2- Softening and dilatation of the cervix uteri prior to surgical pregnancy termination

For the full efficacy of therapy, the use of MIFEGYNE® must be followed, 36 to 48 hours later and not beyond, by surgical termination.

- Risks related to the method

  - Bleeding

    The woman will be informed of the risk of vaginal bleeding which may be heavy, following MIFEGYNE's intake. She should be informed of the risk of abortion prior to surgery (although minimal): she will be informed on where to go in order to check for the completeness of expulsion, or in any case of emergency.

  - Other risks

    They are those of the surgical procedure.

3- in all instances

The use of MIFEGYNE® requires rhesus determination and hence the prevention of rhesus allo-immunisation as well as other general measures taken usually during any termination of pregnancy.

During clinical trials, pregnancies occurred between embryo expulsion and the resumption of menses.

To avoid potential exposure of a subsequent pregnancy to mifepristone, it is recommended that conception be avoided during the next menstrual cycle. Reliable contraceptive precautions should therefore commence as early as possible after mifepristone administration.

Precautions for use

1- in all instances

In case of suspected acute adrenal failure, dexamethasone administration is recommended. 1 mg of dexamethasone antagonises a dose of 400 mg of mifepristone.

Due to the antiglucocorticoid activity of mifepristone, the efficacy of long-term corticosteroid therapy, including inhaled corticosteroids in asthmatic patients, may be decreased during the 3 to 4 days following MIFEGYNE's intake. Therapy should be adjusted.
A decrease of the efficacy of the method can theoretically occur due to the antiprostaglandin properties of non-steroidal anti-inflammatory drugs (NSAIDs) including aspirin (acetyl salicylic acid). Use preferably non-NSAI analgesics.

2- Medical termination of developing intra-uterine pregnancy

Rare serious cardiovascular accidents have been reported following the intra muscular administration of the prostaglandin analogue sulprostone (withdrawn in 1992). No such cases have been reported since analogues of PGE_1 (gemeprost or misoprostol) have been used. For these reasons and as a special precautionary

measure, the medical method is not recommended for use in women over 35 years of age and who smoke more than 10 cigarettes a day.

Method of prostaglandin administration

During intake and for three hours following the intake, the patients should be monitored in the treatment centre, which must be equipped with the appropriate equipment.

3- **for the sequential use of MIFEGYNE® - Prostaglandin, whatever the indication**

The precautions related to the prostaglandin used should be followed where relevant.

4.5 Interaction with other medicinal products and other forms of interactions

No studies to investigate possible interactions between mifepristone and other drugs have been carried out.

4.6 Pregnancy and lactation

In animals (see section 5.3 Pre-clinical safety data), the abortifacient effect of mifepristone precludes the proper assessment of any teratogenic effect of the molecule.

With subabortive doses, isolated cases of malformations observed in rabbits, but not in rats or mice were too few to be considered significant, or attributable to mifepristone.

In humans, the few reported cases of malformations do not allow a causality assessment for mifepristone alone or associated to prostaglandin. Therefore, data is too limited to determine whether the molecule is a human teratogen.

Consequently:

- Women should be informed, that due to the risk of failure of the medical method of pregnancy termination and to the unknown risk to the foetus, the control visit is mandatory (see Section 4.4 special warnings and special precautions for use).
- Should a failure of the method be diagnosed at the control visit *(viable ongoing pregnancy)*, and should the patient still agree, pregnancy termination should be completed by another method.
- Should the patient wish to continue with her pregnancy, the available data is too limited to justify a systematic termination of an exposed pregnancy. In that event, a careful ultra-sonographic monitoring of the pregnancy will be established.

Lactation

Mifepristone is a lipophilic compound and may theoretically be excreted in the mother's breast milk. However, no data is available. Consequently, mifepristone use should be avoided during breast-feeding.

4.7 Effects on ability to drive and to use machines

Not known.

4.8 Undesirable effects

Most frequently reported undesirable effects

- Urogenital
  - Bleeding

    Heavy bleeding occurs in about 5% of the cases and may require hemostatic curettage in up to 1.4% of the cases.
  - Very common uterine contractions or cramping (10 to 45%) in the hours following prostaglandin intake.
  - During induction of second trimester termination of pregnancy or labour induction for foetal death in utero during the third trimester, uterine rupture has been uncommonly reported after prostaglandin intake. The reports occurred particularly in multiparous women or in women with a caesarean section scar.

- Gastrointestinal
  - Cramping, light or moderate.
  - Nausea, vomiting.

- Undesirable effects related to prostaglandin use: nausea, vomiting or diarrhoea, and rarely hypotension (0.25%)

Other undesirable effects

- Hypersensitivity and skin
  - Hypersensitivity: skin rashes uncommon (0.2%), single cases of urticaria.
  - Single cases of erythroderma, erythema nodosum, epidermal necrolysis have also been reported.

- Other systems

  Rare cases of headaches, malaise, vagal symptoms (hot flushes, dizziness, chills have been reported) and fever.

4.9 Overdose

After extensive clinical use, no reports of acute intoxication have been reported.

In the event of accidental massive ingestion, signs of adrenal failure might occur. Signs of acute intoxication may require specialist treatment including the administration of dexamethasone.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

OTHER SEX HORMONE AND MODULATOR OF THE REPRODUCTIVE FUNCTION/ ANTIPROGESTOGEN (GO3 X B01: Urogenital System and Sex Hormones).

Mifepristone is a synthetic steroid with an antiprogestational action as a result of competition with progesterone at the progesterone receptors.

At doses ranging from 3 to 10 mg/kg orally, it inhibits the action of endogenous or exogenous progesterone in different animal species (rat, mouse, rabbit and monkey). This action is manifested in the form of pregnancy termination in rodents.

In women at doses of greater than or equal to 1mg/kg, mifepristone antagonises the endometrial and myometrial effects of progesterone. During pregnancy it sensitises the myometrium to the contraction- inducing action of prostaglandin. During the first trimester, pre-treatment with mifepristone allows the dilatation and opening of the cervix uteri. While clinical data have demonstrated that mifepristone facilitates dilatation of the cervix, no data are available to indicate that this results in a lowering of the rate of early or late complications to the dilatation procedure.

In the event of an early termination of pregnancy, the combination of a prostaglandin analogue used in a sequential regimen after mifepristone leads to an increase in the success rate to about 95 per cent of the cases and accelerates the expulsion of the conceptus.

In clinical trials, according to the prostaglandin used and the time of application, the results vary slightly.

The success rate is up to 95.7% when misoprostol is used orally up to 49 days of amenorrhea, and with gemeprost applied vaginally, it reaches 98.7% up to 49 days of amenorrhea and 94.8% up to 63 days of amenorrhea.

According to the clinical trials and to the type of prostaglandin used, the failure rate varies. Failures occur in 1.3 to 7.5% of the cases receiving sequentially MIFEGYNE® followed by a prostaglandin analog, of which:

- 0 to 1.5% of ongoing pregnancies
- 1.3 to 4.6% of partial abortion, with incomplete expulsion
- 0 to 1.4% of hemostatic curettage

Combinations of mifepristone with other prostaglandin analogues have not been studied.

During the termination of pregnancy for medical reasons *beyond the first trimester*, mifepristone administered at a 600-mg dose, 36 to 48 hours prior to the first administration of prostaglandins, reduces the induction-abortion interval, and also decreases the prostaglandin doses required for the expulsion.

When used for labour induction of foetal death in utero, mifepristone alone induces expulsion in about 60% of cases within 72 hours following the first intake. In that event, the administration of prostaglandin or ocytocics would not be required.

Mifepristone binds to the glucocorticoid receptor. It doesn't bind to mineralocorticoid receptors; therefore, the risk of acute adrenal failure during mifepristone intake is negligible. In animals at doses of 10 to 25 mg/kg it inhibits the action of dexamethasone. In man the antiglucocorticoid action is manifested at a dose equal to or greater than 4.5 mg/kg by a compensatory elevation of ACTH and cortisol.

Mifepristone has a weak anti-androgenic action which only appears in animals during prolonged administration of very high doses.

5.2 Pharmacokinetic properties

After oral administration of a single dose of 600 mg mifepristone is rapidly absorbed. The peak concentration of 1.98 mg/l is reached after 1.30 hours (means of 10 subjects).

There is a non-linear dose response. After a distribution phase, elimination is at first slow, the concentration decreasing by a half between about 12 and 72 hours, and then more rapid, giving an elimination half-life of 18 hours. With radio receptor assay techniques, the terminal half-life is of up to 90 hours, including all metabolites of mifepristone able to bind to progesterone receptors.

After administration of low doses of mifepristone (20 mg orally or intravenously), the absolute bioavailability is 69%.

In plasma mifepristone is 98% bound to plasma proteins: albumin and principally alpha-1-acid glycoprotein (AAG), to which binding is saturable. Due to this specific binding, volume of distribution and plasma clearance of mifepristone are inversely proportional to the plasma concentration of AAG.

N-Demethylation and terminal hydroxylation of the 17-propynyl chain are primary metabolic pathways of hepatic oxidative metabolism.

Mifepristone is mainly excreted in faeces. After administration of a 600 mg labelled dose, 10% of the total radioactivity is eliminated in the urine and 90% in the faeces.

5.3 Preclinical safety data

In toxicological studies in rats and monkeys up to a duration of 6 months, mifepristone produced effects related to its antihormonal (antiprogesterone, antiglucocorticoid and antiandrogenic) activity.

In reproduction toxicology studies, mifepristone acts as a potent abortifacient. No teratogenic effect of mifepristone was observed in rats and mice surviving foetal exposure. In rabbits surviving foetal exposure, however, isolated cases of severe abnormalities occurred (cranial vault, brain and spinal cord). The number of foetal anomalies was not statistically significant and no dose-effect was observed. In monkeys, the number of foetuses surviving the abortifacient action of mifepristone was insufficient for a conclusive assessment.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Colloidal silica anhydrous, maize starch, povidone, magnesium stearate, microcrystalline cellulose.

6.2 Incompatibilities

Not applicable.

6.3 Shelf-life

3 years.

6.4 Special precautions for storage

None.

6.5 Nature and contents of container

3 tablets in blister (PVC / Aluminium).

6.6 Instructions for use and handling

Not applicable.

7. MARKETING AUTHORISATION HOLDER

EXELGYN
6, rue Christophe Colomb
75008 PARIS
France

8. MARKETING AUTHORISATION NUMBER

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

10. DATE OF REVISION OF THE TEXT

Appendix 2

European Patient's Information Leaflet

MIFEGYNE

PATIENT INFORMATION LEAFLET

Please read carefully this leaflet before taking this medicine.
Should you have any question, ask your doctor or your pharmacist to explain any points that are not clear.
Keep this leaflet, you may have to refer to it again later on.

1. TREATMENT IDENTIFICATION

- **NAME OF THE MEDICINAL PRODUCT**

  MIFEGYNE 200 mg, tablets
  (mifepristone)

- **QUALITATIVE AND QUANTITATIVE COMPOSITION**

  Each tablet of MIFEGYNE contains 200 mg of a medicine (active substance) called mifepristone. The tablets also contain the following ingredients: anhydrous colloidal silica, maize starch, povidone, microcrystalline cellulose and magnesium stearate.

- **MAKERS OF MIFEGYNE**

  - **MARKETING AUTHORISATION HOLDER**

    EXELGYN
    6, rue Christophe Colomb
    75008 Paris, FRANCE
    Fax number: 33 1 53 57 37 40

  - **THE MANUFACTURER**

1) What MIFEGYNE does

- **PHARMACEUTICAL FORM AND CONTENTS; PHARMACO THERAPEUTIC GROUP**

  - MIFEGYNE acts by blocking the effects of progesterone, a hormone which is needed for maintenance of pregnancy. This anti-hormone, hence can induce interruption of a pregnancy. It also softens and dilates the external opening of the womb (uterine cervix).

- MIFEGYNE is classified as a sex hormone, antiprogestin, modulator of the reproductive function.

- Tablets. Light yellow, cylindrical, biconvex tablets marked "167B" on one side.

- WHEN SHOULD THIS MEDICINE BE USED?

MIFEGYNE is recommended in the following situations:

1) For medical termination of a developing intra-uterine pregnancy:
   - up to the 49th day following the first day of your last menstrual period,
   - in sequence with another medicine, called a prostaglandin (medicine which increases the womb contractions), administered 36 to 48 hours later after MIFEGYNE's intake.

2) For softening and dilatation of the cervix uteri, prior to surgical termination of pregnancy during the first trimester.

3) As a preparation for the action of prostaglandins for termination of pregnancy for medical reasons *(beyond the first trimester).*

4) To induce labour when the pregnancy is interrupted (death of the fetus in the uterus).
MIFEGYNE is indicated when the use of prostaglandins or oxytocyn is not possible.

2. WARNING BEFORE YOU TAKE MIFEGYNE

a) WHEN SHOULD THE TREATMENT NOT BE USED?

- You should not have the treatment in any of the following cases, if you suffer from:
  - an abnormal function of the adrenal glands (adrenal insufficiency),
  - an allergy to prior use of MIFEGYNE or any ingredients of the tablet,
  - severe asthma which is not well controlled by a specific treatment.

- For the medical termination of a developing intra-uterine pregnancy, you should not have the treatment if:
  - the diagnosis of pregnancy has not been definitely established by biological tests or by ultrasound,

- the first day of your last period was 50 days or more ago,
- an ectopic pregnancy is suspected (the egg implanted in the tubes rather than in your womb),
- due to the need to use prostaglandins in combination with MIFEGYNE, you should not have the treatment if:
  - you have had a bad reaction or allergy to prostaglandins,
  - you suffer or have had cardiovascular problems such as: angina (chest pain due to coronary artery disease), Raynaud's syndrome or disease (circulatory problems in the limbs), cardiac rhythm problems, cardiac insufficiency, severe high blood pressure.

- <u>For patients receiving MIFEGYNE for softening and dilatation of the cervix uteri prior to surgical termination of pregnancy</u>:
  - if the diagnosis of pregnancy has not been definitely established by biological tests or by ultrasound,
  - if the first day of your last menstrual period was 84 days or more ago (according to the law in your country),
  - if an ectopic pregnancy is suspected.

- <u>For use prior to prostaglandins for late termination of pregnancy for medical reasons</u>, the contraindications to the treatment are those of the prostaglandin selected by your doctor to induce expulsion.

- <u>For labour induction to expel a dead fetus</u>

  Should you need prostaglandins to complete the effect of MIFEGYNE, you should be informed of the contraindications of the medicine which will be used *(you may ask further information to your physician).*

b) SPECIAL WARNINGS

MIFEGYNE and the prostaglandin analogues (as well as the follow-up of your treatment), can only be prescribed and administered for termination of pregnancy in accordance with the national legal requirements.

As a consequence, they can only be prescribed by a medical doctor and in a public or private hospital or centre (having approval to undertake terminations of pregnancies) in accordance with the national legal requirements.

The signature of an informed consent letter would certify that you have been fully informed about the medical method of termination of pregnancy with MIFEGYNE and a prostaglandin and of its risks.

Unless decided otherwise by your doctor, it is not advised to use MIFEGYNE if you suffer from:

- renal or liver insufficiency *(severe disease of the liver or of the kidneys)*,
- malnutrition.

1) **For the medical alternative to surgical termination of pregnancy**

This method requires your active involvement and you should be informed of the method's requirements:

- to combine treatment with another medicine (prostaglandin) to be administered at a second visit,
- to return to the clinic for a control visit (3rd visit) within 10 to 14 days after MIFEGYNE's intake in order to check for complete expulsion,
- to terminate the pregnancy by another surgical method in case of treatment failure.

In any case of a pregnancy occurring on a intra-uterine device, this device must be removed before administration of MIFEGYNE.

- Risks related to the method

  Failures:

  The medical method of pregnancy termination with MIFEGYNE and a prostaglandin does not lead to 100% success. Usually, the success rate is about 95%.

  Bleeding:

  You may experience sometimes heavy, and/or prolonged vaginal bleeding (up to 12 days after MIFEGYNE intake). Bleeding occurs in almost all cases and is not in anyway a proof of complete expulsion.

  Therefore, the control visit is mandatory in order to check that the treatment has been successful and well tolerated. This visit may be repeated in case treatment failure is suspected.

  Consequently, you will be advised not to travel far away from the prescribing center until the procedure is completed.

  Due to the risk of heavy bleeding during the medical method of pregnancy termination, should you suffer from hemorrhagic disorders with hypocoagulability (congenital anomaly, etc...) or anemia, the decision to use the medical or the surgical method should be decided by your doctor.

2) For patients receiving MIFEGYNE for dilatation of the cervix uteri prior to surgical termination of pregnancy

For the full efficacy of therapy, the use of MIFEGYNE must mandatorily be followed, 36 to 48 hours later and not beyond, by surgical termination. A shorter or longer time lag may compromise the efficacy of the therapy.

3) In any case

The use of MIFEGYNE requires the prevention of rhesus allo-immunisation (if you are rhesus negative) as well as other general measures taken usually during any pregnancy termination.

It is possible for you to become pregnant again immediately after the termination is complete so you will need to start contraception as early as possible after taking the MIFEGYNE tablets. You should not be pregnant in the menstrual cycle following treatment.

c) PRECAUTIONS FOR USE

1) In any case

Due to specific properties of mifepristone, the efficacy of long-term corticosteroid therapy may be decreased during the 3 to 4 days following MIFEGYNE's intake.

Inform your doctor if you suffer from asthma and if you are taking cortisone treatment in order to have your treatment adjusted if needed.

If you take on a regular basis, non steroidal anti-inflammatory drugs including aspirin as these medications may decrease the method's efficacy.

Should you need to receive pain relief tablets because of painful uterine contractions, do not take any anti-inflammatory medication or aspirin without your doctor advice. You will be prescribed a more appropriate treatment if needed.

2) Medical alternative to surgical termination of pregnancy

As a special precautionary measure and due to rare serious cardiovascular accidents reported following the administration of a certain type of prostaglandin, the medical method is not recommended for use if you are over 35 years of age and smoke more than 10 cigarettes a day.

Method of prostaglandins administration.

During intake and for three hours following the intake, you will be monitored in the treatment centre, which must be equiped with the appropriate monitoring equipment.

3) **For the sequential use of MIFEGYNE – Prostaglandin, whatever the indication**

The precautions related to the prostaglandins used should be followed where relevant. You may ask your doctor for further information.

d) INTERACTIONS WITH OTHER MEDICINES

IN ORDER TO AVOID INTERACTION BETWEEN SEVERAL MEDICATIONS YOU SHOULD TELL YOUR DOCTOR OR YOUR PHARMACIST IF YOU ARE TAKING ANY KIND OF TREATMENT.

e) PREGNANCY - LACTATION

This method of termination of pregnancy may fail.

Therefore, the control visit is mandatory. In the event of failure you will be offered to terminate the pregnancy by another method.

Should the vaginal bleeding persist or in case the next period is missed, inform your hospital doctor *(or clinic)* as soon as possible in order to determine what to do on a case by case basis.

The risks to the fetus in case of an ongoing pregnancy are unknown. Should you change your mind and wish to continue your pregnancy, ask your doctor. You would be proposed prenatal care with repeated ultrasonographies.

There is not data available about MIFEGYNE's excretion in the mother's breast milk. MIFEGYNE use should be avoided during breast-feeding.

AS A GENERAL RULE, YOU SHOULD ALWAYS TELL YOUR DOCTOR OR YOUR PHARMACIST IF YOU ARE BREAST FEEDING BEFORE TAKING ANY MEDICATION.

f) EFFECTS ON ABILITY TO DRIVE AND TO USE MACHINES

Not known.

g) SPORT

Nothing prevents you from exercising unless the side-effects of the treatment make you feeling sick (see section 4).

3. HOW TO USE MIFEGYNE

a) Dosage

– For the medical termination of a developing intra-uterine pregnancy:

The following prescription will be written by your doctor and you should receive the medication in the presence of the doctor or the nurse or midwife.

- 3 tablets of MIFEGYNE to swallow with some water in a single dose.

As a practical guide:

1. After intake of MIFEGYNE, you may go home with another appointment 36 to 48 h. later. You will be given a phone number to use in case you need emergency medical help, especially in case of very heavy bleeding. Bleeding usually starts 1 or 2 days after intake of MIFEGYNE.

   Occasionally, the expulsion may take place before your next appointment for the prostaglandin intake. Nevertheless, complete expulsion must be verified and you must return to the centre for that control.

2. You must then return to the hospital or clinic 2 days later to be given the prostaglandin.

   After you are given the prostaglandin, you should rest at the hospital/clinic for about 3 hours and you can then go home. You will receive, if it is relevant, a prescription for a contraceptive method.

   The products of conception will be expelled during the hours when you will be at the clinic or within the following days. Bleeding usually persists until the follow-up visit.

3. You must return to the hospital/clinic for a mandatory follow-up visit 10 to 14 days after intake of MIFEGYNE. Should your pregnancy be still continuing or the expulsion be incomplete, an appropriate treatment will be prescribed.

   Therefore, you should not travel far away form the prescribing centre until the procedure is completed.

Obviously, if there is any cause for concern, you can either contact the hospital or return to the hospital or centre prior to the appointment time. You will be given a phone number to call in case of concern or emergency.

- For softening of the cervix uteri before surgical termination of pregnancy:

  As a practical guide:

  1. The treatment will consist of intake of one MIFEGYNE tablet by mouth, at the clinic in the presence of the doctor or the nurse.

  2. After administration of MIFEGYNE, you may go home with an appointment 36 to 48 hours later for the surgical procedure.
     Your doctor will explain this to you.
     You may experience vaginal bleeding after MIFEGYNE intake, before surgery. In rare instances, an expulsion may take place before the surgical procedure. You must return to the clinic to check that expulsion is complete.

  3. You will be given a phone number to reach in case of emergency *(or for medical support)*.

  4. You must return to the clinic/hospital for the surgical procedure. After the surgery, you should stay and rest at the centre a few hours. You may then go home with, if relevant, a prescription for a contraceptive method.

- For termination of pregnancy for medical reasons:

  - 3 tablets of MIFEGYNE in a single dose in the presence of the doctor or the nurse or midwife,
  - you will be given an appointment to return to the hospital 36 to 48 hours (2 days) later to be given a prostaglandin which administration may be repeated until the termination has been completed.

- For labor induction to expel a dead fetus:

  3 tablets of MIFEGYNE daily for 2 consecutive days.

b) MODE AND ROUTE OF ADMINISTRATION

Oral route.

c) FREQUENCY AND TIME OF ADMINISTRATION OF THE MEDICATION

According to the medical prescription.

d) DURATION OF TREATMENT

MIFEGYNE is administered in a single dose (see above) but in the case of labor induction to expel a dead fetus, where the treatment is usually prescribed for 2 consecutive days.

e) WHAT TO DO IN CASE YOU TAKE TOO MANY TABLETS

According to the conditions of administration, an overdosage is very unlikely. However, any suggestion of acute intoxication requires treatment in a specialised environment.

f) WHAT TO DO IN CASE ONE OR SEVERAL DOSES HAVE BEEN MISSED

g) AFTER-EFFECTS WHEN MIFEGYNE IS STOPPED

None.

4. POSSIBLE SIDE-EFFECTS

AS WITH ANY MEDICATION, MIFEGYNE MAY, IN SOME PEOPLE, INDUCE ADVERSE REACTIONS.

- Heavy bleeding occurs in about 5% of the cases and may require hemostatic curettage in about 1% of the women.

- Uterine contractions which are often painful, occur frequently: in 10 to 45% of the cases they occur in the hours following prostaglandin intake (The clinic will be able to give you appropriate pain killers).

- During therapeutic termination of pregnancy for medical reasons, rare cases of uterine rupture have been reported after prostagladin intake.
  The reports occurred particularly in multiparous women or in women with a cesarean section scar.

- Gastrointestinal side-effects such as nausea, vomiting, diarrhea are common after the prostaglandin administration.

- Rare cases of blood pressure decrease.

Other rare side-effects

- Allergy such as skin rash or urticaria, and other skin disorders. Headache, dizziness, fever.

Electronic Mail Message

Date: 6/13/00 10:03:07 AM
From: [redacted]
Subject: Medical Abortion in England.

[redacted]

I just spoke with [redacted] London. He was very helpful in explaining their system. Mifepristone has been approved there since approximatedly 1993. All new drugs in the UK are marked with a black triangle for the first 2 years, which alerts practitioners that it is a new drug, and they can then report all AEs, not just serious AEs. There was no initial restriction on the use of mifepristone except as in the current labeling.

Abortions in the UK (both surgical and medical) are provided in Special Family Planning Clinics by specialists in Family Planning or OB/GYN, NOT by general practitioners. Legally, 2 physicians must certify that the patient's psychological or physical well-being is at risk before the procedure can be performed. There is no situation in which the surgical or medical procedure would be performed by a nurse provider or midwife without the direct supervision of a physician.

[redacted]pristone is distributed to the clinic pharmacies and administered at the [redacted]c only, and the patient returns there for the prostaglandin. [redacted] is not aware of any situation where it may be administered at home. Because clinics are located in each region, and patients must attend the facility in their own region, the issue of specifying a given proximity is not addressed.

Although off-label use is possible, [redacted] is not aware of any significant use of different doses or regimens of the drugs. There is some interest on the part of the MCA to look at lower doses, but no sponsor has applied for it, and the available data is old data from a WHO study.

I will keep trying to reach [redacted] who has past experience with the drug in France, and perhaps will call some other European practitioners tomorrow am if I am unable to reach her today.

Will keep you updated.

[redacted]

Electronic Mail Message

Date: 6/14/00 10:38:15 PM
From: [redacted]
Subject: FWD: More info about Europe

Enclosed are French Ab practices.

We are still pulling the data on complications of abs (the spontaneous ab info is lacking, but will pursue). Plan is to send this info and the confidentiality response for you to forward to Dr. Henney around Friday.

Electronic Mail Message

[redacted]

Date: 6/14/00 11:57:03 AM
From: [redacted]
Subject: More info about Europe

I just spoke with [redacted] formerly worked at Exelgyn and is very knowledgeable about the status of mifepristone in Europe. I will try to summarize what I learned.

Mifepristone is distributed directly to clinics in most of Europe, except in Switzerland and Germany, and possibly Austria by now, where abortions are provided by physicians in their own practices, and the product is distributed to their offices in 1 week to 1 month supplies. In Belgium and Spain, distribution is linked to hospital pharmacies.

Medical abortions in France may be delegated by the physician to midwives or nurses. The physician is responsible for the decision to administer the drug, and it is then handled by the nurse-providers with [redacted]ician supervision. The midwives/nurse providers do not perform [redacted]l abortions. The physician is usually in the "ward" but may be [redacted]ble on call in case of a problem.

Surgical abortions and other family planning services are provided in the clinics in France. However, the clinics are closed at night and weekends, so patients are given the phone # of the hospital with 24 hour service and can contact the physician through that number. There is no specific distance requirement. There was a one-hour requirement for the clinical trials only.

The current labeling requires a second visit for administration of the misoprostol. Some physicians allow home administration, but they are cautious as this is not in the approved labeling. It is also administered at home in some places in the UK, but only with misoprostol. (Gemeprost, which is used vaginally in the UK is a more potent prostaglandin and is used with more caution and closer monitoring.) The French regulatory agency is considering changing the requirement for the second visit for misoprostol administration based on US studies by [redacted] (I'm not sure I got the name right)]

Mifepristone along with the more potent prostaglandin gemeprost, which is given vaginally, is approved for gestations up to 63 days in the UK, Norway, and Sweden. The complete abortion rate is 94-97%.

Mifepristone is sometimes used off-label in doses other than 600 mg (most commonly 200 mg, but may be up to 800 mg with vaginal misoprostol 200-600 mcg). The UK was the first to shift to the 200 mg dose, along [redacted]e more potent gemeprost (still off-label, not approved except in [redacted] mg dose)

The need for blood transfusion in France has been 0.1% of patients and

is based on physician judgement, not based on hemoglobin changes.

CONFIDENTIALITY with DIRECT DISTRIBUTION OF MIFEPRISTONE

The main responsibility for ensuring confidentiality falls on the distributor, the FDA investigators who inspect the system, and the providers and patients.

The distributor of the drug will need to ensure that records, receipts, and transactions are kept secure. The distributor will also be tracking the eligibility of providers and receiving credentialing information, all of which must be handled with confidentiality. FDA will be inspecting the distribution system and our record keeping will need to preserve provider confidentiality. Finally, the providers who receive the drug have a role in preserving their own confidentiality as well as patients who receive this treatment from those providers.

FDA Proposed Restricted Distribution System for NDA 20-687 on 6/1/00

Qualifications for Physician Recipients:

1. Must be licensed to practice medicine in the state to which the drug is shipped.
   - acceptable documentation:
     - copy of valid physician's license

2 [redacted]
   - acceptable documentation:
     - sponsor to propose; self-attestation is discouraged

3. Has been trained to and has the ability to assess the age of a pregnancy accurately by ultrasound examination, to monitor abortion by ultrasound examination, and to diagnose an ectopic pregnancy by ultrasound examination.
   - acceptable documentation:
     - sponsor to propose; self attestation is discouraged

4. Has satisfactorily completed training certified by the distributor in the mifepristone treatment procedure, including mechanism of action, appropriate use, proper administration, follow-up, efficacy, adverse events, adverse event reporting, complications, and surgical indications.
   - acceptable documentation:
     - sponsor to propose curricula for review by FDA; sponsor to propose certification tracking system linked to the distribution system

5. Has continuing access (e.g., admitting privileges) to a medical facility equipped for instrumental pregnancy termination, resuscitation procedures, and blood transfusion at the facility or [redacted] drive from the treatment facility.
   - acceptable documentation:
     - a signed letter by the Chief Medical Officer on the medical facility's stationary stating that the facility is properly equipped; sponsor to propose other acceptable documentation

F.D.A. Letter, [redacted] to Arnold, Sandra (February 18, 2000)

COMMENT: "Distribution Plan

We have completed our review of this application, including the restrictions on the distribution and use of this product proposed in your January 21, 2000 submission, entitled "Distribution Plan". We have concluded that adequate information has not been presented to demonstrate that the drug, when marketed in accordance with the terms of distribution proposed, is safe and effective for use as recommended. The restrictions on distribution will need to be amended.

We have thus considered this application under the restricted distribution regulations contained in 21 CFR 314.500 (Subpart H) and have concluded that restrictions as per CFR 314.520 on the distribution and use of mifepristone are needed to assure safe use of this product."

RESPONSE:

The Approvable Letter says that "restrictions as per 21 C.F.R. 314.520 on the distribution and use of mifepristone are needed to assure safe use...." We believe the provision is both inapplicable to mifepristone and unncessary for FDA to obtain appropriate controls on distribution of mifepristone.

As you know, the accelerated approval regulations in "Subpart H" are intended only for those situations where a drug is being considered for use with "a serious or life threatening condition," (See, 314.500, "Scope."), which is clearly not the case with mifepristone. Moreover, as the preambles implementing these "Subpart H" regulations make clear, the products subject to approval under this subpart present marked toxicity profiles or other extreme risk factors that are tolerable only because the disease to be treated is so serious or the benefits of the drug are so much greater than those with existing treatments for such a disease. As a result, the restrictions on conditions for use in part 314.520 were designed for drugs presenting unusually high risks. Application of those principles to mifepristone is not only inappropriate because mifepristone does not meet these criteria, but is also likely to falsely "mark" mifepristone as a highly toxic and risky drug, when, in fact, as FDA knows, it is exceptionally safe and effective. Creating the impression that mifepristone is a subpart H drug could,

just as with an unwarranted black box warning, induce unfounded fears about safety, which could inappropriately deter women from using the drug.[1]

Use of Subpart H here is also totally unnecessary for FDA to satisfy itself that adequate distribution controls are in effect. We have submitted an extensive and detailed distribution plan (Attachment 1), which includes secure manufacturing and shipping procedures, controlled returns, tracking of distribution of individual packages to the patient level, use of a limited number of distributors [redacted], account registration and other detailed ordering requirements for practitioners, direct distribution only to practitioners (not through retail pharmacies), and the use of signed patient agreements. We hereby restate our commitment to carry out this distribution plan.

Our commitment is underscored by the fact that the distribution plan itself (and our monitoring of it) is one of the Phase IV commitments to which we have agreed, and of which FDA has reminded us in the February 18, 2000 Approvable Letter. (That commitment was originally stated in the September 16, 1996 letter from the Population Council to FDA). In addition, a reference to the distribution plan is already incorporated in the package insert for the product, so that when FDA approves the package insert, it will be approving the distribution plan as part of the package insert. Once that is done, we believe FDA would take the position that any significant changes to the distribution plan would require prior approval, and we would not object to that position in this case.

In short, the distribution plan we have proposed is both detailed and comprehensive. It is surely equal to its purpose. In addition, we are firmly committed to carrying it out, and have made that commitment in a form the agency can enforce. Thus, there is no need for FDA to invoke Subpart H to get an excellent distribution plan, even if it were permissible for it to do so.

[1] Not only is Subpart H inapplicable, FDA cannot, in our view, invoke it at this late date (nearly 4 years after the NDA was submitted).

The Danco Group

January 21, 2000

Division of Reproductive and
Urologic Drug Products (HFD-580)
Attention: Document Control Room 17B-20
Office of Drug Evaluation II
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Re: **NDA 20-687, Mifepristone 200mg Oral Tablets**
- Amendment 039 - Mifeprex® – Distribution Plan

Dear

As previously agreed, we are submitting Danco Laboratories, Inc.'s Distribution Plan for Mifeprex®. This is a comprehensive distribution plan that emphasizes control of mifepristone at all points in the supply chain, from manufacturers through to individual patients. This plan has been prepared in light of the unique situation surrounding abortion provision in the United States and not out of any medical safety concerns. However, in preparation of this plan, we have taken into account advice from the FDA that it is considering approving the NDA under "Subpart H—Accelerated Approval of New Drugs for Serious or Life-Threatening Illnesses, Sec. 314.520--Approval with restrictions to assure safe use."

Our position is that we are willing to agree with the FDA on appropriate distribution controls for mifepristone but that the application of Sec. 314.520 under Subpart H seems unnecessary, in light of our voluntary acceptance of some appropriate distribution controls.

Specifically, Sec. 314.520(a) states that the FDA can apply post-marketing restrictions if it "concludes that a drug product shown to be effective can be safely used *only* if distribution or use is restricted" (emphasis added). Regardless of the distribution system for mifepristone, the medical safety of this drug is well documented in our IND application and in the label and, thus, we believe that Sec. 314.520 does not apply.

On the contrary, scientific evidence demonstrates that mifepristone is an exceptionally safe drug. Mifepristone when taken by a woman whose pregnancy is ≤ 49 days LMP is associated with several relatively minor and predictable side effects. More serious adverse events are quite rare and are related to the entire treatment (not mifepristone *per se*), almost always following the use of the prostaglandin. There has never been a death related to the use of mifepristone in combination with misoprostol for medical termination of pregnancy. These details have been discussed and reported in our label and various submissions to the FDA.

In addition to concerns about patient safety, the possibility of teratogenic effects has previously triggered the application of section 314.520, as in the case of Thalomid (Thalidomide). These concerns relate to the inadvertent use of a known teratogen at the early stages of a pregnancy that was not scheduled for termination. In contrast, all women who will receive mifepristone will be known to be in early pregnancy and have elected to terminate that pregnancy. Of course, in the case of a successful application of mifepristone, concerns about teratogenicity are rendered moot as the woman will no longer be pregnant. Similarly, in the case of a failed medical abortion, women should have a surgical intervention to terminate the pregnancy and are counseled to do so before taking mifepristone and misoprostol. To date, there is no compelling evidence to suggest that either mifepristone or misoprostol produces teratogenic effects.

Based on the above reasons, we firmly believe that the NDA for mifepristone should not be approved under Sec. 314.520. In addition, applying Sec. 314.520 might draw increased and unwarranted attention to the product, the FDA, and to Danco and its manufacturers, in particular evoking queries about the product's safety. Nonetheless, given the contentious political climate surrounding *all* abortion provision in the United States, we feel that the distribution of mifepristone should be carefully monitored and controlled. Therefore, we have developed and are implementing a controlled distribution strategy and are submitting the details of this strategy in the enclosed Distribution Plan for your review and comment.

Sincerely,

/S/

President and Chief Executive Officer

/dns
Enclosure

cc:
Sandra P. Arnold – Population Council
Frederick H. Schmidt – Population Council
Patricia C. Vaughan, Esq. – Population Council

MIFEPREX®

DISTRIBUTION PLAN

January 21, 2000

MIFEPREX®

DISTRIBUTION PLAN

CONTENTS

		Page(s)
	EXECUTIVE SUMMARY	3-4
	CONTROLLED DISTRIBUTION FLOWCHART	4a
	PLAN OVERVIEW	5
I.	MANUFACTURING	
	Key Control Points	6
	Process	6
	Packaging	6-7
	Tracking	7
	Security and controls	7-8
	Recall Process	8
II.	LOGISTICS PARTNER	
	Key Control Points	9
	Role	9-10
	Process	10
	Security and controls	11
	Returns Process	11-12
III.	Distributors	
	Key Control Points	13
	Role	13-14
	Process	14-15
	Security and Controls	15-16
	Returns Process	16-17
IV.	PROVIDERS/~~PA~~TIENTS	
	Key Control Points	18
	Process	18
	Communications	18-20
	Training	20-23

MIFEPREX®

DISTRIBUTION PLAN

CONTENTS

EXHIBITS

A. Mock-up of Mifeprex® Package of Three Tablets

B. Conceptual Design of Intermediate Shipper and Case

C. —— Data Tracking Hierarchy

D. ——~—— Letter to DEA

E. Account Registration and Order Form

F. State Abortion Guidelines (sample CDC packet)

G. Patient Information

H. Patient Acknowledgement Form

I. Danco Toll-free Number Schematic

J. Danco Web Site Schematic

K. NAF/CAPS Mifepristone 2000 Seminars

L. Completed Trainings List

MIFEPREX®

DISTRIBUTION PLAN

EXECUTIVE SUMMARY

This Distribution Plan for Mifeprex® demonstrates Danco Laboratories Inc.'s ("Danco") commitment to distributing Mifeprex® safely and efficiently while, at the same time, providing needed services and information to providers and patients in a confidential manner. Danco has a keen awareness of and sensitivity to the regulatory requirements, as well as the market and political dynamics, surrounding introduction of Mifeprex® in the United States. Therefore, Danco has established a **controlled distribution strategy** to best meet the goals of safe, efficient and confidential distribution of Mifeprex®.

This strategy ensures that Danco exerts positive control over distribution of Mifeprex® through all phases of manufacturing, storage, shipment and administration from manufacturer to patient. Key control elements throughout the distribution process include the following:

- Secure manufacturing, receiving and holding areas for Mifeprex®
- Secure shipping procedures, including tamper-proof seals
- Controlled returns procedures
- Tracking system ability to trace individual packages to patient level, while maintaining patient confidentiality
- Use of only [redacted] authorized distributors and a logistics partner, all of whom have necessary expertise, capabilities and industry experience to handle distribution requirements for Mifeprex®
- Required Account Registration and Order Form signed by providers, prior to any Mifeprex® order being shipped
- Mifeprex® availability only to registered providers, not through retail pharmacies
- Documented patient acknowledgment (informed consent), signed by patient and provider

Alongside key control elements, Danco also recognizes the need to provide support and access to training, services and information throughout the supply chain. The support that is built into the distribution system is as follows:

160
1/21/00

Access to multi-media training materials and training programs with continuing medical education (CME) recognition and credits.

- Danco toll-free telephone information network for consumers and providers, with access to medical consultants for providers' medical questions
- Danco web site information network
- Trained service representatives for distributors' questions through the logistics partner

Danco has developed and assembled the infrastructure to ensure that Danco's goal of safe, efficient and confidential distribution of Mifeprex® is attained. The Distribution Plan for Mifeprex® details Danco's controlled distribution strategy, highlighting key control elements at each point in the supply chain.

Exhibit D

Diversion Investigator
US Department of Justice
Drug Enforcement Administration
600 Arch Street, Room 10224
Philadelphia, Pennsylvania 19106

[redacted] is requesting to store non-controlled product in the caged staging area that is in front of our vault. Today no controlled drugs are stored in this limited access area. This request is to store limited quantities (two pallets) of this non-controlled product. This product is controlled by serial number and requires a limited secure access storage area. This product requires special steps to be in place to insure that each package is accountable and secure from the manufacture to the patient.

The product is called Mifeprex (mifepristone). It is an oral antiprogestin agent, which blocks the action of the hormone progesterone and thus requires tracking of the product to the patient level. This is not a short-term request. The business relationship is contracted for three year.

Please consider this request. If there are any questions or if you need further information, my number is [redacted] Thank you in advance for help.

Regards,

[redacted]

Director of Operations

Exhibit E

MIFEPREX®
(Mifepristone tablets 200 mg)

ACCOUNT REGISTRATION LETTER

We are pleased that you wish to become a provider of MIFEPREX® (Mifepristone 200 mg), which is indicated for the medical termination of intrauterine pregnancy through 49 days from the first day of the patient's last menstrual period (see product label for full prescribing information). Product label, patient information and patient acknowledgement forms will be provided together with your initial order of Mifeprex®.

Prior to establishing your account and receiving your first order, you must sign and return this letter to the distributor, indicating that you have met the qualifications outlined below and will observe the guidelines outlined below. If you oversee more than one office facility, you will need to sign and return this letter to the distributor to register each facility prior to shipping the first order. Once each facility is registered with a distributor there are no other restrictions on re-ordering.

Mifeprex® must be provided by or under the supervision of a physician who meets the following qualifications:

- Ability to assess the duration of pregnancy accurately.
- Ability to diagnose ectopic pregnancies.
- Ability to assure patient access to medical facilities equipped to provide emergency treatment of incomplete abortion, blood transfusions and emergency resuscitation, if necessary.

In addition to these qualifications, you must provide Mifeprex® in a manner consistent with the following guidelines.

- You must fully explain the procedure to each patient and obtain each patient's signed acknowledgement. You should not give Mifeprex® to any patient who may be unable to under stand the effects of the treatment procedure or to comply with its regimen.
- Each package of Mifeprex® has a serial number. As part of maintaining complete records for each patient, you must record this identification number in each patient's record.
- While serious adverse events associated with the use of Mifeprex® are rare, you must report any hospitalization, transfusion or other serious event to Danco Laboratories, identifying the patient solely by package serial number to ensure patient confidentiality.
- The patient's follow-up visit is very important to confirm that a complete termination of pregnancy has occurred and that there have been no complications. You must notify Danco Laboratories in the event of an on-going pregnancy, which is not terminated subsequent to the conclusion of the treatment procedure.

By signing the reverse side, you acknowledge receipt of the ACCOUNT REGISTRATION LETTER and agree that you meet these qualifications and that you will follow these guidelines for use.

Highlights of the July 19, 1996 Reproductive Health Drugs Advisory Committee (AC) Meeting On Mifepristone: Outstanding Issues for FDA to Address

1) Further Efficacy Studies Recommendations by Two AC Members

-Advisory Committee Votes
Efficacy: 6 yes, 2 no
Safety: 7 yes, 1 abstention
Benefit/risk: 6 yes, 2 abstentions

In reference to the 6 yes votes to 2 no votes, for demonstration of efficacy one advisory committee member did not feel efficacy was proven and requested "less-selective" patients who are not highly motivated and who had terminations paid for by the clinical trials. (p.278-Henderson) Address this in reviews.

Another advisory committee member wanted to see final U.S. data prior to an approval vote. (p.279-O'Sullivan) Address this in reviews.

2) U.S. Data to Go to the Committee for Review

Dr. O'Sullivan voted no for approval citing need to see U.S. data. (p.279) The committee expressed desire to see all U.S. safety data (p.288) once available. [redacted] stated that if the U.S. data was worse, FDA may hold another AC meeting; if the U.S. data was the same or better, the FDA may mail the results out for comment by the AC (p.290). Was this done?

3) Reconciliation of Differences between Clinical Trials Eligibility, Labeling, and Patient Package Insert (PPI)
The advisory committee (AC) recommends that all conditions of exclusion (cardiovascular diseases and other medical conditions like insulin-dependent diabetes, etc.), information given to patients/physicians, and restrictions in the clinical trials should also be in the physician label and PPI. If there are no data or risks are unknown, state this. (p. 300 Daling, p. 301-2 O'Sullivan, p. 306 Davidson, 308 Zones)

- Exclusion Criteria
Clinical trials prohibited smoking 10 or more cigarettes a day or drinking alcohol during the 48 hours following mifepristone administration and on the day of misoprostol; the AC asks if is this in current physician labeling and PPI? (p.254-Davidson)

Women over the age of 35 were excluded; how is this handled in the label? Why? (p.256-Robbins)

Adolescents were excluded from the trials, is this in the label and PPI? (p.301 Henderson)

-Timing of 2nd Drug

The AC recommends changing the labeling from 36-48 hours for administration of the second drug to "two days" in the medical and patient label. (p.276-Davidson)

4) Labeling Recommendations

-"Safety" Not be Misinterpreted

The term "safety" should not be misinterpreted as "free of adverse effects and free of actually serious adverse effects" and this idea should be in the physician and patient package information. (p.285-Petitti)

-"Acceptability of Adverse Events"

The AC suggests to the extent possible for the Agency, that this method of termination be compared with alternatives in terms of adverse effects and events and this be in the labeling. (p.287-88, Lewis and Davidson)

-Clarify Drug-Drug Interaction Term

Define what are the drugs that cause enzyme induction in the label. (p.302 O'Sullivan)

-Define Risk of Malformation if Pregnancy Continues

Provide information on the risk of malformation for embryo if pregnancy is not terminated with use of drugs; if not known, state. (p.303 O'Sullivan)

-Consideration for Termination if Pregnancy Continues due to Unknown Teratogenic Risk

AC recommends to FDA that all cautions, conditions of exclusion and information given in the clinical trials to patients/physicians be in the label and PPI. Because of the drugs unknown teratogenic risk, the label should read termination of pregnancy should be considered. (p.304-306 discussion, Davidson)

-Decrease in Misoprostol Effectiveness if Administration is Delayed

For information to physicians and patients, state in label and PPI that the effectiveness of misoprostol decreases with delay in its administration and it should be administered as directed. (p.307-Azziz)

-Explain in Label Why Two Days for Misoprostol is Optimal

The label and PPI should explain medically why two days is the optimal time for administering misoprostol. (p. 307 Davidson)

-Patients Should be Asked if they are Taking Other Drugs

Both the physician label and PPI should have statements stating patients should inform their physicians if they are on any other medications. (p.308 Zones)

-Nursing Mothers

Both the misoprostol label and mifepristone label need to be consistent and say to nursing mothers to either not use these drugs or to stop breast-feeding while using them. (p.309-310 Petitti)

-Define Pediatric Patients

Make sure the label and PPI are clear what are the age groups defined when FDA says safety and effectiveness in pediatric patients have not been established. (p.310-O'Sullivan)

-Label Should Mention Efficacy Decreases after Gestational Age of 49 days

The data say there is significant decrease in efficacy occurs for women who carry a fetus of greater than 49 days gestation age. This should be emphasized in label/PPI. (p.310-11 Davidson)

-Label Should State Informed Consent be Written

Physician and PPI should mention written informed consents should be obtained. (p.313-Petitti)

Some suggested wording for the written informed consent: "My physician has discussed with me alternatives to medical abortion, including surgical abortion, continuation of pregnancy...My doctor has confirmed that I am pregnant and that the pregnancy has not lasted more than 49 days..." (p.313 Petitti)

-Label Should Mention Use of Drugs Under Supervision of a Qualified Physician

Nurses can administer this drug, but under the direction of a qualified physician-one who is experienced in handling pregnancies, terminations, and complications of both. (p.314-315 Azziz)

5) Distribution System Issues

The AC proposed the model of the IUD system for tracking distribution of mifepristone. Concern was expressed about not making the tracking system too onerous for physicians. (p.315 Winikoff, O'Sullivan)

Mifepristone ~~would~~ not be distributed to the pharmacy but to physicians directly as proposed by the sponsor. (p.314 Davidson)

-Training of Qualified Physicians through Distributors

The distributors would be responsible for ensuring drug got into hands of physicians who were trained in dating pregnancies, handling complications, identifying ectopic pregnancies, and performing surgical evacuations and emergency procedures. Training seminars for use of mifepristone would be conducted, without financial incentive to physicians, and only those physicians who completed training would be distributed the drug. A tracking system of these physicians would be needed. The AC did not want the

distributor to train non-ob-gyns or non-surgeons the use of this drug and manual vacuum aspiration. Identification of adequate back-up with skills for emergency procedures is needed. FDA must respond by describing qualifications of skills of physicians to whom the drug can be distributed to ensure appropriate use of drug and management of potential complications. There is clearly concern that this drug not be expanded to hands of physicians who are not already skilled in managing pregnancies, terminations, and complications of both. Family practitioners with adequate back up were mentioned as acceptable (p. 316, 318-325Azziz [Davidson 324], 327-328Azziz).

6) Post Market Issues

-Concerns about Compliance with Returning: Study Suggested

The AC expresses concern that compliance with three visits maybe more problematic for minorities, patients with barriers to health care, transportation, child care, etc. and these types of women were not in the clinical trial; can these factors be studied in patients who do and do not return post-marketing to understand appropriate selection of patient population for this drug? (p.269 Henderson, p.270 O'Sullivan, p.280 Henderson, p.291 Henderson, p. 329 Daling) [In response, see p.293 Dr. Zones, on how medical practitioners have historically assessed compliance in their patients as part of what therapeutic options are appropriate. Also see Dr. Daling p.293, who states Planned Parenthood has experience in this population.]

What can be done for patients who complete the medications but cannot afford the surgical terminations, if needed? (p.271 O'Sullivan)

What if the patient does not return to confirm the abortion? (p.296 Dr. Henderson)

-Concerns about Distribution System: Who are the Physicians who Get Drug and Are They Qualified

Concern was raised from p.318-25 that physicians not skilled in handling pregnancies, terminations, or complications from both not be trained to give drug. This should be monitored post-market. (p.326 Henderson)

-Failed Pregnancy Terminations and Resulting Surgical Complications Be Tracked for Everyone being Distributed the Drug

Monitoring the number of failed pregnancy terminations and any resulting surgical complications is advised. (p.326 Henderson) This monitoring is recommended for every physician being distributed the drug for a limited time period (6 months, one year, and two years). (p.328 Azziz) Concern that backup physicians handling complications may appear to have more problems must be adjusted for. (p. 328 O'Sullivan)

-Study Long-term Effects of Both Single and Multiple Use in Patients

Collect data on the long-term effects of both single use and multiple use in patients from a subgroup. (p. 329 Davidson)

-Study Effects of Women over 35, under 20, who Smoke/Don't Smoke

These patients may accept risk to take drug, it would be useful to quantify cardiovascular risk. (p.329 Davidson, Henderson, Daling)

-Study Effects in Pregnancies that Continue after Drugs Administered and No Terminations Result and Further Terminations Not Pursued

What are effects of drug on the fetus, pregnancy, newborn, etc. (p.330 Azziz)?

Reproductive Health Drugs Advisory Committee

FDA Technical Center
Gaithersburg, Maryland
19 July 1996

MINUTES

Members Present	Members Absent
Ezra C. Davidson, Jr, MD (Chair)	Kenneth Ryan, MD
Janet R. Daling, PhD	Edward Wallach, MD
Caseandra E. Henderson, MD	
Thomas S. Kosasa, MD	
Vivian Lewis, MD	
Deborah L. Narrigan, MSN, CMN	
Mary Jo O'Sullivan, MD	
Diana B. Petitti, MD, MPH	
Jane S. Zones, PhD	

Invited Guests

Ricardo Azziz, MD

Executive Secretary

Philip A. Corfman, MD

"We certify that we attended the 19 July 1996 meeting of the Reproductive Health Drugs Advisory Committee and that these Summary Minutes accurately reflect what transpired."

/S/
Philip A. Corfman, MD
Executive Secretary
23 July 1996
Date

/S/
Ezra C. Davidson, MD
Chair
July 23, 1996
Date

The Reproductive Health Drugs Advisory Committee of the Food and Drug Administration met on 19 July 1996 at the Food and Drug Adminstration's Technical Center in Gaithersburg, Maryland. A complete transcript of the meeting is available from the Dockets Management Branch. The following documents are annexed to these Summary Minutes:

1. The Agenda.
2. Questions put to the Committee.
3. A list of Committee members and the Guest invited by the FDA.

The meeting was opened by the Chair with comments concerning the exemplary service of the members whose terms on the Committee have ended, Drs. Janet Daling, Cassandra Henderson, and Jane Zones, and greetings to the Invited Guest, Dr. Ricardo Azziz, who becomes a member of the Committee this year. The Chair also introduced Agency staff at the Committee table: Commissioner David Kessler, Deputy Commissioner Mary Pendergast, and Acting Director of the Reproductive and Urologic Drugs Advisory Committee, Dr. Lisa Rarick.

Subsequent committee meeting dates were confirmed as follows:

20-22 November 1996
13-14 February 1997
5-6 June 1997

Ms. Marina Hooten, the Chief of the Ethics Branch in the Agency's Division of Ethics and Program Integrity, read the Conflict of Interest statement, noting that, due to the possibly apparent conflict of interest, Dr. Zones, though permitted to participate fully in the proceedings, has been asked not to vote, if votes are to be taken.

The Chair then opened the meeting to the principal topic.

NEW DRUG APPLICATION FOR THE USE OF MIFEPRISTONE FOR INTERRUPTION OF EARLY PREGNANCY

After an introduction to the topic by Commissioner David Kessler, the sponsor, the Population Council, presented its findings and recommendations. Presentations were given by Ms. Sandra Arnold, Drs. Ann Robbins, Irvin Spitz, Wayne Bardin, Beverly Winikoff, and Elizabeth Newhall. During these presentations there was discussion of the issues with Committee members. Dr. Robbins concluded the sponsor's presentations.

The next major agenda item was presentations of the Agency's review of the Application by staff of the Reproductive and Urologic Drugs Products Division, including the Acting Director, Dr. Lisa Rarick, and Drs. Alexander Jordan and Ridgely Bennett. There was discussion of the issues with Committee members during and after these presentations.

The afternoon session began with the Open Public Session, with presentations by the following individuals, speaking either as private citizens or on behalf of the organizations they represented:

Office of Congressman Tom Coburn
Member, United States House of Representatives
Michael Schwartz

Alan Guttmacher Institute
Lisa Kaeser, JD

American College of Obstetricians and Gynecologists
Carolyn L. Westoff, MD

American Life League, Inc.
Rebecca Lindstedt

American Medical Student Association
Paul Jung, MD

American Medical Women's Association
Diana Dell, MD

American Public Health Association
Allan Rosenfield, MD

American Victims of Abortion
Olivia L. Gans

Baruch College
Joel Brind, PhD

Private citizen
Randy O'Bannon, speaking for Charles Cargille, MD

Center for Reproductive Law and Policy
Janet Benshoof, JD

Private citizen
Helen M. Donovan, JD

Family Research Council
Gracie S. Hsu, MHS

Feminist Majority Foundation
Eleanor Smeal

Feminist Women's Health Center
Marie Head

Life Issues Institute
Richard D. Glasow, PhD

National Abortion and Reproductive Rights League
Marcy J. Wilder, JD

National Abortion Federation
Paul Blumenthal, MD

National Association of Nurse Practitioners
in Reproductive Health
Susan Wysocki, RNC, NP

National Council of Jewish Women
Donna Gary

National Organization for Women, Inc.
Janice E. Erickson

National Women's Health Network
Cynthia A. Pearson

National Women's Health Organization
Susan Hill

National Women's Law Center
Ann Kolker

Northeast Waterloo Family Practice
M. Louviere, MD

Pharmacists for Life, International
Mary Jasinski Caldwell

Planned Parenthood Federation of America
Gloria M. Feldt

Planned Parenthood of Westchester and Rockland, Inc.
Lynn Borgatta, MD, MPH

Reproductive Health Technologies Project
Marie Bass

Private citizen
Wendy Simonds, PhD

Society of Physicians for
Reproductive Choice and Health
Seymour L. Romney, MD

Southwestern Medical Clinic, PC
Donna J. Harrison, MD

Women's Legal Defense Fund
Joanne L. Hustead

After completion of the Open Public Hearing, the Chair directed the attention of the Committee to the questions.

ANSWERS TO THE QUESTIONS

AGENCY STATEMENT INTRODUCING THE QUESTIONS
"The regimen proposed for the use of mifepristone for the termination of early pregnancy consists of the oral administration of 600 milligrams of mifepristone within 49 days after the beginning of the last menstrual period, followed by oral administration of 400 micrograms of misoprostol 48 hours later."
CHANGE IN STATEMENT
The Committee began its deliberations on the questions by changing the phrase "48 hours" to "2 days" in this statement.

QUESTION 1.

a. Do the results of the open-label, historically controlled studies conducted in France establish the efficacy of this regimen for use in the United States?
ANSWER
The Committee voted 6 in favor and 2 opposed in response to this question.

b. If not, what additional efficacy information should the applicant provide?
ANSWER
In response to this question, the Committee voted unanimously (8 to 0) in favor of the following motion:
"The Committee has some reservations about finally determining efficacy without access to the US data and recommends to the Agency that the Committee would like the opportunity to review the data when they are available."

QUESTION 2.
The safety database for this regimen consists of trials conducted in France, preliminary data from U.S. trials, and foreign post-marketing experience.

a. Do these data adequately demonstrate that the regimen is safe for use in the United States when used for the proposed indication?
In your discussion, please include comments on the following issues:
- o Whether the adverse events associated with the regimen can be adequately managed when the regimen is administered as labeled.
- o The acceptability of the frequency of adverse events.

ANSWER
The Committee voted 7 in favor and 1 in abstention in response to this question. (The Committee provided no specific responses to the two issues on this questions presented by the Agency.)

b. If not, what additional safety information should the applicant provide?
ANSWER
The Committee discussed the issue of safety at length and stated that it would like be to be informed of the final analysis of the safety data from the US studies.

QUESTION 3.
Taking into consideration the overall evidence for safety and effectiveness of the regimen, do you believe the benefits outweigh the risks for use of the regimen for the proposed indication in the United States?
ANSWER
The Committee voted 6 in favor and 2 in abstention in response to this question.

QUESTIONS 4 and 5.

4. If the regimen were to be approved, do you consider the labeling proposed by the applicant on how to administer the regimen and how to monitor patients who receive it to be appropriate?
5. If the regimen were to be approved, what further information, if any, do you recommend be included in the written information to be provided to the patient?

ANSWER
In response to Questions 4 and 5, the Committee made the following statement:
"With regards to labeling for both physicians and the patients, the Committee is concerned that the precautions and conditions employed in the clinical trials - such as under age 18, over age 35, smoking, and certain chronic medical conditions - be described in the labeling and noting that there are as yet no data concerning the safety of the use of the regimen by women with such conditions. The Committee also recommended that patient labeling include what is known about possible teratogenicity in humans, that the risk to fetuses of pregnancies that are not terminated by the regimen is not certain, but women should be offered surgical terminations when failures occur."

QUESTION 6.
If the regimen were to be approved, do you have recommendations concerning the drug distribution system proposed by the applicant?
ANSWER
The Committee voted unanimously (8 to 0) in favor of the following statement:
"We agree in concept with the proposal but have serious reservations on how it is currently described in terms of assuring safe and adequate credentialing of providers."

QUESTION 7.
If the regimen were to be approved, what recommendations, if any, do you have for post-marketing studies?
ANSWER
The Committee recommended that several issues be studied after the regimen is marketed including the following:

- *monitor the adequacy of the distribution and credentialing system by determining, among other end points, the frequency of post-surgical complications;*
- *follow-up on the outcome of all women who have surgical abortion because of method failure;*
- *studies of the long-term effects of multiple use of the regimen;*
- *ascertainment of the number of women who follow the complete regimen of treatment, and follow-up of women who do not;*
- *studies of the efficacy and safety of the regimen in women under age 18, over age 35, and in smokers; and*
- *ascertainment of the effect of the regimen on children born after treatment failure.*

The Committee having completed the agenda, the Chair closed the meeting.

NDA 20-687

SEP 18 1996

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

Dear Dr. Robbins:

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

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

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

Clinical

Please submit a comprehensive description of the proposed distribution system.

Chemistry, Manufacturing, and Controls

Drug Substance:

1.

Drug Product:

Biopharmaceutics

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

1. pH solubility data for mifepristone;

2. condition information at for various media;

3. Tablet dissolution profiles (including raw data and mean data) in various media (i.e., simulated gastric fluid and simulated intestinal fluid, at a range of pH's representative of physiological conditions) that provide adequate conditions with appropriate sampling times to characterize the profile; and

4. Raw data and profiles at different in the dissolution media cited above.

Physician Labeling

General Comments

1. Please excerpt and incorporate sections from the approved labeling for misoprostol that are relevant for single-dose use of misoprostol as provided for in this labeling.

2. Since mifepristone is not an established name as described under section 502(e)(3) of the Federal Food, Drug, and Cosmetic Act, you should apply to the USAN Council for adoption of a name that will comply with that section of the act. They can be reached at the following address:

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

CLINICAL PHARMACOLOGY Section

1. Include a concise description of studies 14 and 24, including:

   a. The number of patients treated and the success rate for the subset of patients with a gestational age $\leq$ 49 days who took $\leq$ 1 dose of misoprostol,

   b. The timing of complete expulsion, and

   c. The success rate after administration of mifepristone only.

2. The "Pharmacokinetics/Metabolism" subsection should be reformatted to include subsections titled "Absorption," "Distribution," "Metabolism," "Excretion," and "Special Populations" with "*Hepatically Impaired Patients*" and "*Renally Impaired Patients*" as subheadings.

3. You state in your proposed package insert that "drugs known to cause enzyme induction may reduce the efficacy of (mifepristone) due to increased metabolism." However, a full investigation of the enzymes involved in the metabolism of mifepristone was not submitted and an extensive search of the biomedical literature did not yield this information. Please submit information to support your statement.

INDICATIONS AND USAGE Section

1. The third paragraph should be revised to read as follows:

   "Two days after receiving mifepristone, patients must return for a second visit. If pregnancy has not been terminated before this second visit as a result of the action of mifepristone alone, 400 μg of misoprostol must be administered (see DOSAGE AND ADMINISTRATION).

2. The first sentence of paragraph four should be deleted.

3. In the second sentence of the fourth paragraph:

   a. Modify the end of the sentence to read ". . . the embryo is exposed to a risk of malformation, and pregnancy termination by surgery should be offered."

b. After this sentence, add "See PRECAUTIONS."

CONTRAINDICATIONS Section

The first sentence of paragraph two should be revised to read:

". . . the treatment procedure is contraindicated where a patient will not be within one hour . . . ."

WARNINGS Section

1. Number each of the three paragraphs and precede each paragraph with the following subheadings:

   "1. Bleeding"

   "2. Confirmation of pregnancy termination"

   "3. Cardiovascular events"

2. Revise the first paragraph (on bleeding) to read as follows:

   a. "Vaginal bleeding occurs in almost all patients during the treatment procedure. In clinical trials, bleeding lasted a mean of nine days, but occasionally lasted for 45 days or longer. Bleeding was reported to last for 69 days in one patient."

   b. Incorporate quantitative information on the frequency of heavy bleeding and the need for treatment of anemia (such as, frequencies of transfusion, and medical and surgical interventions). These frequencies should be based on studies 14 and 24 for women with a gestational age $\leq$ 49 days.

   c. The final sentence should be revised to "The likelihood of a decrease in blood count or hemoglobin concentration increases as the duration of the pregnancy increases . . . ."

PRECAUTIONS Section

General Subsection

1. Revise the first sentence to state that "Administration must be under the supervision of a physician trained in providing abortions."

2. Revise paragraph three to read as follows:

> "There are no data on the safety and efficacy of [product name] in women with chronic medical conditions such as cardiovascular, hypertensive, hepatic, respiratory or renal disease; insulin-dependent diabetes mellitus; severe anemia; or heavy smoking history. Women who are more than 35 years of age and who smoke 10 or more cigarettes per day should be treated with caution because such patients were generally excluded from clinical trials with this product. The use of appropriate prophylactic antibiotics should be considered for patients with underlying cardiac conditions who may require antimicrobial prophylaxis for the prevention of bacterial endocarditis."

3. The last paragraph of this section should be deleted and replaced with the following statement:

> "The effectiveness of [product name] may be lower if misoprostol is administered more than two days after mifepristone administration."

Drug Interactions Subsection

In the last sentence, please provide examples of commonly used drugs known to cause enzyme induction ("...such as ...").

Pregnancy - Teratogenic effects Subsection

Include a concise discussion of the available information from rabbit studies and from human experience.

Nursing mothers Subsection

Revise this section as follows:

> "It is not known whether mifepristone is excreted in human milk. However, many hormones with a similar chemical structure are excreted

Phase 4 Commitments

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

1. To monitor the adequacy of the distribution and credentialing system.

2. To follow-up on the outcome of a representative sample of mifepristone-treated women who have surgical abortion because of method failure.

3. To assess the long-term effects of multiple use of the regimen.

4. To ascertain the frequency with which women follow the complete treatment regimen and the outcome of those who do not.

5. To study the safety and efficacy of the regimen in women (1) under 18 years of age, (2) over age 35, and (3) who smoke.

6. To ascertain the effect of the regimen on children born after treatment failure.

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

1. Retabulate all safety data including results of trials that were still ongoing at the time of NDA submission. The tabulation can take the same form as in your initial submission. Tables comparing adverse reactions at the time the NDA was submitted versus now will facilitate review.

2. Retabulate drop-outs with new drop-outs identified. Discuss, if appropriate.

3. Provide details of any significant changes or findings, if any.

4. Summarize worldwide experience on the safety of this drug product.

5. Submit case report forms for each patient who died during a clinical study or who did not complete a study because of an adverse event.

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

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

Clinical:

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

Drug Substance:

Drug Product:

[redacted]

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

Food and Drug Administration
Division of Drug Marketing, Advertising, and Communications, HFD-40
5600 Fishers Lane
Rockville, Maryland 20857

Within 10 days after the date of this letter, you are required to amend the application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. In the absence of such action FDA may take action to withdraw the application.

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

Should you have any questions, please contact:

[redacted]

Sincerely yours,

[redacted]

1/18/96

cc: Original NDA
HFD-2
HFD-102 (with draft labeling)
HFD-80
HFD-85/
HFD-580
HFD-580/
HFD-40 (with draft labeling)
DISTRICT OFFICE
HFD-580/
Revised HFD-102/

APPROVABLE (AE)

NDA 20-687

Name	Title	Si	Date
			9/16/96
			9/16/96
			9/16/96
			9/16/96
			9/16/96
			9/16/96
			9/16/96

SEP 17 1996

MEMO TO FILE

Date: September 17, 1996

NDA: 20-687

Product: Mifepristone

Sponsor: Population Council

Submission date: March 16, 1996, Received: March 18, 1996

****

The review team has worked hard on this priority application and I agree with the recommendation that the application is approvable.

Chemistry and biopharmaceutics deficiencies, discipline-specific labeling modifications and Phase 4 agreements have been conveyed to the sponsor and are reiterated in the letter being forwarded to ——— for consideration.

——— Group Leader memorandum reviews several outstanding clinical issues which have been discussed with and will continue to be addressed by the sponsor.

Along with the specific items enumerated in the action letter, the sponsor is aware that further items/modifications will require consideration before an approval action would be recommended. These include:

1. Continued update of data from the US clinical trial of this regimen.

2. Appropriate labeling

Along with the modifications suggested in the action letter, we must also consider appropriate changes to the patient labeling once the prescribing information is adequately revised. We also have asked the Division of Drug Marketing, Advertising and Communications to comment on the acceptability of the patient information and will incorporate their comments as labeling discussions continue.

3. Drug Distribution System

I agree with [redacted] conclusion that, if the applicant's proposal for a voluntarily system of limited distribution appears adequate, the imposition of further restrictions would not be warranted. We look forward to receiving a more comprehensive description of the proposed distribution system prior to a final determination on this issue.

4. Phase 4 agreements

As in our letter of August 22nd, with several modifications after discussion with the sponsor on September 12th, the six areas of post-approval monitoring as described in the forwarded action letter have been considered and will be pursued by the applicant after an approval action (as confirmed by a September 16th telefacsimile from the Population Council).

5. Advisory Committee input

Finally, the Reproductive Health Drugs Advisory Committee, which considered this application at a July 19, 1996 meeting, hopes to have the opportunity to comment on modified proposed labeling before approval as well as have the ability to review the final US study results when submitted and we anticipate providing this information as available.

In conclusion, I concur with the review team that an "approvable" letter be communicated to the sponsor at this time for mifepristone 600 mg, followed by 400ug of misoprostol two days later (unless termination has occurred) for pregnancy termination in women whose duration of amenorrhea is no more than 49 days. As agreed by the sponsor, the Center for Drug Evaluation and Research and the Reproductive Health Drugs Advisory Committee, the safe and effective use of this regimen requires certain conditions of use as described in the labeling.

[redacted] 9-17-96

Division of Reproductive and Urologic Drug Products
HFD-580

cc:
NDA 20-687
HFD-580

[redacted]

DF

Memorandum

SEP 16 1996

NDA: 20-687

Drug and indication: Mifepristone for pregnancy termination

Applicant: The Population Council

Submission date: March 14, 1996

Date of MO reviews: June 27, 1996 [NDA review (draft)]
August 28, 1996 and August 29, 1996 (safety update reviews)

Date of Memorandum: September 16, 1996

In this application, the Population Council requests approval for a medical regimen for pregnancy termination in women whose duration of amenorrhea is no more than 49 days. The regimen consists of mifepristone 600 mg, followed by 400 μg of misoprostol two days later unless termination has occurred. The safety and efficacy of this regimen are supported by the results of two historically controlled clinical trials conducted in 2480 French women and sponsored by Roussel Laboratories, and by extensive foreign marketing experience. The results and implications of data in the original NDA submission and in subsequent safety updates have been adequately discussed in [redacted] excellent clinical reviews. I concur with the recommendation that this application is approvable.

Although the data support the safety and efficacy of this regimen, several outstanding clinical issues need to be addressed prior to approval or during phase IV (see below). Additionally, deficiencies in chemistry, manufacturing and controls (CMC), which are discussed in the CMC review (and will not be reiterated in this memorandum), require resolution prior to approval. Despite these deficiencies, an approvable action is recommended at this time because access to this regimen has important public health implications for women; extensive experience with this regimen in European markets suggests that tolerability is acceptable; and the applicant has demonstrated their commitment to address these deficiencies in a responsible and timely manner. Outstanding issues were discussed with the applicant in a meeting on September 12, 1996 and agreement was reached on how to approach their resolution.

Outstanding clinical issues may be summarized as follows:

1. Limited data on use of this regimen in the United States

The reviewed data represent foreign experience in controlled settings (clinical trials and restricted marketing). Safety and efficacy in the U.S. health care setting have not been established at this time, although analysis of U.S. Population Council-sponsored studies is nearing completion. Reassuringly, preliminary analyses of the rate of serious adverse events in

these studies, presented at the July 19, 1996 meeting of the Reproductive Health Drugs Advisory Committee, were similar to experience in French trials and suggest that foreign safety data are generalizable to U.S. women treated in controlled settings. The sponsor has committed to submitting full study reports of the U.S. trials promptly after their completion. An executive summary of these results will be forwarded to Advisory Committee members and we anticipate that the label will be revised to incorporate U.S. data at that time.

2. Professional and patient labeling

The clinical sections of the product labeling require extensive revision, as noted in the appended labeling review (Attachment 1). Of particular note, the label should provide practitioners with: a) information relevant to single dose use of misoprostol; b) quantitative information from clinical trials on the success rate and the risk of serious adverse experience with this regimen; and c) any available information on the teratogenic risk of this regimen in animals and humans. Revisions have also been requested that reflect labeling comments from members of the Reproductive Health Drugs Advisory Committee regarding lack of data in women excluded from clinical trials (such as those with chronic medical conditions, at extremes of age, or with a heavy smoking history).

Comments from the Division of Drug Advertising, Marketing and Communications on the Patient Package Insert are pending and will be forwarded to the applicant upon completion.

3. Drug distribution

The applicant has appropriately proposed that drug distribution be limited to licensed physicians (with prior training in assessing the length of pregnancy, in diagnosing ectopic pregnancy, and [redacted] who will attend educational seminars on the safe use of this regimen. Based on concerns raised at the July 19, 1996 Advisory Committee meeting, the applicant has revised the initial distribution proposal to eliminate plans for training physicians in surgical abortion.

However, while we concur with the concept of limiting drug distribution to credentialed providers, the adequacy of the proposed plan can not be fully evaluated at this time because sufficient information on its implementation has not been submitted. The applicant has acknowledged this deficiency and has agreed to submit a comprehensive description of the distribution system for review, when available. Further, because the applicant has voluntarily proposed a system of limited distribution, imposition of further distribution restrictions under the Agency's Subpart H regulations does not appear warranted.

4. Phase IV commitments

Members of the Reproductive Health Drugs Advisory Committee recommended that several issues be addressed during Phase IV. These issues were reiterated in a letter to the applicant on August 22, 1996, and discussed during the September 12, 1996 meeting. During this meeting, the applicant committed to pursue Phase 4 studies with the following objectives:

a. To monitor the adequacy of the distribution and credentialing system;
b. To follow-up on the outcome of a representative sample of women who have surgical abortion because of method failure;
c. To assess the long-term effects of multiple use of the regimen;
d. To ascertain the frequency with which women follow the complete treatment regimen and the outcome of those who do not;
e. To study the safety and efficacy of the regimen in women under 18 years of age, over age 35, and in smokers; and
f. To ascertain the effect of the regimen on children born after treatment failure.

The review team members, including [redacted] should be congratulated for their excellent work on this priority application.

[redacted]

HFD-580

cc:
NDA20-687
HFD-580/[redacted]

D.F

NDA 20-687
Mifepristone

The Population Council
August 29,1996

Review of United States Safety Data Dated July 14, 1996

Submission dated July 14, 1996 is a summary report of the serious adverse events from Protocols 166 A and B during the United States clinical trials. All of these reports have been submitted previously in

A total of fifty-two subjects had at least one SAE. There was more than one adverse event reported for most subjects. The most frequently reported SAE was hemorrhage (41 reports). This was followed by fainting/dizziness (20 reports) which includes all of the following events: fainting, feeling faint or lightheaded, dizziness, syncope, vasovagal reaction and passing out. Other serious adverse events that were reported by at least four subjects are listed in the summary below.

Total No. of Patients	Total No. of Clinics	Total No. of Adverse Events	Total Number of Treatments				Total No. Hospitalized
			D&C/ Asp.	Meth./ oxy.	IV Fluids	Transfusion	
52	13	Hemorrhage 41 Faint/Dizziness 20 Cramping 14 Vomiting 06 Hypotension 05 Tachycardia 04	34	15	28	04	26

These serious adverse events resulted in the hospitalization of twenty-six subjects. Four subjects received transfusions. A total of twenty-eight subjects received IV fluids (including 3 of the subjects that also had transfusions). A total of thirty-four subjects received a D&C or aspiration. All but two of the subjects who had a D&C or aspiration reported hemorrhage. Fifteen subjects recieved methergine or oxytocin for treatment of bleeding, although eleven of these subjects eventually had a surgical procedure.

It is not possible to make a complete comparison of the serious adverse events reported in the United States trial and the pivotal French studies in the NDA, due to different definitions of SAEs and different adverse event reporting requirements in the two countries. Also, the safety analysis of the United States trials has not been conducted, since the good clinical practice audit of the clinics is currently being completed. Therefore, at this time comparisons between the United States and NDA pivotal studies can only be made with the serious adverse events

reported from these fifty-two United States subjects, rather than other less serious adverse events that will be uncovered during the safety analysis of the entire United States database. However, some general comparisons can be made. The total number of subjects enrolled in United States Protocol 166A/B was 2,121. This is slightly less than the number of subjects (2480) enrolled in the pivotal French trials in the NDA. The number of transfusions is identical (4) in both studies and the number of hospitalizations is similar (26 in the United States trials and 21 in the pivotal trials). The number of reported cases of hemorrhage, metrorrhagia or excessive bleeding was similar in the two studies. Hemorrhage was reported by forty-one subjects in the United States studies. In the NDA pivotal studies, fifty-two subjects reported metrorrhagia or excessive bleeding, which was categorized as severe in twenty-one subjects. However, the manner in which the bleeding was treated differed in the two studies. In the Unites States trials, thirty-two of the thirty-four surgical interventions (D&C or aspiration) were performed on subjects experiencing hemorrhage. In the NDA pivotal trials, a total of fifteen subjects received surgical interventions for bleeding. The greater number of surgical interventions by United States investigators is not unexpected, due to their initial lack of experience in the control of bleeding during medical abortion. This was the first clinical trial of medical abortion in the United States, but medical abortion had been available in France for several years prior to the conduct of the French studies of mifepristone and misoprostol. The United States investigators have noted that as they gained experience with the bleeding that occurs during medical abortion, they were less likely to surgically intervene.

There were five cases of hypotension, in the United States trials, although blood pressure readings were given for only two of these subjects. There were seven cases of clinically relevant hypotension, one rated as severe, in the NDA pivotal trials. There were also a similar number of reports of tachycardia for United States subjects and in the pivotal trials (4 and 5 reports, respectively).

The incidence of other adverse events reported in the United States subjects, such as cramping or vomiting, cannot at this time be fairly compared to the numbers of these adverse events reported from all subjects in the NDA pivotal studies. This comparison must await the safety analysis of the United states database.

Conclusion:

The SAEs reported during the United States trial do not appear to differ significantly from those reported in the pivotal NDA trails, although a full comparison is not possible at this time. The higher incidence of surgical intervention in the United States trials may be explained by the initial inexperience of United States clinicians in providing medical abortion. Investigators in the United States trials have indicated that there was a learning curve associated with the treatment of bleeding during the trial. The incidence of other events such as hemorrhage, transfusions, and hospitalizations were similar in the two studies.

In summary, the current comparison of SAEs between the United States trial and the NDA pivotal trials indicated that medical abortion can be safely delivered in a wide variety of United States settings.

7/9/96

Population Council
Center for Biomedical Research
1230 York Avenue
New York, NY 10021

FAXED 14 July '96

Fed Ex 15 July 96

Fax from Ann Robbins, Ph.D
Phone: 212-327-8748
Fax: 212-327-7678

Number of Pages (including this sheet): 12

Send to Facsimile Number: [redacted]

Date: 14 July 1996

Send to Company: FDA,
Division of Reproductive
and Urologic Drug Products

Send to Person: [redacted]

Subject: U.S. Safety Data

[redacted]

As requested during our teleconference call of 10 July 1996, attached please find a summary report of the serious adverse events (SAE) from Population Council Protocol 166A/B that have been reported to the FDA. The tables provide a listing of all subjects who experienced a serious adverse event during the U.S. trial, as well as the location of each reported SAE in the Population Council's [redacted] and NDA 20-687. This summary was generated solely for Council use in preparation for the upcoming July 19 advisory committee meeting. There is no new information in this summary that the agency has not received from us previously in the IND, NDA or NDA safety update--it is just presented in a different format and organization here. However, if you would like me to officially amend our IND and/or NDA with this summary, please inform me of this and I will do so.

I hope this information is helpful for you and other members of your division. Please contact me if you have further questions.

Best regards,

Ann Robbins, Ph.D.
Scientist

cc:S. Arnold

SUMMARY OF SERIOUS ADVERSE EVENTS REPORTED IN PROTOCOL 166A/B

Introduction

This internal Population Council report was generated in preparation for the upcoming Mifepristone NDA 20-687 advisory committee meeting on July 19, 1996. The goal was to summarize all serious adverse events (SAEs) that occurred during the conduct of Protocol 166A/B. SAEs are defined as those events reported to the Council from the clinics which the Council then reported to the FDA on Medwatch forms. All of these SAEs reports have been previously submitted to the FDA in [redacted] as well as documented in NDA 20-687.

Results

The data relevant to SAEs have been summarized in the following three tables. Table 1 lists each participating clinic by clinic number, principal investigator name, location and type of clinic. Table 2 identifies, in chronological order of occurrence, each subject for whom a SAE was reported to the FDA on a Medwatch form. The nature of the adverse event(s) is recorded as well as the need for a dilatation and curettage (D&C) or aspiration, intravenous fluids, transfusion or hospitalization. When available, the subject's duration of amenorrhea and ethnicity is provided. Finally, the IND submission number and date the Medwatch form was submitted to the IND are listed.

The summary of Table 2 indicates that a total of 52 subjects had at least one SAE. There was more than one adverse event reported for most subjects on the Medwatch forms. The most frequently reported SAE was hemorrhage (41 reports). This was followed by fainting/dizziness (20 reports) which includes all of the following events: fainting, feeling faint or lightheaded, dizziness, syncope, vasovagal reaction and passing out. Other serious adverse events that were reported by at least 4 subjects are listed in the Summary of Table 2.

These serious adverse events resulted in the hospitalization of 26 subjects. Four subjects received transfusions. A total of 28 subjects received IV fluids (including 3 of the subjects that also had transfusions). A total of 34 subjects received a D&C or aspiration. All but two of the subjects who had a D&C or aspiration reported hemorrhage. Fifteen (15) subjects received methergine or oxytocin for treatment of bleeding, although 11 of these subjects eventually had a surgical procedure.

The Drug Surveillance Department of Roussel Uclaf maintains a database of all serious adverse events associated with mifepristone for any medical use. At the request of Roussel, the Council sends to them information on all SAEs from the U.S. clinical trials that were reported to the FDA. Roussel assigns an "International Drug Surveillance Number" (IDSN) to each SAE and then provides a medical code for the reported SAE. These SAEs from the U.S. trial are thus captured in Roussel's database and are included in their quarterly reports of international SAEsa associated with mifepristone use. The SAEs from the Council's U.S. study have been reported in the NDA by this IDSN, in order to correspond to the report numbering system of other SAEs included in our NDA from international use of mifepristone in clinical trials and during post-marketing surveillance. However, this has caused some confusion in identification of subjects in the U.S. clinical trial for three reasons: 1) one subject may be assigned more than one IDSN by Roussel, depending upon how many adverse events occurred, since the IDSN is associated with an adverse event, not a subject; and 2) the medical code for the SAE assigned by Roussel may not precisely correspond to the description of the SAE as reported on the Medwatch form submitted to the FDA by the Council and 3) Roussel has made some mistakes in their coding of subject's identification. The purpose of Table 3 is to clarify the relationship between a subject in the U.S. trial and the IDSN(s) assigned to that subject by Roussel. In Table 3, each subject with an SAE in the Council's trial is identified and the IDSN(s), as assigned by Roussel, that are associated with that subject are listed. The medical code assigned by Roussel for the SAE(s) of each subject is also included.

For four subjects in the U.S. trial, Roussel has not yet assigned an IDSN or medical code (subject 123, clinic 01; subject 076, clinic 03; subject 070, clinic 02; and subject 159, clinic 01). The location in the NDA of the line listing of the SAE, as identified by the IDSN, is also indicated on Table 3. Line listings of all of the SAEs in the U.S. clinical trial were included in either the original NDA submission of March 14, 1996 (Volume 1.66, p. 32) or the NDA Safety Update Report of June 20, 1996 (Volume 3.2, p. 10).

Comparison of U.S. trials and pivotal NDA trials

It is not possible to make a complete comparison of the serious adverse events reported in the U.S. trial and the pivotal French studies in the NDA, due to different definitions of SAEs and different adverse event reporting requirements in the two countries. Also, the safety analysis of the U.S. trials has not been conducted, since the good clinical practice audit of the clinics is currently being completed. Therefore, at this time comparisons between the U.S. and NDA pivotal studies can only be made with the serious adverse events reported from these 52 U.S. subjects who had a Medwatch report, rather than other less serious adverse events that will be uncovered during the safety analysis of the entire U.S. database. However, some general comparisons can be made. The total number of subjects enrolled in U.S. Protocol 166A/B was 2,121. This is slightly less than the number of subjects (2480) enrolled in the pivotal French trials in the NDA. The number of transfusions is identical (4) in both studies and the number of hospitalizations is similar (26 in the U.S. trials and 21 in the pivotal trials). The number of reported cases of hemorrhage, metorrhagia or excessive bleeding was similar in the two studies. Hemorrhage was reported by 41 subjects in the U.S. studies who required a Medwatch report. In the NDA pivotal studies, 52 subjects reported metorrhagia or excessive bleeding, which was categorized as severe in 21 subjects. However, the manner in which the bleeding was treated differed in the two studies. In the U.S. trials, 32 of the 34 surgical interventions (D&C or aspiration) reported on the Medwatch forms were performed on subjects experiencing hemorrhage. In the NDA pivotal trials, a total of 15 subjects

received surgical interventions for bleeding. The greater number of surgical interventions by U.S. investigators is not unexpected, due to their initial lack of experience in the control of bleeding during medical abortion. This was the first clinical trial of medical abortion in the U.S., but medical abortion had been available in France for several years prior to the conduct of the French studies of mifepristone and misoprostol. The U.S. investigators have noted that as they gained experience with the bleeding that occurs during medical abortion, they were less likely to surgically intervene.

There were 5 cases of hypotension reported on Medwatch forms, although blood pressure readings were given for only 2 of these subjects. There were 7 cases of clinically relevant hypotension, one rated as severe, in the NDA pivotal trials. There were also a similar number of reports of tachycardia on the Medwatch forms for U.S. subjects and in the pivotal trials (4 and 5 reports, respectively).

The incidence of other adverse events reported on Medwatch forms of the U.S. subjects, such as cramping or vomiting, cannot at this time be fairly compared to the numbers of these adverse events reported from all subjects in the NDA pivotal studies. This comparison must await the safety analysis of the U.S. database.

Conclusions

The SAEs reported during the U.S. trial do not appear to differ significantly from those reported in the pivotal NDA trials, although a full comparison is not possible at this time. The higher incidence of surgical intervention in the U.S. trials may be explained by the initial inexperience of U.S. clinicians in providing medical abortion. Investigators in the U.S. trial have indicated that there was a learning curve associated with the treatment of bleeding during the trial. The incidence of other events such as hemorrhage, transfusions, and hospitalizations were similar in the two studies. In summary, the current comparison of SAEs between our U.S. trial and the NDA pivotal trials indicated that medical abortion can be safely delivered in a wide variety of U.S. settings.

Table 1

Clinics in Population Council US Studies Protocol 166A/B

Clinic Number	Investigator Name	Location	Type of Clinic*	Protocol A or B
01	Mishell	Los Angeles, CA	University Hospital	A
02	Haskell	Des Moines, IA	Planned Parenthood	A
03	Poppema	Seattle, WA	Other	A
04	Tyson	Burlington, VT	Planned Parenthood	A
05	Blumenthal	Baltimore, MD	University Hospital	A
06	Borgotta	White Plains, NY	Planned Parenthood	A
07	Malloy	Atlanta, GA	Other	A
08	Rothenberg	Shrewsburg, NJ	Planned Parenthood	A
21	Poindexter	Houston, TX	Planned Parenthood	B
22	Vargas	Denver, CO	Planned Parenthood	B
23	[redacted]		Planned Parenthood	B
24	Westhoff	New York, NY	University Hospital	B
25	Nichols	Portland, OR	Other	B
26	Sheehan	San Diego, CA	Planned Parenthood	B
27	Dean	St. Louis, MO	Other	B
28	Creinin	Pittsburgh, PA	University Hospital	B
29	Sogor	Cleveland, OH	Other	B

* Other = Clinic or Private Office.

Table 2

IND Safety Reports (Med Watch) Submitted t[illegible]

Patient No.	Clinic No.	Adverse Event	D&C/ Asp.	Meth./ oxy.	IV Fluids	Trans-fusion	Hosp.	DA	Race	IND No. and Date
C01 (005)	22	Hemorrhage	X		X	X	X	63		107 11/21/94
036	02	Hemorrhage Vomiting Fainting	X		X			44		108 12/01/94
033	02	Vomiting Diarrhea Dehydration			X			49		108 12/01/94
027	02	Hemorrhage Cramping	X			X	X	53	East Asian	109 12/07/94
042	02	Hemorrhage Cramping Dizziness	X		X		X	51	Cau-casian	109 12/07/94
(057)	01	Hemorrhage Dizziness Headache Hypotension (BP 88/55, pulse 101) Tachycardia	X		X	X		44		110 12/20/94
015	25	Hemorrhage Cramping	X+					46		113 01/18/95
012	25	Hemorrhage Cramping	X					49		113 01/18/95
061	01	Hemorrhage Weak Nausea Pale & Cold			X			57		113 01/18/95
076	02	Hemorrhage Vomiting Cramping Chlamydial infection								113 01/18/95
033	03	Hemorrhage Syncope Pallor	X	X				52		113 01/18/95
022	25	Hemorrhage Cramping Feeling Faint	X		X		X	56		114 01/23/95
050	03	Hemorrhage Dizziness Postural Hypotension (BP 60/ palpable)	X				X	30		114 01/23/95

Table 2 (Cont'd)

Patient No.	Clinic No.	Adverse Event	D&C/ Asp.	Meth./ oxy.	IV Fluids	Trans-fusion	Hosp.	DA	Race	IND No. and Date
009	26	Hemorrhage Cramping Syncope	X		X		X	57		115 02/07/95
062	01	Hemorrhage Cramping	X				X	57	His-panic	118 02/15/95
107	01	Vomiting Dizziness			X					118 02/15/95
114	01	Hemorrhage	X	X			X	62	His-panic	118 02/15/95
123	01	Hemorrhage Dizziness Headache		X	X			53		118 02/15/95
037	04	Hemorrhage	X		X			65		118 02/15/95
109	01	Hemorrhage Fever	X		X		X	45		119 02/17/95
116	01	Chest Pain					X			119 02/17/95
048	03	Hemorrhage Tachycardia	X				X	51		120 03/03/95
076	03	Hemorrhage Cramping		X						121 03/06/95
060	24	Hemorrhage Hypotension Tachycardia			X	X		54		122 03/10/95
017	23	Hemorrhage Orthostatic Hypotension	X	X	X			57		123 03/13/95
070	02	Gunshot					X			123 03/13/95
030	23	Hemorrhage Syncope Tachycardia Hypotension	X		X			52		124 04/11/95
032	23	Vasovagal reaction			X					124 04/11/95
035	23	Hemorrhage		X	X					124 04/11/95
037	23	Hemorrhage Dizziness Shortness of Breath	X	X	X			51		124 04/11/95
081	26	Hemorrhage Syncope/neck injury	X+				X	51		124 04/11/95
158	02	Hemorrhage Weakness	X	X	X			54		125 04/19/95

Table 2 (Cont'd)

Patient No.	Clinic No.	Adverse Event	D&C/ Asp.	Meth./ oxy.	IV Fluids	Trans-fusion	Hosp.	DA	Race	IND No. and Date
159	01	Hemorrhage	X+	X	X			50		125 04/19/95
036	27	Pneumonia					X			132 06/07/95
012	29	Hemorrhage Cramping Faintness	X				X	53		132 06/07/95
028	04	Hemorrhage Dizziness		X						132 06/07/95
075	04	Nausea Dizziness			X					132 06/07/95
004	28	Hemorrhage	X	X			X	55		132 06/07/95
027	28	Hemorrhage Vomiting Lightheaded	X		X		X	50		133 06/13/95
071	23	Hemorrhage Vomiting Dizziness	X		X		X	55	Afro-Amer-ican	136 07/18/95
030	28	Hemorrhage								136 07/18/95
033	28	Hemorrhage	X				X	46		138 07/25/95
063	28	Anxiety attack Depression Threatened suicide					X	50		139 07/28/95
147	27	Viral meningitis					X			141 08/04/95
074	28	Hemorrhage Passed out	X	X	X		X	60		143 08/09/95
088	28	Hemorrhage (2 Med Watch reports)	X	X	X		X	62		143 08/09/95 144 08/10/95
018	07	Abdominal pain	X					42		145 08/15/95
019	07	Hemorrhage								145 08/15/95
104	28	Hemorrhage Cramping	X	X	X		X	62		146 08/25/95
108	28	Cramping Fever, tender uterus	X	X			X	63		147 09/01/95

Table 2 (Cont'd)

Patient No.	Clinic No.	Adverse Event	D&C/ Asp.	Meth./ oxy.	IV Fluids	Trans-fusion	Hosp.	DA	Race	IND No. and Date
116	24	Hemorrhagia Cramping Fever Endometritis	X		X			61		149 09/21/95
165	25	Hemorrhage Dizziness	X		X		X	60		154 11/02/95

Summary of Table 2

Total No. of Patients	Total No. of Clinics	Total No. of Adverse Events	Total Number of Treatments				Total No. Hospitalized
			D&C/ Asp.	Meth./ oxy.	IV Fluids	Transfusion	
52	13	**Hemorrhage 41** **Faint/Dizziness** 20** **Cramping 14** **Vomiting 06** **Hypotension 05** **Tachycardia 04**	34	15	28	04	26

* Listed in chronological order as reported to the FDA.
+ Surgical procedure not reported on Med Watch form.
D&C/Asp = Dilatation and Curettage/Aspiration.
Meth/oxy = Methergine/Oxytocin.
Hosp. = Hospitalizations.
DA = Number of days of amenorrhea.
** includes fainting, feeling faint or lightheaded, dizziness, vasovagal reaction, syncope and passing out.

Table 3

Correlation between Population Council Subject and Serious Adverse Event Coded by Roussel

Patient No.	Clinic No.	IDSN*	SAE** Coded by Roussel	Location in NDA Volume Page
C01 (005)	22	199500076RU	Metrorrhagia Anemia	Vol. 1.66 p.32
		199500439RU	Metrorrhagia Abdominal pain	Vol. 3.2 p.10
036	02	199500072RU	Metrohagia Vomiting Malaise	Vol. 1.66 p.32
033	02	199500442RU	Dehydration Nausea Vomiting Diarrhea	Vol. 3.2 p.10
027	02	199500074RU	Abdominal pain Anemia Metrorrhagia	Vol. 1.66 p.32
042	02	199500075RU	Abdominal pain Metrorrhagia Anemia	Vol. 1.66 p.32
—057)	01	199500071RU	Metrorrhagia Hypotension Anemia	Vol. 1.66 p.32
		199500440RU	Metrorrhagia Hypotension Headache	Vol. 3.2 p.10
015	25	199500066RU	Metrorrhagia	Vol. 1.66 p.32
012	25	199500067RU	Metrorrhagia	Vol. 1.66 p.32
061	01	199500068RU	Hypotension	Vol. 1.66 p.32
076	02	199500069RU	Urogenital Disorder	Vol. 1.66 p.32
033	03	199500070RU	Metrorrhagia Syncope	Vol. 1.66 p.32
		199500444RU	Metrorrhagia Dizziness Headache	Vol. 3.2 p.10
022	25	199500441RU	Abdominal Pain Hypotension	Vol. 3.2 p.10
		199500064RU	Metrorrhagia	Vol. 1.66 p.32

Table 3 (Cont'd)

Patient No.	Clinic No.	IDSN*	SA** Coded by Roussel	Location in NDA Volume Page
050	03	199500065RU	Metrorrhagia Postural hypotension	Vol. 1.66 p.32
009	26	199500077RU	Metrorrhagia	Vol. 1.66 p32
062	01	199500102RU	Metrorrhagia	Vol. 1.66 p.32
107	01	199500443RU	Vomiting Nausea Dizziness	Vol. 3.2 p.10
114	01	199500104RU	Metrorrhagia	Vol. 1.66 p.32
123	01	NA***	NA	Vol. 1.66 p.32
037	04	199500106RU	Metrorrhagia	Vol. 1.66 p.32
109	01	199500100RU	Metrorrhagia Fever	Vol. 1.66 p32
116	01	199500101RU	Chest pain	Vol. 1.66 p.32
048	03	199500140RU	Metrorrhagia	Vol. 1.66 p.32
076	03	NA	NA	Vol. 1.66 p.32
060	24	199500139RU	Metrorrhagia Hypotension	Vol. 1.66 p.32
017	23	199500135RU	Metrorrhagia Postural Hypotension	Vol. 1.66 p.32
070	02	NA	NA	Vol. 1.66 p.32
030	23	199500175RU	Metrorrhagia Syncope	Vol. 1.66 p.32
032	23	199500446RU	Syncope	Vol. 3.2 p.10
035	23	199500447RU	Metrorrhagia	Vol. 3.2 p.10
037	23	199500176RU	Metrorrhagia	Vol. 1.66 p.32
081	26	199500172RU	Metrorrhagia Syncope	Vol. 1.66 p.32
158	02	199500179RU	Metrorrhagia	Vol. 1.66 p.32
159	01	NA	NA	Vol. 1.66 p.32
036	27	199500247RU	Pneumonia	Vol. 1.66 p.32

Table 3 (Cont'd)

Patient No.	Clinic No.	IDSN*	SAE** Coded by Roussel	Location in NDA Volume Page
012	29	199500248RU	Metrorrhagia	Vol. 1.66 p.32
028	04	199500249RU	Metrorrhagia	Vol. 1.66 p.32
075	04	199500448RU	Dehydration	Vol. 3.2 p.10
004	28	199500251RU	Metrorrhagia	Vol. 1.66 p.32
027	28	199500455RU	Metrorrhagia	Vol. 3.2 p.10
071	23	199500329RU 199500449	Vomiting Metrorrhagia Dizziness	Vol. 1.66 p.32 Vol. 1.66 p.32
030	28	199500330RU	Metrorrhagia	Vol. 1.66 p.32
033	28	199500454RU	Metrorrhagia	Vol. 1.66 p.32
063	28	199500340RU	Depression	Vol. 1.66 p.32
147	27	199500342RU	Meningitis	Vol. 3.2 p.10
074	28	199500450RU 199500355RU	Metrorrhagia Hypotension Metrorrhagia Hypotension Anemia	Vol. 3.2 p10 Vol. 3.2 p.10
088	28	199500356RU 199500451RU	Metrorrhagia Metrorrhagia	Vol. 3.2 p.10 Vol. 3.2 p.10
018	07	199500365RU	Abdominal pain	Vol. 3.2 p.10
019	07	199500366RU	Metrorrhagia	Vol. 3.2 p.10
104	28	199500452RU	Metrorrhagia Uterine spasm	Vol. 3.2 p.10
108	28	199500375RU	Abdominal pain Fever	Vol. 3.2 p.10
116	24	199500453RU	Metrorrhagia Endometrial disorder	Vol. 3.2 p.10
165	25	199500427RU	Metrorrhagia Malaise	Vol. 3.2 p.10

*IDSN= International Drug Surveillance Number.
**SAE = Serious Adverse Event.
***NA = Not available, not yet assigned by Roussel.

D.F

SEP 11 1996

NDA 20-687
Mifepristone

The Population Council
August 28, 1996

Medical Officer's Summary of Safety Update Dated
June 20, 1996

Included in the Safety Update Report received June 27, 1996 are two new clinical study reports as well as new information regarding study reports previously submitted.

The first new clinical study report is entitled, "The Efficacy and Safety of Mifepristone 600 mg in a Single Dose in Combination with Intravenously Administered Sulprostone (Nalador) in Therapeutic Termination of Second Trimester Pregnancy". The second new clinical report is entitled "Role of Cortisol in the Thermal Response to Alimentation: Effect of Mifepristone" and consisted of twelve healthy, male volunteers, six of whom received a single 600 mg tablet and six of whom received a placebo.

Neither of the two new clinical study reports reveal any additional safety concerns not identified in the two pivotal clinical studies.

Newly completed clinical trials include three studies of labor induction, two studies of breast cancer, and the United States clinical trials of early pregnancy termination. Laboratory data from these completed studies have not yet been analyzed and, therefore, no information on laboratory data are reported in this safety update. Final data analysis and study reports for these six studies have not been completed. The results for termination of pregnancy studies conducted in the United States are expected to be in full agreement with the two pivotal clinical studies. No unanticipated safety issues were raised in these studies. Preliminary examination of information from the United States studies as it was forwarded weekly from the clinics directly to the sponsor during the course of the trials indicates that the final, analyzed results will be similar to those obtained in similar clinical trials of the same medical regimen.

The literature update includes eleven articles published in 1995 and one article published in 1996. Three articles are of particular interest. One is the publication of one of the pivotal clinical studies (FF/92/486/24) by Aubeny et.al. The second is entitled "A Comparative Analysis of Fall in Hemoglobin Following Abortions Conducted By Mifepristone (600 mg) and Vacuum Aspiration" by Thonneau et. Al. The investigators found significant blood loss in the two weeks following abortions by the mifepristone/sulprostone protocol while hemoglobin concentrations remained stable in women who had vacuum aspiration. Women who took mifepristone experienced a mean fall of 0.7 g/dl in hemoglobin two weeks after the abortion. The third article entitled "Clinical, Hormonal, and Sonographic Predictors of Successful RU-486-Induced Abortions" was by Menashe et.al. A small hematoma, seen as a localized detachment of the gestational sac, was observed in the decidua capsularis in women who aborted successfully. A significant decrease in plasma levels of estradiol and progesterone and significantly increased cortisol levels in the plasma of the patients who aborted were observed by the seventh day following treatment.

Table four of the Safety Update Report contains adverse reactions from all sources reported to Roussel Uclaf which were summarized in the quarterly line listings covering July 1, 1995 to September 30, 1995; October 1, 1995 to December 31, 1995; January 1, 1996 to March 31, 1996 and reported in the Periodic Safety Update No. 3 dated January 1996 for the period June 1, 1995 to November 30, 1995.

Of a total of forty eight patient reports of adverse experiences listed in Table 4, twenty-eight were reported from patients enrolled in the United States studies (protocols 166A and B). Of these twenty-eight reports, nineteen were metrorrhagia, three were abdominal pain, two were dehydration, and there were one each of depression, viral meningitis, vomiting, and syncope. Vacuum aspiration or D&C was performed in twelve cases of metrorrhagia and a blood transfusion was given in one case of metrorrhagia. Concomitant hypotension was also reported in four patients with severe metrorrhagia. The patient with syncope presented with a marked vasovagal reaction fifteen minutes after misoprostol administration.

In the section of the Safety Update Report entitled "Tolerance of RU 486 During United States Studies" there is Table 1 which was submitted to the sponsor by Russell Uclaf June 7,1995 which indicates that there were forty-seven serious adverse events plus 8 non serious adverse events in the United States studies (protocols 166 A and B). Table 2 indicates that of the forty-seven serious adverse events forty-one were related to bleeding, two to hypotension, and one each to vomiting, chest pain, infection, and accidental injury.

Two deaths have occurred in clinical trials conducted by Roussel Uclaf. One was a male in a study evaluating mifepristone in the treatment of Cushing syndromes by ectopic ACTH secretion or adrenal tumor. The other was an eighty-three year old female with an unresectable meningioma who suffered a stoke like event leading to death. Seven other deaths were reported in patients enrolled in compassionate use protocols. One of these deaths was a seventy-one year old woman with an acute myocardial infarction.

Also included is a half page document entitled "Notifications Report to Roussel Uclaf from Study English PMS" which lists seven reactions occurring in five patients. There were three reports of uterine hemorrhage, one incomplete abortion with bleeding, one convulsion, one congenital nail disorder, and one report of lack of efficacy.

Also included is a section entitled "New Foreign Marketing Information" which consists only of a core product information document from the product manufacturer revised in March 1995.

Since the start of the use of mifepristone until November 30, 1995, Roussel Uclaf has recorded fifty-three cases of continued pregnancy after the intake of mifepristone for early pregnancy termination (alone or associated with a postaglandin analog).

Among these fifty-three cases:

Nineteen pregnancies were delivered at term (or close to it):

Fifteen were uneventful pregnancies with children normal at birth.
One was normal but born prematurely (33-34 weeks) from caesarean section
One was normal except for common slight bilateral talipes.
One case involves unilateral fingernail defects.
One child was reported as strictly normal at birth but it was known that when she was three months old, the infant was diagnosed as having an autoimmune disorder with chronic giant cell hepatitis and immunohemolytic anemia and later died of severe infectious pneumonia likely exacerbated by immuno-suppressive drugs. The reporting physician's opinion (an expert in teratogenicity) was that the onset of the autoimmune disorder was coincidental and that the role of mifepristone could be reasonably excluded.

In fifteen cases information on further condition of the fetus was made available, mainly in the cases where pregnancy is known to have been terminated later:

In nine cases, termination was performed voluntarily and information either from histologic examination or from ultrasound was that the fetus was normal.

In one case, at therapeutic termination the fetus was noted to have sirenomelia associated with other fetal malformations. The opinion of the consulting embryologists to whom the case was submitted by Roussel Uclaf was that the role of mifepristone was very unlikely. This case has been published (Pons J.C. and all : Lancet, 1991, 328: 763).

In five cases of ongoing pregnancy, the latest available information during second trimester examination indicated normal pregnancy and fetus development.

In six cases, no information on the fetus could be obtained but pregnancy was known to have been ~~terminated~~ later.

In thirteen cases, no further information was made available; in most cases patients were lost to follow-up, and in some cases pregnancy is still ongoing.

Comment: This Safety Update does not reveal any unexpected, unanticipated safety issues that were not made known in the original submission of the NDA.

[redacted]

Concur: [redacted]

DIF

FEB 17 2000

Memo
New Drug Application

NDA: 20-687

Sponsor: **Population Council, Inc.**

Drug: **[Tradename] (mifepristone) 200mg tablet for oral administration**

Indication: **Termination of intrauterine pregnancy up to 49 days since Last Menstrual Period (LMP)**

Date received: **Original NDA: March 18, 1996**
Approvable letter issued: September 18, 1996
Complete Response received: August 18, 1999

Date of Memo: February 17, 2000

In this complete response to the approvable letter issued in September 1996, the applicant has presented further information in support of the use of mifepristone for the termination of pregnancy from diagnosis and up to seven weeks (49 days) of amenorrhea. In this setting mifepristone is ingested orally as three 200mg tablets followed 48 hours later by two 200ug tablets of misoprostol.

Clinical/Statistical

Results from several studies to establish the safety and efficacy of mifepristone plus misoprostol were reviewed as a result of the application submitted March 18, 1996. The two "pivotal" trials, both conducted in France, included in this original application revealed a complete abortion rate of 95% (for intrauterine pregnancies ≤ 49 days since last menstrual period—LMP). Although preliminary results from a large US trial were submitted for review with the original 1996 application, the current resubmission contains the final study report for this US trial.

The trial results are extensively described and analyzed in the Medical Officer review. Of the 2,121 women enrolled in the US, 859 were in the ≤ 49 days amenorrhea group. Efficacy was 92% in this group. Effectiveness was less beyond 49 days of amenorrhea. The original French studies reported an average duration of bleeding of 9 days. For the US studies this average was 14 days. Adverse event reporting was higher in the US population as compared to the French results but remained acceptable. The most common adverse event reported was abdominal cramping—an expected outcome. In the ≤ 49 days amenorrhea group, excessive bleeding led to transfusion in one US patient and an additional 2 women were treated in the emergency setting for excessive bleeding. The MO review describes data in comparison to surgical abortion. In the end, I agree with the MO conclusion that mifepristone plus misoprostol as described in the clinical studies is effective for termination of pregnancies up to 49 days since LMP and has an acceptable safety profile.

Clinical Audits

In 1996, two French sites were audited and found acceptable. For this review cycle, three US sites were selected by the review team and were audited by the Division of Scientific Investigations. All three (sites in California, Washington and Iowa) were found acceptable.

Clinical Pharmacology and Biopharmaceutics

The outstanding question of appropriate dissolution specifications has been considered. The chemists and the Office of Clinical Pharmacology and Biopharmaceutics have described revised specifications. These specifications will be conveyed in the action letter.

Pharmacology/Toxicology

Adequate non-human studies have been performed and found acceptable. Labeling comments will be included in the action letter.

Chemistry

Our September 18, 1996 requests that the sponsor apply to USAN for an established name. The March 1997 correspondence from the sponsor indicates that they did not understand this request as they refer to determining a "tradename" rather than applying for an established name. In a further correspondence dated June 25, 1999 the applicant has indicated that they have obtained approval of the USAN council for adoption of the name, mifepristone.

The proposed tradename "Mifeprex" was found to not be acceptable by the Office of Post-marketing Drug Risk Assessment. The alternative name proposed——— was found to be acceptable at this time.

As the chemistry reviews describe, several outstanding questions remain regarding both drug substance and drug product. Also, the drug substance manufacturing site has failed GMP inspection. Resolution of the chemistry and inspection issues will be required prior to an approval action.

Advisory Committee Activities

The Reproductive Health Drugs Advisory Committee met in July 1996 to consider this application and recommended approval. The committee expressed interest in seeing the final US study report as well as final labeling. The US study results, as published in an April 30, 1998 issue of the New England Journal of Medicine, were sent to the members of the Advisory Committee on November 1, 1999. No specific comments were received from this mailing.

Final labeling will be sent to the Advisory Committe members on approval of this application.

Labeling—prescription and patient

Our September 18, 1996 approvable letter requires submission of revised labeling. The sponsor has responded to these labeling requests in correspondence dated March 28, 1998 and again on June 25, 1999. The review team, along with the Division of Drug Marketing, Advertising and Communication have addressed the proposed labeling during this review cycle. All team comments have been collated and discussed. Our recommendations for labeling changes are provided in a "strike-out/underline" version and will be conveyed with the action letter. Major areas for consideration include:

1. We recommend that the labeling include a black boxed warning describing the major requirements and conditions for use.
2. The sponsor has proposed that the medication given on day 2 of the regimen (misoprostol) could be given either in the office/clinic (as per the clinical trials) or at home. The Division and Office have

discussed this proposal and find it acceptable. No changes in safety or efficacy are expected based on the location of ingestion of the misoprostol.

3. DDMAC has provided extensive comments regarding the patient labeling including the proposed "acknowledgement" section.

Distribution System and Subpart H recommendations

Under 21CFR 314 Subpart H, the agency can determine that a drug can be approved with restrictions to assure safe use. We have concluded that mifepristone is a candidate for Subpart H 314.520 when and if the product is approved. 314.520 states:

a If FDA concludes that a drug product shown to be effective can be safely used only if distribution or use is restricted, FDA will require such postmarketing restrictions as are needed to assure safe use of the drug product, such as:
   1 Distribution restricted to certain facilities or physicians with special training or experience; or
   2 Distribution conditioned on the performance of specified medical procedures.

b The limitations imposed will be commensurate with the specific safety concerns presented by the drug product.

The sponsor submitted a distribution plan proposal in January 2000. After consideration of their proposal, we have concluded that the Subpart H provisions are appropriate for approval of this product. The distribution plan will need to be revised to include adequate training and certification of providers. The labeling and training materials will need to include information on reporting of events to both the sponsor and to the FDA. The distribution system will need to include a quality assurance/quality control component. As the system is developed, we can work with the applicant in order to incorporate a data collection component for the various Phase 4 commitments listed below.

Subpart H approval will also allow the FDA to impose similar distribution restrictions and system on any future generic mifepristone approved for this indication.

Phase 4 Commitments

The approvable letter of September 1996 describes six areas of commitment made by the applicant for Phase 4 study. In this complete response of August 1999, the applicant addresses each commitment and proposes approaches to each of the commitments made. These commitments will again need to be included in the current action letter. The commitments include:

1. To monitor the adequacy of the distribution and credentialing system.
2. To follow-up on the outcome of a representative sample of mifepristone-treated women who have surgical abortion because of method failure.
3. To assess the long-term effects of multiple use of the regimen.
4. To ascertain the frequency with which women follow the complete treatment regimen and the outcome of those who do not.
5. To study the safety and efficacy of the regimen in women (a) less than 18 years of age, (b) over age 35 and (c) who smoke.
6. To ascertain the effect of the regimen on children born after treatment failure.

Other Petitions/Correspondence

A letter dated June 21, 1999 was sent to [redacted] Center for Drug Evaluation and Research (CDER), requesting a discussion of confidentiality issues for the drug substance

JAN 27 2000

D/F

MEDICAL OFFICER'S REVIEW OF AMENDMENTS 024 AND 033
FINAL REPORTS FOR THE U.S. CLINICAL TRIALS INDUCING ABORTION UP TO 63 DAYS GESTATIONAL AGE AND COMPLETE RESPONSES REGARDING DISTRIBUTION SYSTEM AND PHASE 4 COMMITMENTS

NDA Number: 20-687

Applicant: Population Council
One Dag Hammarskjold Plaza
New York, New York 10017

Dates of Submission: June 3, 1999 and August 18, 1999

Dates Submissions Received: June 4, 1999 and August 19,1999

Date Review Completed: October 28, 1999

Date Review Revised: November 19, 1999

Date Review Finalized: November 22,1999

I. General Information:

A. Name of Drug:
1. Established Name: Mifepristone
2. Trade Name: None designated as yet.

3. Laboratory Code Name: RU 38486 (RU-486).

B. Pharmacologic Category: Antiprogestational and antiglucocorticoid agent.

C. Proposed Indication: Medical termination of intrauterine pregnancy through 49 days' pregnancy.

D. Dosage Form and Route of Administration: Tablet for oral administration.

E. Strength: Each tablet contains 200 mg of mifepristone.

F. Dosage: Three 200 mg tablets (600 mg) of mifepristone are taken as a single oral dose. Unless abortion has occurred, the patient takes two 200 μg tablets (400 μg) of misoprostol orally two days after ingesting mifepristone.

G. Related Drugs: None marketed.

H. Table of Contents:

1. General Information 1
2. Manufacturing Controls Reference 2
3. Pharmacology and Pharmacodynamics Reference 2
4. Clinical Background 2
5. Regulatory Background 3
6. Statistical Consultation Reference 6
7. Clinical Studies 6
8. Reviewer's Comments, Evaluation, and Conclusions 15
9. Labeling Evaluation Reference 20
10. Conclusion 20
11. Recommended Phase 4 Studies 20
12. Consideration of Advisory Committee Member's Comments .. 21
13. Recommendation 29

II. Manufacturing Controls: Please refer to chemist's review for details.

III. Pharmacology and Pharmacodynamics: Please refer to pharmacologist's review for details.

IV. Clinical Background:

Mifepristone is a synthetic steroid that was approved for the termination of pregnancy in France in December 1988 (launched September 1989), in Sweden in 1992, in the United Kingdom in 1991, and in China in 1988. (It should be noted that mifepristone used in China is not manufactured by Roussel Uclaf but by domestic companies). When administered alone in total doses of 1400-1600 mg over 1-10 days, the success rate was 64-85%. Subsequent studies demonstrated that the administration of mifepristone followed by a synthetic prostaglandin analog increases the success rate to over 95%. In a preliminary study of 100 women, the success rate of 600 mg mifepristone and 0.2 mg misoprostol was 95% for pregnancies of no more than 49 days of amenorrhea. Misoprostol is a synthetic prostaglandin E_1 analog that is approved in the United States and Europe for the prevention of nonsteroidal anti-inflammatory drug-induced gastric ulcers in an oral dose of 0.2 mg. q.i.d. In the United States misoprostol is available as Cytotec® (G.D. Searle and Co.).

Nine phase 2 clinical studies to determine the most effective dose and dosage regimen for mifepristone used alone for the interruption of pregnancy were conducted in France between 1983 and 1986. Patients in these studies were entered with a target gestational age of less than or equal to 41 days of amenorrhea. One thousand patients were exposed to doses ranging from 100 mg for one to four days to 800 mg for one day.

Following completion of the phase 2 studies, nine phase 3 clinical trials employing a single 600 mg dose of mifepristone were conducted to evaluate the efficacy and the

safety of this dose. The target population was patients with pregnancies having a gestational age ≤42 days of amenorrhea. A total of 2,459 patients were studied.

The advantage of combining mifepristone 600 mg with a prostaglandin (sulprostone 250μg I.M. 36-48 hours later) for pregnancy interruption was demonstrated in 1985. A series of ten clinical trials were conducted between 1987 and 1991 to confirm and extend these initial observations. In addition to sulprostone, other prostaglandins including gemeprost, [redacted] were evaluated. During the ten studies, a total of 19,947 patients were exposed to mifepristone administered as a single 600 mg dose. One of these studies enrolled over 16,000 patients. Very rare cases of hypotension and one myocardial infarction were reported. Successful termination of early pregnancy was achieved in 82.6 to 100% of the patients enrolled in these studies and the safety of mifepristone was confirmed.

The efficacy and safety of mifepristone given as a single 600 mg oral dose in combination with misoprostol 0.4 mg orally administered approximately 36 to 48 hours after mifepristone for termination of pregnancy was evaluated in two historically controlled, pivotal clinical trials conducted in France. The first study included women with intrauterine pregnancies of ≤ 49 days and the second study included women with intrauterine pregnancies of ≤63 days. In the second study, a second dose of 200 μg of misoprostal was given 3 hours after the first dose if complete abortion had not occurred. In the first study of 1205 evaluable patients, the complete abortion rate was 95.4% and in the second study of 1104 evaluable patients, the complete abortion rate was 92.8%. These two studies were evaluated in the review of a new drug application that was submitted March 16, 1996.

V. Regulatory Background:

A. Contract between Roussel and Population Council signed in 1982 allowing study of mifepristone in the U.S.

B. The first protocol submitted to study mifepristone as an abortifacient was included in an amendment dated December 2, 1983 to [redacted]. Subsequent protocols were submitted to study various dosage regimens for abortion.

C. A letter from Dr. David Kessler, Commissioner of Food and Drugs dated December 14, 1992 to Dr. Edourard Sakiz, President of Roussel-Uclaf began FDA's contact with Roussel-Uclaf.

D. Dr Sakiz replied to Dr. Kessler in a letter dated December 17, 1992 that Roussel-Uclaf was reviewing its strategy to start clinical trials in the United States and should be able to come up with some proposals by the end of January, 1993.

E. President Clinton sent a memorandum to the Secretary of Health and Human Services January 22, 1993 directing her to promptly assess initiatives by which

the Department could promote the testing, licensing, and manufacturing in the United States of RU-486 or other antiprogestins.

F. Dr. Kessler wrote Dr. Sakiz January 22, 1993 requesting a meeting in early February to discuss possible therapeutic uses of anti-progestational drugs and, in particular, FDA's interest in receiving a new drug application for approval of mifepristone for interruption of early pregnancy.

G. Dr. Kessler wrote Professor Wolfgang Hilger, President of the Board of Hoechst AG February 3, 1993 informing him directly of FDA's interest in discussing the availability of mifepristone in the United States for research and marketing and the opportunity to review a new drug application for RU-486 for termination of early pregnancy.

H. Dr. Kessler met with Dr. Sakiz February 24, 1993 to discuss mifepristone along with senior FDA and Roussel-Uclaf representatives.

I. A letter from Roussel-Uclaf dated February 26, 1993 to [redacted] Deputy Commissioner of Food and Drugs enclosed a copy of an agreement dated July 17, 1984 between Population Council and Roussel-Uclaf.

J. Secretary Shalala wrote a letter to Professor Hilger March 12, 1993 urging him to eliminate Hoechst corporate barriers to the introduction of RU-486 into the United States.

K. Dr. Sakiz wrote Secretary Shalala March 18, 1993 informing her that her letter to Professor Hilger would greatly contribute to further progress in any decision to make RU-486 available in the United States.

L. Professor Hilger wrote Secretary Shalala March 23, 1993 stating that at a later stage a common decision would be made on how to proceed in the USA.

M. Professor Hilger wrote Dr. Kessler April 15, 1993 indicating that Dr. Sakiz would be representing Hoechst at a meeting April 20, 1993 with Dr. Kessler.

N. FDA met with Roussel-Uclaf and Population Council April 20, 1993, at which meeting Roussel-Uclaf agreed to transfer the technology necessary to produce mifepristone to Population Council and Population Council agreed to move as soon as possible to submit an NDA to the FDA.

O. [redacted] (HHS) wrote a note to [redacted] Assistant Secretary for Health September 14, 1993 informing him of discussions he had that day with FDA and Population Council in which he was informed that Roussel had now retained a law firm (Swindler and Berlin) to try to work out a tripartite agreement with the U.S. government regarding RU-486 which would provide four

guarantees to Roussel regarding legislation and indemnification.

P. On September 23, 1993, approved talking points released by Population Council indicated that negotiations with Roussel-Uclaf were ongoing, but that Roussel-Uclaf had recently re-raised issues that were beyond the capacity of the Council to resolve.

Q. A briefing memorandum from FDA to the Chief of Staff, HHS was transmitted September 30, 1993 in preparation for a meeting that took place October 4, 1993 with senior Department officials and legal representatives of Roussel-Uclaf in which current marketing of RU-486 (outside of the U.S.), discussions with Roussel-Uclaf regarding testing of RU-486, and FDA's analysis regarding legislation and indemnification were discussed.

R. A revised draft of the proposed distribution requirements for mifepristone as discussed by the legal representatives of Roussel-Uclaf and Population Council was provided to ———— April 11, 1994 and a rerevised draft was provided April 14, 1994.

S. A briefing memorandum from FDA to the Secretary, HHS was transmitted April 12, 1994 in preparation for a meeting April 14, 1994 with senior HHS officials, Roussel-Uclaf, and Population Council on the status of their negotiations regarding mifepristone.

T. An agenda for a meeting May 6, 1994 between Dr. Kessler and Roussel-Uclaf was submitted April 25, 1994 by Roussel-Uclaf to ———— in which measures to protect and inform patients and the labeling were to be discussed.

U. Population Council submitted the protocols to ———— August 3, 1994 to evaluate the efficacy, safety, and acceptability of mifepristone to induce abortion in women with amenorrhea of up to 63 days in U.S. medical facilities.

V. A new drug application was submitted March 16, 1996 (received March 18 1996). The medical officer, in his review signed June 27, 1996 recommended approval of the NDA provided that the data from the U.S. studies currently being analyzed by the applicant did not differ adversely significantly from the two pivotal French clinical studies contained in the NDA.

W. The NDA for mifepristone for interruption of early pregnancy was presented and discussed at a meeting of the FDA Reproductive Health Drugs Advisory Committee July 19, 1996. The committee concluded in a 6 to 0 vote (with 2 abstentions) that the benefits of a mifepristone and misoprostol regimen for terminating early pregnancies outweighed its risks. The advisory committee also agreed in concept with, but expressed reservations about, the applicant's proposal

for a restricted distribution system under controlled conditions, with mifepristone available to patients only in registered or approved facilities. The committee also recommended post-marketing studies to gather further information about the actual application of this regimen in the United States.

X. An approvable letter was sent to the sponsor September 18, 1996 with a request for submission of the proposed distribution system and a reminder of their commitments to perform phase 4 studies.

Y. The final reports of the clinical trials conducted in the United States were submitted in amendment 024 June 3, 1999 and complete responses regarding the distribution system and phase 4 commitments were submitted in amendment 033 August 18, 1999.

VI. Statistical Consultation: None required

VII. Clinical Studies:

The efficacy and safety of mifepristone was evaluated in two prospective, open-label, multicenter clinical trials in the United States according to two identical protocols (166A and 166B) at 17 centers (University hospitals, Planned Parenthood clinics, and free-standing clinics). The studies were conducted at centers that could perform abortions by either vacuum aspiration or dilatation and curettage and had access to facilities that provided blood transfusions and performed routine emergency resuscitation procedures. The studies included patients in three gestational age groups:

Group 1: amenorrhea of ≤49 days
Group 2: amenorrhea of 50-56 days
Group 3: amenorrhea of 57-63 days

Data from the two studies were combined in the following evaluation.

A. Investigators:

Dr. Paul Blumenthal	Baltimore, Maryland
Dr. Lynn Borgatta	White Plains, New York
Dr. Mitchell Crenin	Pittsburgh, Pennsylvania
Dr. Catherine Dean	St. Louis, Missouri
Dr. Susan Haskell	Des Moines, Iowa
Dr. Tyrone Mallory	Atlanta, Georgia
Dr. Daniel Mishell, Jr.	Los Angeles, California
Dr. Mark Nichols	Portland, Oregon
Dr. Alfred Poindexter	Houston, Texas
Dr. Suzanne Poppema	Seattle, Washington

Dr. Eugene Rothenberg	Shrewsbury, New Jersey
Dr. Katherine Sheehan	San Diego, California
Dr. Laszlo Sogor	Cleveland, Ohio
Dr. Judith Tyson	Burlington, Vermont
Dr. Peter Vargas	Aurora, Colorado
Dr. Carolyn Westhoff	New York, New York

B. Objectives of the Study:

The study was conducted to evaluate the effectiveness, safety, acceptability, and feasibility of using mifepristone and misoprotol in a variety of clinical settings within the United States health care system for the induction of abortion in women whose duration of amenorrhea was no more than 63 days.

C. Rationale for the Study:

Extensive experience has been gained outside the United States with the use of mifepristone and various prostaglandin analogs, including misoprostol, for the termination of pregnancies up to 63 days, with complete abortion rates ranging from 92.7% to 99%. The applicant wished to confirm the efficacy and safety of the regimen in the United States.

D. Method of Assignment to Treatment:

Eligible patients fulfilling all of the inclusion criteria and none of the exclusion criteria were assigned to one of the three treatment groups, based on gestational age.

E. Number of Subjects:

A total of 2,121 patients were enrolled including 859 patients in groups 1,722 patients in group 2, and 540 patients in group 3.

F. Duration of Clinical Trial:

Patients were to receive mifepristone on day 1 and misoprostol on day 3 and were to be observed in the clinical setting for at least 4 hours after misoprostol administration. Patients were to return for evaluation on day 15.

G. Inclusion Criteria:

1. Was at least 18 years of age and in good general health.

2. Requested a voluntary termination of pregnancy.

3. Had a positive urine pregnancy test.

4. Had an intrauterine pregnancy with a duration of amenorrhea of ≤63 days (from the first day of her last menstrual period) that was confirmed by uterine size on pelvic examination and by vaginal ultrasound evaluation.

5. Agreed to have a surgical termination of pregnancy if the study procedures failed to terminate her pregnancy.

6. Was a resident of the United States.

7. Gave written informed consent to participate in the study and was willing and able to participate.

H. Exclusion Criteria:

1. Had evidence of any disorder which represented a contraindication to the use of mifepristone (such as adrenal disease or a condition requiring chronic corticosteroid administration) or misoprostol (such as asthma, glaucoma, mitral stenosis, arterial hypotension, sickle cell anemia, or a known allergy to prostaglandins).

2. Had a history of severe liver, respiratory, or renal disease or thromboembolism.

3. Had a cardiovascular disease, e.g. angina, valve disease, arrhythmia, cardiac failure, or insulin dependent diabetes.

4. Had hypertension that was being treated on a chronic basis or had blood pressure of greater than 140/90mmHg.

5. Was anemic (hemoglobin < 10 g/dL or hematocrit < 30%).

6. Had a known clotting defect or was receiving anticoagulants.

7. Had an IUD *in situ*.

8. Was breastfeeding.

9. Had adnexal masses or tenderness on pelvic examination that suggested pelvic inflammatory disease.

10. Had an ectopic pregnancy or threatened abortion.

11. Was over 35 years of age and smoked more than 10 cigarettes per day, and

had another risk factor for cardiovascular disease such as diabetes mellitus, hyperlipidemia, hypertension, or a family history of ischemic heart disease.

12. Was unlikely to understand and comply with the requirements of the study.

13. Lived or worked more than one hour from the emergency care facility that served the abortion center.

I. Trial Period:

September 13, 1994 to September 12, 1995

J. Dosage and Mode of Administration:

Patients were not to eat during the one hour before and after the administration of mifepristone. In the presence of the investigator, each patient was administered three 200 mg mifepristone tablets by mouth with no more than 240 mL of water. Patients were informed that they should not smoke during the 48 hours following mifepristone administration and on the day misoprostol was to be administered. Unless the investigator could verify unequivocally that complete abortion had occurred, patients were administered two 200 μg misoprostol tablets by mouth with no more than 240 mL of water in the presence of the investigator 36 to 60 hours after the administration of mifepristone.

K. Efficacy Assessments:

Pelvic examinations were performed before mifepristone administration at visit 1, before misoprostol administration at visit 2, during the 4 hour observation period after misoprostol administration, and at the visit 3 evaluation. At visit 1, patients also had transvaginal ultrasound examinations and quantitative hCG β subunit pregnancy tests performed. At visits 2 and 3, ultrasound examinations were performed at the discretion of the investigator.

The outcome of treatment was classified as follows:

1. Complete abortion: pregnancy termination and complete expulsion of the products of conception without the need of surgical intervention.

2. Incomplete abortion: pregnancy termination with either partial expulsion or nonexpulsion of the products of conception diagnosed at visit 3 or at study end if later than visit 3 with surgery required.

3. Ongoing pregnancy: a viable pregnancy diagnosed at visit 3 based on fetal heartbeat and/or fetal growth indicating gestations that are

two weeks older than at visit 1; surgery required.

4. Medical intervention: before visit 3, the investigator judged that a surgical intervention was medically indicated.

5. Patient request: before visit 3, the patient chose not to proceed with the medical method of abortion and requested surgical intervention.

In the analyses of treatment outcome, complete abortion only was classified as a treatment success. All other categories resulted in a surgical procedure and , therefore, were classified as treatment failures.

L. Safety Assessments:

Adverse events were summarized and evaluated.

M. Disposition of Patients:

A total of 2121 patients were enrolled. Of these, 2015 (95.0%) were included in the efficacy analyses. There were 106 patients excluded from the efficacy analyses because of failure to show up for visit 3, thus preventing confirmation of a final outcome. For 92 of these patients, there was some information suggesting a successful outcome. For one excluded patient, there was evidence that suggested failure. The remaining 13 women were lost to followup; 5 had continuing pregnancies when last seen at visit 2. All 2121 patients were evaluable for safety. A total of 827 patients in Group 1, 678 patients in Group 2, and 510 patients in Group 3 were included in the efficacy evaluation.

N. Demographic Characteristics:

Most patients were Caucasian (71%), 20-29 years of age (61%; mean age of 26.9 years), of normal body mass index (71%), nulliparous (55%) and had a previous elective abortion (51%). The differences among the three gestational age groups in race distribution and mean age, weight, and body mass index were small and not of clinical significance.

O. Results:

1. Efficacy:

Success and failure rates are summarized in Table 1.

Table 1
(Sponsor's Table 4.1)
Treatment Outcomes by Gestational Age (Evaluable Patients)

Treatment Outcomes	Group 1 ≤ 49 days N = 827	Group 2 50-56 days N = 678	Group 3 57-63 days N = 510
Total Successes	762 (92%)	563 (83%)	395 (77%)
RU-486 alone	40 (5%)	12 (2%)	4 (< 1%)
Plus misoprostol	722 (87%)	551 (81%)	391 (77%)
Total Failures	65 (8%)	115 (17%)	115 (23%)
Med intervention	13 (2%)	26 (4%)	21 (4%)
Patient request	5 (< 1%)	13 (2%)	12 (2%)
Incomplete ab	39 (5%)	51 (8%)	36 (7%)
Ongoing preg	8 (< 1%)	25 (4%)	46 (9%)

Failures are discussed in this review in the "Safety" section of "Results."

Complete abortion rates according to time of occurrence are displayed in Table 2 as confirmed by the investigators.

Table 2
(Sponsor's Table 5.1)
Time to Occurrence of Complete Abortion

Occurrence Time	Group 1 ≤ 49 days N =827	Group 2 50-56 days N=678	Group 3 57-63 days N=510
Mifepristone alone	40 (4.8%)	12 (1.8%)	4 (0.8%)
≤ 4h after misoprostol	376 (45.5%)	312 (46.0%)	178 (34.9%)
> 4h & < end of day 4	178 (21.5%)	118 (17.4%)	118 (23.1%)
After day 4	168 (20.3%)	121 (17.8%)	95 (18.6%)
Surgical intervention	65 (7.9%)	115 (17.0%)	115 (22.5%)

2. Safety:

Adverse events, regardless of causality, were reported for at least 99% of the patients in each gestational age group. More than one adverse event was reported for most patients. The majority of adverse events were of mild or moderate severity. Approximately 23% of the adverse events in each gestational age group were judged to be severe. The most common adverse event was abdominal pain, including uterine cramping. This was to be expected since the treatment procedure is designed to induce the uterine cramping (and bleeding) necessary to produce an abortion.

Other commonly reported adverse events were nausea, vomiting, headache, diarrhea, and dizziness. No serious adverse events were reported in tolerance studies in healthy non-pregnant female and healthy male subjects where mifepristone was administered in single doses greater than threefold that recommended for termination of pregnancy. Table 3 shows that the rates of most, but not all, adverse events that occurred in patients whose gestational age was ≤ 49 days were not significantly different from the rates across all gestational age groups.

Table 3

Most Commonly Reported Adverse Events

Adverse Event	Group 1 ≤ 49 days N=859 Percentage	Groups 1, 2, and 3 ≤ 63 days N=2121 Percentage
Abdominal pain (cramping)	96	97
Nausea	61	67
Headache	31	32
Vomiting	26	34
Diarrhea	20	23
Dizziness	12	12
Fatigue	10	9
Back pain	9	9
Uterine hemorrhage	5	7
Fever	4	4
Viral infections	4	4
Vaginitis	3	4
Rigors (chills/shaking)	3	3
Dyspepsia	3	3
Insomnia	3	2
Asthenia	2	2
Leg pain	2	2
Anxiety	2	2
Anemia	2	2
Leukorrhea	2	2
Sinusitis	2	2
Syncope	1	2

Table 4 shows the rates of adverse events in any gestational age group which were significantly different across gestational age groups.

Table 4
Adverse Events Significantly Different Across Gestational Age Groups

Adverse Event	Group 1 ≤ 49 days Percentage	Group 2 50-56 days Percentage	Group 3 57-63 days Percentage
Nausea	61	71	72
Vomiting	26	38	41
Diarrhea	20	23	26
Uterine hemorrhage	5	8	10

No patient was discontinued from the study because of an adverse event and there were no deaths.

The median bleeding duration for group 1 was 14 days and 15 days for groups 2 and 3.

The proportions of patients who received any medications for bleeding increased with increasing gestational age form 5.7% in group 1 to 10.7% in group 3. A total of 146 patients (6.9%) received uterotonics (ergot-type medications or oxytocin) for bleeding.

Fourteen patients (0.7%) were hospitalized for an adverse event. Of these patients, 2 of 4 in the ≤ 49 days group, 3 of 5 in the 50-56 days group, and 3 of 5 in the 56-63 days group had adverse events (severe excessive bleeding) which were considered to be study drug related. The other patients were hospitalized for reasons unrelated to study treatment (pneumonia, meningitis, automobile accident, depression, shooting injury, endometritis).

Nineteen patients (0.9%) had emergency room visits that did not result in hospitalization. Sixteen of these 19 patients had excessive bleeding (2, ≤ 49 days; 7, 50-56 days; 7, 57-63 days). The other three visits were for chest pain, nausea and vomiting, and cramping.

Four patients received blood transfusions (1, ≤ 49 days; 2, 50-56 days; 1, 57-63 days). Three of these patients were hospitalized.

IV fluids were administered for various reasons to 9 (1.0%) patients in the ≤ 49 days group, 19 (2.6%) in the 50-56 days group, and 18 (3.3%) in the 57-63 days group.

The following five potentially serious adverse events occurred:

A 34 year old patient with a 20 year history of seizures and a pregnancy of

46 days gestational age had a mild seizure (convulsion) on the day of mifepristone administration and received 250 mg of dilantin. In the opinion of the investigator, the patient's seizure was not related to treatment with mifepristone and she received misoprostol 47 hours after the mifepristone.

A 28 year old of 54 days gestational age with a negative gastrointestinal history reported possible blood in her stool a month after misoprostol administration. In the opinion of the investigator, the patient's melena was not related to study treatment.

A 23 year old of 57 days gestational age developed moderate purpura (body bruises) that lasted for one day without treatment ten days after receiving misoprostol. In the opinion of the investigator, the patient's purpura was not related to study treatment.

A 21 year old of 57 days gestational age developed severe viral meningitis 6 days after receiving misoprostol and was hospitalized. In the opinion of the investigator, the patient's meningitis was not related to study treatment.

A 27 year old of 60 days gestational age with a negative gastrointestinal history reported blood in her stool 3 days after receiving misoprostol. At the time of last contact with the patient three weeks later, no further incidents of melena had been reported. In the opinion of the investigator, the patient's melena was not related to study treatment.

The proportions of patients with a decrease in hemoglobin or hematocrit of more than 20% from their pre-mifepristone administration levels increased significantly with increasing gestational age, from 3.1% in the ≤ 49 days group to 8.0% in the 57-63 days group.

Of the 1028 patients with hemoglobin measurements before and after misoprostol administration, 131 had a decrease of at least 2mg/dL (7.8%, ≤49 days; 15.0%, 50-60 days; 17.4% 57-63 days).

Hypotension after administration of misoprostol occurred in 0.3% - 1.4% of all treated patients.

Hypertension after administration of misoprostol occurred in 1.5% - 1.7% of all treated patients.

Decrease in heart rate by > 20% after administration of misoprostol occurred in 18.2% - 21.3% of all patients.

Increase in heart rate by >20% after administration of misoprostol occurred in 11.8% - 14.1% of all patients.

For the subgroup of patients with a full panel of laboratory tests, the median changes were small and not of clinical significance.

Failure of the mifepristone - misoprostol procedure required surgical intervention which is an additional safety concern, albeit small. A total of 295 patients were classified as having failed medical abortion. Of these patients, 79 (27%) had ongoing pregnancies, 126 (43%) had incomplete abortions, 30 (10%) requested and had surgical terminations, and the remaining 60 (20%) patients had surgical terminations performed because of medical indications directly related to the medical procedure. In group 1 (≤ 49 days gestation), of the 65 failures, 8 (12%) patients had ongoing pregnancies, 39 (60%) patients had incomplete abortions, 5 (8%) requested and had surgical terminations performed, and the remaining 13 (20%) patients had surgical terminations directly related to the medical procedure. The failure rates for medical intervention, patient request, incomplete abortion, and ongoing pregnancy were significantly higher in groups 2 and 3 than in group 1.

For each gestational age group, the adverse event rates were highest at Planned Parenthood clinics and lowest at Free-Standing clinics, with university hospital clinics in the middle.

VIII. Reviewer's Comments, Evaluation, and Conclusions:

Two studies were conducted according to two identical protocols at 17 centers to evaluate a mifepristone - misoprostol regimen for the termination of pregnancies in the United States health care system. The studies included patients in three gestational age groups:

Group 1: amenorrhea of ≤ 49 days
Group 2: amenorrhea of 50-56 days
Group 3: amenorrhea of 57-63 days

The studies included women who requested a voluntary termination of pregnancy, had a positive pregnancy test, and a documented intrauterine pregnancy. Women with liver, respiratory, renal, adrenal, or cardiovascular disease, thromboembolism, hypertension, anemia, insulin-dependent diabetes mellitus, coagulopathy, or allergy to prostaglandins were excluded, as were women less than 18 years of age or those more than 35 years of age who smoked more than ten cigarettes per day and had another cardiovascular risk factor. Women were also excluded if they had intrauterine devices, were breast-feeding, were receiving anticoagulation or long-term glucocorticoid therapy, had adrenal masses, had