for individual amenorrhea group and all groups combined. The various effects examined using the multinomial logistic models will also be exhibited in tables and/or figures.

8.2.4. Analysis of factors associated with early abortion (Days 1-3) or late abortion (Days 4-15) or Failure will be undertaken by a variety of multivariate techniques. This analysis pertains to aspects of efficacy, safety and acceptability.

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8.2.5. Baseline/Safety Analysis. Qualitative baseline and safety variables will be systematically summarized in appropriate patient groupings for examination by the medical reviewer. Descriptive statistics for baseline and safety variables that are suitable for quantitative analysis will be displayed in tables and figures. Furthermore, these variable will be evaluated across amenorrhea groups using linear models, applied to continuous or categorical variables. Continuous variables expected to markedly deviate from normality will be rank transformed to obtain nonparametric tests of significance. Any baseline variable found to exhibit a meaningful difference across amenorrhea groups, will be considered for use as covariate or blocking factor in the efficacy analysis. As a conservative measure to increase statistical power, variables exhibiting p-values of 0.20 or less will be singled out to assess their potential relevance to the safety and efficacy of the study drug.

Analysis of variables associated with need for transfusion and with severe cardiovascular adverse events will be undertaken.

8.2.6. Acceptability Analysis: Analysis of variables associated with acceptability within each duration of amenorrhea and overall shall be undertaken using both univariate and multivariate techniques.

9. RISK-BENEFIT ASSESSMENT

Experience gained to date with the use of mifepristone and prostaglandin for the termination of early pregnancy indicates that this has few side effects and a frequency of short-term complications that is comparable to that observed after vacuum aspiration. The most common complaints during treatment, particularly following administration of the prostaglandin, are lower abdominal pain, nausea, vomiting and diarrhea. In addition, bleeding for several days is common. For these complaints, appropriate medication can be prescribed when required. Occasionally, heavy uterine bleeding may necessitate emergency curettage and, very rarely, blood transfusion.

The approximate failure rate, according to the experience gained from women who have had this treatment in Europe, up to 49 days is 5%. Therefore approximately 5% of the subjects in this trial treated up to 49 days of amenorrhea will be expected to undergo surgical termination of pregnancy. It is possible the failure rate will be higher in the older pregnancies.

Following a treatment regimen involving the intramuscular injection of the prostaglandin analog sulprostone, in a very low percentage of cases (one in 20,000), serious cardiovascular complications have been observed, including one case of fatal myocardial infarction. These complications have been most often associated with subjects who were heavy smokers, and still these complications are extremely rare. There is no evidence that misoprostol, a different class of prostaglandin, which is widely prescribed for longterm use in the prevention and treatment of peptic ulcer disease, is associated with any such cardiovascular side effects.

All subjects will be informed as to the potential complications. Centers participating in the trial will ensure that qualified personnel and necessary equipment and supplies are available at all time to deal with any complications.

Studies conducted in mice and rats have shown that mifepristone does not have any teratogenic effects. There are insufficient data to evaluate the effects of mifepristone on the human fetus. In one subject in France who took mifepristone and failed to abort, pregnancy was terminated at 18 weeks because of fetal abnormalities. The precise relationship to mifepristone could not be established[7]. Thus, in the event of a continuing pregnancy, surgical abortion should be performed. Misoprostol has been reported to be teratogenic and is reported to be associated with malformations of the scalp, cranium and other abnormalities[7].

The benefits of this form of medical termination of pregnancy are that most women participating in the study can be expected to have a complete abortion and will not be exposed to the risks associated with surgical abortion, particularly the risks of physical trauma (e.g., cervical laceration, uterine perforation, etc). Nor does medical abortion carry any anesthetic-related risk.

No financial renumeration will be offered to potential study participants.

10. SIGNATURES

I have read the forgoing protocol and agree to conduct the study as outlined.

_____ / / _____

Signature of Investigator M D Y

_____ / / _____

Signature of Sponsor M D Y

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Table 1

	Visit 1	Visit 2	Visit 3
Counseling	X		
Medical, OB-GYN History	X		
Medical Examination	X	X	X
Pelvic Examination	X	X	X
Urine Pregnancy Test	X		X*
Vaginal Ultrasound	X	X*	X*
Blood Typing including Rh	X		
Hemoglobin Determination	X		X*
Administration of Mifepristone	X		
Administration of Rhogam		X*	
Administration of Misoprostol		X	
Interview and Review of Diary		X	X

* - To be conducted if indicated

00186

References

1. Spitz, I.M. and Bardin, C.W., "RU 486-A modulator of progestin and glucocorticoid action," *N Engl J Med*, pp. 404-12, 1993.

2. Ulmann, A., Silvestre, L., Chemma, L., Rezvani, Y., Renault, M., Aguillaume, C.J., and Baulieu, E.E., "Medical termination of early pregnancy with mifepristone (RU 486) followed by a prostaglandin analogue," *Acta Obstet Gynecol Scand*, vol. 71, pp. 278-83, 1992.

3. Klitsch, M., "Antiprogestin and the abortion controversy. A progress report.," *Fam. Plan. Perspectives*, vol. 23, pp. 275-81, 1991.

4. Peyron R., Aubeny, E., Targosz, V., Silvestre, L., Renault, M., Elkik, F., Leclerc, P., Ulmann, A., and Baulieu, E.E., "Early termination of pregnancy with mifepristone (RU 486) and the orally active prostaglandin misoprostol," *New Engl. J. Med.*, vol. 328, pp. 509-1513, 1993.

5. Thong, K.J. and Baird, D.T., "Induction of abortion with mifepristone and misoprostol in early pregnancy,:" *Br. J. Obstet. Gynaecol.*, vol. 99, pp. 1004-7, 1992.

6. Pons, J.C., Imbert, M.C., Elefant, E., Roux, C., Herschkorn, P., and Papiernik, E., "Development after exposure to mifepristone in early pregnancy," *Lancet*, vol. 338, p. 763, 1991.

7. Fonesca, W., Alencar, A.J.C., Mota, F.S.B., and Coelho, H.L.L., "Misoprostol and congenital malformations," *Lancet*, vol. 338, pp. 56-142, 1983.

July 15, 1994

APPENDIX 1

PROTOTYPE INFORMED CONSENT

1. Purpose and aims of the study

It is possible to induce abortion in women with unwanted pregnancies by taking mifepristone in combination with a prostaglandin (misoprostol). Mifepristone is a drug which blocks the action of progesterone, a hormone needed to maintain pregnancy. One of mifepristone's actions is to interrupt pregnancy in its early stages. Prostaglandins are natural substances made by the lining of the womb during menstruation and cause contraction of the womb. During the early stages of pregnancy, mifepristone plus misoprostol cause abortion in approximately 95 per cent of women. Major advantages of this method of pregnancy termination are that no surgical instruments are pushed into the womb. Approximately 250,000 women in 20 countries have used mifepristone and a prostaglandin as a medical method of pregnancy interruption. Mifepristone and misoprostol have been used by over 50,000 women at the dose to be used in this study. The dosage to be studied has been approved legally for routine use in France for women who are pregnant and have experienced seven weeks or less since the last menses. Mifepristone in combination with a prostaglandin has also been approved for use in China, Britain and Sweden. In the latter two countries, it is used in women who are pregnant and have experienced nine weeks or less since the last menstrual period.

The aims of these studies are to determine the safety, efficacy and acceptability of mifepristone plus misoprostol for pregnancy termination in women who have experienced amenorrhea (i.e., absence of menstruation) of 63 days or less from the first day of bleeding from the last menstrual period. These factors will be examined in three groups of women with durations of less than 50 days; 50 through 56 days and 57 through 63 days from the first day of bleeding from the last menstrual period. This study is being performed as a requirement for registration of mifepristone plus misoprostol with the U.S. Food and Drug Administration (FDA) so that these products can be used for pregnancy termination in the U.S.

APPEARS THIS WAY
ON ORIGINAL

2. Clinic visits

I understand that at my initial visit (visit 1) I will receive counseling about the method, a physical examination and an ultrasound examination using a small instrument that is placed in my vagina. The aim is to verify the duration of my pregnancy. In order to terminate my pregnancy, I will take three tablets of mifepristone (first medication) orally in the presence of study personnel. Two days later, I will return to the clinic (visit 2) and will take two misoprostol tablets (second medication) by mouth. The duration of my stay at the clinic at the second visit will be approximately four hours, during which time I will be closely monitored by the study team. During this time, there is an 60-80% chance that abortion will occur. I understand that if the abortion does not occur at the clinic, it is likely to occur at home and I may continue to have uterine bleeding similar to a heavy menstrual period for several days.

A further appointment will be made for me to return to the clinic two weeks after taking the first tablet (visit 3), to ensure that the treatment has been effective. If the treatment has not been effective, then a surgical procedure called vacuum aspiration or dilatation and curettage will be carried out at that time to complete the abortion. This is the same surgical procedure that would have been used had I elected to undergo surgical abortion in the first instance. Since it is possible to become pregnant again after the abortion; I will be asked to select and use a contraceptive method.

3. Benefits

I understand that an advantage of the mifepristone/misoprostol medical method for pregnancy termination is that it avoids a surgical procedure. There is no anesthesia-related risks or risk of uterine perforation or cervical canal injury which may rarely be observed after surgical termination of pregnancy. Another benefit is the satisfaction of participating in the study that will make mifepristone/misoprostol available to women in the U.S.

APPEARS THIS WAY
ON ORIGINAL

4. Risks and discomforts

I understand that experience gained so far with the combination of drugs and the termination of early pregnancy indicates that this therapy has few side effects. The frequency of short-term complications are comparable to that observed after surgical abortion performed by vacuum aspiration. The most common complaint during treatment (particularly following administration of the second medication) is lower abdominal pain or cramps which are similar to those associated with a very heavy menstrual period. I will receive appropriate medication for pain when required. I understand that I should not take aspirin, Motrin®, ibuprofen (Advil® or any other drug known to block the action of prostaglandins. However, I may take Tylenol® and I may receive stronger medications for pain from my doctor. I understand that cramps and abdominal pains are usual and an expected part of the abortive process. Nausea, vomiting, and diarrhea have been observed following administration of the second medication. Therefore, at the second visit it is necessary to remain at the clinic under appropriate medical supervision for approximately four hours before returning home. Uterine bleeding, similar to a heavy period and lasting at least one week, may be expected. In rare instances very heavy uterine bleeding may occur requiring surgical abortion and/or blood transfusion.

I understand that abortion after mifepristone/misoprostol is successful in termination of pregnancy in approximately 95% of treated women. When abortion is incomplete or does not occur, it is essential that a surgical abortion be performed by vacuum aspiration or dilatation and curettage.

I understand that it is not advisable to allow a pregnancy to continue after taking mifepristone and/or misoprostol, since the full effects of mifepristone on the fetus are not know and misoprostol administration in early pregnancy has been associated with abnormal development of the fetus.

There have been no serious heart conditions in the 52,000 women using the combination of drugs in the study for pregnancy termination. However, serious cardiovascular complications, including one fatal heart attack occurred during medical abortion using a different drug combination. These heart conditions have occurred usually in women who are heavy smokers or have increased blood fats, diabetes, high blood pressure, or family history of heart disease. This risk also increased in women who are over 35 years of age. These complications have been seen only following an injected prostaglandin and are rare (one in 20,000 cases). To date there is no evidence that the oral prostaglandin (misoprostol) that I will be taking in this study and which has been used widely for prolonged periods of time in the prevention of stomach ulcers, is associated with such cardiovascular side effects.

5. Alternative Statement

I know that my pregnancy could be terminated by a surgically performed abortion procedure (dilatation and curettage or vacuum aspiration). The possible advantages and disadvantages of a surgical rather than a medical termination have been explained to me. The advantages of surgical termination of pregnancy is that this is a one day procedure. The risks associated with surgical abortion are minimal. These include the risk of an anesthetic procedure. In the U.S., less than 1% of patients who undergo a surgical abortion experience a major complication associated with the procedure such as a serious pelvic infection, cervical tear, bleeding requiring a blood transfusion or unintended major surgery (for a uterine perforation).

6. Physical Injury Statement

If I require medical treatment as a result of physical injury arising from my participation in this study, immediate, essential, short-term medical care and treatment as determined by the doctors in this study will be made available without charge to me. There will be no monetary compensation for any other care, but medical consultation and appropriate referral services are available. Further information on the availability of medical care and treatment for any physical injury resulting from my participation in this study may be obtained from the Investigator, Dr. _____ (telephone:_____).

7. Whom to Call in an Emergency

I understand that if severe uterine bleeding, or abdominal pain, or any other medical emergency arises in association with this method, I will report immediately to (institute, address, telephone no.) In addition, I will contact Dr. _____

(telephone:_____). If he or she cannot be reached in a medical emergency related to the study, I may contact Dr. _____ (telephone:_____).

8. Offer to Answer Questions and Freedom to Withdraw from the Study

I have been told that I may withdraw from the study at any time without jeopardy to my present or future medical care from the hospital or clinic. I have been told to contact Dr. _____(telephone:_____ or Dr. _____ (telephone:_____ if I have any questions about the research. These physicians may appoint their associates to answer my questions.

I also understand that the Principal Investigator may require me to withdraw from the study, if in his/her medical judgement it is in the best interest of my health or if it becomes impossible for me to follow the experimental procedure of this study.

9. Confidentiality

I understand that information obtained in this study will be transmitted only in a form that cannot be identified with me. I understand that the Population Council or their designated monitors, as well as the U.S. Food and Drug Administration may request access to my medical records.

INFORMED CONSENT:

"I am willing ( ), or I am not willing () to be interviewed by a representative of the sponsor. I understand that I can change my mind at any time. If I do not agree to be interviewed, this will not affect my present or future medical care from the hospital or the clinic, or my participation in the study. The interview, conducted in the language I speak, will verify that I understand the risks, benefits, procedures, and the experimental nature of the study. All information will be kept confidential."

10. Subject's Statement

I understand that the purpose of this research is to study the safety, efficacy and acceptability of mifepristone and misoprostol for terminating pregnancy.

I understand that my participation in this study is wholly voluntary that I may withdraw from the study at any time, without the need to justify my decision.

I, the undersigned, agree to take part as a volunteer in this research project. I have reviewed the information sheet which describes the abortion process and all my questions have been satisfactorily answered.

I have been informed verbally and in writing whom to contact in case of an emergency. I agree to participate in this study as a volunteer subject.

_____ _____

Date Signature of Volunteer

APPEARS THIS WAY
ON ORIGINAL

July 15, 1994

11. Investigator's Statement

I, the undersigned, have explained to the volunteer in the language which she speaks the procedures to be followed in this study and the risks and benefits involved.

Date	Signature of Investigator
Date	Signature of Witness to the Above Signature and Explanation

APPEARS THIS WAY
ON ORIGINAL

The Population Council

Center for
Biomedical Research

1230 York Avenue
New York, New York 10021
Cable: Popblomed, New York
Facsimile: (212) 327-7678
Telephone: (212) 327-8731
Telex: 238274 POBI UR

ORIGINAL

September 1, 1994

———— Division of Metabolism and
Endocrine Drug Products, HFD-510
Center for Drug Evaluation and Research
Document Control Room, 14B-03
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Re: *IND* ———— ***Mifepristone Tablets, 200 mg***
Submission Serial Number: 102
Information Amendment: Chemistry, Manufacturing, and Controls

Dear ————

We refer to our above Investigational New Drug Application (IND) which provides for the upcoming initiation studies with mifepristone in inducing abortion. We also refer to the telephone conversation of July 13, 1994 between Dr. Irving Spitz of The Population Council and ———— of your office regarding the investigational drug supplies to be provided by Roussel Uclaf for conducting the study.

In our recent amendment of August 4, 1994 (Submission Serial Number 100), we described the tablet dosage form of the investigational product and the general methods of labeling and distribution we planned to undertake in connection with the clinical studies. This description was based on the assumption that the product to be supplied to us by Roussel would be the European commercial tablet in blister packaging, as described in the amendment. In his conversation of July 13 with ———— , Dr. Spitz discussed that we had been informed by Roussel that the product might differ from the commercial product in that the tablets likely would not bear the product identification code on one face and the Roussel logo on the other. ———— advised that the IND should be amended to provide dissolution information on the differing product.

We have now received a bulk shipment of tablets from Roussel and wish to amend our IND with the following information on the product received and the repackaging and labeling activities we propose to undertake with the product for distribution to investigators.

1. Description of Investigational Product Received from Roussel Uclaf

A bulk shipment consisting of — metallic containers, each containing ———— tablets in a polyethylene bag, has been received from Roussel Uclaf. A copy of the labeling for the containers is provided in Attachment I. Attachment II is a copy of the Certificate of Analysis for the product. As stated in the Certificate of Analysis, the product complies with current manufacturer specifications, but the tablet dosage form does not bear engraved markings on either face. The specifications for the product include a dissolution requirement and results

DATE RECEIVED:
☐ LETTER ☐ FAX
CSO INITIALS

of the test are provided in the Certificate of Analysis.

2. Description of Repackaging, Labeling, and Distribution Procedures.

The bulk drug supplies received by The Population Council are inventoried and kept in secure storage facilities. For distribution to individual study centers, the tablets will be repackaged by the pharmacy _____ into amber plastic, light-protective, child-resistant dispensing vials. A stability study will be initiated on the product in the dispensing vials.

Attachment III is an example of the investigational label which will be applied to the vials. The number of tablets specified on the label can vary depending on whether the drug supply is for the pilot or major study.

An inventory system will be maintained which will record information on quantities and ultimate disposition of drug supplies provided to investigators.

Please contact me should there be any questions or comments regarding this amendment.

Sincerely yours,

C. Wayne Bardin

C. Wayne Bardin, M.D.
Director

Attachments

APPEARS THIS WAY
ON ORIGINAL

IND ———

MEMO OF TELEPHONE CONVERSATION

I called Dr. Irving Spitz at the Population Council (212-327-8734) on Monday, August 8, with a response to the questions he posed on Thursday, August 4. (Refer to e-mail dated Aug. 4.)

I told Dr. Spitz that ——— had consulted with ——— HFD- regarding the acceptability of separate dissolution profiles for the tablets with and without the logo embossed [for establishing bioequivalence with clinical supplies.] The dissolution profile, as shown in the data sheet provided to the Population Council by Roussel UCLAF and faxed to me by Dr. Spitz on August 4, was given as an example. Both ——— said they could accept individual dissolution PROFILES for each type tablet - rather than a comparative dissolution study - to meet the requirements of their respective disciplines. ——— had stated that it was important to have the dissolution profiles conducted by the same company using the same equipment, if at all possible. He said that usually discrepancies are magnified when the tests are done using different equipment and staff, so it is to the applicant's advantage to have the tests done by the same company. I reiterated that dissolution PROFILES were needed.

Dr. Spitz did not know whether the Pop. Council would be able to get Roussel to do the profile for the tablets without any logo, but we speculated that they might need to do it for release of the lot. In any case, he was pleased that the problem of requiring comparative testing of both tablets had been resolved.

/S/ 8-11-94

cc: Arch. IND ——— (+attachments)
HFD-510
HFD-510 ———
HFD-426 ———

APPEARS THIS WAY
ON ORIGINAL

e Population Council
ter for
nedical Research

1230 York Avenue
New York, New York 10021
Cable: Popbiomed, New York
Facsimile: (212) 327-7678
Telephone: (212) 327-8731
Telex: 238274 POBI UR

FACSIMILE TRANSMITTAL SHEET ATTACHMENT 2a

Number of Pages (including this sheet 5

Send to Facsimile Number 301- 443. 9282

Date 8 1 4 94

Send to Company

Send to Person

Subject

Comments:

Dear —, Here is the material as promised. Please call me if you need further clarification.

Thanks,

Tony

Tel. 212- 327-8754

BEST POSSIBLE COPY

Electronic Mail Message

Date: 9/12/00 5:17:29 PM
From:
To: See Below
Subject: FWD: Mifepristone phase4

Everyone,

Please see the attachment. This is revised version of the phase 4 protocol designs. This version incorporates the comments from this morning's meeting.

Due to prior commitments, I'm not sure that OPDRA members will be able to attend tomorrow's t-con with the sponsor. I will check OPDRA availability in the morning (and talk with

And will check with ODE/Repro to see if OPDRA comments 'as is' are appropriate or if further negotiations by the ODE/Repro/sponsor may be necessary.

Thanks.

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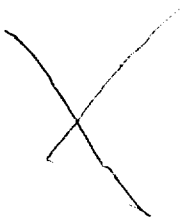

Printed by [redacted]

Electronic Mail Message

Sensitivity: COMPANY CONFIDENTIAL

Date: 12-Sep-2000 05:17pm
From: [redacted]
Dept: HFD-440 PKLN 15B18
Tel No: [redacted] FAX [redacted]

TO: See Below
Subject: FWD: Mifepristone phase4

Everyone,

Please see the attachment. This is [redacted] revised version of the phase 4 protocol designs. This version incorporates the comments from this morning's meeting.

Due to prior commitments, I'm not sure that OPDRA members will be able to attend tomorrow's t-con with the sponsor. I will check OPDRA availability in the morning (and talk with [redacted]

And will check with ODE/Repro to see if OPDRA comments 'as is' are appropriate or if further negotiations by the ODE/Repro/sponsor may be necessary.

Thanks,
[redacted]

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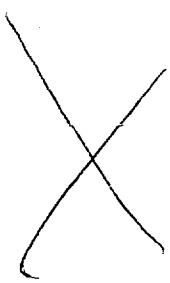

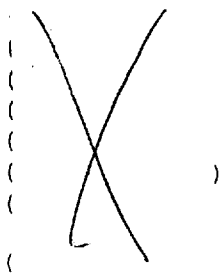

Electronic Mail Message

Date: 09/10/2000 10:13:02 PM
From: [redacted]
To: See Below
Subject: Re: Mifepristone Update

>FYI,
>
>I spoke to [redacted] PMS-580) a few minutes ago and wanted to update the office on the Mifepristone
>application. As you all know a meeting with 580 and ODE III has been scheduled for Tuesday at 8:30 a.m.
>(see RCM) to discuss OPDRA's review of the applicant's Phase 4 commitment proposals [redacted] indicated
>that they plan to send the applicant a letter on Wednesday morning which contains the following.
>
>1. Final Medication Guide comments
>2. Final Labeling comments
>3. OPDRA's Phase 4 comments
>
>At least this advance notice allows us the opportunity to finalize OPDRA's comments prior to Tuesday's
>meeting.
>
>Thanks.
[redacted]
>
>
Thanks for working on this for OPDRA.

[redacted]

To:
To:
To:
To:
To:
To:

Electronic Mail Message

Date: 9/8/00 3:50:23 PM
From:
Subject: Mifepristone Update

FYI,

I spoke to 580) a few minutes ago and wanted to update the office on the Mifepristone application. As you all know a meeting with 580 and ODE III has been scheduled for Tuesday at 8:30 a.m. (see RCM) to discuss OPDRA's review of the applicant's Phase 4 commitment proposals. ndicated that they plan to send the applicant a letter on Wednesday morning which contains the following.

1. Final Medication Guide comments
2. Final Labeling comments
3. OPDRA's Phase 4 comments

At least this advance notice allows us the opportunity to finalize OPDRA's comments prior to Tuesday's meeting.

Thanks.

Electronic Mail Message

Date: 09/08/2000 3:50:23 PM
From:
To: See Below
Subject: Mifepristone Update

FYI,

I spoke to 580) a few minutes ago and wanted to update the office on the Mifepristone application. As you all know a meeting with 580 and ODE III has been scheduled for Tuesday at 8:30 a.m. (see RCM) to discuss OPDRA's review of the applicant's Phase 4 commitment proposals. indicated that they plan to send the applicant a letter on Wednesday morning which contains the following.

1. Final Medication Guide comments
2. Final Labeling comments
3. OPDRA's Phase 4 comments

At least this advance notice allows us the opportunity to finalize OPDRA's comments prior to Tuesday's meeting.

Thanks.

To:
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Printed by [redacted]

Electronic Mail Message

Sensitivity: COMPANY CONFIDENTIAL

Date: 08-Sep-2000 05:36pm
From: [redacted]

Dept: HFD-103 PKLN 13B45
Tel No: [redacted] FAX [redacted]

TO: See Below
Subject: Mifepristone final review package

Please note that final labeling discussion with the company will be happening next week (Tues/Wed) and hopefully we will get agreement on the phone.

[redacted], please schedule a telecon with Pop Council after our internal meeting on labeling (including label, patient agreement, prescriber's agreement). Med guide final comments will be given to company later.

Please finalize your reviews [redacted], will do a brief Division note. Division final reviews due to Office 9/15 noon!

[redacted] please track to make sure this happens. The package will then be looked at by ORM and Dr. Henney.

Distribution:

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Electronic Mail Message

Date: 9/8/00 2:47:26 PM
From:
To: See Below
Subject: Re: Mifepristone Label

In follow-up to the meeting yesterday, I would like to remind everyone that labeling comments need to be communicated to me by 12:00PM on Monday, September 11, 2000. The Office is requesting that the sponsor receive information on the morning of the 13th from us. If you would like to fax your changes, I can be reached at . Please do not hesitate to contact me if there are any problems.

Just as a reminder, any comments regarding the MedGuide should be directed to . Any comments regarding the Phase 4 section of the application should be directed to OPDRA . Any comments regarding the Q&As should be directed toward

Thanks,

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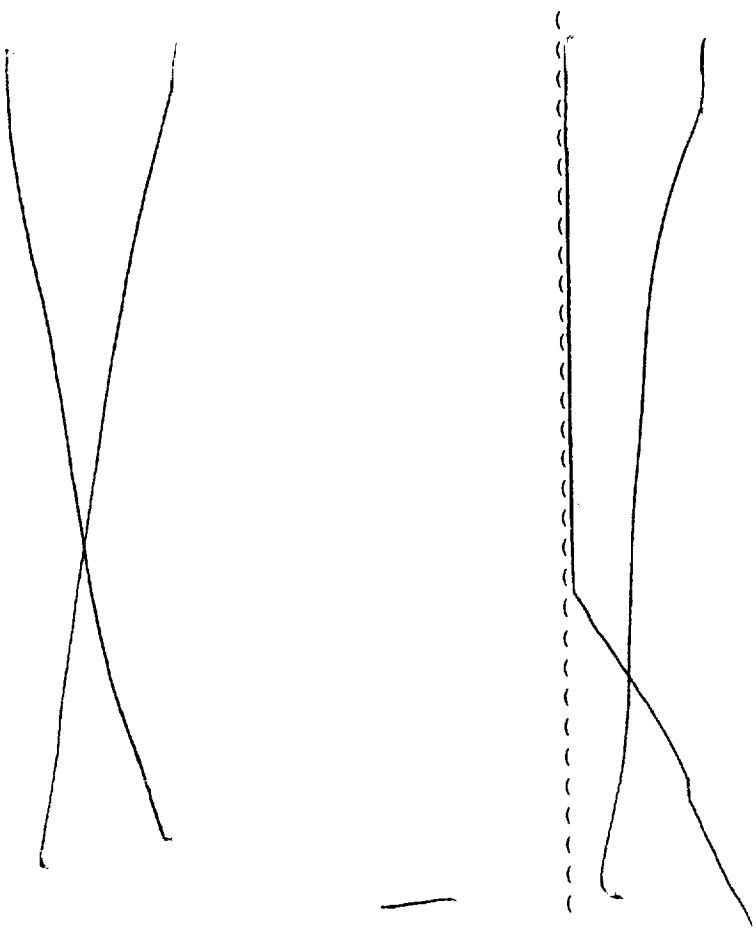

Electronic Mail Message

Date: 9/7/00 7:32:57 PM
From:
To: See Below
Subject: Please check RCM---meeting scheduled for Tuesday, 09/12/00 at 8:30 AM

Everyone,

An internal meeting with OPDRA/Repro/ODE has been scheduled for Tuesday, 09/12/00, at 8:30 AM in Room 13B-45.

This Tuesday meeting is an action item resulting from 09/07/00 meeting.

Agenda is to discuss the OPDRA review of the applicant's proposed Phase 4 studies.

Thanks,

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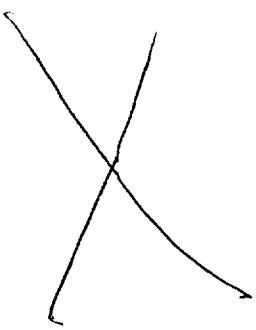

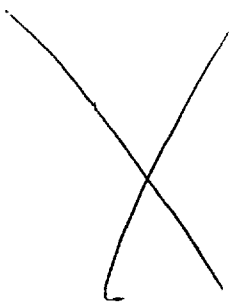

Electronic Mail Message

Date: 9/7/00 5:16:08 PM
From:
Subject: OPDRA Action Item following Pop Council meeting today

As a follow to the Pop Council Meeting today, the action item for OPDRA entailed an internal meeting with the recipients of this email to discuss the Phase 4 studies. OPDRA will review and discuss Pop Council's Sept 7th proposed Phase 4 documents. _____ will schedule this meeting for approximately Tuesday (Sept 12th) of next week. A follow up telecon with the sponsor may or may not be indicated following this meeting, and if so, will be scheduled by HFD-580.

Thank You,
_____

Electronic Mail Message

Date: 9/7/00 5:16:08 PM
From: [redacted]
To: See Below
Subject: OPDRA Action Item following Pop Council meeting today

As a follow to the Pop Council Meeting today, the action item for OPDRA entailed an internal meeting with the recipients of this email to discuss the Phase 4 studies. OPDRA will review and discuss Pop Council's Sept 7th proposed Phase 4 documents. [redacted] will schedule this meeting for approximately Tuesday (Sept 12th) of next week. A follow up telecon with the sponsor may or may not be indicated following this meeting, and if so, will be scheduled by HFD-580.

Thank You,
[redacted]

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Electronic Mail Message

Date: 09/07/2000 5:16:08 PM
From: [redacted]
To: See Below
Subject: OPDRA Action Item following Pop Council meeting today

As a follow to the Pop Council Meeting today, the action item for OPDRA entailed an internal meeting with the recipients of this email to discuss the Phase 4 studies. OPDRA will review and discuss Pop Council's Sept 7th proposed Phase 4 documents. [redacted] will schedule this meeting for approximately Tuesday (Sept 12th) of next week. A follow up telecon with the sponsor may or may not be indicated following this meeting, and if so, will be scheduled by HFD-580.

Thank You,
[redacted]

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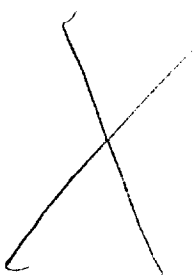

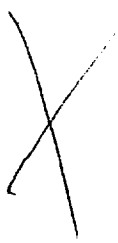

Electronic Mail Message

Date: 9/5/00 3:10:51 PM
From: [redacted]
To: [redacted]
Cc: [redacted]
Cc: [redacted]
Cc: [redacted]
Cc:
Subject: FWD: Mifeprisone - followup info re. misoprostol use at home

FYI... [redacted] has provided copies of his IND review for [redacted] as well as his updated draft review for mifepristone which includes available published references for use with misoprostol at home.

I will bring those down to you for your information.

[redacted]

Electronic Mail Message

Date: 8/28/00 8:28:36 AM
From:
To: See Below
Subject: Mifeprex Medication Guide

Attached is the latest version of the Mifeprex Medication Guide. Based on comments from a variety of sources, there have been several changes since the last version. These changes are summarized at the beginning of the document.

We plan to send the Medication Guide to the company on Wednesday. Therefore, we must have your comments by close of business on Tuesday. We apologize for the short time frame.

Send your comments to

Thanks

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E L E C T R O N I C M A I L M E S S A G E

Sensitivity: COMPANY CONFIDENTIAL

Date: 13-Sep-2000 03:59pm EDT
From:

Dept: HFD-103 PKLN 13B45
Tel No:

Subject: DDMAC review of Mifepristone

Nancy Buc stated Pop Council would submit their launch materials on Monday for review. They believe they will do a "rolling" review for the immediate 120 days as they are late in development. This means as they develop stuff, they will submit rather than wait for completing all materials used in the first 120 days. We had agreed to this last month.

Printed by [redacted]

Electronic Mail Message

Sensitivity: COMPANY CONFIDENTIAL

Date: 11-Sep-2000 12:24pm
From: [redacted]

Dept: HFD-006 WOC2 6049
Tel No: [redacted] FAX [redacted]

TO: See Below
Subject: RU-486 Timeline

Attached is the timeline for RU-486. There are still a few blanks to be filled in, but I can revise the timeline as more info becomes available.

Copies have been sent to Dr. Henney and [redacted] thru FDA ExSec.

[redacted]

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Electronic Mail Message

Date: 9/11/00 12:24:05 PM
From: [redacted]
To: See Below
Subject: RU-486 Timeline

Attached is the timeline for RU-486. There are still a few blanks to be filled in, but I can revise the timeline as more info becomes available.

Copies have been sent to Dr. Henney and [redacted] thru FDA ExSec.

[redacted]

To: [redacted]
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Electronic Mail Message

Date: 9/20/00 10:33:13 AM
From:
To:
Cc:
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Subject: RU 486 2nd review done

I have integrated your and _____ comments into this, I believe, final document. It is ready for your and _____ signatures. I will bring the paper copy to you at our meeting at 10:30 today. I believe that the signed document needs to be at HFD-580 by this Friday so that all documents can be delivered to Dr. Henney by 27th.

Attached please find a copy of the document. If you or _____ has any changes, please let me know.

Electronic Mail Message

Date: 9/18/00 2:01:20 PM
From: [redacted]
To: See Below
Subject: DRAFT mife action letter (for comment and correction)

Attached is the most recent version of the DRAFT action letter for the mifepristone application. Please note the citations for Subpart H, the distribution system, Medication Guide and Phase 4.

You may email me any corrections or edits or fax them to [redacted]

Thanks,

[redacted]

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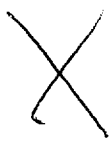

Electronic Mail Message

Date: 9/18/00 1:50:26 PM
From:
To:
Cc:
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Subject: Internal Q&As

Attached is the latest version of the internal Q&As that we did not get to review this morning. These have been reviewed by

I will pass the message to that comments should be sent to you by 11:00 on Tues.

Electronic Mail Message

Date: 9/18/00 1:50:26 PM
From:
To:
Cc:
Cc:
Cc:
Subject: Internal Q&As

Attached is the latest version of the internal Q&As that we did not get to review this morning. These have been reviewed by

I will pass the message to
that comments should be sent to you by 11:00 on Tues.

Electronic Mail Message

Date: 9/14/00 4:33:58 PM
From: [redacted]
To: See Below
Subject: FWD: Internal Q's and A's

Attached are the internal Q&As for your review. There may be a few more tomorrow. [redacted] has reviewed these and her changes are incorporated.

An earl review would be appreciated since they need to go to GC tomorrow ASAP

Thanks

[redacted]

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This is a listing of documents sent to the Office of Legislation (OL) in response to a Congressional document request. I did not keep copies of the document.

DOCUMENT LISTING -- RU-486

DATE	FROM	TO	SUBJECT
11/03/88	Dr. Irving M. Spitz Population Council	Division of Metabolic & Endocrine Drug Products	Letter (and enclosures) in response to FDA's request for adverse reaction reports (ADRs) for IND
11/17/88	Dr. Irving M. Spitz		Letter (and enclosures) regarding ADRs.
11/19/90	Dr. Irving M. Spitz		Letter (and enclosures) regarding ADRs.
11/18/94	Dr. Irving M. Spitz	FDA	IND Safety Report
11/21/94	Dr. C. Wayne Bardin		Letter (and enclosures) regarding ADRs.
12/01/94	Dr. C. Wayne Bardin Population Council		Letter (and enclosures) regarding ADRs.
12/02/94	Dr. Irving Spitz	FDA	IND Safety Report
12/07/94	Dr. C. Wayne Bardin		Letter (and enclosures) regarding ADRs.
12/14/94	Dr. Fred Schmidt Population Council	FDA	IND Safety Report
12/20/94	Dr. C. Wayne Bardin		Letter (and enclosures) regarding ADRs.
01/18/95	Dr. C. Wayne Bardin		Letter (and enclosures) regarding ADRs.
01/23/95	Dr. C. Wayne Bardin		Letter (and enclosures) regarding ADRs.
02/07/95	Dr. C. Wayne Bardin		Letter (and enclosures) regarding ADRs.
02/10/95	Dr. Fred Schmidt	FDA	IND Safety Report
02/15/95	Dr. C. Wayne Bardin		Letter (and enclosures) regarding ADRs.
02/17/95	Dr. C. Wayne Bardin		Letter (and enclosures) regarding ADRs.

DATE	FROM	TO	SUBJECT
02/17/95	Population Council	FDA	IND Safety Report
02/17/95	Dr. Fred Schmidt	FDA	IND Safety Report
02/24/95	Dr. Fred Schmidt	FDA	IND Safety Report
03/95	Sirkku Larsson	FDA	Final Clinical Report of Interruption of Early Pregnancy with RU-486 with Addition of a Prostaglandin (E_1), Gemeprost 24 Hours or 48 Hours after RU-486 Administration
03/03/95	Dr. C. Wayne Bardin		Letter (and enclosures) regarding ADRs.
03/06/95	Dr. C. Wayne Bardin		Letter (and enclosures) regarding ADRs.
03/09/95	Dr. Fred Schmidt	FDA	IND Safety Report
03/10/95	Dr. C. Wayne Bardin		Letter (and enclosures) regarding ADRs.
03/13/95	Dr. C. Wayne Bardin		Letter (and enclosures) regarding ADRs.
04/11/95	Dr. C. Wayne Bardin		Letter (and enclosures) regarding ADRs.
04/19/95	Dr. C. Wayne Bardin		Letter (and enclosures) regarding ADRs.
06/02/95	Dr. Fred Schmidt	FDA	IND Safety Report
06/07/95	Dr. C. Wayne Bardin		Letter (and enclosures) regarding ADRs.
06/07/95	Dr. André Ulmann		Tolerance of RU-486 during U.S. Studies
06/13/95	Dr. C. Wayne Bardin		Letter (and enclosures) regarding ADRs.
07/95	Roussel Uclaf	FDA	International Safety Report

DATE	FROM	TO	SUBJECT
07/18/95	Dr. C. Wayne Bardin		Letter (and enclosures) regarding ADRs.
07/25/95	Dr. C. Wayne Bardin		Letter (and enclosures) regarding ADRs.
07/28/95	Dr. Fred Schmidt	FDA	IND Safety Report
07/28/95	Dr. C. Wayne Bardin		Letter (and enclosures) regarding ADRs.
08/03/95	Dr. Fred Schmidt	FDA	IND Safety Report
08/04/95	Dr. C. Wayne Bardin		Letter (and enclosures) regarding ADRs.
08/08/95	Dr. Fred Schmidt	FDA	IND Safety Report
08/08/95	Dr. Fred Schmidt	FDA	IND Safety Report
08/09/95	Dr. C. Wayne Bardin		Letter (and enclosures) regarding ADRs.
08/10/95	Dr. C. Wayne Bardin		Letter (and enclosures) regarding ADRs.
08/15/95	Dr. C. Wayne Bardin		Letter (and enclosures) regarding ADRs.
08/25/95	Dr. C. Wayne Bardin		Letter (and enclosures) regarding ADRs.
09/01/95	Dr. C. Wayne Bardin		Letter (and enclosures) regarding ADRs.
09/21/95	Dr. C. Wayne Bardin		Letter (and enclosures) regarding ADRs.
10/04/95	Roussel Uclaf	FDA	Quarterly Safety Line Listing
11/02/95	Dr. C. Wayne Bardin		Letter (and enclosures) regarding ADRs.
01/04/96	Population Council	Dr. Stonier Hoechst Roussel LTD	Quarterly Safety Line Listings 10/1/95 through 12/31/95
04/12/96	Roussel Uclaf	FDA	Quarterly Safety Line Listings

DATE	FROM	TO	SUBJECT
06/20/96	Dr. Ann Robbins Population Council		Letter (and enclosures) regarding ADRs.
07/14/96	Dr. Ann Robbins	Division of Reproductive and Urologic Drug Products	Letter (and enclosures) regarding ADRs.
07/25/96	Dr. Ann Robbins	Div. of Reproductive and Urologic Drug Products	Letter (and enclosures) in response to FDA request for a summary of the international post-marketing surveillance data on the use of RU-486.
01/22/97	Clinical Investigations Branch	Dr. Elizabeth Aubeny Clinical Investigator Broussais Hospital	Letter (and 26 enclosures) that resulted from FDA's 6/26/96 inspection.
01/22/97		Dr. H. Quiquempois Clinical Investigator Center Hospitalier de Valenciennes	Letter (and 40 enclosures) that resulted from FDA's 07/01/96 inspection.
11/21/97	Dr. Fred Schmidt		Letter (and enclosures) regarding ADRs.
Undated			Spontaneous Notifications Reported to Roussel Uclaf 01/01/93 through 10/12/94
Undated	Population Council	FDA	Periodic Safety Update 06/01/95 through 11/30/95

DATE: SEPTEMBER 28, 2000

FROM: [redacted], DIVISION OF IMPORT OPERATIONS & POLICY (HFC-170)

SUBJ: CANCELLATION OF IMPORT ALERT #66-47, "AUTOMATIC DETENTION OF ABORTIFACIENT DRUGS"

TO: IMPORT PROGRAM MANAGERS

This alert has been cancelled. Districts may refer to Import Alert #66-41 for current guidance concerning the abortifacient product, mifepristone.

FOI: No purging required

PREPARED BY: DIOP, Operations & Policy Branch

DATE LOADED INTO FIARS: September 28, 2000

/s/

DATE: SEPTEMBER 28, 2000

FROM: [redacted]ISION OF IMPORT OPERATIONS & POLICY (HFC-170)

SUBJ: REVISION OF IMPORT ALERT #66-41, "UNAPPROVED NEW DRUGS PROMOTED IN THE U.S."

TO: IMPORT PROGRAM MANAGERS

NOTE: This revision updates the alert into the current format. Additional changes are bracketed by asterisks (***).

TYPE OF ALERT: ***Detention Without Physical Examination (DWPE)***

(Note: This import alert contains guidance to FDA field personnel only. It does not establish any requirements, or create any rights or obligations on FDA or on regulated entities.)

PRODUCT: Unapproved new drugs

PRODUCT CODE: ***See attachment***

PROBLEM: Unapproved drugs promoted in the U.S.

OASIS CHARGE CODE: UNAPPROVED

PAF: AAP (Approvals)

***PAC: 56008H
63001***

COUNTRY: All

MANUFACTURER/ CHIPPER: See attachment

REFERENCE: ***Regulatory Procedures Manual Chapter 9, Subchapter "Coverage of Personal Importations" issued 12/11/89. (Note: This subchapter, previously designated as RPM 9-71, was issued to consolidate guidance that previously existed in RPM Chapters: 9-71, "Mail Importations" and Chapter 9-72, "Coverage of Importations Contained in Personal Baggage," and the Pilot Guidance for Release of Mail Importation dated July 29, 1988.)***

Compliance Policy Guide (CPG) 120.500 (formerly 7150.10) gives extensive background on health fraud, and the indirect risks of relying on unproven remedies. Health fraud has been defined by the agency as the promotion of unproven medical products.

CHARGE: "The article is subject to refusal of admission pursuant to Section 801(a)(3) in that it appears to be a new drug within the meaning of Section 201(p) without an effective new drug application (NDA) [Unapproved New Drug, Section 505(a)".]

RECOMMENDING OFFICE: Division of Import Operations and Policy (HFC-170)

REASON FOR ALERT: Media reports concerning FDA'S guidance for release of importations for personal use have inaccurately suggested that any unapproved drug may be imported through the mail for personal use. The pilot guidance and subsequent Regulatory Procedures Manual Subchapter, "Coverage of Personal Importations," that issued is much more restrictive than reported. The RPM subchapter provides guidance for use in those instances in which field personnel determine that the exercise of discretion regarding the admissibility of an unapproved drug might be appropriate. The guidance is by its very terms discretionary, and does not provide anyone with a right to import any drug.

The guidance provides that release of an unapproved drug for personal use may be appropriate if, among other considerations, the drug is intended for a serious condition for which effective treatment may not be available domestically either through commercial or clinical means, and it is not considered to represent an unreasonable risk. The guidance is intended to apply only to: (1) persons who have received treatment in a foreign country with an unapproved drug which is not available in the United States, and who, upon returning to the United States, have imported the drug for their personal use in an effort to continue the treatment started abroad; and (2) persons who have made their own arrangements for obtaining an unapproved drug from foreign sources, when the drug has not been promoted in the United States.

When there is evidence of promotion of unapproved drugs to persons in the United States, the products should be considered for detention. Evidence of promotion may consist of solicitations for mail orders, press releases, advertising materials, and other public announcements that are directed to persons residing in the U.S.

The subchapter of the RPM on coverage of personal importations provides guidance for FDA personnel on when it is appropriate to recommend import alerts involving unapproved products likely to be imported for personal use. Such recommendations are appropriate when an unapproved product represent a health fraud, as defined in CPG 120.500 or an unapproved foreign product is promoted for mail-order shipments. Thus, the field may recommend an import alert when an unapproved product poses either a direct health risk or indirect health risk.

GUIDANCE: Districts may detain without physical examination any unapproved drug listed in the attachment.

Districts may also detain without physical examination any other unapproved drug that fails to meet the discretionary release criteria in the RPM. When detained products that appear to meet these criteria and are not listed in the attachment, districts should forward documentation to DIOP for consideration for inclusion in this alert.

SPECIAL NOTE: Districts should continue to enforce, as appropriate, related import alerts restricting fraudulent, dangerous, and

commercial unapproved drug importations.

FOI: No purging required.

KEYWORDS: New drugs, unapproved new drugs

PREPARED BY: DIOP, Operations and Policy SDWG: HFC-172, [redacted]
DATE LOADED
INTO FIARS: September 28, 2000

/s/

ATTACHMENT TO IMPORT ALERT #66-41

Unapproved new drugs that may be subject to DWPE

Note: The full attachment identifying the products that may be subject to this guidance was not reissued with the text revision of this alert.

DATE: SEPTEMBER 28, 2000

FROM: [redacted] DIVISION OF IMPORT OPERATIONS & POLICY (HFC-170)

SUBJ: REVISION OF THE ATTACHMENT TO IMPORT ALERT #66-41, "UNAPPROVED NEW DRUGS PROMOTED IN THE U.S."

TO: IMPORT PROGRAM MANAGERS

The following product has met the criteria for detention without physical examination:

PRODUCT/ PRODUCT CODE	SOURCE	COUNTRY
Mifepristone 65J[] [] [] []/ 65D[] [] [] []	All	All

FDA has determined that unapproved versions of mifepristone manufactured outside the U.S. are being promoted in this country for use to end pregnancy. Due to the risks to the safety of the user in inadequately controlled settings, mifepristone should be considered inappropriate for release under the Personal Import Guidance. Districts encountering entries of mifepristone should determine whether the importer of record for the article being entered is Danco Laboratories, LLC, New York, New York (distributor of the U.S. approved product) or whether the article is being entered under an IND that is in effect. In such circumstances (when the article is being imported by the distributor of the U.S. approved product or under an IND that is in effect), the article is outside the scope of this guidance.

(Districts should contact CDER for verification of IND status.)

Please add this product to the attachment for Import Alert #66-41.

RECOMMENDED BY: DIOP (HFC-170)

FOI: No purging required

PREPARED BY: DIOP, Operations & Policy Branch

DATE LOADED INTO FIARS: September 28, 2000

/s/

UNIVERSITY OF
ROCHESTER
MEDICAL CENTER

EASTMAN DENTAL CENTER
SCHOOL OF MEDICINE AND DENTISTRY
SCHOOL OF NURSING
STRONG MEMORIAL HOSPITAL
UNIVERSITY MEDICAL FACULTY GROUP

DEPARTMENT OF FAMILY MEDICINE
UNIVERSITY OF ROCHESTER/HIGHLAND HOSPITAL

9-1-00

To. _____

From: Eric Seleff, MD

IND - _____

INTERNET - CALL FOR MIFEPRISTONE

Respected DOCTORS

We are pleased to inform you that we will start selling 200MG / 25MG
MIFEPRISTONE tablet dose along with misnprostol From 1 september 2000 onward.

Keeping in mind possiablity's of longterm association with you/other Doctors/Hospital's in various country's we are giving a purposal which as below:-

The selling price for Mifepristone tablet/dose will be same as prevailing in purchaser country but they will get 15 to 25% discount in form of free products such as pregnancy test/Lh ovulation/FSH/OTHER cassette/strip and or tibolone / other o&g segment tablet/ capsule/injection.(In This regard we are sending our products list by SEPERATE E-MAIL)

please advise prevailing price of mifepristone in your country as well as how many tablet/dose you can buy at a time enabling us to give you our best (15 to >25% free product discount).If possiable please send us contact information of known O&G Doctors/hospital either in your country or in other country's AND ALSO CONTACT INFORMATION OF O&G DOCTORS ASSOCIATION IN YOUR COUNTRY/ANY OTHER COUNTRY'S.

looking forward to your reply
best regards
DILIP CHOUDHURY
DIVERSIFIED CORP.,
INDIA

Jacob W. Holler Family Medicine Center
885 South Avenue
Rochester, New York 14620
(716) 442-7470 Fax: (716) 442-8319

Danco Laboratories, LLC

VIA FACSIMILE:

September 26, 2000

Center for Drug Evaluation
and Research
Food and Drug Administration
Woodmont Office Complex 2
1451 Rockville Pike
Rockville, MD 20852

Dear

Further to your inquiries regarding please be advised as follows:

- The Population Council has indicated, through Sandra P. Arnold, that they have had no relationship in any way with
- Danco's has also indicated that they have had no business dealings or relationship with

Separately, the port of entry for importation of Danco's Drug Substance is and Danco is amenable to notifying the FDA ahead of each importation. Please let me know how and to whom you wish us to provide this information.

Sincerely,

/S/

/dns

cc: Sandra P. Arnold – Population Council

This document constitutes trade secret and confidential commercial information exempt from public disclosure under 21 C.F.R. 20.61. Should FDA tentatively determine that any portion of this document is disclosable in response to a request under the Freedom of Information Act, Danco Laboratories, LLC requests immediate notification and an opportunity for consultation in accordance with 21 C.F.R. 20.45. Contact telephone number is

MIFEPRISTONE NDA

STATUS

Brief Summary of Publicly Available Information

- The sponsor, The Population Council, Inc., initially submitted an NDA for Mifepristone (RU-486) in March 1996.

- The NDA contained the results of two large clinical trials performed in the European Union and preliminary data from an on-going U.S. trial in support of the indication: Medical termination of intrauterine pregnancy through 49 days' gestational age. (Pregnancy is dated from the first day of the last menstrual period).

- The NDA was reviewed on a 6-month regulatory clock, and issues were presented and discussed at an open advisory committee meeting in July 1996. The sponsor received an approvable letter on September 18, 1996, which conveyed the conclusion that the drug, used under specific conditions, was found safe and effective for the indication.

- The letter also outlined various deficiencies that required response before the application could be approved, including a list of chemistry and manufacturing controls requirements as well as label modifications and postmarketing surveillance commitments.

- The advisory committee discussion included recommendations for labeling, postmarketing surveillance, and a well-controlled distribution system for the drug. The committee also requested the opportunity to review the final U.S. study report once available.

Brief Summary of Non-Public Information

FACSIMILE TRANSMISSION RECORD

DIVISION OF PRESCRIPTION DRUG COMPLIANCE & SURVEILLANCE
OFFICE OF COMPLIANCE
CENTER FOR DRUG EVALUATION & RESEARCH
FOOD AND DRUG ADMINISTRATION
METROPARK NORTH I, HFD-330
7520 STANDISH PLACE, ROCKVILLE, MD. 20855

FAX #: 301-594-5998 PHONE #: 301-594-0101

DATE: 9/26/00 NUMBER OF PAGES 13

FROM:

TO:

FAX#: 4-6197 PHONE #:

COMMENTS:

Confidential

NOTE: THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW. If you are not the addressee, or a person authorized to deliver the document to the addressee, you are hereby notified that any review, disclosure, dissemination, copying, or other action based on the content of this communication is not authorized. If you have received this document in error, please notify us immediately by telephone and return this document to us at the above address by mail. Thank you.

NDCLIST_ALL QUERY

Tradename:MIFEPRISTONE			Rx/OTC:R
Firm:	NDC:064877-0001 Status:DC 27-APR-1999 Owner:DRLS		
Ingred:MIFEPRISTONE	100	%WW	0129613AA A

Drug Class	Package	Size	Type
	064877-0001-**	AS ORDERED	DRUM

*** NOTE ***
THIS SCREEN MAY CONTAIN TRADE SECRET INFORMATION. PLEASE TAKE CARE!!
> PRESS PF2 FOR DOSAGE, ROUTE & APPL INFO PRESS PF3 FOR MANUFACTURERS INFO <
Up/Down ARROWS MOVE THRU RECORDS, Return/Backspace MOVE THRU BLOCKS,PF4 EXITS.

Count: *1 <Replace>

NDCLIST_ALL QUERY

Tradename:MIFEPRISTONE Rx/OTC:R

Firm: NDC:064877-0001 Status:DC 27-APR-1999 Owner:DRLS

DOSAGE & ROUTE INFORMATION

DOSAGE CODE	DOSEFORM	ROUTE CODES	ROUTE FORM	APPLICATION NUMBER
313	NOT APPLIC	135	OTHER	

*** NOTE ***
THIS SCREEN MAY CONTAIN TRADE SECRET INFORMATION. PLEASE TAKE CARE!!
> PRESS PF2 FOR DOSAGE, ROUTE & APPL INFO PRESS PF3 FOR MANUFACTURERS INFO <
Up/Down ARROWS MOVE THRU RECORDS, Return/Backspace MOVE THRU BLOCKS, PF4 EXITS.

<Replace>

Count: *1

NDCLIST_ALL QUERY ------ MANUFACTURERS FOR NDC: 064877-0001
Tradename:MIFEPRISTONE

CFN	Lblcode	Shortname	Longname	State	Foreign
FCCH499	064877	SHANGHAI HUALIAN	SHANGHAI HUALIAN PHARMACEU		CH
	ADDRESS:MINLE RD PUDONG DEVELOPMENT AREA/SHANGHAI,				

Press Previous Screen to return to detail screen. For Help - Press CTRL K

Count: *1

<Replace>

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

DRUG PRODUCT LISTING

(In accordance with Public Law 92-387)

Form Approved: OMB No. 0910-0045, Expiration Date: September 30, 1997. See OMB Statement on Reverse.

NAME AND ADDRESS OF FIRM
SHANGHAI HUALIAN PHARMACEUTICAL CO,LTD
370 JIANG WAN ROAD, WEST
SHANGHAI 200083, CHINA

LABELING REVISION
CHANGE OF
☐ RTE OF A ADMIN ☐ INDICATION
☐ NAME / DOSE / STR / MFGR
☐ OTHER (Specify)

LI 156,027

NATIONAL DRUG CODE: LABELER [redacted] PRODUCT 0648-7700-01

SEC | S | U | PRODUCT TRADE NAME OR CATALOG NAME
01 | | | MIFEPRISTONE Per SOP

FDA APPLICATION NO. | REPORT DATE MO DA YR | TYPES OF BUSINESS | PRODUCT TYPE | PRODUCT DISCONTINUED | BASIS OF CONCENTRATION WHOLE NUMBERS DECIMAL UNIT
[redacted] | 03 25 99 W | OTHER (Specify) | HIZ | IR | APR 05 1999 | 1 | KG

RECEIVED
APR 05 1999

DOSAGE FORM | ROUTES OF ADMINISTRATION | SEC | S | U | PKG CODE | PACKAGE SIZE | PACKAGE TYPE
31313 5 | | 03 | | ** AS ORDERED | DRM
03
[redacted] 03
MO YEAR MO YEAR MO YEAR 03
03

NOTICE: This report is required by law (21 C.F.R. 207.30). Failure to report can result in misbranded for not more than one year or a fine of not more than $1,000, or both (FD&C Act, Section 303)

SEC | S | U | INGR SEQ | FT | ESTABLISHED NAME OF PRODUCT AND / OR INGREDIENT(S) OR BIOLOGIC PROPER NAME, TEST OBJECTIVE / EQUIPMENT / REAGENT NAME, ETC | AMOUNT WHOLE NUMBER DECIMAL | UNIT
05 | A | MIFEPRISTONE | 100 | %WW
05
05
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RECEIVED
MAY 03 1999
PIMB

SEC | S | U | DUNS OR FIRM ESTABLISHMENT REGISTRATION NUMBER | ACTUAL MANUFACTURING SITE OF THE ABOVE DRUG PRODUCT | STATE | FOREIGN COUNTRY | NDC LABELER CODE | SHUNT NAME
07 | F | C | H | 41519 | SHANGHAI HUALIAN PHARMACEUTICAL CO LTD | CHINA
07 | MINLEI ROAD PUDONG DEVELOPMENT AREA
07 | SHANGHAI 201419

FORM FDA 2657 (10/94) PREVIOUS EDITION IS OBSOLETE

PAGE 1 OF 1 PAGES

MIF 005082

Original sent under separate

Food and Drug Administration
CDER/OIT/DDMS/IMT, HFD-095
5600 Fishers Lane
Rockville, MD 20857

Attn:

RECEIVED
MAY 03 1999
PIMB

April 26, 1999

Re: LI 156027
Product: Mifepristone
Manufacturer: Shanghai HuaLian Pharmaceutical Co., Ltd.

Dear

This is in regard to our recent telephone conversation pertaining to the Drug Listing submission for Mifepristone manufactured by the Shanghai HuaLian Pharmaceutical Co., Ltd.

As indicated to you, Mifepristone is the Active Pharmaceutical Ingredient (API) involved in NDA 20-687 for Mifepristone Tablets, 200 mg. This NDA has been reviewed by the Agency and it is considered "*approvable*" pending an adequate response to some technical aspects pertaining to this submission (Agency letter of September 18, 1996, pertinent excerpt attached).

Therefore, please be so kind as to proceed with the pertaining Drug Listing as requested earlier.

Thank you for your attention.

Sincerely,

Encl.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

4.13.99

RECEIVED
MAY 0 3 1999
PIMB

Shanghai Hualian Pharmaceutical

We are returning copies of your FDA Form(s) 2657 submitted under the requirements of the Drug Listing Act of 1972 for the reason(s) indicated below:

Preliminary Requirements

- ☐ A separate Form FDA 2657 must be submitted for each product.
- ☐ Reporting firm's (submitter) name and/or address is missing from the form.
- ☐ Reporting firm's (submitter) name and /or address does not match our records.
- ☐ Reporting firm (submitter) is not registered. Please resubmit this form and all labeling for this product along with a completed Form FDA 2656 (Registration of Drug Establishment).
- ☐ Current label(s) and/or package insert(s) is/are missing.

Section 01

- ☐ Product trade name is missing.
- ☐ Labeler code is missing or incorrect. The labeler code must reflect that of the reporting firm.
- ☐ Product code is missing or incorrect. Please assign a product code according to your chosen NDC configuration.
- ☐ Product code belongs to a different product. Please assign a new product code.
- ☐ For finished dosage form prescription drugs, an FDA application number (NDA/ANDA) or an initial marketing date is required. Please fill in one or the other.
- ☐ Business and/or product type, and/or legal status is missing.

Section 03

- ☐ Package code, package size, and/or package type is missing.
- ☐ NDC configuration is incorrect. Product and package codes must be assigned as explained in 21 CFR 207.35(b).

Section 05

- ☐ Active ingredient(s), amount(s) and/or unit(s) is/are missing.

Section 07

- ☐ The actual manufacturer of the product is missing.
- ☐ Please indicate the actual site or firm establishment registration number (also known as the CFN) and/or the actual manufacturer's labeler code.
- ☐ Manufacturer in Section 07 is not registered. The manufacturer must be registered and/or list before this form can be processed.

See back page for additional comments.

Comments

- ☐ We are unable to determine from the attached Form(s) FDA 2657 the type of update and/or changes you are requesting. Please explain in more detail.
- ☐ Attached Form(s) FDA 2657 appears to be an update of an existing product. However, the original form(s) cannot be located. Please resubmit a copy of the originally submitted Form(s) FDA 2657 along with the appropriate label(s) and/or package insert(s).
- ☐ Manufacturer must submit Form FDA 2657 for this product before this form can be processed.

Other

- ☐ This product is not considered a drug and is not required to be listed with CDER. finished dosage
- ☐ Please provide name of approved drug product of which this is an active ingredient.

We request that you send the corrected form(s) and this letter within 20 working days to:

Food and Drug Administration
CDER/OIT/DDMS/IMT, HFD-095
5600 Fishers Lane
Rockville, MD 20857

If you need assistance, please contact _____

Enclosure(s)

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

DRUG PRODUCT LISTING

(In accordance with Public Law 92-387)

Form Approved: OMB No. 0910-0045. Expiration Date: September 30, 1997. See OMB Statement on Reverse.

NAME AND ADDRESS OF FIRM
SHANGHAI HUALIAN PHARMACEUTICAL CO.,LTD.
370 JIANG WAN ROAD, WEST
SHANGHAI 200083, CHINA

LABELING REVISION
CHANGE OF
☐ RTE OF A DMIN ☐ INDICATION
☐ NAME / DOSE / STR / INGR
☐ OTHER (Specify)

LI 156,027

SEC	S	U	PRODUCT TRADE NAME OR CATALOG NAME	NATIONAL DRUG CODE LABELER	PRODUCT
01			MIFEPRISTONE		06487-7000-01

FDA APPLICATION NO	REPORT DATE MO	DA	YR	TYPES OF BUSINESS	PRODUCT TYPE	PRODUCT DISCONTINUED OTHER (Specify)	BASIS OF CONCENTRATION WHOLE NUMBERS	DECIMAL	UNIT
.	02	25	99	W	HZ	R	1		KG

RECEIVED
APR 05 1999

DOSAGE FORM	ROUTES OF ADMINISTRATION	SEC	S	U	PKG CODE	PACKAGE SIZE	PACKAGE TYPE
313135		03			**	AIS ORDERED	DRM
		03					
		03					
MO YEAR	MO YEAR	MO YEAR 03					
.		03					

PRIME

NOTICE: This report is required by law (21 C.F.R. 207.30). Failure to report can result in misbranding and may result in fines of not more than one year or a fine of not more than $1,000, or both (FD&C Act, Section 303).

SEC	S	U	ESTABLISHED NAME OF PRODUCT AND / OR INGREDIENT(S) OR BIOLOGIC PROPER NAME, TEST OBJECTIVE / EQUIPMENT / REAGENT NAME, ETC.	AMOUNT WHOLE NUMBER	DECIMAL	UNIT
05			A MIFEPRISTONE	100		%WW
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SEC	S	U	ESTABLISHMENT REGISTRATION NUMBER	ACTUAL MANUFACTURING SITE OF THE ABOVE DRUG PRODUCT	STATE	FOREIGN COUNTRY	NDC LABELER CODE	SHORT NAME
07			FCCH419	SHANGHAI HUALIAN PHARMACEUTICAL CO LTD		CHINA		
07				MINLEI ROAD PUDONG DEVELOPMENT AREA				
07				SHANGHAI 201419				

FORM FDA 2657 (8/91) PREVIOUS EDITION IS OBSOLETE.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

4.27.99

Shanghai Huqian Pharmaceutical

Bar Code #

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- ☐ Manufacturer must submit Form FDA 2657 for this product before this form can be processed.

Other

- ☐ This product is not considered a drug and is not required to be listed with CDER.
- ☐ NDA is not approved yet. Product is not in commercial distribution. Resubmit when NDA is approved.

We request that you send the corrected form(s) and this letter within 20 working days to:

Food and Drug Administration
CDER/OIT/DDMS/IMT, HFD-095
5600 Fishers Lane
Rockville, MD 20857

If you need assistance, please contact _____

Enclosure(s)

Food and Drug Administration
CDER/OIT/DDMS/IMT, HFD-095
5600 Fishers Lane
Rockville, MD 20857

Attn:

April 26, 1999

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Thank you for your attention.

Sincerely,

Encl.

Fax Note 7671 | 4/26 | 5

What Do We Know about Induced Abortion in the United States

Induced Abortion Data:

- In 1996, a total of 1.22 million induced abortions were reported to CDC. At same year, a provider survey showed a slightly higher number, 1.37 million abortions performed, representing an abortion rate of 22.9 per 1,000 women aged 15-44 in the United States[1,2].
- Approximately one third of all abortions were performed at 7 or fewer weeks of gestation. Additional 20 percent were at 8 weeks of gestation[2].
- In 1996, approximately 4,200 medical abortions were performed and the remaining were surgical abortions[2].
- Four states, i.e. California, New York, Florida and Texas, accounted for about 50 percent of all abortions in the United States (Table 1)[2].

Who Seeks Abortion Service:

- Women aged 19 or younger obtained approximately 20 percent of all abortions while women aged 35 and older accounted for about 10 percent of the total[1].
- The abortion rate for black and Hispanic women were approximately 2-3 times the rates for white women even if white women account 60 percent of all abortions[1,2].
- Older women were more likely to obtain abortion earlier in pregnancy than were younger women[1].

Who Provides Abortion Service:

- In 1996, 78,910 physicians (MDs) were registered as family practice physicians and 38,424 as Ob/Gyns[3].
- In 2000, 12 percent of Ob/Gyns and 2 percent of family practice physicians routinely perform elective surgical abortions[4].
- In 1996, abortion services were provided in 2,042 facilities, including 703 hospitals, 452 abortion clinics, 417 other clinics and 470 physician offices[2].
- 22 percent of the facilities accounted for 80 percent of abortions performed in the United States[2].

Access to Abortion Service:

- Only 1 percent of abortions (14,070) was reported in nonmetropolitan counties, where 18 percent of women of reproductive age lived[2].
- Of the country's 320 metropolitan area, approximately one third (102) had no known abortion provider or had a provider that together reported fewer than 50 abortions[2].

Safety of Abortion Service:

- In 1992, 10 women died as a result of complication from legal induced abortion and the case fatality rate was 0.7 abortion-related deaths per 100,000 legal induced abortions[1].

Created on 08/28/00 8:43 AM

MIF 005090

Efficacy and Safety of Mifepristone:

- In US clinical trials, the success rate were 92 percent (762/827) in the 49 days group, 83 percent (563/678) in the 50-to-56 days group, 77 percent (395/510) in the 57-to-63 days group. In addition, approximately 51 percent of women in the study had a previous elective abortion and success rate tends to be lower among women who had previous elective abortions[5].
- Hospitalization, surgical interventions, and intravenous-fluid administration were reported for 2 percent of the women in the <49-days group and for 4 percent of those in each of the other groups, mostly due to excessive bleeding[5].
- Excessive bleeding necessitated blood transfusions in four women[5].

Safe and Effective Use of Mifepristone:

- In France, 80 percent of women who terminate their pregnancies before the seventh week choose the drug over surgical methods. Mifepristone accounts for 30 percent of all abortions in France[6].
- At Planned Parenthood of Greater Iowa, one of 17 sites that participated in US Mifepristone clinical trials, 80 percent (238/301) eligible patients choose Mifepristone when it was offered[7].
- 44 percent of Ob/Gyns and 31 percent of family practice physicians would be likely or very likely to prescribe Mifepristone after FDA's approval (Table 2)[4].
- 5 percent (106/2121) of US clinical trial participants failed to return for the last visit (visit 3)[5].

Reference

1. Koonin LM, Strauss LT, Chrisman CE, Montalbano MA, Bartlett LA and Smith JC. Abortion surveillance - United States, 1996, MMWR 1999;48(No. SS-4):1-52
2. Henshaw SK. Abortion incidence and service in the United States, 1995-1996. Family Planning Perspectives 1998;30:263-270.
3. American Medical Association. Physician Characteristics and Distribution in the US 1997/1998, Chicago, 1997.
4. KFF. Views of Women's Health Care Providers on Abortion: An Update on Mifepristone. The Henry J. Kaiser Family Foundation, Publication No. 3027, June 2000.
5. Spitz B, Bardin W, Benton L, Robbins A. Early pregnancy termination with mifepristone-misoprostol in the United States. N Engl J Med 1998;338:1241-7.
6. Abortion pill to be tested here. St. Louis Post-Dispatch, April 7, 1995 Pg 1A
7. Blinder V, Elul B and Winikoff B. Mifepristone-misoprostol medical abortion: who will use it and why? Am J Obstetrics and Gynecology 1998;179:

Table 2. Characteristics of Ob/Gyn and Family Practice Physicians participated in Kaiser Family Foundation's Survey (June 2000)

	Obstetricians and Gynecologist (n=566)	Family Practice Physician (n=201)
% aged 50 or less	52%	15%
% male	72%	86%
% solo practice	32%	54%
% rural practice site	15%	33%

Created on 08/28/00 8:43 AM

MIF 005093

b(5)
post funeral

3 pages

b(4)

37 pages

November 22, 1999

Regulatory Background Documentation

NDA 20-687

mifepristone

DATE: SEPTEMBER 28, 2000

FROM: [redacted], DIVISION OF IMPORT OPERATIONS & POLICY (HFC-170)

SUBJ: CANCELLATION OF IMPORT ALERT #66-47, "AUTOMATIC DETENTION OF ABORTIFACIENT DRUGS"

TO: IMPORT PROGRAM MANAGERS

This alert has been cancelled. Districts may refer to Import Alert #66-41 for current guidance concerning the abortifacient product, mifepristone.

FOI: No purging required

PREPARED BY: DIOP, Operations & Policy Branch

DATE LOADED INTO FIARS: September 28, 2000

/s/

DATE: SEPTEMBER 28, 2000

FROM: [redacted]ISION OF IMPORT OPERATIONS & POLICY (HFC-170)

SUBJ: REVISION OF IMPORT ALERT #66-41, "UNAPPROVED NEW DRUGS PROMOTED IN THE U.S."

TO: IMPORT PROGRAM MANAGERS

NOTE: This revision updates the alert into the current format. Additional changes are bracketed by asterisks (***).

TYPE OF ALERT: ***Detention Without Physical Examination (DWPE)***

(Note: This import alert contains guidance to FDA field personnel only. It does not establish any requirements, or create any rights or obligations on FDA or on regulated entities.)

PRODUCT: Unapproved new drugs

PRODUCT CODE: ***See attachment***

PROBLEM: Unapproved drugs promoted in the U.S.

OASIS CHARGE CODE: UNAPPROVED

PAF: AAP (Approvals)

***PAC: 56008H
63001***

COUNTRY: All

MANUFACTURER/ SHIPPER: See attachment

REFERENCE: ***Regulatory Procedures Manual Chapter 9, Subchapter "Coverage of Personal Importations" issued 12/11/89. (Note: This subchapter, previously designated as RPM 9-71, was issued to consolidate guidance that previously existed in RPM Chapters: 9-71, "Mail Importations" and Chapter 9-72, "Coverage of Importations Contained in Personal Baggage," and the Pilot Guidance for Release of Mail Importation dated July 29, 1988.)***

Compliance Policy Guide (CPG) 120.500 (formerly 7150.10) gives extensive background on health fraud, and the indirect risks of relying on unproven remedies. Health fraud has been defined by the agency as the promotion of unproven medical products.

CHARGE: "The article is subject to refusal of admission pursuant to Section 801(a)(3) in that it appears to be a new drug within the meaning of Section 201(p) without an effective new drug application (NDA) [Unapproved New Drug, Section 505(a)".]

RECOMMENDING OFFICE: Division of Import Operations and Policy (HFC-170)

REASON FOR ALERT:

Media reports concerning FDA'S guidance for release of importations for personal use have inaccurately suggested that any unapproved drug may be imported through the mail for personal use. The pilot guidance and subsequent Regulatory Procedures Manual Subchapter, "Coverage of Personal Importations," that issued is much more restrictive than reported. The RPM subchapter provides guidance for use in those instances in which field personnel determine that the exercise of discretion regarding the admissibility of an unapproved drug might be appropriate. The guidance is by its very terms discretionary, and does not provide anyone with a right to import any drug.

The guidance provides that release of an unapproved drug for personal use may be appropriate if, among other considerations, the drug is intended for a serious condition for which effective treatment may not be available domestically either through commercial or clinical means, and it is not considered to represent an unreasonable risk. The guidance is intended to apply only to: (1) persons who have received treatment in a foreign country with an unapproved drug which is not available in the United States, and who, upon returning to the United States, have imported the drug for their personal use in an effort to continue the treatment started abroad; and (2) persons who have made their own arrangements for obtaining an unapproved drug from foreign sources, when the drug has not been promoted in the United States.

When there is evidence of promotion of unapproved drugs to persons in the United States, the products should be considered for detention. Evidence of promotion may consist of solicitations for mail orders, press releases, advertising materials, and other public announcements that are directed to persons residing in the U.S.

The subchapter of the RPM on coverage of personal importations provides guidance for FDA personnel on when it is appropriate to recommend import alerts involving unapproved products likely to be imported for personal use. Such recommendations are appropriate when an unapproved product represent a health fraud, as defined in CPG 120.500 or an unapproved foreign product is promoted for mail-order shipments. Thus, the field may recommend an import alert when an unapproved product poses either a direct health risk or indirect health risk.

GUIDANCE:

Districts may detain without physical examination any unapproved drug listed in the attachment.

Districts may also detain without physical examination any other unapproved drug that fails to meet the discretionary release criteria in the RPM. When detained products that appear to meet these criteria and are not listed in the attachment, districts should forward documentation to DIOP for consideration for inclusion in this alert.

SPECIAL NOTE:

Districts should continue to enforce, as appropriate, related import alerts restricting fraudulent, dangerous, and

commercial unapproved drug importations.

FOI: No purging required.

KEYWORDS: New drugs, unapproved new drugs

PREPARED BY: DIOP, Operations and Policy SDWG: HFC-172, [redacted]
DATE LOADED
INTO FIARS: September 28, 2000

/s/