| TREATMENT | DOSAGE mg/kg | CHANGE IN THE ENDOMETRIUM IN McPHAIL UNITS |
|---|---|---|
| Progesterone (subcutaneously) | 0.2 | 3.2 |
| Product of Example 4 (by mouth) | 0.3 | 0 |
| | 1.0 | 0 |
| | 3.0 | 0 |
| | 10.0 | 0 |
| | 30 | 0 |
| Progesterone (subcutaneously) | 0.2 | 3.0 |
| Progesterone 0.2 mg (subcutaneously) + the compound of example 4 (by mouth) | 0.3 | 2.8 |
| | 1 | 2.1 |
| | 3 | 1.4 |
| | 10 | 0.6 |
| | 30 | 0 |

[A] Technique described by D. A. Morgenty, L. P. Anderson, and H. B. McCullough Endocrin. 1939, 24, 659.

Groups of three immature female rabbits weighing about 1 kg were topically treated on the dorsal skin with 25 μg of estradiol in 10 μl of ethanol on day 1. On day 4 the product to be tested dissolved in 0.1 ml of sesame oil containing 5% benzyl alcohol was introduced into a part of the uterus isolated between two ligatures. On the sixth day the animals were sacrificed, their uterines retained and fixed in Bouin's solution for histological examination. Changes in the uterine endometrium were noted after the method of McPhail.

The following results were obtained.

| TREATMENT | DOSE μg/RABIT | CHANGE IN THE ENDOMETRIUM |
|---|---|---|
| Product of Example 4 | 30 | 0 |
| | 300 | 0 |
| Progesterone | 10 | 2.7 |
| Progesterone 10 μg + Product of Example 4 | 1 | 1.6 |
| | 3 | 1.3 |
| | 10 | 1.0 |
| | 30 | 0.6 |
| | 90 | 0.6 |

Conclusion:

This product tested is devoid of progestomimetic activity while on the contrary it possesses a remarkable antiprogestomimetic activity.

## V. ANTI-IMPLANTATION AND ABORTIVE ACTIVITIES IN FEMALE RATS

The first day of gestation is determined by the presence of sperm in the vagina. The product of example 4 is administered by mouth 3 consecutive days at the rate of 5 ml per kilogram as a suspension of 0.5% of carboxymethyl cellulose in water containing 0.2% Tween.

The animals were sacrificed between the 5th and 8th day after the last treatment and the uterus was examined.

The following results were obtained:

| DAYS OF TREATMENT | DOSE mg/kg/day | RESULTS |
|---|---|---|
| 1,2,3 | 10 | Non-implantation |
| 1,2,3 | 2 | No action |
| 4,5,6 | 10 | Non-implantation |
| 4,5,6 | 2 | Non-implantation |
| 7,8,9 | 10 | Abortion |
| 7,8,9 | 2 | Abortion |
| 10,11,12 | 10 | Abortion |
| 10,11,12 | 2 | Abortion |
| 13,14,15 | 10 | Abortion |
| 13,14,15 | 2 | Abortion in 50% of the animals |

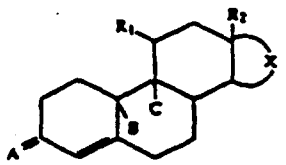
Conclusion:

This product tested showed anti-implantation activity and abortive activity in the rat at all times of the period of gestation.

Various modifications of the products and methods of the invention may be made without departing from the spirit or scope thereof and it is to be understood that the invention is intended to be limited only as defined in the appended claims.

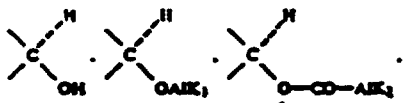
What we claim is:

1. An antiprogestomimetic composition comprising an anti-progestomimetically effective amount of at least one compound selected from the group consisting of 19-nor steroids and 19-nor-D-homo-steroids of the formula




I

wherein $R_1$ is an organic radical of 1 to 18 carbon atoms containing at least one atom selected from the group consisting of nitrogen, phosphorous and silicon with the atom immediately adjacent to the 11-carbon atom being carbon, $R_2$ is a hydrocarbon of 1 to 8 carbon atoms, X is selected from the group consisting of a pentagonal ring and a hexagonal ring optionally substituted and optionally containing a double bond, B and C together form a double bond or an epoxy group, the ring C=A group at position 3 is selected from the group consisting of C=O, ketal,

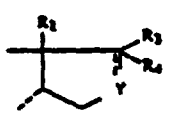



>C=NOH, >C=NOAlK$_3$ and $CH_2$, AlK$_1$, ALK$_2$ and AlK$_3$ are selected from the group consisting of alkyl of 1 to 8 carbon atoms and aralkyl of 7 to 15 carbon atoms and their non-toxic, pharmaceutically acceptable acid addition salts and an inert carrier.

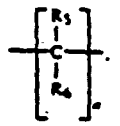
2. A composition of claim 1 wherein B and C form a double bond.

3. A composition of claim 1 wherein $R_2$ is methyl.

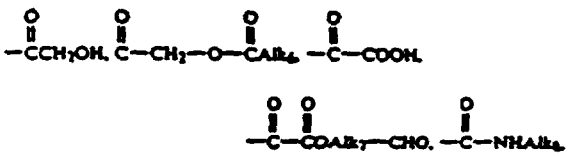
4. A composition of claim 1 wherein X and the carbons to which it is attached form the ring of the formula



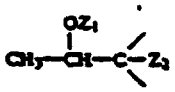
wherein $R_2$ has the above definition, the dotted line in the 16,17-position is an optional double bond, Y is the group



n is 1 or 2, $R_5$ is selected from the group consisting of hydrogen, alkyl of 1 to 8 carbon atoms, alkenyl and alkynyl of 2 to 8 carbon atoms, aryl of 6 to 14 carbon atoms and aralkyl of 7 to 15 carbon atoms, $R_6$ may be the same as $R_5$ and may be selected from the same group of members as $R_5$ or —OH, $R_3$ and $R_4$ are individually selected from the group consisting of hydrogen, —OH, —$OAlk_4$, —$OCOAlk_5$, alkenyl and alkynyl of 2 to 8 carbon atoms,



and —CN wherein $Alk_4$, $Alk_5$, and $Alk_8$ are selected from the group consisting of alkyl of 1 to 8 carbon atoms and aralkyl of 7 to 15 carbon atoms, $Alk_6$ is selected from the group consisting of optionally substituted alkyl of 1 to 8 carbon atoms and aralkyl of 7 to 15 carbon atoms and $Alk_7$ is alkyl of 1 to 8 carbon atoms and $R_3$ and $R_4$ form the group



and $Z_1$ is selected from the group consisting of hydrogen, alkyl of 1 to 8 carbon atoms and acyl of an organic carboxylic acid of 1 to 8 carbon atoms and $Z_2$ is alkyl of 1 to 8 carbon atoms.

5. A composition of claim 4 wherein the D ring is saturated, $R_5$ and $R_6$ are hydrogen and n is 1.

6. A composition of claim 1 wherein the C=A group is C=O.

7. A composition of claim 1 wherein $R_1$ is a hydrocarbon of 1 to 18 carbon atoms containing at least one nitrogen atom.

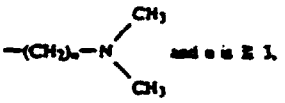
8. A composition of claim 7 wherein $R_1$ is a primary, secondary or tertiary alkyl of 1 to 8 carbon atoms containing at least one heteroatom of the group consisting of nitrogen, sulfur and oxygen at least one being nitrogen or substituted with a heterocycle containing at least one nitrogen atom.

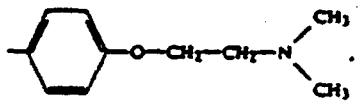
9. A composition of claim 7 wherein $R_1$ is heterocycle containing at least one nitrogen atom optionally substituted with an alkyl of 1 to 8 carbon atoms.

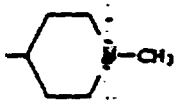
10. A composition of claim 7 wherein $R_1$ is aryl or aralkyl containing the group

wherein $R_7$ and $R_8$ are alkyl of 1 to 8 carbon atoms or primary, secondary or tertiary alkyl of 1 to 8 carbon atoms containing at least one heteroatom of the group consisting of nitrogen, sulfur and oxygen of which at least one is nitrogen or substituted with a heterocycle containing at least one nitrogen atom.

11. A composition of claim 10 wherein $R_1$ is selected from the group consisting of 2-pyridyl, 3-pyridyl, 4-pyridyl,





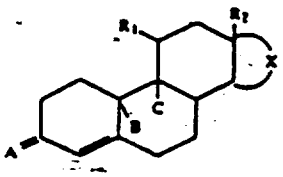


12. A composition of claim 1 wherein $R_1$ contains an oxidized nitrogen atoms.

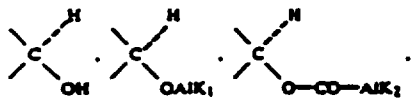
13. A composition of claim 1 wherein the active compound is selected from the group consisting of 11β-[4-(N,N-dimethylaminoethoxy)-phenyl]-17α (prop-1-ynyl)-$\Delta^{4,9}$-estradiene-17β-ol-3-one, 11β-[4-(N,N-dimethylamino)-phenyl]-17α-(prop-1-ynyl)-$\Delta^{4,9}$-estradiene-17β-ol-3-one, N-oxide of 11β[4-(N,N-dimethylamino)-phenyl]-21 chloro-19-nor-$\Delta^{4,9}$-pregnadiene-20-yne-17β-ol-3-one, N-oxide of 9α,10α-epoxy-11β[4-(N,N-dimethylamino)-phenyl]-21-chloro 19-nor-17α-$\Delta^4$-pregnene-20-yne-17β-ol-3-one-11β-[4(N,N-dimethylamino)-phenyl]-17α-(prop-2-ynyl)-$\Delta^{4,9}$-estradiene-17β-ol-3-one, N-oxide of 11β-[4-(N,N-dimethylamino)-phenyl]-17α-(prop-1-ynyl)-$\Delta^{4,9}$-estradiene-17β-ol-3-one and their non-toxic, pharmaceutically acceptable acid addition salts.

14. The composition of claim 1 wherein the active compound is 11β-/4-(N,N-dimethylamino)phenyl/17α-(prop-1-ynyl)$\Delta^{4,9}$ estradiene-17β-ol-3-one.

15. A method of inducing menses in warm-blooded animals comprising administering to warm-blooded animals, when progesterone plays a physiologically essential role, an anti-progestomimetically effective amount of at least one compound selected from the group consisting of 19-nor steroids and 19-nor-D-homo-steroids of the formula



wherein $R_1$ is an organic radical of 1 to 18 carbon atoms containing at least one atom selected from the group consisting of nitrogen, phosphorous and silicon with the atom immediately adjacent to the 11-carbon atom being carbon, $R_2$ is a hydrocarbon of 1 to 8 carbon atoms, X is selected from the group consisting of a pentagonal ring and a hexagonal ring optionally substituted and optionally containing a double bond, B and C together form a double bond or an epoxy group, the ring C=A group at position 3 is selected from the group consisting of C=O, ketal,



>C=NOH, >C=NOAlK$_3$ and $CH_2$, AlK$_1$, AlK$_2$ and AlK$_3$ are selected from the group consisting of alkyl of 1 to 8 carbon atoms and aralkyl of 7 to 15 carbon atoms and their non-toxic, pharmaceutically acceptable acid addition salts.

16. A method of claim 15 comprising administering to women an antiprogestomimetically effective amount of at least one compound of claim 1 during the luteal phase.

17. A method of claim 16 wherein the compound is administered at the end of luteal phase.

18. A method of claim 15 of interrupting pregnancy comprising administering to warm-blooded animals an antiprogestomimetically effective amount of at least one compound of claim 1.

19. A method of claim 15 wherein the compound is administered orally or locally.

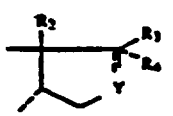
20. A method of claim 16 wherein the compound is administered orally or locally.

21. A method of claim 15 wherein the compound is administered during 1 to 5 days.

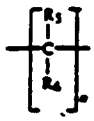
22. A method of claim 15 wherein B and C form a double bond.

23. A method of claim 15 wherein $R_2$ is methyl.

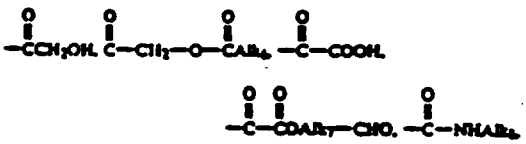
24. A method of claim 15 wherein X and the carbons to which it is attached from the ring of the formula



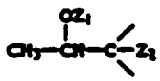
wherein $R_2$ has the above definition, the dotted line in the 16,17 position is an optional bond, Y is the group



a is 1 or 2, $R_5$ is selected from the group consisting of hydrogen, alkyl of 1 to 8 carbon atoms, alkenyl and alkynyl of 2 to 8 carbon atoms, aryl of 6 to 14 carbon atoms and aralkyl of 7 to 15 carbon atoms, $R_6$ may be the same as $R_5$ and may be selected from the same group of members as $R_5$ or —OH, $R_3$ and $R_4$ are individually selected from the group consisting of hydrogen, —OH, —OAlK$_4$, —OCOAlK$_5$,alkenyl and alkynyl of 2 to 8 carbon atoms,



and —CN wherein AlK$_4$, AlK$_5$ and AlK$_8$ are selected from the group consisting of alkyl of 1 to 8 carbon atoms and aralkyl of 7 to 15 carbon atoms, AlK$_4$ is selected from the group consisting of optionally substituted alkyl of 1 to 8 carbon atoms and aralkyl of 7 to 15 carbon atoms and AlK$_7$ is alkyl of 1 to 8 carbon atoms and $R_3$ and $R_4$ form the group



and $Z_1$ is selected from the group consisting of hydrogen, alkyl of 1 to 8 carbon atoms and acyl of an organic carboxylic acid of 1 to 8 carbon atoms and $Z_2$ is alkyl of 1 to 8 carbon atoms.

25. A method of claim 24 wherein the D ring is saturated, $R_5$ and $R_6$ are hydrogen and a is 1.

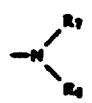
26. A method of claim 15 wherein the C=A group is C=O.

27. A method of claim 15 wherein $R_1$ is hydrocarbon of 1 to 18 carbon atoms containing at least one nitrogen atom.

28. A method of claim 27 wherein $R_1$ is a primary, secondary or tertiary alkyl of 1 to 8 carbon atoms containing at least one heteroatom of the group consisting of nitrogen, sulfur and oxygen at least one being nitrogen or substituted with a heterocycle containing at least one nitrogen atom.

29. A method of claim 27 wherein $R_1$ is heterocycle containing at least one nitrogen atom optionally substituted with an alkyl of 1 to 8 carbon atoms.

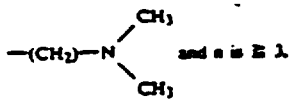
30. A method of claim 27 wherein $R_1$ is aryl or aralkyl containing the group



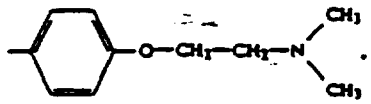
wherein $R_7$ and $R_8$ are alkyl of 1 to 8 carbon atoms or primary, secondary or tertiary alkyl of 1 to 8 carbon

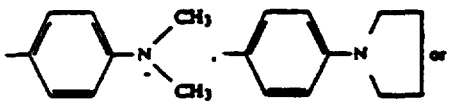
atoms containing at least one heteroatom of the group consisting of nitrogen, sulfur and oxygen of which at least one is nitrogen or substituted with a heterocycle containing at least one nitrogen atom.

31. A method of claim 30 wherein $R_1$ is selected from the group consisting of 2-pyridyl, 3-pyridyl, 4-pyridyl,

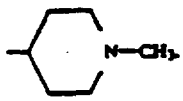


and n is ≧ 1.





or



32. A method of claim 15 wherein $R_1$ contains an oxidized nitrogen atom.

33. The method of claim 15 wherein the active compound is selected from the group consisting of 11β-[4-(N,N-dimethylaminoethoxy)-phenyl]-17α-(prop-1-ynyl)-$\Delta^{4,9}$-estradiene-17β-ol-3-one, 11β-[4-(N,N-dimethylamino)-phenyl]-17α-(prop-1-ynyl)-$\Delta^{4,9}$-estradiene-17β-ol-3-one, N-oxide of 11β-[4-(N,N-dimethylamino)-phenyl]-21-chloro-19-nor-$\Delta^{4,9}$-pregnadiene-20-yne-17β-ol 3-one, N-oxide of 9α,10α-epoxy-11β-[4-(N,N-dimethylamino)-phenyl]-21-chloro-19-nor-17α-$\Delta^{4}$-pregnene-20-yne-17β-ol-3-one, 11β-[4-(N,N-dimethylamino)-phenyl]-17α-(prop-2-ynyl)-$\Delta^{4,9}$-estradiene-17β-ol-3-one, N-oxide of 11β-[4-(N,N-dimethylamino)-phenyl]-17α-(prop-1-ynyl)-$\Delta^{4,9}$-estradiene-17β-ol-3-oneand their non-toxic, pharmaceutically acceptable acid addition salts.



34. The method of claim 16 wherein the active compound is selected from the group consisting of 11β-[4-(N,N-dimethylaminoethoxy)-phenyl]-17α-(prop-1-ynyl)-$\Delta^{4,9}$-estradiene-17β-ol-3-one, 11β-[4-N,N-dimethylamino)-phenyl]-17α-(prop-1-ynyl)-$\Delta^{4,9}$-estradiene-17β-ol-3-one, N-oxide of 11β-[4-N,N-dimethylamino)-phenyl]-21-chloro-19-nor-$\Delta^{4,9}$-pregnadiene-20-yne-17β-ol-3-one, N-oxide of 9α,10α-epoxy-11β-[4-(N,N-dimethylamino)-phenyl]-21-chloro-19-nor-17α-$\Delta^{4}$-pregnene-20-yne-17β-ol-3-one, 11β-[4-N,N-dimethylamino)-phenyl]-17α-(prop-2-ynyl)-$\Delta^{4,9}$-estradiene-17β-ol-3-one, N-oxide of 11β[4-(N,N-dimethylamino)-phenyl]-17α-(prop-1-ynyl)-$\Delta^{4,9}$-estradiene-17β-ol-3-one and their non-toxic, pharmaceutically acceptable acid addition salts.

35. The method of claim 15 wherein the active compound is 11β-/4-(N,N-dimethylamino)phenyl/17α-(prop-1-ynyl)$\Delta^{4,9}$ estradiene-17β ol-3-one.

36. The method of claim 16 wherein the active compound is 11β-/4-(N,N-dimethylamino)phenyl/17α-(prop-1-ynyl)$\Delta^{4,9}$ estradiene 17β ol-3-one.

* * * * *

**US Patent No.: 4,626,531**

The Population Council
Center for
Medical Research

1230 York Avenue
New York, New York 10021
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Facsimile: (212) 327-7678
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To Whom It May Concern:

The undersigned declares that Patent No. 4,626,531 covers the formulation, composition, and/or method of us of Mifepristone [trade name undertermined]. This product is the subject of this application for which approval is being sought.

Signed on: October 3, 1995

for The Population Council

C. Wayne Bardin, MD

C. Wayne Bardin, M.D.
Vice President

APPEARS THIS WAY
ON ORIGINAL

# United States Patent [19]

Elger et al.

[11] Patent Number: 4,626,531

[45] Date of Patent: Dec. 2, 1986


[54] **PROSTAGLANDINS AND ANTIGESTAGENS FOR INDUCTION OF LABOR AND FOR ABORTION**


[75] Inventors: Walter Elger; Sybille Beier, both of Berlin, Fed. Rep. of Germany

[73] Assignee: Schering Aktiengesellschaft, Berlin and Bergkamen, Fed. Rep. of Germany



[21] Appl. No.: 660,358

[22] Filed: Oct. 12, 1984

[30] Foreign Application Priority Data

Oct. 12, 1983 [DE] Fed. Rep. of Germany ..... 3337450

[51] Int. Cl.[4] ..... A61K 31/56

[52] U.S. Cl. ..... 514/171

[58] Field of Search ..... 514/171



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| 4,447,424 | 5/1984 | Tesarik et al. | 424/240 |



*Primary Examiner*—Elbert L. Roberts

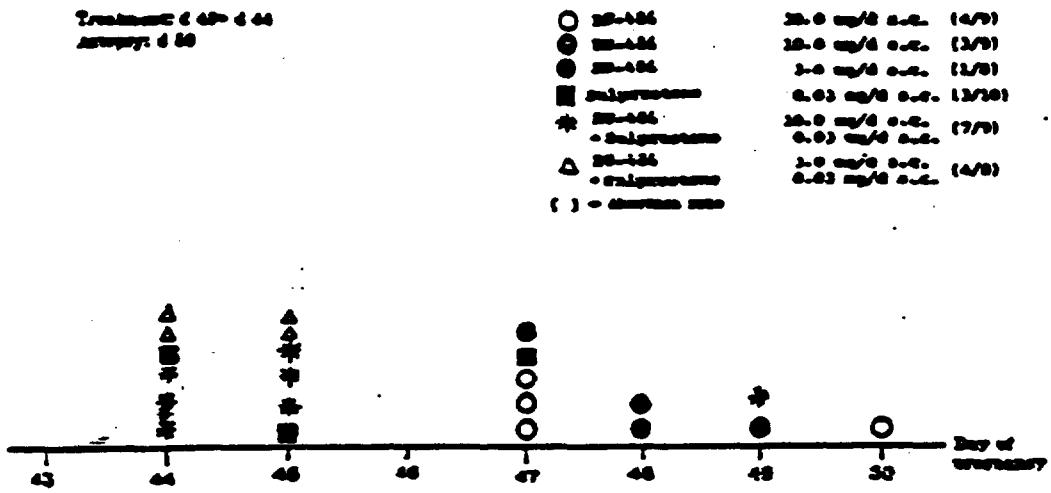
*Attorney, Agent, or Firm*—Millen & White



[57] ABSTRACT

A pharmaceutical composition containing a prostaglandin and an antigestagen is suitable for induction of labor and for abortion.


31 Claims, 5 Drawing Figures



Treatment: d 43+ d 44
Autopsy: d 50

| | | | |
|---|---|---|---|
| ○ | RU-486 | 30.0 mg/d s.c. | (4/9) |
| ⊜ | RU-486 | 10.0 mg/d s.c. | (3/9) |
| ⊜ | RU-486 | 3.0 mg/d s.c. | (1/8) |
| ■ | Sulprostone | 0.03 mg/d s.c. | (3/10) |
| ✱ | RU-486 + Sulprostone | 10.0 mg/d s.c. 0.03 mg/d s.c. | (7/9) |
| △ | RU-486 + Sulprostone | 3.0 mg/d s.c. 0.03 mg/d s.c. | (4/8) |

( ) = Abortion rate

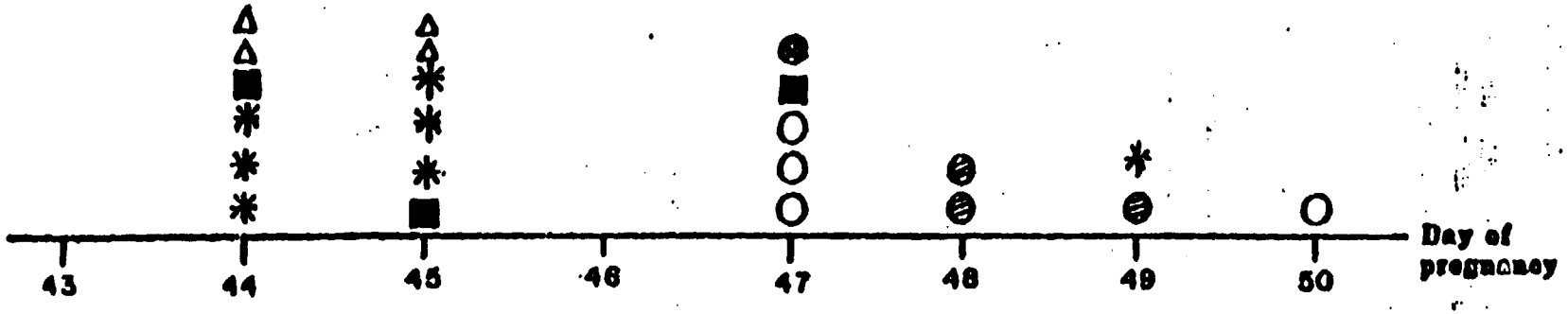



FIG. 1

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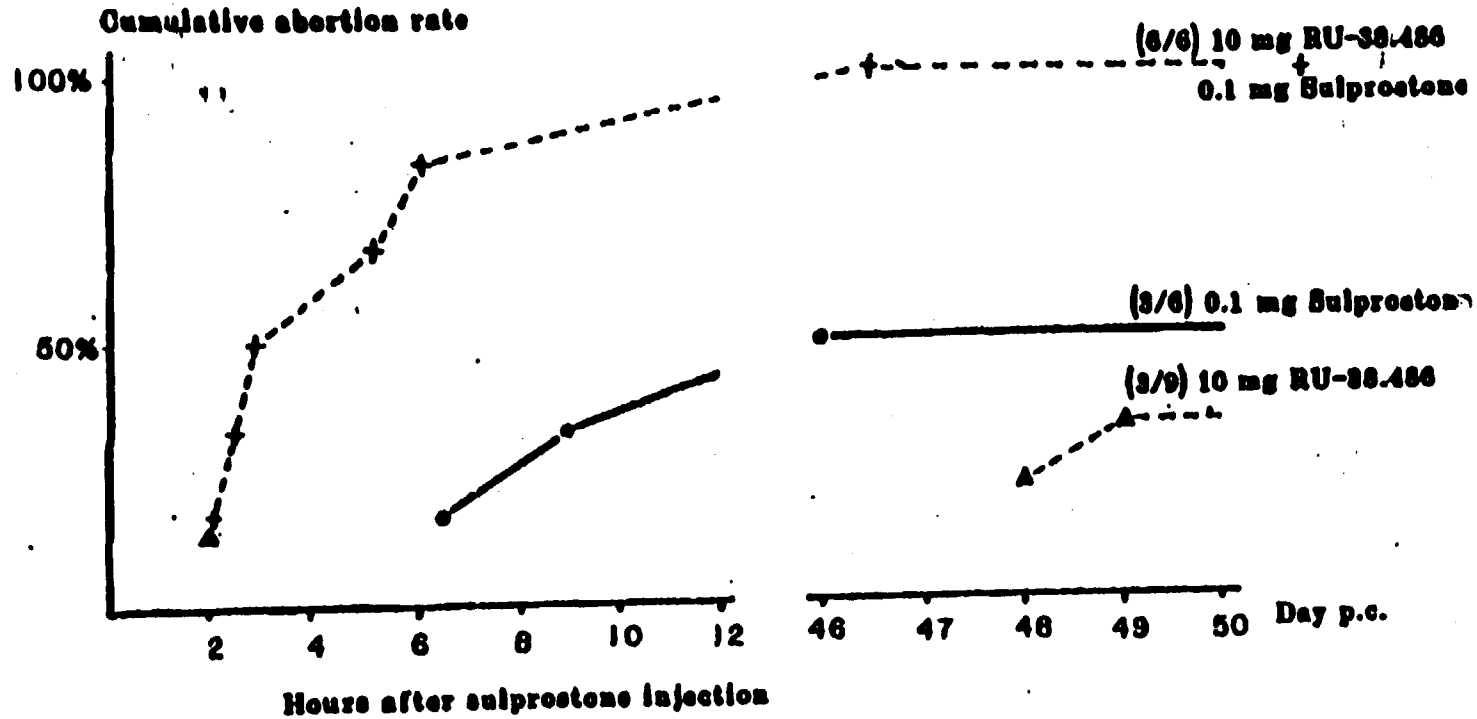
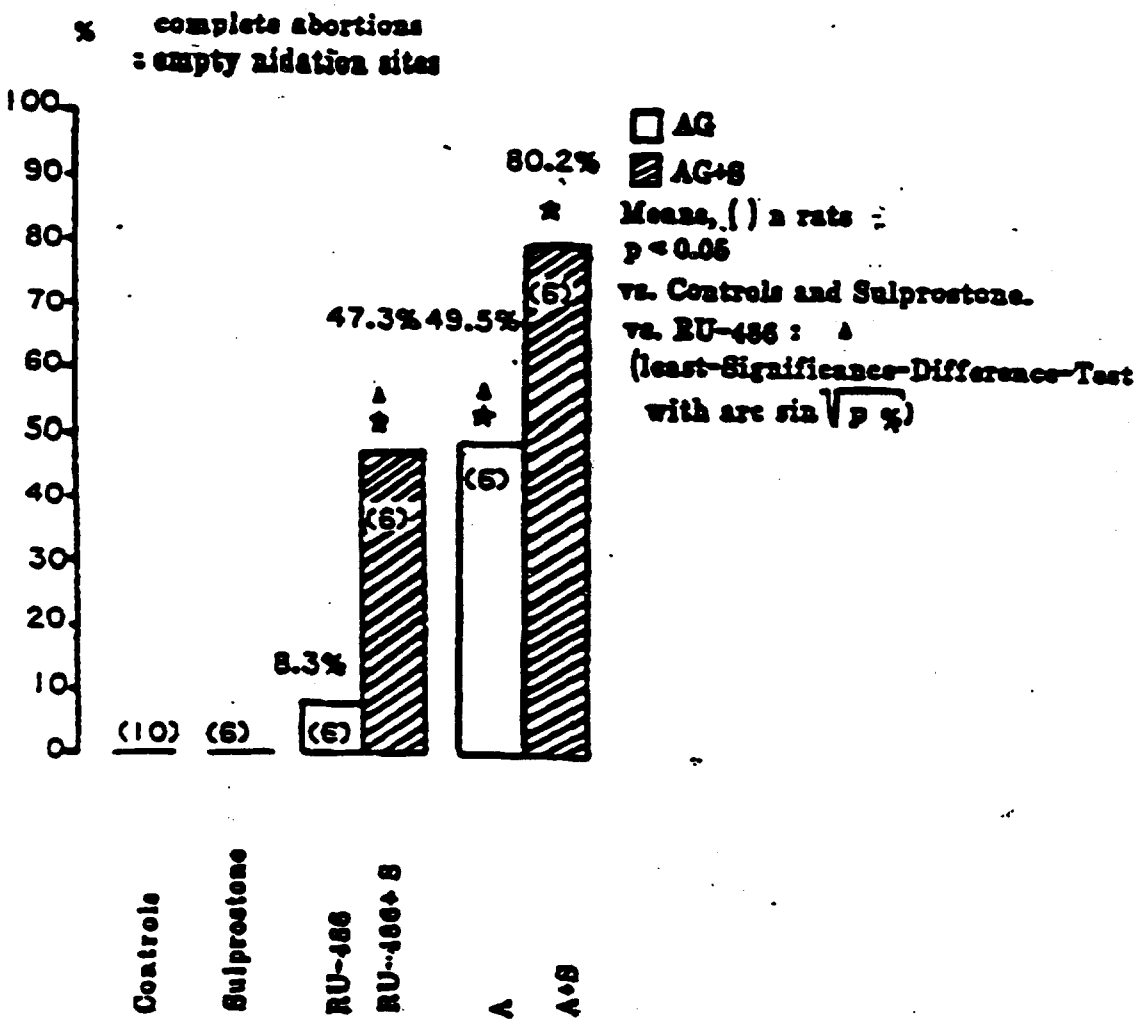



FIG. 2

88




RU-486 = 11β-(4-N,N-Dimethylaminophenyl)-17β-hydroxy-17α-propinyl-4,9(10)-estradien-3-one

A = 11β-(4-Dimethylaminophenyl)-17α-hydroxy-17β-(3-hydroxypropyl)-13α-methyl-4,9-gonadien-3-one

FIG. 3

FIG. 4-1

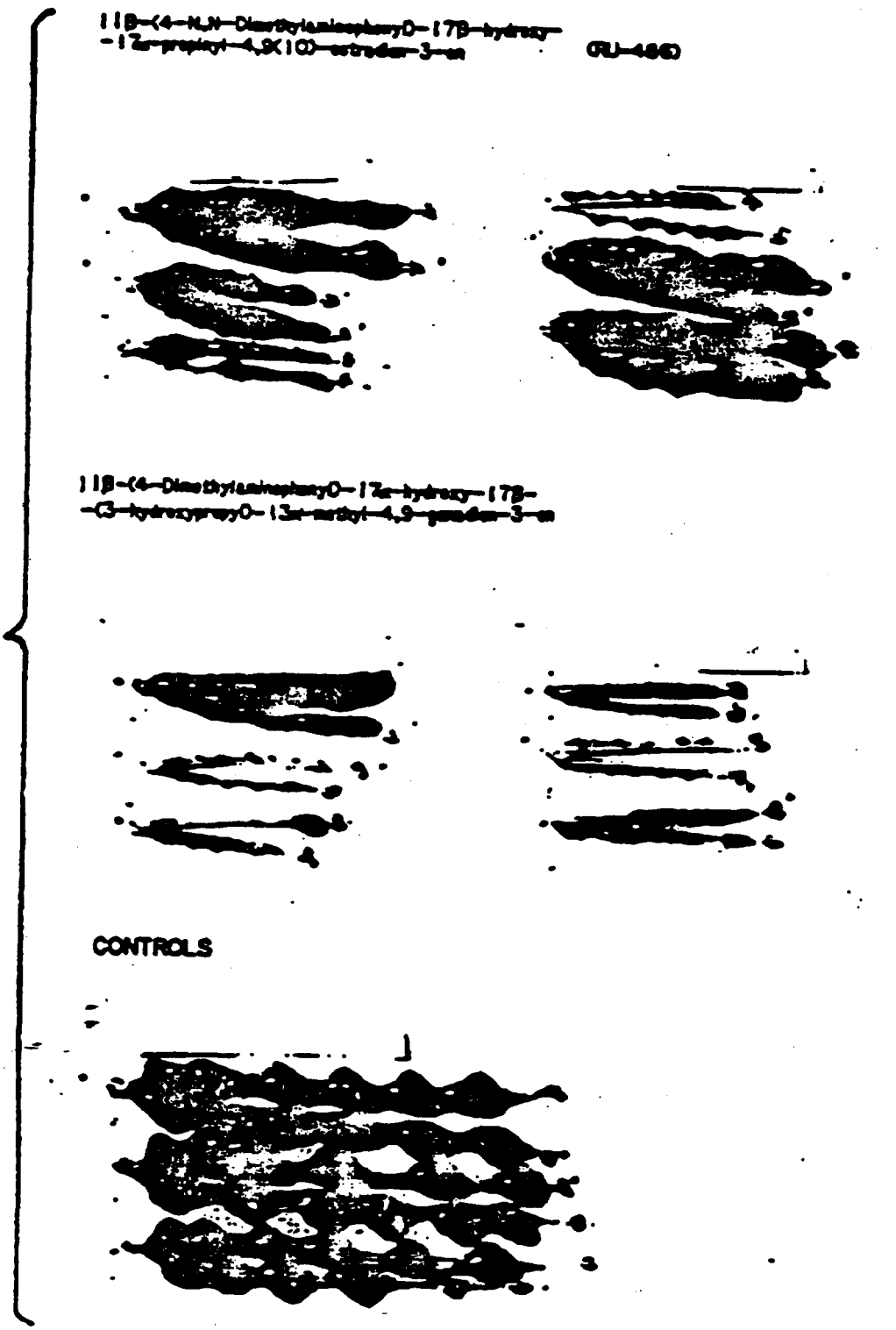
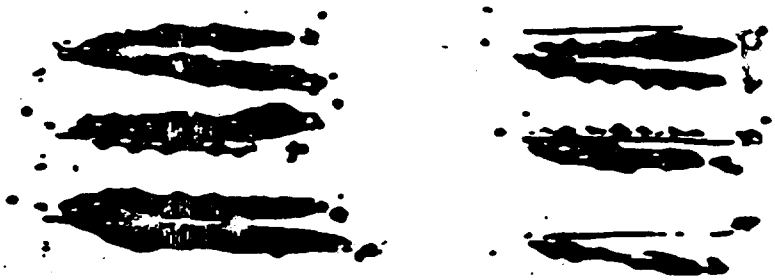
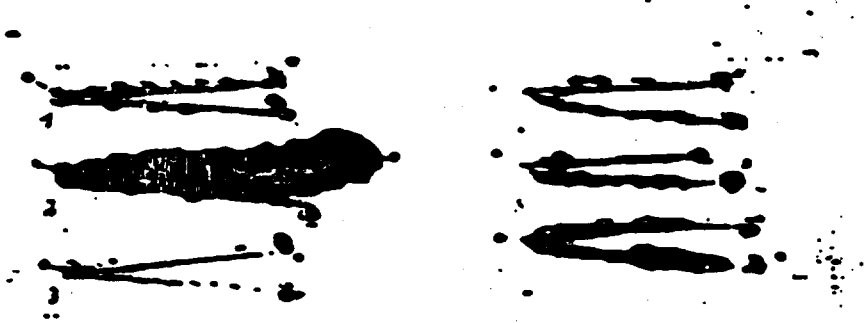


FIG. 4-2

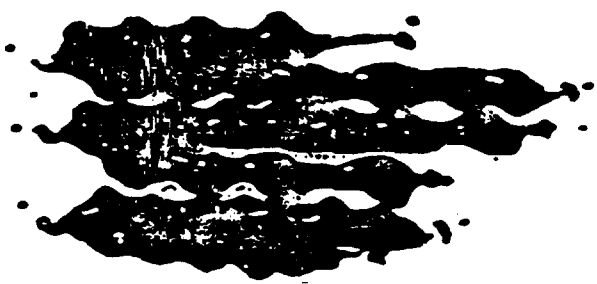
RU-486 4S



11B-(4-Dimethylaminophenyl)-12a-hydroxy-17B-
-(3-hydroxypropyl)-13a-methyl-4,9-gonadien-3-one 4S



SULPROSTONE



# PROSTAGLANDINS AND ANTIGESTAGENS FOR INDUCTION OF LABOR AND FOR ABORTION

## BACKGROUND OF THE INVENTION

This invention relates to a combination product for combined use in the induction of labor or for abortion.

To avert danger for the mother and/or child, it is sometimes necessary to induce labor artificially or to terminate a pregnancy before term. Surgical techniques and pharmacological methods are available for this purpose.

A favorable pharmacological method is vaginal or intramuscular application of prostaglandins which, in the case of abortion, are taken in the first or second three-month period of pregnancy (Contraception 1983, Vol. 27, 51–60 and Int. J. Gynaecol. Obstet. 1982, Vol. 20, 383–386. Advantages of prostaglandins include their simple administrability and their applicability for use over a long period of pregnancy. Disadvantages include acute side effects such as pain and nausea; moreover, the success rate in the case of abortion in advanced phases of pregnancy is not over 90% even with a long period of prostaglandin treatment.

Another possibility of terminating a pregnancy consists in the application of an antigestagen (Med. et Hyg. :982, Vol 40, 2087–2093). Antigestagens are better tolerated than prostaglandins but have a greater latency and individual variability of onset of action in comparison with prostaglandins.

## SUMMARY OF THE INVENTION

Accordingly, it is an object of this invention to provide a new composition and method for induction of labor or abortion, which significantly ameliorates these problems.

Upon further study of the specification and appended claims, further objects and advantages of this invention will become apparent to those skilled in the art.

These objects have been attained based in part on this finding, that the PG type and AG type disadvantages are avoided or significantly ameliorated if prostaglandins (PG) and antigestagens (AG) are used together for these purposes.

## BRIEF DESCRIPTION OF THE DRAWINGS

Various other objects, features and attendant advantages of the present invention will be more fully appreciated as the same becomes better understood when considered in conjunction with the accompanying drawings wherein:

FIG. 1 illustrates the results of tests involving the termination of pregnancy in guinea pigs. The day of abortion is shown under various treatment conditions;

FIG. 2 shows the results of a comparative test of the abortive action of sulprostone (PG) and RU-38.486 (AG) and the sequential use of both substances in pregnant guinea pigs (s.c. administration); and

FIGS. 3 and 4 show the results of an evaluation of synergistic antigestagen (AG)/Sulprostone(S) actions in advanced pregnancy in rats. Antigestagen: 3.0 mg/d s.c. days 13–15 p.c., Sulprostone: 0.1 mg 2×day 15 p.c., autopsy day 17 p.c.

## DETAILED DISCUSSION

Surprisingly, the amounts by weight of prostaglandin and antigestagen can be greatly reduced in combined use in comparison with the usual amounts employed when they are used alone. Further surprising is the fact that the success rate of abortions or labor induction can even be increased as a result. The prostaglandin and antigestagen are advantageously used separately, simultaneously and/or sequentially. The weight ratio of prostaglandin to antigestagen is generally 1:20 to 1:6000, preferably 1:10[1] to 1:500.

These weight ratios are based on appropriate values for the most preferred active ingredients, i.e., sulprostone as the prostaglandin and 11β-[(4-N,N-dimethylamino)-phenyl]-17β-hydroxy-17α-propinyl-4,9(10)-estradiene-3-one as the antigestagen. Corresponding weight ratios for any other ingredients can be readily determined using fully conventional techniques, e.g., involving differential potency studies using conventional protocols.

Prostaglandins suitable for use according to the invention are all prostaglandins suitable for abortion or inducing labor. These are well known. They particularly include prostaglandins of the E and F types. There can be mentioned for example: prostaglandin $E_2$, prostaglandin $F_{2\alpha}$, prostaglandin E derivatives, e.g., 16-phenoxy-ω-17,18,19,20-tetranor-$PGE_2$-methylsulfonylamide (sulprostone), 16,16-dimethyl-trans-Δ 2-$PGE_1$-methyl ester (Gemeprost), 9-deuxo-16,16-dimethyl-9-methylene-$PGE_2$ (Metenoprost), prostaglandin F derivatives, e.g. 15-methyl-$PGF_{2\alpha}$-methyl ester, (5Z,13E)-(9R,11R,15R)-9-chloro-11,15-dihydroxy-16,16-dimethyl-5,13-prostadienoic acid (DE-OS No. 29 50 027), (5Z,13E)-(9R,11R,15R)-11,15-dihydroxy-9-fluoro-16-phenoxy-17,18,19,20-tetranor-5,13-prostadienoic acid (DE-OS No. 31 26 924), (5Z,13E)-(9R,11R,15R)-11,15-dihydroxy-16,16-dimethyl-9-fluoro-5,13-prostadienoic acid (DE-OS No. 31 26 924), (5Z,13E)-(9R,11R,15R)-9-bromo-11,15-dihydroxy-16-phenoxy-17,18,19,20-tetranor-5,13-prostadienoic acid (DE-OS No. 31 48 743), or (5Z,13E)-(9R,11R,15R)-9-bromo-11,15-dihydroxy-16,16-dimethyl-5,13-prostadienoic acid (DE-OS 31 48 743), etc.

This listing is exemplary only. Many other prostaglandins can be used.

The prostaglandins can be used in amounts that are clearly lower than the generally normal amounts for abortion or induction of labor. The amount to be used according to the invention conventionally depends, inter alia, on the hormone level, the period of the pregnancy, etc., of the patient and the manner of application. Precise dosages can be routinely determined using conventional techniques in view of this disclosure. When sulprostone is used as the prostaglandin, as a rule 0.03 to 0.5 mg per day suffices. Application can, for example, be made locally, topically, enterally or parenterally. Upon intramuscular injection or intravenous infusion, for example, amounts of about 0.1 to 0.3 mg of sulprostone per day are satisfactory. Upon local application, for example extra-amniotically or intravaginally, about 0.03 to 0.5 mg of sulprostone per day is used. For topical application, transdermal systems, such as skin plasters, can be used. According to this invention, biologically equivalent amounts of other prostaglandins can be used instead of sulprostone. These bioavailability equivalent amounts can be determined routinely and conventionally, e.g., by performing differential potency studies using fully routine pharmacological protocols, e.g., W. Elger, Animal Reproduction Science 2 (1979), 133.

The combined treatment with prostaglandin and antigestagen occurs as a rule over 1 to 4, preferably 1 to 2

days, during which time the prostaglandin and antigestagen can be applied preferably separately and simultaneously, or also separately and sequentially. The prostaglandin and antigestagen can also be combined in a single dosage unit. In sequential therapy, preferably, first the antigestagen is applied for 1 to 4 days and then the prostaglandin alone; or the prostaglandin and additional antigestagen together, over 24 hours. The application of the antigestagen for 1 or for 4 days depends on the period of pregnancy and on the progesterone level.

All compounds are suitable as antigestagens for this invention which have a strong affinity for the gestagen receptor (progesterone receptor) and yet show no progestational activity of their own, thus functioning as antigestagens. For example, the following steroids are suitable as such competitive progesterone antagonists:

11β-[(4-N,N-dimethylamino)-phenyl]-17β-hydroxy-17α-propinyl-4,9(10)-estradien-3-one,

11β-[(4-N,N-dimethylamino)-phenyl]-17β-hydroxy-18-methyl-17α-propinyl-4,9(10)-estradien-3-one,

11β-[4-N,N-dimethylamino)-phenyl]-17aβ-hydroxy-17aα-propinyl-D-homo-4,9(10),16-estratrien-3-one, (European patent application No. 82400025.1—Publication No. 0 057 115);

11β-p-methoxyphenyl-17β-hydroxy-17α-ethinyl-4,9(10)-estradien-3-one (Steroids 37 (1981) 361–382), or

11β-(4-dimethylaminophenyl)-17α-hydroxy-17β-(3-hydroxypropyl)-13α-methyl-4,9-gonadien-3-one.

Also suitable for use in this invention are antigestagens which antagonize the effect of gestagens per se, i.e., operate by a route different from competing with the gestagen receptor. Suitable such antigestagens include the derivatives of triloxane (U.S. Pat. No. 4,160,027).

The foregoing listing is exemplary only. Many other antigestagens can be used, e.g., as disclosed in Fertility and Sterility 40, 253 (1982), Steroids 37, 361 (1981).

The antigestagens according to this invention are used in amounts that as a rule are also lower than the generally normal amounts for abortion or labor induction. In general, 10–200 mg of 11β-[(4-N,N-dimethylamino)-phenyl]-17β-hydroxy-17α-propinyl-4,9(10)-estradien-3-one per day or a biologically equivalent amount of another antigestagen suffice. Precise dosages can be routinely determined using conventional techniques in view of this disclosure. The mentioned bioequivalent amounts can be determined conventionally and routinely, e.g., by performing differential potency studies using fully routine pharmacological protocols, e.g., Fertility and Sterility 40, 253 (1982), Steroids 37, 361 (1981).

The antigestagens can, for example, be applied locally, topically, enterally or parenterally.

For the preferred oral application of either component, tablets, coated tablets, capsules, pills, suspensions or solutions are suitable. These can be produced in the usual way using the admixtures and vehicles customary in galenicals, most notably those well known for formulations of PG and AG compounds. For local or topical application, for example, vaginal suppositories or transdermal systems such as skin plasters are suitable.

A dosage unit generally contains about 10 to 200 mg of antigestagen. Suitable hosts are mammals including humans. Other than as indicated herein, administration will be analogous to that of the known active ingredients alone.



Without further elaboration, it is believed that one skilled in the art can, using the preceding description, utilize the present invention to its fullest extent. The following preferred specific embodiments are, therefore, to be construed as merely illustrative, and not limitative of the remainder of the disclosure in any way whatsoever. In the following example(s), all temperatures are set forth uncorrected in degrees Celsius; unless otherwise indicated, all parts and percentages are by weight.

## EXAMPLE 1

Composition of a freeze-dried sulprostone formulation per ampoule

| | |
|---|---|
| 0.1 mg | Sulprostone |
| 5.0 mg | Polyvinylpyrrolidone (K value = 15–18) |
| 1.75 mg | Tris(hydroxymethyl)aminomethane hydrochloride (trometamol.HCl) (from 1.5 mg trometamol and 1N hydrochloric acid) |
| 7.05 mg | |

For dosage and application, the content of the ampoule is dissolved with isotonic saline solution for intramuscular injection or intravenous infusion for extra-amniotic application.

Production of the dry substance

Sulprostone is brought to solution by addition to an ice-cooled solution of polyvinylpyrrolidone and trometamol in distilled water. The pH of the solution is adjusted to 5.0 by addition of 1N hydrochloric acid with strong cooling. Then the solution was filled to the required volume. After filtering with a membrane filter, the solution is dosed in ampoules.

The solution is then frozen by immersion of the ampoules in an acetone/dry ice freezing mixture and immediately freeze-dried in a precooled freeze-dry unit for about 48 hours. After completion of the freeze-drying, the ampoules are immediately sealed.

## EXAMPLE 2

Composition of a film with sulprostone for vaginal application

| | |
|---|---|
| 0.1 mg | Sulprostone |
| 19.8 mg | Hydroxypropyl cellulose |
| 0.12 mg | Polyoxyethylene/polyoxypropylene polymer (Pluronic F 68 ®) |
| 20.02 mg | |

The film has a length of 3 cm.

## EXAMPLE 3

Composition of a film with sulprostone for buccal application

| | |
|---|---|
| 0.3 mg | Sulprostone |
| 9.16 mg | Hydroxypropyl cellulose |
| 9.16 mg | Cellulose fibers |
| 0.15 mg | Polyoxyethylene/polyoxypropylene polymer (Pluronic F 68 ®) |
| 18.77 mg | |

The surface of the film is 1.2 × 1.2 cm.

## EXAMPLE 4

Composition of a tablet with sulprostone for vaginal application

| | |
|---|---|
| 0.1 mg | Sulprostone |
| 236.9 mg | Lactose |
| 100.0 mg | microcrystalline cellulose |
| 1.0 mg | Magnesium stearate |
| 338.0 mg | |

## EXAMPLE 5

Composition of another tablet with 11β-[(4-N,N-Dimethylamino)-phenyl]-17β-hydroxy-17α-propinyl-4,9(10)-estradien-3-one for oral application

| | |
|---|---|
| 10.0 mg | 11β-[(4-N,N—Dimethylamino)-phenyl]-17β-hydroxy-17α-propinyl-4,9(10)-estradien-3-one |
| 140.5 mg | Lactose |
| 69.5 mg | Corn starch |
| 2.5 mg | Polyvinylpyrrolidone 25 |
| 2.0 mg | Aerosil |
| 0.5 mg | Magnesium stearate |
| 225.0 mg | Total weight |

Pharmacological observations

The prostaglandin sulprostone and the antigestagens 11β-[(4-N,N-dimethylamino)-phenyl]-17β-hydroxy-17α-propinyl-4,9(10)-estradien-3-one (RU 38486) and 11β-(4-dimethylaminophenyl)-17α-hydroxy-17β-(3-hydroxypropyl)-13α-methyl-4,9-gonadien-3-one were selected as model substances for a pilot test on pregnant guinea pigs and rats. The doseges tested can be gathered from Table 1 and FIGS. 1 to 4.

(1) Research on pregnant guinea pigs

(1.1) Testing of the combination

Description of the test

Pregnant guinea pigs with a body weight of about 800 g were taken on the 42nd day of pregnancy for the test (the second day of the vaginal opening in the mating season was counted as the first day of pregnancy). Pregnancy was checked by palpation before beginning of the test. The treatment took place with the selected test substances or the combination by daily injection on the 43rd and 44th day of pregnancy. For this purpose, the test substances were dissolved in benzyl benzoate+castor oil (ratio of the mixture in the case of sulprostone: 1+2; RU 38486: 2+4.5) and the daily dose was injected s.c. in a volume of 0.4 ml (sulprostone) or of 1.0 ml (RU 38486). The possible expulsion of the fetus was checked during and after treatment several times daily. On the 50th day of pregnancy, the animals were sacrified. The uteri were examined and the fetuses found.

Results:

The results of the tests for induction of abortion in pregnant guinea pigs with combined administration of antigestagen and prostaglandin are summarized in Table 1.

TABLE 1

Comparative examination of the abortive action of sulprostone (PG), RU-38,486 (competitive progesterone antagonist) and the combination of both substances in pregnant guinea pigs. Treatment (43. and 44. autopsy on 45th

| Dose mg/d s.c. | a animals with abort/ 5 total animals Sulprostone (S) | RU-38,486 | S-/RU - combination | |
|---|---|---|---|---|
| 30.0 | — | 6/9 | 0.03 s.c. Sulprostone | |
| 10.0 | — | 3/9 | + | 7/9 |
| 3.0 | — | 1/8 | 10.0 mg RU-38,486 | |
| 1.0 | — | | 0.03 mg Sulprostone | |
| 0.3 | 10/10 | | + | 4/8 |
| 0.1 | 5/10 | | 3.0 mg RU-38,486 | |
| | 0/10* | | | |
| 0.03 | 3/10 | | | |
| 0.01 | 0/9 | | | |

(* = "natural abortions")

Sulprostone:

The abortifacient action of sulprostone was dependent on dosage. An abortion rate of 30% (=abortion in 3 out of 10 animals treated) was found in the case of a dose of 0.03 mg/d s.c. Expulsion of the embryos from the uterus occurred with this dose with a latency of about 1-2 days (see FIG. 1).

Antigestagens:

With antigestagen RU 38486 a termination of an existing pregnancy with 30 mg/d s.c. was to be obtained in 4 out of 9 animals treated. With a dose of 10.0 mg/d the abortion rate was 3/9 animals treated. After 3.0 mg/d s.c. only 1 out of 8 animals treated aborted. The abortions occurred with latency of 4 to 7 days from the beginning of treatment (see FIG. 1).

AG/PG combination:

The combination of subabortive antigestagen doses (3.0 mg or 10.0 mg RU 38486/d s.c.) with a marginally effective sulprostone dose of 0.03 mg/d s.c. led, in comparison with only antigestagen treatment, in each case to a clearly higher abortion rate and to a far faster induction of abortions. The interval of induction of abortion was also shorter than with only PG treatment, to the extent that the latter caused expulsion of the primordium as all (see table 1 and FIG. 1).

1.2 Testing with sequential treatment

Description of the test

Pregnant guinea pigs with a body weight of about 800 g were taken on the 42nd day of pregnancy for the tests (the second day of the vaginal opening in the mating season was counted as the first day of pregnancy). Pregnancy was checked by palpation before beginning of the test. The treatment took place with the selected antigestagens by daily injection on the 43rd and 44th day of pregnancy. The prostaglandin was applied on the 45th day. For this purpose the antigestagen was dissolved in benzyl benzoate+castor oil (mixture ratio 2+4.5) and the daily dose injected subcutaneously in a volume of 1.0 ml. The sulprostone was put in the galenical preparation of the Nalador ® ampoule and injected subcutaneously. The possible expulsion of fetuses was checked during and after treatment several times daily. On the 50th day of pregnancy the animals were sacrificed. The uteri were inspected and the fetuses found.

Results:

The results of the tests for induction of abortion in pregnant guinea pigs in sequential application of antigestagen and prostaglandins are summarized in FIG. 2.

Salprostone:

With a dose of 0.1 mg salprostone/d s.c. an abortion rate of 50% (=abortion in 3 out of 6 animals treated) was found. Expulsion of embryos from the uterus occurred with this dose with a latency of about 6–24 hours (see FIG. 2).

Antigestagens:

With antigestagen RU 38486 a termination of an existing pregnancy with 10 mg/c s.c. in 3 out of 9 animals treated was achieved. However, the abortion occurred only on the 48th or 49th day, i.e., with a latency of 5 to 6 days from the beginning of treatment (see FIG. 2).

AG/PG sequential treatment:

With sequential administration of the above mentioned marginally effective AG and PG doses, termination of pregnancy in all guinea pigs (6/6 animals) occurred (see FIG. 2), in which the latency period was much shorter than with only PG treatment, to the extent that the latter was successful at all (median value: 4 hours versus 12 to 24 hours).

(2) Research on pregnant rats

Description of test

The tests were conducted on female Wistar rats of an in-house breed with a weight of about 200 g. After mating had occurred, the beginning of pregnancy was assured by determination of sperm in a vaginal smear.

The day of determination of sperm is considered as day 1 of pregnancy (=d1 p.c.).

The antigestagens were dissolved in a benzyl benzoate-castor oil mixture (ratio 1+4). The vehicle volume per individual dose was 0.2 ml. The treatment was subcutaneous.

The dosages selected can be gathered from FIG. 3.

The prostaglandin salprostone was dissolved in a mixture of ethanol+benzyl benzoate+castor oil (ratio 1+5+12). The vehicle volume of the selected individual dose of 0.1 mg was 0.2 ml. Salprostone was applied subcutaneously.

Pregnancy was checked by palpation before beginning of the test. Assignment of the pregnant animals to the various test groups was done randomly (n=6/group). With administration only of the antigestagens selected, the treatment took place by injection from d13–d15 of pregnancy. Groups, which were given a combined antigestagen/prostaglandin treatment, received, in addition, 2×0.1 mg salprostone/animal s.c. on d15 p.c.

Only salprostone (2×0.1 mg/animal s.c. on d15 p.c.) was administered to another group. From d13–15 p.c. 0.2 ml of the benzyl benzoate-castor oil vehicle was applied daily to the control group. The rats were sacrificed on d17 p.c. and the uteri were examined for living and dead fetuses, retained placentas and empty nidation sites. The percentage of complete abortions (by definition: empty nidation site) was calculated per group.

Results:

The results of the tests for induction of abortion in pregnant rats are documented in FIGS. 3 and 4.

Treatment with effective antigestagens led to induction of abortions in rats. However, there is a tendency to incomplete abortions, in part, the abortions go along with prolonged, continuous vaginal bleeding. (A corresponding behavior was observed in the first clinical research with RU-486 e.g. the case of suppressed menstruation.)

The percentage of complete abortions with 3-day s.c. administration of 3.0 mg/d s.c. was 49.5% for the test substance 11β-(4-dimethylaminophenyl)-17α-hydroxy-17β-(3-hydroxypropyl)-13α-methyl-4,9-gonadien-3-one. After administration of 3.0 mg of RU-486/d s.c., the rate of complete abortions was 8.3%. Additional salprostone administration of 2×0.1 mg/d s.c. on day 15 could clearly increase the abortive effectiveness of 11β-(4-dimethylaminophenyl)-17α-hydroxy-17β-(3-hydroxypropyl)-13α-methyl-4,9-gonadien-3-one and RU-486 (see FIGS. 3 and 4).

The preceding examples can be repeated with similar success by substituting the generically or specifically described reactants and/or operating conditions of this invention for those used in the preceding examples.

From the foregoing description, one skilled in the art can easily ascertain the essential characteristics of this invention, and without departing from the spirit and scope thereof, can make various changes and modifications of the invention to adapt it to various usages and conditions.

What is claimed is:

1. A pharmaceutical composition comprising a labor or abortion inducing prostaglandin and a labor or abortion inducing antigestagen, the total amount of the combination of the prostaglandin and the antigestagen being effective to induce labor or an abortion.

2. A pharmaceutical composition of claim 1 wherein the amount of the prostaglandin and the amount of the antigestagen are both lower than the amount at which each is effective to induce labor or abortion when used alone.

3. A pharmaceutical composition of claim 1, wherein at least one of the amount of the prostaglandin and the amount of the antigestagen is lower than the amount at which it is effective to induce labor or abortion when used alone.

4. A pharmaceutical composition of claim 1, wherein the prostaglandin and antigestagen are contained in a weight ratio of 1:20 to 1:6000.

5. A pharmaceutical composition of claim 1, wherein the prostaglandin and the antigestagen are contained in separate dosage units.

6. A pharmaceutical composition of claim 1, wherein the prostaglandin and the antigestagen are contained in the same dosage unit.

7. A pharmaceutical composition of claim 1, wherein the prostaglandin is 0.03–0.5 mg of 16-phenoxy-ω-17,18,19,20-tetranor-$PGE_2$-methylsulfonylamide or a biologically equivalent amount of another prostaglandin.

8. A pharmaceutical composition of claim 1, wherein the antigestagen is 10–200 mg of 11β-[(4-N,N-dimethylaminophenyl]-17β-hydroxy-17α-propinyl-4,9(10)-estradien-3-one or a biologically equivalent amount of another antigestagen.

9. A pharmaceutical composition of claim 1, wherein the prostaglandin is prostaglandin $E_2$, prostaglandin $F_{2\alpha}$, 16-phenoxy-ω-17,18,19,20-tetranor-$PGE_2$-methylsulfonylamide, 16,16-dimethyl-trans-$\Delta^2$-$PGE_1$-methyl ester, 9-deoxo-16,16-dimethyl-9-methylene-$PGE_2$, a prostaglandin F derivative, 15-methyl-$PGF_{2\alpha}$-methyl ester, (5Z,13E)-(9R,11R,15R)-9-chloro-11,15-dihydroxy-16,16-dimethyl-5,13-prostadienoic acid, (5Z,13E)-(9R,11R,15R)-11,15dihydroxy-9-fluoro-16-phenoxy-17,18,19,20-tetranor-5,13-prostadienoic acid, (5Z,13E)-(9R,11R,15R)-11,15-dihydroxy-16,16-dimethyl-9-fluoro-5,13-prostadienoic acid (DE-OS 31 26 924), (5Z,13E)-(9R,11R,15R)-9-bromo-11,15-dihydroxy-16-phenoxy-17,18,19,20-tetranor-5,13-prostadienoic acid.

or (5Z,13E)-(9R,11R,15R)-9-bromo-11,15-dihydroxy-16,16-dimethyl-5,13-prostadienoic acid.

10. A pharmaceutical composition of claim 1, wherein the antigestagen is
11β-[(4-N,N-dimethylamino)-phenyl]-17β-hydroxy-17α-propinyl-4,9(10)-estradien-3-one,
11β-[(4-N,N-dimethylamino)-phenyl]-17β-hydroxy-13-methyl-17α-propinyl-4,9(10)-estradien-3-one,
11β-(4-N,N-dimethylamino)-phenyl]-17aβ-hydroxy-17a$_a$-propinyl-D-homo-4,9(10),16-estratrien-3-one,
11β-p-methoxyphenyl-17β-hydroxy-17α-ethinyl-4,9(10)-estradien-3-one, or
11β-(4-dimethylaminophenyl)-17α-hydroxy-17β-(3-hydroxypropyl)-13α-methyl-4,9-gonadien-3-one.

11. A pharmaceutical composition of claim 7 wherein the prostaglandin is 0.1 to 0.3 mg of 16-phenoxy-ω-17,18,19,20-tetranor-PGE$_2$-methylsulfonylamide or a biologically equivalent amount of another prostaglandin and the composition is adapted for i.m. or i.v. administration.

12. A pharmaceutical composition of claim 7 wherein the prostaglandin is 0.03 to 0.5 mg of 16-phenoxy-ω-17,18,19,20-tetranor-PGE$_2$-methylsulfonylamide or a biologically equivalent amount of another prostaglandin and the composition is adapted for local administration.

13. A pharmaceutical composition of claim 4, wherein the amount of antigestagen is 10-200 mg per dosage unit of 11β-[(4-N,N-dimethylamino)-phenyl]-17β-hydroxy-17α-propinyl-4,9(10)-estradien-3-one or a biologically equivalent amount of another antigestagen.

14. A method of inducing an abortion in a pregnant patient comprising administering to the patient an effective amount of a composition of claim 1.

15. A method of inducing labor in a pregnant patient comprising administering to the patient an effective amount of a composition of claim 1.

16. A method of claim 14, wherein the administration of the prostaglandin and the antigestagen is simultaneous.

17. A method of claim 14, wherein the administration of the prostaglandin and the antigestagen is sequential.

18. A method of claim 14, wherein the prostaglandin and the antigestagen are administered in separate dosage units.

19. A method of claim 15, wherein the administration of the prostaglandin and the antigestagen is simultaneous.

20. A method of claim 15, wherein the administration of the prostaglandin and the antigestagen is sequential.

21. A method of claim 15, wherein the prostaglandin and the antigestagen are administered in separate dosage units.

22. A method of inducing an abortion in a pregnant patient comprising administering to the patient an effective amount of a composition of claim 3.

23. A method of inducing labor in a pregnant patient comprising administering to the patient an effective amount of a composition of claim 3.

24. A method of inducing an abortion in a pregnant patient comprising administering to the patient an effective amount of a composition of claim 7.

25. A method of inducing labor in a pregnant patient comprising administering to the patient an effective amount of a composition of claim 7.

26. A method of inducing an abortion in a pregnant patient comprising administering to the patient an effective amount of a composition of claim 8.

27. A method of inducing labor in a pregnant patient comprising administering to the patient an effective amount of a composition of claim 8.

28. A method of inducing an abortion in a pregnant patient comprising administering to the patient an effective amount of a composition of claim 9.

29. A method of inducing labor in a pregnant patient comprising administering to the patient an effective amount of a composition of claim 9.

30. A method of inducing an abortion in a pregnant patient comprising administering to the patient an effective amount of a composition of claim 10.

31. A method of inducing labor in a pregnant patient comprising administering to the patient an effective amount of a composition of claim 10.

* * * * *



APPEARS THIS WAY
ON ORIGINAL

UNITED STATES PATENT AND TRADEMARK OFFICE

# CERTIFICATE OF CORRECTION

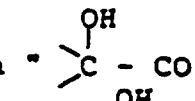
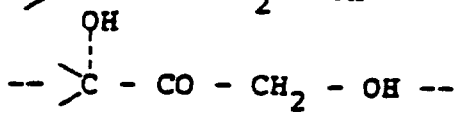
PATENT NO. : 4,386,085

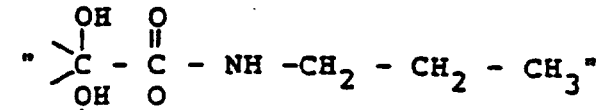
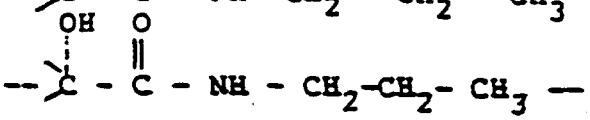
DATED : May 31, 1983

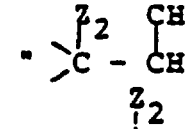
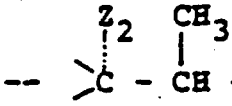
INVENTOR(S) : JEAN G. TEUTSCH ET AL.



It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Column 3, line 50: The formula "  " should read 

Column 3, line 55: The formula "  " should read 

Column 3, line 60: The formula "  " should read 

Column 6, line 34: "epxoide" should read -- epoxide --.

Column 8, line 51: "bisox-" should read -- bisoxy]- --.

Column 8, line 52: Delete "y]-".

Column 8, line 60: "17Δ" should read -- 17α --.

Column 8, line 61; Column 28, lines 11 and 21; Column 41, line 57; Column 43, line 66: "ethaned-" should read — ethane- —.

Column 8, line 62; Column 28, line 12 and 22; Column 41, line 58; Column 43, line 67: "iyl" should read -- diyl --.

UNITED STATES PATENT AND TRADEMARK OFFICE

# CERTIFICATE OF CORRECTION

PATENT NO. : 4,386,085 

DATED : May 31, 1983

INVENTOR(S) : JEAN G. TEUTSCH ET AL.

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Column 30, line 31: "dimethylaminoe-" should read -- dimethylamino- --.

Column 30, line 32: "thoxy" should read -- ethoxy --.

Column 30, line 36; Column 34, line 6; Column 37, last line: "1-" should read -- 10- --.

Column 30, line 37; Column 34, line 7; Column 38, first line: Delete "0".

Column 32, line 7: "alcol" should read -- alcohol --.

Column 39, line 11: "(propa-1,21" should read -- (propa-1,2 --.

Column 41, line 48: "17β1-ol" should read -- 17-β-ol --

Column 41, line 65: Delete "b".

Column 46, line 30: "$\Delta^6$" should read -- $\Delta^9$ --.

Column 47, line 53: "17βol" should read -- 17β-ol --.

Column 49, line 2: "19-nor-17β" should read -- 19-nor-17α --.

Column 51, line 46: "hydrox-" should read -- hydroxy- --

Column 51, line 47: "yimino" should read -- imino --.

Column 51, line 50: "phenyl]-B 17-hydroxyimino" should read -- phenyl]-17-hydroxyimino --.

Column 57, line 63: Delete "1"

Column 57, line 64: "0α" should read -- 10α --

APPEARS THIS WAY
ON ORIGINAL

UNITED STATES PATENT AND TRADEMARK OFFICE

# CERTIFICATE OF CORRECTION

PATENT NO. : 4,386,085 Page 3 of 3

DATED : May 31, 1983

INVENTOR(S) : JEAN G. TEUTSCH ET AL.

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Column 62, 3rd last line: "to 7 to 15" should read -- of 7 to 15 --.

Column 64, line 55: " $-\overset{O}{\overset{\|}{C}}CH_2-OH$" should read -- $-\overset{O}{\overset{|}{C}}CH_2OH$ --

Signed and Sealed this

Eighteenth Day of October 1983

[SEAL]

Attest:

GERALD J. MOSSINGHOFF

Attesting Officer Commissioner of Patents and Trademarks

APPEARS THIS WAY
ON ORIGINAL

## A Request for Logistic Regression Analyses

Contact: _____ or
_____ cder.fda.gov

**Statistical Software to be Used:** Stata, SPSS or SAS

**Final Product:** Original computer printout, including but are not limited to, names and coding of the dependent and independent variables, number of observations, odds ratio, standard error, and p-value or 95%CI.

**Logistic Models:** (Two Models with different dependent and independent variables)

Model #1:

1. Dependent variable: Q9- How likely to prescribe it if FDA approves mifepristone (please code "very likely" and "somewhat likely" as 1, and all others as 0")
2. Independent variables:
   Specialty: please code ObGyn as 1 and FPP as 0
   Sex (Q27): please code Male as 1 and Female 0
   Age (Q26): please code "24-39" and "40-49" as 1 and all others as 0
   Practice Site (Q22): please create two dummy variables for "Urban", "Suburban" and "Rural"
   Type of practice (Q21): please code "Solo" as 1 and all others as 0
   Surgical abortion (Q1): please code Response A as 1 and all others as 0
3. Modeling: please force all independent variables into the model

Model #2:

1. Dependent variable: Q12(g) - if (INSERT), would you be more or less likely to prescribe mifepristone, or would it have no effect (please code "no effect" and "more likely" as 1 and all others as 0)
2. Independent variables:
   Specialty: please code ObGyn as 1 and FPP as 0
   Likelihood to prescribe (Q9): please code "very likely" and "somewhat likely" as 1, and all others as 0
   Sex (Q27): please code Male as 1 and Female 0
   Age (Q26): please code "24-39" and "40-49" as 1 and all others as 0
   Practice Site (Q22): please create two dummy variables for "Urban", "Suburban" and "Rural"
   Type of practice (Q21): please code "Solo" as 1 and all others as 0
   Surgical abortion (Q1): please code Response A as 1 and all others as 0
3. Modeling: please force all independent variables into the model

Printed by

# Electronic Mail Message

**Sensitivity:** COMPANY CONFIDENTIAL

**Date:** 12-Apr-1999 11:40am
**From:**

**Dept:** HFD-820 PKLN 14B45
**Tel No:**

**TO:** See Below
**Subject:** Re: FWD: Inspection schedule for RU-486

We do have a drug
and less of a problem in terms of getting it inspected. I don't know all the particulars as yet, but , will be getting the necessary information soon. Primarily I wanted to alert you since the DS site is in China. Due to the nature of the drug, the firm is very concerned with ANY identification with the product. The Population Council is even exploring mechanisms to try to keep the actual DP manufacturers name off the labels.

>
>We have given the heads up to the necessary DEIO folks for inspection
>planning and will attempt to meet the July inspection request. However,
>we will need further information, such as the firms complete name,
>address, phone numbers and contacts in order to plan the inspection.
To
>the best of my knowledge, we have no inspectional history of Hualian...

>
>We will need such information as soon as it is available so that we can
>begin the inspection process.
>
>While OC does not directly schedule the inspection trips, I expect that
>there may be multiple trips to India. Given the visibility of RU-483,
>we are well aware of this high priority.
>
>This does lead to a secondary question. Has The Population Council
>found an alternate finished dosage manufacturer? Who will be
>manufacturing the finished dosage?
>
>Thanks,
>

**Distribution:**

**TO:**

**CC:**
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Printed by

# Electronic Mail Message

**Sensitivity:** COMPANY CONFIDENTIAL

**Date:** 12-Apr-1999 08:54am
**From:**
**Dept:** HFD-322 MPN1 272
**Tel No:**

**TO:** See Below
**Subject:** Re: FWD: Inspection schedule for RU-486

We have given the heads up to the necessary DEIO folks for inspection planning and will attempt to meet the July inspection request. However, we will need further information, such as the firms complete name, address, phone numbers and contacts in order to plan the inspection. To the best of my knowledge, we have no inspectional history of Hualian...

We will need such information as soon as it is available so that we can begin the inspection process.

While OC does not directly schedule the inspection trips, I expect that there may be multiple trips to India. Given the visibility of RU-483, we are well aware of this high priority.

This does lead to a secondary question. Has The Population Council found an alternate finished dosage manufacturer? Who will be manufacturing the finished dosage?

Thanks,

**Distribution:**

**TO:**

**CC:**
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**CC:**
**CC:**

Printed by [redacted]

# Electronic Mail Message

**Sensitivity:** COMPANY CONFIDENTIAL

**Date:** 12-Apr-1999 08:39am
**From:** [redacted]

**Dept:** HFD-322 MPN1 272
**Tel No:** [redacted]

**TO:** [redacted]

**Subject:** FWD: Inspection schedule for RU-486

Printed by

# Electronic Mail Message

**Date:** 12-~~Apr~~-1999 06:20am
**From:**

**Dept:** HFD-820 PKLN 14B45
**Tel No:**

**Subject:** FWD: Inspection schedule for RU-486

The Population Council has evidently finally found a manufacturer for RU-486 for the US market. This amendment has not yet been filed to the NDA and the manufacturer of drug substance is in China. The firm has indicated that they are ready for inspection now, but they are having a consultant look a second time at their facility to be sure it meets cGMPs. They have indicated that they should be ready by July. They have also indicated that they have heard that a team is headed into China for inspections around that time and would like to get on the schedule for that trip if possible.

Due to the visible nature of this NDA and the problems associated with getting inspections done in mainland China, we would like to get this on the schedule before the submission is received, particularly if an inspection trip to the region is already being planned. This is not a goal date that I would want to miss due to inspection scheduling problems. I would like to add this topic to the EES group discussions to see what we can do.

Thanks,

Printed by [redacted]

# Electronic Mail Message

**Sensitivity:** COMPANY CONFIDENTIAL

**Date:** 11-Oct-2000 12:46pm
**From:** [redacted]

**Dept:** HFD-324 MPN1 265
**Tel No:** [redacted]

**TO:** [redacted]

**Subject:** Request for RU-486 records

[redacted]

Please allow the record to show the following:

Although, our EES shows that I received the Establishment Inspection Report (EIR) of [redacted] into EES and corresponded with the District Office (DO) on the status of their inspection of this drug, the record should also show the following. I neither reviewed that EIR nor any other record associated with this drug. My review was not necessary since the DO acted on it first. [redacted]

However, I also believe in the good that this agency does in bringing to market drugs that alleviate pain and suffering and heal. Hence I choose to stay here and work for the good which is greater.

[redacted] FDA Consumer Safety Officer

Printed by [redacted]

# Electronic Mail Message

**Sensitivity:** COMPANY CONFIDENTIAL

**Date:** 05-Oct-2000 09:58am
**From:** [redacted]

**Dept:** HFD-005 WOC2 6027
**Tel No:** [redacted]

**TO:** subscribers:

**CC:** [redacted]
**CC:**
**CC:**
**CC:**
**Subject:** FOI Requests for Records - RU 486

The FDA has received several Freedom of Information Act (FOIA) requests for documents related to RU-486, mifepristone, Mifeprex, or NDA 20-687. Each office, division, or organizational unit in CDER must review all files in its possession, custody, or control for any documents which refer or relate to any of these terms. Additionally, each CDER employee must search his/her personal files, including e-mails, for any such documents. Records that are responsive to the FOIA requests might include, but are not limited to, division files, personal files, e-mail correspondence (personal and divisional), memoranda, handwritten notes, and documentation of telecons. The all-subscriber e-mail of last week does not need to be submitted. No documents relating to any of the identified terms should be destroyed at this time.

Please send copies (not the originals) of all documents, with a cover page or note indicating the sender, to [redacted] in HFD-205 for evaluation. Email records should be sent in hard copy, not forwarded electronically. You should send copies of all identified documents, regardless of whether or not you believe a document is releasable. HFD-205 will review all of the documents to determine whether they are subject to release; sending a copy of a document to HFD-205 does not mean that the document will automatically be released.

We need copies of all documents by close of business on Friday, October 18, 2000. It is extremely important that we receive the copies by this time, so you should not wait until that afternoon to begin collecting them. Again, please retain the originals.

If you have any questions, please call [redacted]

Printed by [redacted]

# Electronic Mail Message

**Sensitivity:** COMPANY CONFIDENTIAL

**Date:** 05-Oct-2000 09:58am
**From:** [redacted]

**Dept:** HFD-005 WOC2 6027
**Tel No:** [redacted]

**TO:** subscribers:

**CC:** [redacted]
**CC:** [redacted]
**CC:** [redacted]
**CC:** [redacted]
**Subject:** FOI Requests for Records - RU 486

The FDA has received several Freedom of Information Act (FOIA) requests for documents related to RU-486, mifepristone, Mifeprex, or NDA 20-687. Each office, division, or organizational unit in CDER must review all files in its possession, custody, or control for any documents which refer or relate to any of these terms. Additionally, each CDER employee must search his/her personal files, including e-mails, for any such documents. Records that are responsive to the FOIA requests might include, but are not limited to, division files, personal files, e-mail correspondence (personal and divisional), memoranda, handwritten notes, and documentation of telecons. The all-subscriber e-mail of last week does not need to be submitted. No documents relating to any of the identified terms should be destroyed at this time.

Please send copies (not the originals) of all documents, with a cover page or note indicating the sender, to [redacted] for evaluation. Email records should be sent in hard copy, not forwarded electronically. You should send copies of all identified documents, regardless of whether or not you believe a document is releasable. HFD-205 will review all of the documents to determine whether they are subject to release; sending a copy of a document to HFD-205 does not mean that the document will automatically be released.

We need copies of all documents by close of business on Friday, October 18, 2000. It is extremely important that we receive the copies by this time, so you should not wait until that afternoon to begin collecting them. Again, please retain the originals.

If you have any questions, please call [redacted]

Printed by [redacted]

# Electronic Mail Message

**Sensitivity:** COMPANY CONFIDENTIAL

**Date:** 02-Oct-2000 08:10am
**From:** [redacted]

**Dept:** HFD-322 MPN1 272
**Tel No:** [redacted]

**TO:** [redacted]

**CC:** [redacted]
**Subject:** Re: Chinese Inspection Records/DMFs

We copied all the files for Southwest. Is this a new congressional request for Shanghai Pharmaceutical #12. We haven't heard that one before. We have an inspection file on Shanghai Pharmacceutical No. 12. The only inspection was in 1990 and the firm is now inactive. Its unusual, but this file does contain a copy of a 1989 ammendment to [redacted]

Printed by

# Electronic Mail Message

**Sensitivity:** COMPANY CONFIDENTIAL

**Date:** 29-Sep-2000 01:26pm
**From:**

**Dept:** HFD-322 MPN1 272
**Tel No:**

**TO:**

**Subject:** Re: Need Inspection Reports for Chinese Firms

The Shaghai Hua Lain file is about 2 inches and the Soutwest file is about 3/4 inch thick. We already copied these two files Wednesday per request of for the Committee holding the counterfeit bulk drug hearing next week. There were given to the same day. Is that the same committee?

Printed by

# Electronic Mail Message

**Sensitivity:** COMPANY CONFIDENTIAL

**Date:** 27-Sep-2000 11:30am
**From:**

**Dept:** HFD-322 MPN1 272
**Tel No:**

**TO:**

**Subject:** Re: FW: Chinese Inspection records -- URGENT!!

We copied the two Shanghai Hua Lian EIRs & exhibits, the Firms' responses following both inspections, our untitled letter, our internal documents.

We have no DMFs and have advised to have someone else get them from files. is delivering the inspectional copies to

Printed by [redacted]

# Electronic Mail Message

**Sensitivity:** COMPANY CONFIDENTIAL

**Date:** 26-Sep-2000 09:16am
**From:** [redacted]

**Dept:** HFD-322 MPN1 272
**Tel No:** [redacted]

**TO:** [redacted]
**TO:** [redacted])

**Subject:** Re: Request for Information

1. [redacted] was not identified as the agent for Shanghai Hua Lian. [redacted] was identified as the consultant and was present during the inspections and submitted all correspondence. Danco Group in New York is identified in the July EIR as the U.S. Agent and importer.

2. The re-inspection was July 24-28, 2000. I think [redacted] sent you a copy of the EIR. I am writing a summary of both inspections for GC and I will send you a copy when done. Mifepristone is the subject of an NDA which has not yet been approved. The firm only shipped a few test batches of the bulk drug to the US so far.

3. I am not aware of any relationship between [redacted] or Danco. I think they are competitors, but Danco may be a broker. I know of no connection between Shanghai Hua Lian and [redacted]

4. The initial inspection in Oct. 99 found that the analytical methods were being used were different than what was submitted. We did not beleive this was fraud however, and was corrected by submission of a supplement with the correct methods.

Printed by

# Electronic Mail Message

**Date:** 24-May-2000 12:41pm
**From:**

**Dept:** HFD-322 MPN1 272
**Tel No:**

**TO:**
**TO:**

**Subject:** FWD: Shanghai Hualian

I thought so...

Printed by [redacted]

# Electronic Mail Message

**Date:** 24-May-2000 12:41pm
**From:** [redacted]

**Dept:** HFD-322 MPN1 272
**Tel No:** [redacted]

**TO:** [redacted]
**TO:** [redacted]

**Subject:** FWD: Shanghai Hualian

I thought so...

Printed by [redacted]

# Electronic Mail Message

**Date:** 24-May-2000 11:31am
**From:** [redacted]
**Dept:**
**Tel No:**

**Subject:** Shanghai Hualian

Due date was moved to 30 Sept. per [redacted] Will try and get this done before that date.

Printed by [redacted]

# Electronic Mail Message

**Date:** 24-May-2000 11:31am
**From:** [redacted]
**Dept:**
**Tel No:**

**Subject:** Shanghai Hualian

Due date was moved to 30-Sept, per [redacted] Will try and get this done before that date.

[redacted]

Printed by [redacted]

# Electronic Mail Message

**Sensitivity:** COMPANY CONFIDENTIAL

**Date:** 13-Apr-2000 05:26pm
**From:** [redacted]

**Dept:** HFD-324 MPN1 265
**Tel No:** [redacted]

**TO:**

**CC:**
**CC:**
**CC:**
**CC:**
**Subject:** Reinspection of Chinese facility for NDA # 20687

Good Afternoon,

The purpose of this message is to respond to your email to [redacted] (attached below) regarding the inspection of [redacted] for NDA 20687, located in China.

We have received the request for the inspection and notified the appropriate office to begin the inspection trip preparations. We received a package from [redacted] today, which will also assist in the reinspection of this facility.

I noticed in your email, that you want this resubmission to meet the 6 month timeframe. Currently, EES references a UF date of 5/21/00. Which is the correct timeframe. Our office and the Office of Regulatory Affairs is aware of the high profile nature of this application and would appreciate clarification regarding the intended UF date which must be met. This will assist in the inspection planning process.

We will continue to monitor this application. Should you wish to contact me, I can be reached directly at [redacted]

/s/

[redacted]

Investigations and Preapproval Compliance Branch, HFD-324
CDER/Office of Compliance

[redacted] was talking to me about the recent resubmission (3/31/00) of the application from the Population Council, Mifepristone. My approvable letter to them on 2/18/2000 listed deficiencies with GMPs. Knowing the Pop Council would be responding shortly to this approvable letter, the Reproductive division sent a request to compliance for reinspection of the Chinese plant on 2/25/00. Given the high profile nature of this drug, I would appreciate if you could make sure we are on track for reinspection within the 6 month review period. Thanks so much for your assistance. Let me know if you need more information.

[redacted]

Printed by [redacted]

# Electronic Mail Message

**Sensitivity:** COMPANY CONFIDENTIAL

**Date:** 12-Apr-2000 08:31am
**From:** [redacted]

**Dept:** HFD-324 MPN1 265
**Tel No:** [redacted]

**TO:** [redacted]
**TO** [redacted]

**Subject:** FWD: Reinspection Chinese Plant on Population Council Application

FYI - Please give me an update on this status.

[redacted]

Printed by [redacted]

# Electronic Mail Message

**Sensitivity:** COMPANY CONFIDENTIAL

**Date:** 12-Apr-2000 10:02am
**From:** [redacted]
**Dept:** HFD-322 MPN1 272
**Tel No:** [redacted]

**TO:** [redacted] ( [redacted] )

**Subject:** Re: FWD: Reinspection Chinese Plant on Population Council Application

We are still waiting for [redacted] Review division, to give us information on issues to be covered during the inspection. I will try to call him as soon as possible. The request for a reinspection was entered into EES and forwarded to DEIO. DEIO is trying to schedule, but the last word we have from the review division is that they would get us additional information, and that the firm had not yet replied to the deficiency letter.

Printed by [redacted]

# Electronic Mail Message

**Date:** 12-Apr-2000 11:14am
**From:** [redacted]

**Dept:** HFD-580 PKLN 17B31
**Tel No:** [redacted]

**TO:** [redacted]

**CC:** [redacted]
**CC:** [redacted]
**Subject:** NDA 20-687

I just sent you a package with addition information for NDA 20-687. If you have any questions about this package, please contact me.

Thank you,

[redacted]

Printed by

# Electronic Mail Message

**Date:** 12-Apr-2000 11:18am
**From:**

**Dept:** HFD-580 PKLN 17B31
**Tel No:**

**TO:**

**Subject:** NDA 20-687

I forgot to ask you what your internal mail address is.

Printed by

# Electronic Mail Message

**Sensitivity:** COMPANY CONFIDENTIAL

**Date:** 12-Apr-2000 11:26am
**From:**

**Dept:** HFD-322 MPN1 272
**Tel No:**

**TO:**

**Subject:** Re: NDA 20-687

thanks

Printed by [redacted]

# Electronic Mail Message

**Sensitivity:** COMPANY CONFIDENTIAL

**Date:** 12-Apr-2000 11:27am
**From:** [redacted]

**Dept:** HFD-322 MPN1 272
**Tel No:** [redacted]

**TO:** [redacted]

**Subject:** Re: NDA 20-687

HFD-
I am in Metro Park North I

Printed by

# Electronic Mail Message

**Date:** 11-Apr-2000 07:24pm
**From:**

**Dept:** HFD-301 MPN1 254
**Tel No:**

**Subject:** FWD: Reinspection Chinese Plant on Population Council Application

Printed by [redacted]

# Electronic Mail Message

**Date:** 05-Apr-2000 03:59pm
**From:** [redacted]

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

**Subject:** Reinspection Chinese Plant on Population Council Application

[redacted] was talking to me about the recent resubmission (3/31/00) of the application from the Population Council, Mifepristone. My approvable letter to them on 2/18/2000 listed deficiencies with GMPs. Knowing the Pop Council would be responding shortly to this approvable letter, the Reproductive division sent a request to compliance for reinspection of the Chinese plant on 2/25/00. Given the high profile nature of this drug, I would appreciate if you could make sure we are on track for reinspection within the 6 month review period. Thanks so much for your assistance. Let me know if you need more information.

Printed by

# Electronic Mail Message

**Date:** 13-Mar-2000 11:37am
**From:**

**Dept:** HFD-580 PKLN 17B31
**Tel No:**

**TO:**

**Subject:** Re: NDA 20-687 Mifepristone

I will do that. I noticed that a withhold recommendation was made today on my request for inspection of the Chinese facility. Do I need to resubmit another request?

Thanks,

>If you can get us something within about 2 weeks, it would be helpful in
>planning the inspection.

Printed by

# Electronic Mail Message

**Date:** 13-Mar-2000 08:28am
**From:**

**Dept:** HFD-580 PKLN 17B31
**Tel No:**

**TO:**

**Subject:** Re: NDA 20-687 Mifepristone

How soon do you need the details? I need to take a look at an IND in another Division that is using DS manufactured at this site.

Thanks,

>I see that this NDA has been reentered into EES for the Chinese API
>manufacturer. Per our earlier discussion, can you provide any additional
>background on what should be covered during the inspection.

Printed by

# Electronic Mail Message

**Date:** 09-Apr-1999 03:04pm
**From:**

**Dept:** HFD-580 PKLN 17B45
**Tel No:**

**Subject:** Inspection schedule for RU-486

As I discussed this afternoon, I am providing the following information for the inspection:

1. NDA 20-687

2. AE letter was issued on September 18, 1996

3. They are planning to submit an amendment in response to the AE letter in June, 1999, which will trigger the review clock of 6-month.

4. The manufacturing sites of the drug substance is in China and its name is Hualian (no information on the address yet) which manufactured 3 batches. More detailed information will be submitted in the near future.

5. They like to have this site inspected in July.

I will greatly appreciate it, if you could bring this issue during your meeting with OC this month, so that the inspection can be scheduled in July for this NDA.

Thank you for your help.

Printed by [redacted]

# Electronic Mail Message

**Sensitivity:** COMPANY CONFIDENTIAL

**Date:** 29-Jun-2000 08:18am
**From:** [redacted]
**Dept:**
**Tel No:**

**TO:** [redacted]

**Subject:** Re: Request for Documentation

Thank you. I don't need the exhibits. However, if there was a Chinese version of the response, I'd like a copy of that, too. You can mail me the documents at:

[redacted]

I appreciate your help.

> -----Original Message-----
> [redacted]
> Sent: Thursday, June 29, 2000 8:09 AM
> To: [redacted]
> Subject: Re: Request for Documentation
> Sensitivity: Confidential
>
> Yes, we can get you a copy of the Oct 99 EIR & response. The firm's name
> is Shanghai Hua Lian Pharmacceutical Factory. Do you also want the
> exhibits fromthe inspection? I will have them copied, where are you
> located?
>
> A reinspection is planned for July. I am not sure exactly when. It was
> scheduled to check on the corrections from the previous inspection and not
> just to look into these allegations.
>
> You can contact me [redacted] for copies & information, but if I am not
> here, call [redacted] She handles all our files.
>

Printed by

# Electronic Mail Message

**Date:** 25-Sep-2000 04:03pm
**From:**

**Dept:**
**Tel No:**

**TO:**

**Subject:** Request for Information

As you may have heard, another letter came in from regarding Mifepristone. Can you provide me the following information:
1) Is the US agent for Shanghai Hualian Pharmaceutical (and if not, who is the US agent)
2) The findings of FDA's March 2000 inspection of Shanghai Hualian Pharmaceutical (if possible, a copy of the summary would be appreciated)
3) The relationship between Shanghai Hualian and Danco Group regarding Mifepristone and its importation to the US
4) Any indication of the possibility of fraud involving Mifepristone

If you have any questions, please don't hesitate to ask. Thank you in advance for your assistance.

Printed by

# Electronic Mail Message

**Sensitivity:** COMPANY CONFIDENTIAL

**Date:** 24-May-2000 10:23am
**From:**

**Dept:** HFD-324 MPN1 265
**Tel No:**

**TO:**

**CC:**
**Subject:** FWD: RE: Reinspection of Chinese facility for NDA # 20687

Looks like drop dead UF date is 9/30/00 for this application - have we any feedback from DEIO that we WILL make the UF date for this high priority, high visibility application?

# Electronic Mail Message

**Date:** 5/17/00 12:09:51 PM
**From:**
**Subject:** NDA 20-687 Mifepristone

Hi Everyone,
Attached are draft meeting minutes. Please comment and correct by COB, 5/24/00.
Thanks,

# Electronic Mail Message

**Date:** 4/28/00 7:51:17 AM
**From:**
**To:**
**Subject:** FWD: Environmental information for 20-687

FYI

# Electronic Mail Message

**Date:** 4/28/00 6:53:09 AM
**From:** [redacted]
**Subject:** Environmental information for 20-687

The information that they submitted to address the chemistry deficiency (submit a categorical exclusion under 21 CFR 25.31(b) for the drug substance manufacturer) is fine.

However in this packet of information they say they have submitted a categorical exclusion claim for the drug product. I have a completed environmental assessment and finding of no significant impact in my files for this application. These were signed 7/11/96. Could you look into this and let me know what is going on?

Thanks,

[redacted]

Printed by

# Electronic Mail Message

**Sensitivity:** COMPANY CONFIDENTIAL

**Date:** 14-Feb-2000 10:00am
**From:**

**Dept:** HFD-324 MPN1 265
**Tel No:**

**TO**
**TO**
**TO**

**CC:**
**CC**
**Subject:** Re: fwd:

Hi

Thanx for promptly getting back with us on this. We will be in touch, if we need further info.

r

>
>Good Morning.
>
>The following message was provided this morning by CSO regarding
>the reinspection of If you require further
>information, please let us know. We can arrange for a call if needed. If
>not, thanks for your assistance.
>
>
>
>
>
>
>
>----------[Original Message]----------
>
>I closed out the inspection on Friday and will send a recommendation
>to approve NDA #20-687 to this morning. I made two 483 comments. The
>first was regarding the labeling of vials - they labeled a few vials
>incorrectly on their but the data itself was not affected. The
>second was regarding labeling of stability samples - they labeled the
>stability sample with the wrong place of storage, but the ACTUAL place and

>condition of storage was observed to be correct. I also spent a considerable
>amount of time on the [redacted] issue, and no deviations were observed.
>
[redacted]
>

Printed by [redacted]

# Electronic Mail Message

**Date:** 14-Feb-2000 07:24am
**From:** [redacted]
**Dept:**
**Tel No:**

**TO:** [redacted]
**TO:** [redacted]

**Subject:** fwd: [redacted]

Good Morning.

The following message was provided this morning by CSO [redacted] regarding the [redacted] reinspection of [redacted] If you require further information, please let us know. We can arrange for a call if needed. If not, thanks for your assistance.

[redacted]

----------[Original Message]----------

I closed out the inspection at [redacted] on Friday and will send a recommendation to approve NDA #20-687 to [redacted] this morning. I made two 483 comments. The first was regarding the labeling of [redacted] vials - they labeled a few vials incorrectly on their [redacted], but the data itself was not affected. The second was regarding labeling of stability samples - they labeled the stability sample with the wrong place of storage, but the ACTUAL place and condition of storage was observed to be correct. I also spent a considerable amount of time on the [redacted] issue, and no deviations were observed.

[redacted]

Printed by [redacted]

# Electronic Mail Message

**Date:** 14-Feb-2000 07:56am
**From:** [redacted]

**Dept:**
**Tel No:**

**TO:**
**TO**

**Subject:** fwd: [redacted]

FYI...The Investigator finished the follow-up [redacted] on NDA 20-687...see message below. [redacted] will enter the District's recommendation to approve today. Pls contact me if there are remaining questions.

----------[Original Message]----------

I closed out the inspection at [redacted] on Friday and will send a recommendation to approve NDA #20-687 to [redacted] this morning. I made two 483 comments. The first was regarding the labeling of [redacted] vials - they labeled a few vials incorrectly on their [redacted] but the data itself was not affected. The second was regarding labeling of stability samples - they labeled the stability sample with the wrong place of storage, but the ACTUAL place and condition of storage was observed to be correct. I also spent a considerable amount of time on the [redacted] issue, and no deviations were observed.

Printed by [redacted]

# Electronic Mail Message

**Sensitivity:** COMPANY CONFIDENTIAL

**Date:** 11-Feb-2000 01:56pm
**From:** [redacted]
**Dept:** HFD-324 MPN1 265
**Tel No:** [redacted]

**TO** [redacted]
**TO** [redacted]

**CC** [redacted]
**CC** [redacted]
**CC:** [redacted]
**Subject:** Re: [redacted] NDA 20-687

[redacted]

I assume you mean without the company. If so, we would be available about 10:30 AM for tel-con with [redacted] Try [redacted] first; if no answer try my number which is [redacted] Thanx

[redacted] and I met with [redacted] yesterday. They have made a lot of
>corrective actions and provided much more clarification on the
>issue. Although different from what they originally explained, it seems to be
>more reasonable. [redacted] is working on confirming the other corrective actions
>and trying to determine if there are any other related issues. We briefly
>discussed a conference call on Monday if you or you and [redacted] are available.
>Hopefully there will be enough information to make a final decision. So far
>things are looking good.
>
>Please advise when you might be available. Morning may be better for [redacted] in
>case he has to go out again, but I will try to find out. I will also check
>with [redacted]
>
>Thanks for your help.
>
>[redacted]
>
>[redacted]
>
>[redacted]:der.fda.gov Wrote:
>| FROM too long. Original FROM is
>| [redacted]
>|
>|
>| ---------- Original Message Follows
>| ----------
>|
>| Hi [redacted]
>|
>| I got your message that you folks were starting the follow/up
>| Wednesday. Thanx
>|

> Do you have a rough idea which way this will go at this
> point?
>
> Thanx
>
>
>
>
>
>
>

Printed by [redacted]

# Electronic Mail Message

**Date:** 11-Feb-2000 11:32am
**From:** [redacted]

**Dept:**
**Tel No:**

**TO:** [redacted]

**CC:** [redacted]
**CC** [redacted]
**Subject:** Re: [redacted] NDA 20-687

[redacted] and I met with [redacted] yesterday. They have made a lot of corrective actions and provided much more clarification on the [redacted] issue. Although different from what they originally explained, it seems to be more reasonable. [redacted] is working on confirming the other corrective actions and trying to determine if there are any other related issues. We briefly discussed a conference call on Monday if you or you and [redacted] are available. Hopefully there will be enough information to make a final decision. So far things are looking good.

Please advise when you might be available. Morning may be better for [redacted] in case he has to go out again, but I will try to find out. I will also check with [redacted]

Thanks for your help.

[redacted]

[redacted] :der.fda.gov Wrote:

FROM too long. Original FROM is [redacted]

[redacted] der.fda.gov>

---------- Original Message Follows ----------

Hi [redacted]

I got your message that you folks were starting the follow/up
Wednesday. Thanx

Do you have a rough idea which way this will go at this point?

Thanx

[redacted]

Printed by

# Electronic Mail Message

**Date:** 08-Feb-2000 09:00am
**From:**

**Dept:**
**Tel No:**

**TO:**

**CC:**
**Subject:** Follow-up

Good Morning.

I wanted to let you know that the follow-up inspection will be initiated tomorrow 2/9/00. We will update you as soon as possible. Please feel free to call me directly if you need information.

Thanks.

Printed by

# Electronic Mail Message

**Date:** 03-Feb-2000 03:13pm
**From:**

**Dept:**
**Tel No:**

**TO**

**Subject:** Re: NDA 20-687 reinspection at

Hi

I will know more tomorrow. has been out this week and will be in tomorrow. is out until Monday. I have an investigator and possibly an analyst, but I have the same concern. I will discuss it as early as possible with and get back to you.

Thanks.

cder.fda.gov Wrote:

> FROM too long. Original FROM is
> der.fda.gov>
>
> ---------- Original Message Follows ----------
>
> Hi
>
> Do you have any idea when you might start the reinspection of the
> subject firm?
>
> We are concerned that it be completed in enough time to process the
> report, if it be lengthy.
>
> Thanx

MIF 003463

Printed by

# Electronic Mail Message

**Sensitivity:** COMPANY CONFIDENTIAL

**Date:** 03-Feb-2000 01:48pm
**From:**
**Dept:** HFD-324 MPN1 265
**Tel No:**

**TO:**
**TO:**

**CC:**
**CC:**
**Subject:** NDA 20-687 reinspection at

Hi

Do you have any idea when you might start the reinspection of the subject firm?

We are concerned that it be completed in enough time to process the report, if it be lengthy.

Thanx

Printed by

# Electronic Mail Message

**Sensitivity:** COMPANY CONFIDENTIAL

**Date:** 02-Feb-2000 12:57pm
**From:**

**Dept:** HFD-324 MPN1 265
**Tel No:**

**TO:**
**TO:**

**Subject:** Re: reinspection at for NDA 20-687

as not sure of the process. Hence my response.

>
>I was under the impression that this was the district's decision, did
expect CDER to issue the reinspection?

>
>
>

>
>CDER will not issue another assignment for reinspection, if
>reinspecition to verify corrections can be accomplished within the next
>few days. Please keep in mind that we are fast approaching the 2/19/00
>PDUFA date.
>
>Thanx

Printed by

# Electronic Mail Message

**Sensitivity:** COMPANY CONFIDENTIAL

**Date:** 02-Feb-2000 09:04am
**From:**

**Dept:** HFD-324 MPN1 265
**Tel No:**

**TO:**
**TO:**
**TO:**

**CC:**
**Subject:** reinspection at for NDA 20-687

Folks,

CDER will not issue another assignment for reinspection, if reinspecition to verify corrections can be accomplished within the next few days. Please keep in mind that we are fast approaching the 2/19/00 PDUFA date.

Thanx

Printed by [redacted]

# Electronic Mail Message

**Date:** 27-Jan-2000 03:05pm
**From:** [redacted]
**Dept:**
**Tel No:**

**TO:** [redacted]

**CC:** [redacted]
**Subject:** fwd: Re: [redacted] 20-687 Mifepristone

[redacted]

Comments:

Our server is now up...I just received [redacted] evaluation of [redacted], [redacted] response (FDA483 . I asked him to look at it since they referred to this as an "industry practice". Their explanation is being FedEx'd to your attention...you should receive it tomorrow. Sorry for the confusion....

[redacted]

----------[Original Message]----------

Hi [redacted]
[redacted] response to the [redacted] question is satisfactory. According to their response, the SOP for their method states that [redacted]

[redacted]

>Hi [redacted]
>I'm faxing you a further response from [redacted] re: their reply to 483 Observation
the use of [redacted] sample injections for the calibration of [redacted] systems. I know you had some issues with their initial

>explanation. Pls advise me if this helps to explain it further.
>Thanks for your help.
>[redacted]

>

Printed by

# Electronic Mail Message

**Date:** 26-Jan-2000 09:22am
**From:**
**Dept:**
**Tel No:**

**TO:**

**CC:**
**CC:**
**Subject:** - NDA 20-687 Mifepristone

submitted two responses (11/10&30/99) regarding the 483 observations. We reviewed them along with reviewer) and sent a reply to the firm on 1/11/00. While their corrective actions appear appropriate (for the most part), we advised the firm that a reinspection is indicated to verify their corrective actions. If you can forward me your fax number, I'll fax over our letter to the firm. has copies of the firm's responses, which are too lengthy to fax).

Is there a timeframe for approval?

Printed by [redacted]

# Electronic Mail Message

**Sensitivity:** COMPANY CONFIDENTIAL

**Date:** 16-Jul-1996 11:20am
**From:** [redacted]

**Dept:** HFD-070 PKLN 8B45
**Tel No:** [redacted]

**TO:** All ALL-IN-1 users on this node ( SUBSCRIBERS: )

**Subject:** Meeting Alert

From [redacted]

On Friday, July 19, the Advisory Committee for Reproductive Health Drugs will meet at the FDA Technical Center on Industrial Drive to consider mifepristone for interruption of early pregnancy. We want you to be aware of unusual restrictions concerning attendance and parking at this meeting.

The meeting is scheduled to begin at 9 am. An overflow room with live video will be set up at the Gaithersburg Hilton, 620 Perry Pkwy, Gaithersburg. Because of the limited seating capacity and very limited parking at the Technical Center, FDA employees who have not been directly involved in the meeting (your name would be on a list), but who are interested in watching this meeting, are encouraged to do so from the Gaithersburg Hilton. With a few exceptions, access to the Technical Center will be only by shuttle bus starting at 7 am from the Gaithersburg Hilton or Montgomery County Fairgrounds, (no walk-ins will be allowed) and limited to approximately the first 200 people, depending on room capacity. FDA observers would be included in this group. FDA participants who are on the list, but who do not have reserved parking will be bused to the site from the Oak Grove Complex (2094-2098), located on Gaither Road, south of Shady Grove Road. FDA staff, of course, have the right to attend the meeting with the general public, but, as noted, space will be limited.

Printed by [redacted]

# Electronic Mail Message

**Sensitivity:** COMPANY CONFIDENTIAL

**Date:** 18-May-1999 10:05am
**From:** [redacted]

**Dept:** HFD-322 MPN1 272
**Tel No:** [redacted]

**TO:** [redacted]

**CC:** [redacted]
**CC:**
**Subject:** FWD: [redacted] RU486

FYI

MIF 003471

Printed by [redacted]

# Electronic Mail Message

**Date:** 10-May-1999 03:29pm
**From:** [redacted]

**Dept:** HFD-322 MPN1 272
**Tel No:** [redacted]

**Subject:** Re: FWD: RU-486

Thanks for the feedback. Are you all aware of Population Council asking [redacted] RU-486?

I found no evidence in the application via EES that this site was approved for such an operation. Is this a contact with one of the manufacturers?

We have reason to believe, based on a pre-operational review that this firm, intended to [redacted] RU-486.

Appreciate your assistance,

[redacted]

DAN COATS
INDIANA

404 RUSSELL SENATE OFFICE BUILDING
(202) 224-5623

INDIANAPOLIS OFFICE:
1180 MARKET TOWER, 10 WEST MARKET STREET
INDIANAPOLIS, IN 46204
(317) 226-5555

United Stat
WASHINGTON,

OPTIONAL FORM 99 (7-90)
FAX TRANSMITTAL
To
Fax #
# of pages ▶
Phone #
NSN 7540-01-317-7368 5099-101 GENERAL SERVICES ADMINISTRATION

April 11, 1996

The Honorable Donna E. Shalala
Secretary
Department of Health and Human Services
200 Independence Avenue, Southwest
Washington, D.C. 20201

**SPECIAL**

Dear Secretary Shalala:

As chairman of the Senate Committee on Labor and Human Resources Subcommittee on Children and Families, I request copies of documents in the possession of the Food and Drug Administration, including any of its advisory committees, relating to the drug known as RU 486 (mifepristone), developed by the company Roussel Uclaf SA.

I understand that the Population Council has an active investigational new drug application (IND) to use RU 486 for abortion. Several reports indicate extensive communications between representatives of the Clinton administration and private companies and organizations, including the Population Council, concerning the future availability of RU 486 for use as an abortion pill in the United States. These reports, together with issues raised in a Citizens' Petition on RU 486 submitted last year to the FDA, have generated serious concern for public safety and the integrity of the drug approval process. Consequently, I request that you provide the following information:

(1) Any and all written or recorded communications, including electronic or telephonic communications, involving one or more of the persons listed below and relating to RU 486 from January 1, 1992, up to the present (i.e., up until the time the document search is conducted).

When used in the above request, the word "communication" includes, but is not limited to: correspondence, electronic mail, memoranda, notes of conversations, calendars, notes of meetings (including the agenda, the list of those in attendance and the time, date and location of each meeting), telephone logs, message slips, and the travel logs of administration employees. It also includes all communications that do not specifically mention RU 486 but that may relate to its possible approval by FDA for use as an abortifacient (e.g., communications relating to the acceptability of foreign data in the drug approval process, communications with drug companies that produce a prostaglandin that is or could be used in conjunction with RU 486, etc.).

For each such communication, please indicate the date of the communication, the names and the professional or organization affiliations of all persons involved or present, and the offices within the FDA from which the communications were obtained. Also, please indicate which communications, if any, are confidential and may not be disclosed to the public.

This request includes all communications involving the following persons from January 1, 1992, up to the present:

President Clinton, Mrs. Clinton, and White House staff
Other administration officials or personnel, including yourself, _____, _____, and _____ of the Endocrine Drugs Division of the FDA
Edouard Sakiz, Dr. Andre Ulmann, and other officers, employees, or representatives of Roussel Uclaf
Margaret Catley-Carlson, Dr. Wayne Bardin, and other officers, employees, and representatives of the Population Council
David A. Grimes, M.D.
Daniel R. Mishell, M.D.
Suzanne Poppema, M.D.
Officers, employees and representatives of the following companies and organizations:
- Hoechst AG of Germany
- Hoechst Celanese Corporation
- Hoechst-Roussel Pharmaceuticals
- Rhone-Poulenc of France
- Schering AG of Germany
- G.D. Searle Company
- Upjohn Company
- Gynopharma, Inc.
- Cabot Medical Corporation
- Aurora Medical Services
- Fund for the Feminist Majority
- Planned Parenthood Federation of America
- Reproductive Health Technologies Project
- National Abortion Federation
- National Abortion and Reproductive Rights Action League (formerly the National Abortion Rights Action League)
- Oregon Science Health University of Portland, Oregon
- Center for Reproductive Law and Policy
- National Organization for Women
- Women's Issues Network

(2) Any and all documents relating to the implementation of President Clinton's January 22, 1993, memorandum for the Secretary of Health and Human Services regarding the importation of RU 486.

In this memorandum, the President asked the Secretary to take the following three actions:

a) "promptly instruct the FDA to determine whether there is sufficient evidence to warrant exclusion of RU 486 from the list of drugs that qualify for the personal use importation exemption";

b) " immediately take steps to rescind Import Alert 66-47" if the "FDA concludes that RU 486 meets the criteria for the personal use importation exemption"; and

c) "promptly assess initiatives by which the Department of Health and Human Services can promote the testing, licensing, and manufacturing in the United States of RU 486 and other antiprogestins."

When used in the above request, the word "document" includes, but is not limited to: internal and external documents of the Food and Drug Administration, documents prepared by persons or offices outside the FDA (including documents prepared by non-governmental persons, organizations, or companies), correspondence, electronic mail, memoranda, notes of conversations, calendars, notes of meetings (including the agenda, the list of those in attendance and the time, date and location of each meeting), and telephone logs, message slips, and travel logs of administration employees. It also includes all documents that do not specifically mention RU 486 but which may relate to its possible approval by FDA for use as an abortifacient (e.g., criteria for the acceptance of foreign data, the use of a prostaglandin with RU 486, etc.). For each such document, please indicate the date of the document, the author or authors of the document, the persons to whom it was given or sent, and the offices within the Department from which the documents were obtained. Please separate the documents in this second request into three categories based on which of the three actions requested by the President the documents address. Again, please indicate which communications, if any, are confidential and may not be disclosed to the public.

With respect to both requests (1) and (2) above, I ask that the information provided be complete, and that you not withhold documents or excise portions of documents on grounds of relevancy. If you assert executive privilege as to any document, please identify each one by providing the following information: the type of document and a summary of its contents; the date, author(s), and recipient(s) of document, the basis for withholding it from Congress, and an explanation if that basis was asserted on any document(s) in the 103rd Congress.

Please inform me if any communications (particularly, but not exclusively, e-mails) have been destroyed and the policy of the FDA on the destruction of e-mail messages. I request that every person involved in filling this requests, be asked if he or she has had e-mail messages related to RU 486 that have been destroyed and, if so, to provide a description of the subjects of those messages.

Finally, I wish to know the process used to comply with this letter, and to receive copies of all communications (memos, electronic mail, letters, etc.) produced in furtherance of filling this request for documents.

Thank you for your attention to this inquiry. I look forward to receiving the information by May 15, 1996. If you foresee any difficulty in fulfilling this request by that date, please notify me immediately. Vince Ventimiglia of my staff will be available to work with you if you have any questions. He can be reached at 202-224-1133.

Sincerely,

Dan Coats
U.S. Senator

**SPECIAL**

cc: Dr. David A. Kessler

APPEARS THIS WAY
ON ORIGINAL

04-16-1996-0005

TOM A. COBURN, M.D.
2D DISTRICT, OKLAHOMA
COMMITTEE ON COMMERCE
SUBCOMMITTEES
TELECOMMUNICATIONS AND FINANCE
HEALTH AND ENVIRONMENT
ENERGY AND POWER

511 CANNON HOUSE OFFICE BUILDING
WASHINGTON, DC 20515
(202) 225-2701
(202) 225-3038 (FAX)
215 STATE STREET, SUITE 515
MUSKOGEE, OK 74401
(918) 687-2533
(918) 682-8503 (FAX)

# Congress of the United States
## House of Representatives
Washington, DC 20515–3602

November 10, 1995

Dr. David A. Kessler
Commissioner
U.S. Food and Drug Administration
Room 14-71
5600 Fishers Lane
Rockville, Maryland 20857

Dear Dr. Kessler:

As a member of the House Commerce Committee's Subcommittee on Health and the Environment, I write to request copies of documents in the possession of the Food and Drug Administration, including any of its advisory committees, relating to the drug known as RU 486 (mifepristone), developed by the company Roussel Uclaf SA.

I understand that the Population Council has an active investigational new drug application (IND) to use RU 486 for abortion. Several reports have appeared which indicate extensive communications between representatives of the Clinton administration and private companies and organizations, including the Population Council, concerning the future availability of RU 486 for use as an abortion pill in the United States. These reports, together with issues raised in a Citizens' Petition on RU 486 recently submitted to the FDA, have generated serious concern for public safety and the integrity of the drug approval process. Consequently, I am requesting that you provide the following information:

1) Any and all written or recorded communications, including electronic or telephonic communications, to or from the persons listed below relating to RU 486 from January 1, 1992 up to the present (i.e., up until the time the document search is conducted).

When used in the above request, the word "communication" includes, but is not limited to: correspondence, electronic mail, memoranda, notes of conversations, notes of meetings, copies of the calendars of meetings, and telephone logs and message slips. It also includes all communications which do not specifically mention RU 486 but which may relate to its possible approval by FDA for use as an abortifacient (eg., communications relating to the acceptability of foreign data in the drug approval process).

For each such communication, please indicate the date of the communication, the names and the professional or organizational affiliations of all persons involved or present, the locations of meetings, and the offices within the FDA from which the communications were obtained. Also, please indicate which communications, if any, are confidential and may not be disclosed to the public.

This request includes all communications sent to or by the following persons from January 1, 1992 up to the present:

President Clinton, Mrs. Clinton, and White House staff
Other administration officials or personnel, including yourself, [redacted] and [redacted] of the Endocrine Drugs Division of the FDA
Edouard Sakiz, Dr. Andre Ulmann, and other officers, employees, or representatives of Roussel Uclaf
Margaret Catley-Carlson, Dr. Wayne Bardin, and other officers, employees, and representatives of the Population Council
David A. Grimes, M.D.
Daniel R. Mishell, M.D.
Suzanne Poppema, M.D.
Officers, employees and representatives of the following companies and organizations:
Hoechst AG of Frankfurt, Germany
Hoechst Celanese Corporation of Somerville, New Jersey
Hoechst-Roussel Pharmaceuticals of Somerville, New Jersey
Rhone-Poulenc of Paris
Schering AG of Berlin, Germany
G.D. Searle Company of Skokie, Illinois
Upjohn Company of Kalamazoo, Michigan
Gynopharma, Inc. of Somerville, New Jersey
Cabot Medical Corporation of Langhorne, Pennsylvania
Aurora Medical Services of Seattle, Washington
Fund for the Feminist Majority
Planned Parenthood Federation of America
Reproductive Health Technologies Project
National Abortion Federation
National Abortion and Reproductive Rights Action League (formerly the National Abortion Rights Action League)
Oregon Science Health University of Portland, Oregon
Center for Reproductive Law and Policy
National Organization for Women
Women's Issues Network

2) Any and all documents relating to the implementation of President Clinton's January 22, 1993, memorandum for the Secretary of Health and Human Services regarding the importation of RU 486.

In this memorandum, the President asked the Secretary to take the following three actions:

a) "promptly instruct the FDA to determine whether there is sufficient evidence to warrant exclusion of RU-486 from the list of drugs that qualify for the personal use importation exemption;"

b) "immediately take steps to rescind Import Alert 66-47" if the "FDA concludes that RU-486 meets the criteria for the personal use importation exemption;" and

c) "promptly assess initiatives by which the Department of Health and Human Services can promote the testing, licensing, and manufacturing in the United States of RU-486 and other antiprogestins."

When used in the above request, the word "document" includes, but is not limited to: internal and external documents of the Food and Drug Administration, documents prepared by persons or offices outside the FDA (including documents prepared by non-governmental persons, organizations, or companies), correspondence, electronic mail, memoranda, notes of conversations, notes of meetings, copies of the calendars of meetings, and telephone logs and message slips. It also includes all documents which do not specifically mention RU 486 but which may relate to its possible approval by FDA for use as an abortifacient (eg., criteria for the acceptance of foreign data, etc.). For each such document, please indicate the date of the document, the author or authors of the document, the persons to whom it was given or sent, and the offices within the Department from which the documents were obtained. Please separate the documents in this second request into three categories based on which of the three actions requested by the President the documents address. Again, please indicate which communications, if any, are confidential and may not be disclosed to the public.

Thank you for your attention to this inquiry. A similar request for documents has been submitted to Secretary Shalala. I look forward to receiving the information by December 1, 1995. If you foresee any difficulty in fulfilling this request by that date, please notify me immediately. Roland Foster on my staff will be available to work with you if you have any questions.

Sincerely,

Tom A. Coburn, M.D.
Member of Congress

CDER
CRA

Page 1 **ADDITIONAL RU-486 DOCUMENTS FOR CONGRESSIONAL DOCUMENT REQUEST FROM REP. COBURN**

| Trac # | Corres. Date | To | From | Subject |
|---|---|---|---|---|
| 92 2781 | 3/31/92 | Dr. Kessler | Pro-Choice Resources TFischman, LRoper-Batker, Dconway | Urges FDA to allow testing and dist. of RU486 |
| 92 4417 | 5/14/92 | Mr. Benson | G Miyoshi (State of HI) | Transmits copy of State of HI House Resolution re; RU486 |
| 92 4494 | 6/29/92 | Mr. Myoshi | Dr. Kessler | Responds to State of HI resolution on RU486 |
| 92 4775 | 6/9/92 | Dr. Kessler | M Susser | APHA write to request brief paper on FDA psition of RU486 for pub in APHA Journal. Has attached article as ref. By Banwell/Paxman |
| 92 5600 | 7/15/92 | Dr. Kessler | Judi Brown, American Life League | Defends import alert on RU486 (doesn't want RU486 avail in US). |
| 92 7024 | 10/8/92 | "Interested Parties" | Doug Johnson, NRTL | National Right to Life sends fax re: Bogus ABC New Report on Admin Position on RU486 Breast Cancer Research (several attachments + f/u fax later in the same day) |
| 92 7511 | 11/4/92 | Dr. Kessler | J Taylor, Du Page Senior Citizens Council | Supports efforts to ensure medical research testing of RU486 for breast cancer and aging diseases. |
| 92 7612 | 11/6/92 | Dr. Kessler | Alan Stone,M.D. of Harvard University | Write re his research assistnat doing paper on RU486. Asks Kessler to send materials to help in her research. |
| 92 7612 | 1/21/93 | [redacted] | Dr. Kessler | Response to [redacted] 11/6/92 letter. Encloses matericals that discuss drug approval process and RU486 import restrictions (copies NOT in scanner and not attached). |
| 92 8091 | 12/8/92 | Dr. Kessler | Dr. Hanita Blumfield, AJ Congress | Provides petitions gathered by Commission for Women's Equality of American Jewish Congress support testing of RU486 in the US. |
| 92 8287 | 12/18/92 | [redacted] | Bro. Ronald J.J. DeMello of Nat'l Catholic Pro-Life Program | Opposes RU486. Wants to know why FDA supports RU486 ("aborting unborn babies.") |
| 92 8287 | 2/2/93 | DeMello | [redacted] | Reply to 12/18/92 letter. |

 **ADDITIONAL RU-486 DOCUMENTS FOR CONGRESSIONAL DOCUMENT REQUEST FROM REP. COBURN**

| Trac # | Corres. Date | To | From | Subject |
|---|---|---|---|---|
| 93 0037 | 12/29/92 | Dr. Kessler | F. Mayer, PPSI | Pharmacists Planning Service, Inc. - writes (enclosing several letters/docs - ATTACHED) re: PPSI's request to have FDA release RU486 for use in the US. |
| 93 0169 | 1/13/93 | Kessler/ [redacted] | [redacted] | Letter requesting that FDA grant her an IND for RU486 to treat a meningeal brain tumor (MANY ATTACHMENTS - redacted for patient identifiers). |
| 93 0255 | 1/13/93 | Dr. Kessler | Dr. Hanita Blumfield, AJ Congress | Submits (more) petitions gathered by Commission for Women's Equality of American Jewish Congress. Supports testing of RU486 in the US (petitions NOT in scanner) |
| 93 0320 | 1/22/93 | SF Chronicle (Editor) | Carol Scheman | Response to column by Beverly Zakarian about RU486 |
| 93 0510 | 1/27/93 | Dr. Kessler | [redacted] | Reports on hazard re: RU486 and increased risk of breast cancer. |
| 93 0899 | 2/19/93 | Dr. Kessler/ [redacted] | [redacted] & family | On behalf of patient [redacted] requesting IND to use RU486 to treat her inoperable meningioma of the brain. (Multiple attachments - all need redaction for patient identifiers) |
| 93 0928 | 2/11/93 | Secy Shalala | Sharon Belton, Mpls City Council | Writes in support of S. 222 to require FDA to collect same info on RU486 as is required for submission by a mfr. Supports Clinton admin position on RU486 (favors its use). |
| 93 0930 | 2/16/93 | Dr. Billy Jones (cc: to Secy of HHS) | L Sepersky and S Hollander (City of New York Community Board # 6) | Encloses resolution passed at the Board's 2/10/93 meeting re: moratorium on R-U pharmaceutical products and petition to R-U to begin testing of RU486 by FDA. |
| 93 1341 | 3/3/93 | Secy Shalala | [redacted] | Advises Secy that his company has expressed interest to R-U in a license to develop and market RU486 in North America (attaches copies of correspondence between them and R-U.) |
| 93 2172 | 4/20/93 | Dr. Kessler | [redacted] | Supports availability of RU486. |
| 93 2202 | 4/21/93 | Dr. Kessler | D. Stone, Physicians for RU486 | Wants Kessler/FDA to keep his organization abreast of developments affecting status of RU486. |

 **ADDITIONAL RU-486 DOCUMENTS FOR CONGRESSIONAL DOCUMENT REQUEST FROM REP. COBURN**

| Trac # | Corres. Date | To | From | Subject |
|---|---|---|---|---|
| 93 2202 | 5/28/93 | D. Stone | [redacted] | Response to 4/21/93 letter. |
| 93 2755 | 5/20/93 | Dr. Kessler | [redacted] | Opposes Dr. Kessler's "advocacy of abortion" re: avail of RU486. Asks Kessler to resign. |
| 93 2998 | 4/1/93 | Dr. Kessler | Wedi Lehman, Right to Life League of S. CA | Distressed over FDA attempts to introduce RU486 in the US as an abortifacient. |
| 93 2998 | 6/23/93 | Ms. Lehman | [redacted] | Response to 4/1/93 letter. |
| 93 3016 | 5/24/93 | Dr. Kessler | E Kornreich, Association of the Bar of City of NY | Requests report on status of FDA's reconsideration of prior admin's decision to exclude RU486 from FDA's exemption allowing individual (personal) import of 3-months' supply of uapproved new drug for serious medical condition. |
| 93 3016 | 6/30/93 | Kornreich | [redacted] | Response to 5/24/93 ltr. |
| 93 3894 | 8/6/93 | [redacted] | Kenneth Shine, IOM | Invitation to dinner and briefing on IOM's report on RU486 evaluating current state of science regarding clinical uses of antiprogestins. |
| 93 3895 | 8/6/93 | Dr. Kessler | Kenneth Shine, IOM | Same invite as above. |
| 93 3948 | 8/2/93 | Dr. Kessler | [redacted] Disciple Renewal | Comments on Disciples of Christ resolution urging FDA to take immediate steps to check safety/efficacy of RU486 and other anti-protgesterone drugs. Opposes use of RU486 for abortfacient purposes. |
| 93 4035 | 8/11/93 | [redacted] | S Snedeker & H Hadley of TV 12 (Wast Palm Beach, FL) | Thank you for [redacted] interview on 7/29/93 on RU486. |
| 93 4520 | 9/14/93 | Dr. Kessler | Molla Donaldson, IOM/NAS | Encloses copy of IOM report "Clinical Applications of Mifepristone (RU 486) and Other Antiprogestins: Assessing the Science and Recommending a Research Agenda. (Copy of report NOT in scanner). |
| 93 4671 | 9/15/93 | Dr. Kessler | Geoffrey Dalander, Group 486 | Wants to know if generic form of RU486, mfgd under Pop Council patent expect to be given as swift an approval by FDA as the R-U form could expect? |

 **ADDITIONAL RU-486 DOCUMENTS FOR CONGRESSIONAL DOCUMENT REQUEST FROM REP. COBURN**

| Trac # | Corres. Date | To | From | Subject |
|---|---|---|---|---|
| 93 5076 | 11/9/93 | [redacted] | G Dalander, Group 486 | Same letter (above) as to Kessler. |
| 93 4671 & 5076 | 1/21/94 | Dalander/Moritz | [redacted] | Responds to 9/15 ltr. And 11/9/93 letter re: swift approval for generic version of RU486. Note: don't have copy of Secy letter mentioned in MKP response. |
| 93 4824 | 9/11/93 | [redacted] | [redacted] an individual) | Requests FDA allow her to market RU486. (Needs redaction?) |
| 93 4824 | 10/12/93 | [redacted] | [redacted] | Response to 9/11/93 letter. Tells her, despite her interest, FDA needs official "sponsor" in order to supply info on safety/effectiveness to FDA. |
| 93 9731 | 12/3/93 | [redacted] | Etienne Baulieu | Provides copy of paper delivered at the Ciba Foundation meeting on "The role of the media in science communication" in Stockholm 12/7-8/93 re:presentation of RU486 in the media. |
| 94 0565 | 1/11/94 | [redacted] | John Fleder (Olsson, Frank, & Weeda) | Expresses thanks on behalf of client for help re: import of RU486 to treat a cancer patient. Patient identifiers have been REDACTED. |
| 94 5321 | 6/3/94 | Dr. Kessler | Judie Brown, American Life League, Inc. | Concerned about FDA's activism in bringing RU486 to the US as an abortifacient (opposed). Requests info from FDA. |
| 94 5321 | 6/13/94 | Judie Brown | [redacted] | Respone to 6/3/94 letter to Kessler. Encloses requested info (document not in scanner). |
| 94 5703 | 6/10/94 | FDA | [redacted] | Submits proposed study and voluminous materials re: RU486 vs Arsenic poisioning vs Nembutol Treatment (makes allegations of suppression of intellectual ideas by Waterloo University in Canada?) |
| 94 5703 | 7/11/94 | [redacted] | [redacted] | Response to 6/10/94 submission (general info on how drugs are studied/approved) |
| 94 5908 | 5/21/94 | Mrs. Clinton | [redacted] patient) | Requests compassionate use of RU486 to treat a meningioma (brain tumor). Patient identifiers REDACTED |
| 95 2698 | 3/16/95 | Dr. Kessler | [redacted] | Requests restrictions on distribution of RU486 only to MDs with surgical privileges & those able to do D & C procedures. |

 **ADDITIONAL RU-486 DOCUMENTS FOR CONGRESSIONAL DOCUMENT REQUEST FROM REP. COBURN**

| Trac # | Corres. Date | To | From | Subject |
|---|---|---|---|---|
| 95 2698 | 4/6/95 | [redacted] | [redacted] | Response to 3/16/95 letter to Dr. Kessler. |
| 95 3751 | 4/11/95 | [redacted] | [redacted] | Responds to [redacted] letter of 4/6/95 re: RU486. |

Drafted: [redacted] HF-40:1/2/96
486index.abc

APPEARS THIS WAY
ON ORIGINAL

D. N COATS
INDIANA

404 RUSSELL SENATE OFFICE BUILDING
(202) 224-5623

INDIANAPOLIS OFFICE
1180 MARKET TOWER, 10 WEST MARKET STREET
INDIANAPOLIS, IN 46204
(317) 226-5555

# United States Senate

WASHINGTON, DC 20510

COMMITTEES
ARMED SERVICES
LABOR AND HUMAN RESOURCES

April 11, 1996

Dr. David A. Kessler
Commissioner
U.S. Food and Drug Administration
Room 14-71
5600 Fishers Lane
Rockville, Maryland 20857

Dear Dr. Kessler:

As chairman of the Senate Committee on Labor and Human Resources Subcommittee on Children and Families, I request copies of documents in the possession of the Food and Drug Administration, including any of its advisory committees, relating to the drug known as RU 486 (mifepristone), developed by the company Roussel Uclaf SA.

I understand that the Population Council has an active investigational new drug application (IND) to use RU 486 for abortion. Several reports indicate extensive communications between representatives of the Clinton administration and private companies and organizations, including the Population Council, concerning the future availability of RU 486 for use as an abortion pill in the United States. These reports, together with issues raised in a Citizens' Petition on RU 486 submitted last year to the FDA, have generated serious concern for public safety and the integrity of the drug approval process. Consequently, I request that you provide the following information:

(1) Any and all written or recorded communications, including electronic or telephonic communications, involving one or more of the persons listed below and relating to RU 486 from January 1, 1992, up to the present (i.e., up until the time the document search is conducted).

When used in the above request, the word "communication" includes, but is not limited to: correspondence, electronic mail, memoranda, notes of conversations, calendars, notes of meetings (including the agenda, the list of those in attendance and the time, date and location of each meeting), telephone logs, message slips, and the travel logs of administration employees. It also includes all communications that do not specifically mention RU 486 but that may relate to its possible approval by FDA for use as an abortifacient (e.g., communications relating to the acceptability of foreign data in the drug approval process, communications with drug companies that produce a prostaglandin that is or could be used in conjunction with RU 486, etc.).

96-2902
MIF 003485

For each such communication, please indicate the date of the communication, the names and the professional or organization affiliations of all persons involved or present, and the offices within the FDA from which the communications were obtained. Also, please indicate which communications, if any, are confidential and may not be disclosed to the public.

This request includes all communications involving the following persons from January 1, 1992, up to the present:

President Clinton, Mrs. Clinton, and White House staff
Other administration officials or personnel, including yourself, [redacted], and [redacted] of the Endocrine Drugs Division of the FDA
Edouard Sakiz, Dr. Andre Ulmann, and other officers, employees, or representatives of Roussel Uclaf
Margaret Catley-Carlson, Dr. Wayne Bardin, and other officers, employees, and representatives of the Population Council
David A. Grimes, M.D.
Daniel R. Mishell, M.D.
Suzanne Poppema, M.D.
Officers, employees and representatives of the following companies and organizations:
- Hoechst AG of Germany
- Hoechst Celanese Corporation
- Hoechst-Roussel Pharmaceuticals
- Rhone-Poulenc of France
- Schering AG of Germany
- G.D. Searle Company
- Upjohn Company
- Gynopharma, Inc.
- Cabot Medical Corporation
- Aurora Medical Services
- Fund for the Feminist Majority
- Planned Parenthood Federation of America
- Reproductive Health Technologies Project
- National Abortion Federation
- National Abortion and Reproductive Rights Action League (formerly the National Abortion Rights Action League)
- Oregon Science Health University of Portland, Oregon
- Center for Reproductive Law and Policy
- National Organization for Women
- Women's Issues Network

(2) Any and all documents relating to the implementation of President Clinton's January 22, 1993, memorandum for the Secretary of Health and Human Services regarding the importation of RU 486.

In this memorandum, the President asked the Secretary to take the following three actions:

a) "promptly instruct the FDA to determine whether there is sufficient evidence to warrant exclusion of RU 486 from the list of drugs that qualify for the personal use importation exemption" ;

b) " immediately take steps to rescind Import Alert 66-47" if the "FDA concludes that RU 486 meets the criteria for the personal use importation exemption"; and

c) "promptly assess initiatives by which the Department of Health and Human Services can promote the testing, licensing, and manufacturing in the United States of RU 486 and other antiprogestins."

When used in the above request, the word "document" includes, but is not limited to: internal and external documents of the Food and Drug Administration, documents prepared by persons or offices outside the FDA (including documents prepared by non-governmental persons, organizations, or companies), correspondence, electronic mail, memoranda, notes of conversations, calendars, notes of meetings (including the agenda, the list of those in attendance and the time, date and location of each meeting), and telephone logs, message slips, and travel logs of administration employees. It also includes all documents that do not specifically mention RU 486 but which may relate to its possible approval by FDA for use as an abortifacient (e.g., criteria for the acceptance of foreign data, the use of a prostaglandin with RU 486, etc.). For each such document, please indicate the date of the document, the author or authors of the document, the persons to whom it was given or sent, and the offices within the Department from which the documents were obtained. Please separate the documents in this second request into three categories based on which of the three actions requested by the President the documents address. Again, please indicate which communications, if any, are confidential and may not be disclosed to the public.

With respect to both requests (1) and (2) above, I ask that the information provided be complete, and that you not withhold documents or excise portions of documents on grounds of relevancy. If you assert executive privilege as to any document, please identify each one by providing the following information: the type of document and a summary of its contents; the date, author(s), and recipient(s) of document, the basis for withholding it from Congress, and an explanation if that basis was asserted on any document(s) in the 103rd Congress.

Please inform me if any communications (particularly, but not exclusively, e-mails) have been destroyed and the policy of the FDA on the destruction of e-mail messages. I request that every person involved in filling this requests, be asked if he or she has had e-mail messages related to RU 486 that have been destroyed and, if so, to provide a description of the subjects of those messages.

Finally, I wish to know the process used to comply with this letter, and to receive copies of all communications (memos, electronic mail, letters, etc.) produced in furtherance of filling this request for documents.

Thank you for your attention to this inquiry. A similar request for documents has been submitted to Secretary Shalala. I look forward to receiving the information by May 15, 1996. If you foresee any difficulty in fulfilling this request by that date, please notify me immediately. Vince Ventimiglia of my staff will be available to work with you if you have any questions. He can be reached at 202-224-1133.

Sincerely,

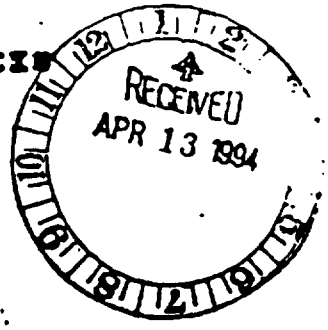
Dan Coats
U.S. Senator

APPEARS THIS WAY
ON ORIGINAL

cc: Honorable Donna.E. Shalala

DEPARTMENT OF HEALTH AND HUMAN SERVICES

April 12, 1994




TO: The Secretary
Through: DS _____
COS _____
ES _____
ASH /s/ _____ APR 12 1994

FROM: Deputy Commissioner/Senior Advisor to the Commissioner of Food and Drugs

SUBJECT: Pre-Meeting on RU-486 on April 13, 1994, at 5:30 p.m.--BRIEFING

PURPOSE

This is to prepare you for a meeting to be held on April 14, 1994, at 4:00 p.m., with representatives from Hoechst/Roussel Uclaf and the Population Council, on the status of their negotiations concerning RU-486.

PARTICIPANTS in APRIL 14 Meeting

Outside the Department

**Hoechst**
Lester Hyman and _____ Swidler and Berlin

**Roussel Uclaf**
_____ (new president)
_____ Business Development

**Population Council**
Margaret Catley Carlson
- Jim Boynton, attorney

HHS Officials

_____

_____

David Kessler

BACKGROUND - It has been over a year since President Clinton executed a memorandum to you, directing the assessment of initiatives to promote the testing, licensing, and manufacturing in the United States of RU-486 (mifepristone) (Tab A). It has also been a year since the April 1993 meeting at FDA, at which Roussel Uclaf expressed publicly its willingness to modify its contract with the Population Council and permit the Population Council and its sublicensees to produce and distribute RU-486 in the United States. Negotiations between the Population Council

FILE COPY

| OFFICE | SURNAME | DATE | OFFICE | SURNAME | DATE | OFFICE | SURNAME | DATE |
|---|---|---|---|---|---|---|---|---|
| | | | | | | | | |
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MIF 003489

and Hoechst/Roussel Uclaf have been ongoing since that time, however, a final contract has not been negotiated or signed. There has been a great deal of Congressional and media interest in RU-486 and speculation as to the reasons why the negotiations between Hoechst/Roussel Uclaf and the Population Council have not been concluded. A description of specific proactive activities that the Department has undertaken in relation to RU-486 is attached at Tab B. An overview chronology of all RU-486 activities is attached at Tab C.

CURRENT STATUS

The parties have been negotiating sporadically since the April 1993 meeting at the FDA.

The parties will have just concluded a face-to-face meeting on Tuesday, April 12th before meeting with you.

ISSUES THAT MAY BE RAISED BY THE PARTIES

OTHER EVENTS

A summary of other events related to RU-486, including the import alert, the status of Benten v. Kessler, women's groups activities, a hearing on RU-486, and Mr. Lawrence Lader's efforts, is attached at Tab E.

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Attachments
Tab A: President Clinton's Directive
Tab B: Proactive Activities by the Department
Tab C: Overview Chronology of RU-486
Tab D:
Tab E: Other Events of Interest
Tab F: Proposed Distribution Scheme for RU-486
Tab G: Import Alert Memoranda

THE WHITE HOUSE

WASHINGTON

January 22, 1993

MEMORANDUM FOR THE SECRETARY OF HEALTH AND HUMAN SERVICES

SUBJECT: Importation of RU-486

In Import Alert 66-47, the Food and Drug Administration ("FDA") excluded the drug Mifepristine -- commonly known as RU-486 -- from the list of drugs that individuals can import into the United States for their "personal use," although the drugs have not yet been approved for distribution by the FDA. (See FDA Regulatory Procedures Manual, Chapter 9-71.) Import Alert 66-47 effectively bans the importation into this Nation of a drug that is used in other nations as a nonsurgical means of abortion.

I am informed that in excluding RU-486 from the personal use importation exemption, the FDA appears to have based its decision on factors other than an assessment of the possible health and safety risks of the drug. Accordingly, I hereby direct that you promptly instruct the FDA to determine whether there is sufficient evidence to warrant exclusion of RU-486 from the list of drugs that qualify for the personal use importation exemption. Furthermore, if the FDA concludes that RU-486 meets the criteria for the personal use importation exemption, I direct that you immediately take steps to rescind Import Alert 66-47.

In addition, I direct that you promptly assess initiatives by which the Department of Health and Human Services can promote the testing, licensing, and manufacturing in the United States of RU-486 or other antiprogestins.

You are hereby authorized and directed to publish this memorandum in the Federal Register.

William J. Clinton

APPEARS THIS WAY
ON ORIGINAL

MIF 003492

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL

TAB C

# RU-486 OVERVIEW CHRONOLOGY

| | |
|---|---|
| 6/6/89 | FDA Commissioner Frank Young directed that an "import alert" on abortifacient drugs be issued. |
| 4/17/90 | The import alert was revised to include a list of the various chemical names for RU-486. This version of the import alert is currently in effect. |
| 11/19/90 | Congressional hearings were held by Congressman Ron Wyden before the Subcommittee on Regulation, Business Opportunities, and Energy of the Committee on Small Business, House of Representatives, on "RU 486: The Import Ban and Its Effect on Medical Research" |
| 1/3/92 | Letter from Dr. Ulmann of Roussel Uclaf to the review division confirming that Roussel agrees to help U.S. investigators perform clinical studies with RU-486, provided that (1) the studies are not in relation to abortion; (2) the protocols are medically and ethically acceptable; and (3) the investigators will comply with FDA rules and internal Roussel procedures with regards to reporting of side-effects, publications, etc. |
| 7/1/92 | The legality of the import alert was challenged by Ms. Benten who attempted to bring the drug into the U.S. (Benten v. Kessler, Civ. No. 92-3161, U.S. District Court for the Eastern District of New York.) The district court issued a preliminary injunction directing FDA to release the drug to Ms. Benten; the Court of Appeals stayed the district court's order the same day; three days later, the Supreme Court denied plaintiffs' request to lift the stay. Subsequently, Ms. Benten had a surgical abortion. |
| 9/92 | The Court of Appeals dismissed the appeal as moot and vacated the district court's decision. Both the government and plaintiffs filed motions before the district court which subsequently were withdrawn without prejudice to refiling at a future time. The government stated that it would inform the court when a decision was made by HHS on FDA's recommendation regarding the import alert. |
| 12/92 | FDA begins extensive contact with Roussel Uclaf, the manufacturer of RU-486, —— the company to submit a New Drug Application (NDA) for RU-486 for interruption of early pregnancy. On December 14, Dr. Kessler wrote to Roussel Uclaf on this drug; in response, on 12/17/92, Roussel Uclaf informed FDA that it was reviewing its strategy for beginning clinical trials in the U.S. and that it should have some proposals by the end of January 1993, at which time further discussions with the Agency would be pursued. |
| 12/16/92 | 34 newly elected House members urged Hoechst AG to begin studies of the abortifacient use in the U.S., stating that "American women should have the same choice as women in other nations to terminate a pregnancy in a safe and |

responsible manner."

1/22/93 President Clinton executed a memorandum to the Secretary, directing her to assess initiatives to promote the testing, licensing, and manufacturing in the United States of RU-486 (mifepristone) and to direct the FDA to reassess whether RU-486 qualifies for importation under FDA's personal use importation policy.

1/22/93 Dr. Kessler wrote to Dr. Sakiz, President of Roussel Uclaf, requesting a meeting during the first three days of February to discuss possible therapeutic uses of anti-progestational drugs and, in particular, FDA's interest in receiving an NDA for RU-486 for interruption of early pregnancy.

2/3/93 Dr. Kessler wrote to Prof. Hilger of Hoechst AG to inform him directly of FDA's interest in this matter and that FDA wants the opportunity to review an NDA for RU-486 for termination of early pregnancy. The letter asks for Prof. Hilger to expedite the process.

2/24/93 Senior representatives of FDA and Roussel Uclaf met to discuss clinical and manufacturing data on the drug that FDA would need in considering an NDA for an abortifacient indication. At that meeting, FDA received a strong commitment from Roussel Uclaf to continue to make the drug available for research on other potential uses. While asserting that RU-486 should be made available in the United States, the firm emphasized the importance of finding a way to achieve that goal without the involvement of Roussel Uclaf. FDA and Roussel Uclaf agreed to continue to work on this matter until remaining issues can be resolved.

3/2/93 FDA initiated a meeting with representatives from NIH's National Institute of Child Health and Human Development, National Cancer Institute, and Office of Research on Women's Health, to discuss with the NIH initiatives that were ongoing, and which could be planned, to respond to the President's directive to assess initiatives by which the Department can promote the testing in the United States of RU-486 and other antiprogestins.

3/12/93 The Secretary wrote to the president of Hoechst, the parent company of Roussel Uclaf, to urge him to eliminate corporate barriers to the introduction of RU-486 into the United States.

3/19/93 Letter to the Editor published in the Wall Street Journal from Searle, the manufacturer of Cytotec, indicating that Searle "strongly opposes any efforts to approve its (Cytotec) use with RU-486 in abortion, either in the U.S. or elsewhere."

3/31/93 Mr. Lawrence Lader, one of the plaintiffs in the pending litigation and President of Abortion Rights Mobilization (ARM), Inc., wrote to the Secretary indicating that ARM's scientists had manufactured a version of RU-486 at a U.S. lab and that ARM planned to apply to FDA for permission to test its version of the drug.

4/14/93 Attempts are made to encourage Prof. Hilger of Hoechst to attend the 4/20 meeting. In a 4/15/93 letter, Prof. Hilger indicates his unwillingness to attend and indicates that Dr. Sakiz of Roussel Uclaf will represent Hoechst at the 4/20 meeting. Prof. Hilger also outlines Hoechst's position that Hoechst will not be involved in the marketing or production of RU-486 for the U.S. market, and that its eventual distribution can only be done through third parties.

4/20/93 A meeting was held at which Roussel Uclaf indicated its willingness to modify the contract that it entered into with the Population Council, a non-profit scientific and technical organization, in 1983. These modifications would permit the Population Council and its sublicensees to produce and distribute RU-486 in the United States. The Population Council, with the active participation of Roussel Uclaf, agreed to work to identify a manufacturer for RU-486 for the United States market and to begin a clinical trial to test the drug in the United States. The Population Council expected this trial to be conducted in parallel with preparation of the NDA and agreed to move as soon as possible to submit an NDA. FDA indicated that it is prepared to expedite the review of a marketing application for RU-486, if one is submitted, based on established legal and scientific criteria.

5/4/93 ——— and others meet with FDA review division representatives to discuss the development of a non-French mifepristone as an abortifacient in the United States. At this meeting, the director of the review division indicated that if —— —— intended to pursue the development of his own mifepristone, FDA requirements would ———— ———— group could show bioequivalence to the Roussel Uclaf mifepristone, provide the chemical identity of the product, and receive permission to reference the Population Council's IND.

5/5/93 Roussel Uclaf submits to the review division additional data intended to support its proposed "training protocol" for the use of mifepristone for termination of early pregnancy to be conducted in the United States.

5/13/93 Stipulation and Order in which FDA agreed to advise the court and plaintiffs in the Benten case as to whether a recommendation had been made to the Secretary in response to the President's directive by July 15, 1993.

7/14/93 FDA forwarded a recommendation to PHS on the RU-486 import alert. In preparing the action memorandum, FDA contacted responsible individuals from the countries in which RU-486 is available in order to understand and describe the tightly controlled distribution system used in each country.

8/2/93 FDA is notified by the Population Council's lawyer that Roussel Uclaf has retained a law firm to try to work out a tripartite agreement with the government regarding RU-486 which would provide Roussel with several guarantees:

- o legislation guaranteeing patient right to access to all participating clinical study sites and providing criminal penalties for any attempted interference with product, testing, distribution, etc.;
- o assurance that federal authorities would enforce the legislation;
- o indemnification to Roussel and Hoechst for any losses due to a possible boycott; and
- o legislative exemption regarding product liability.

The Population Council was informed that Roussel's lawyers would request an early meeting with the Secretary or White House.

9/9/93 IOM issues its report and recommendations on the "Clinical Applications of Mifepristone (RU 486) and Other Antiprogestins."

9/23/93 The Population Council issued a statement indicating that negotiations with Roussel Uclaf are ongoing and that it had expected a signed agreement by mid-September; that the company recently re-raised issues that are beyond the capacity of the Council to resolve and that has delayed completion of the contract; that they hope these difficulties can be overcome in the next week or two; that the Council has prepared a protocol to amend its IND, negotiated with a management team and subcontractors to conduct a clinical trial, hired additional staff, developed and sent questionnaires to about 60 sites and investigators to help in selection of trial locations, amassed information about potential companies for manufacture and distribution and established criteria, worked on informational materials for providers and clients, and arranged for funding. The Council states that it has gone as far as it can go in making commitments without a signed contract.

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| 10/4/93 | Meeting with [redacted] Roussel Uclaf's lawyers from Swindler and Berlin [redacted] during which it is explained that the [redacted] |
| October '93 - March '94 | Parties continue negotiations |
| 2/94 | Attorneys representing Hoechst submit proposed revisions to H.R. 796. |

APPEARS THIS WAY
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