MEMORANDUM
Public Affairs Office

Date: March 12, 1992

To: Division of Regulatory Affairs (HFD-365,)
Office of Compliance

Subject: Consumer comments re: RU486

From: [redacted] /BOS-DO

Name
Date last spoke

The attached letter was received by this office. I am forwarding the writer's concerns to your office for consideration, per her request.

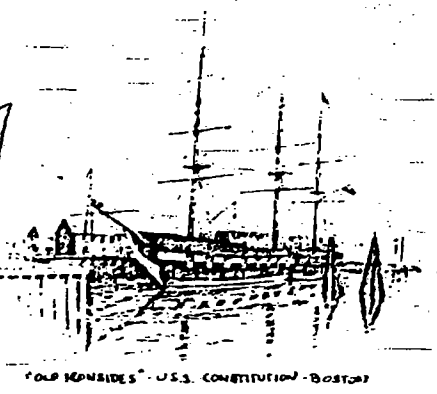
/S/

/S/
RU486

Public Affairs Office
Boston District Office

APPEARS THIS WAY
ON ORIGINAL

Ru 2
078-007
3/26/92



...on
...ery Parkway
...thersburg, MD 20877
...tact: _____

Preprinted Requisition
 # E-094495

EXPENDITURES FOR ADVISORY COMMITTEE MEETING

Advisory Committee for Reproductive Health Drugs — July 19, 1996
(24-hour hold on one days)

CONFERENCE ROOM RENTAL one days at $2400 per day		$2,400.00
[redacted] (2) easels at $10 ea.		$ 20.00
TELEPHONE FOR REGISTRATION TABLE		$ 25.00
TOTAL CONFERENCE ROOM EXPENSES		$2,445.00

[redacted]

MAILTBOX		
2X2 CAROUSEL SLIDE PROJECTOR W/REMOTE		
MIC W/PODIUM AND LIGHT		
FLOOR MIC (2)		
TABLE MICS (10)		
OVERHEAD PROJECTOR		
SCREEN		
LASER POINTER		
MIXERS (16 CHANNEL)		
LAVALIER		
PROFESSIONAL AUDIO TECHNICIAN (10 HOURS)		
EXTRA SLIDE PREVIEWERS		

SET UP FEE **(first day only)** 18% x $2,445 = $440.10		$440.10
TOTAL AUDIO VISUAL EXPENSES	$	
TOTAL CONFERENCE RM. EXPENSES	$ 2,885.10	
GRAND TOTAL	$ 2,885.10	

TAX EXEMPT NUMBER - 30005004

SET UP AND SPECIAL INSTRUCTIONS: (NO ADDITIONAL CHARGE)

[redacted]

THEATRE STYLE SEATING
WATER STATION - OUTSIDE OF CONFERENCE ROOM OR IN BACK OF ROOM
6' SKIRTED REGISTRATION TABLE IN FOYER WITH TWO CHAIRS

[redacted]

DEPARTMENT OF
HEALTH AND HUMAN SERVICES
PURCHASE/SERVICE/STOCK REQUISITION

BPA and Call No. _____

REQUISITION NUMBER: F07836
OFFICE CODE/SYMBOL: ACS:HFD-21

TO: DHHS/FDA/DCGM (HFA-13)
REQUEST FOR: ☐ PURCHASE ☐ SERVICE ☐ STOCK ISSUE ☒ RENTAL/LEASE
REQUESTING ORGANIZATION: Food and Drug Administration
CUSTODIAL AREA: CDER
DATE: 09/06/96
OBJECT CLASS: 25.9Z
FOR REFERENCE CALL:
EXTENSION:
APPROPRIATION: 7560600 223200 20
DELIVER TO:
FDA/CDER/ACS
5600 Fisher Lane (HFD-21)
Rockville, MD 20857
CAN: 6-6992862 D-52004
DATE REQUIRED: 07/19/96

ITEM NO.	DESCRIPTION (INCLUDE STOCK NUMBER, MODEL/PART NO., ETC.)	QUANTITY REQUIRED	UNIT OF ISSUE	COST UNIT	COST TOTAL
	Use and reconfiguration of National Narrowcast Network's ISDN line for 7/19/96 Reproductive Health Drugs Advisory Committee Meeting. TITLE OF MEETING: Reproductive Health Drugs Advisory Committee LOCATION: FDA Tech., Center Gaithersburg, MD DATE: July 19,1996 TIME: 8:00am-6:00pm JUSTIFICATION: See attached.	reconfiguration			$143.50
				TOTAL	$143.

I certify that the property/services requested are required for Government business, and are not available from stores or current stocks.*

FUNDS AVAILABLE (Signature/Title)
Director, ACS

DATE: 9/6/96

REQUESTED BY (Signature/Title)*
Deputy Director, AC...
DATE: 9/6/96

RECOMMEND APPROVAL (Signature/Title)*
DATE:

APPROVED BY (Signature/Title)*
Director, ACS
DATE: 9/6/96

PROPERTY MANAGEMENT OFFICER (Signature)*
DATE:

RECEIVING OFFICIAL - I certify that the quantities indicated in the "Quantity Required" column above have been received in total or as annotated.

RECEIVING OFFICIAL (Signature/Title)
DATE:

ORDER NO. (PO, DO, FEDSTRIP, ETC.)
ORDER DATE:

VOUCHER NO.
VOUCHER DAT

MIF2007 009310

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration

Memorandum

Date September 6, 1996

From [redacted]dvisors and Consultants Staff

Subject Requisition for Narrowcast Network

To [redacted]

Office of Facilities, Acquisitions and Central Services, HFA-512

On July 19, 1996, the Reproductive Health Drug Advisory Committee held a meeting at the FDA Technical Center. Due to the the large public interest in the meeting an overflow room was reserved at the Hilton Hotel in Gaithersburg, Maryland. Since a large number of people requested time to speak it was necessary to change the agenda for the meeting. As originally planned the meeting was scheduled to finish at 5:30 p.m. However, the meeting ran later and ended after 6:30 p.m.

At the meeting we learned the company responsible for the broadcasting the video from the FDA Technical Center to the Hilton Hotel had been able to reserve a satellite transponder only until 6:00 p.m. The company was unable to obtain additional time on a transponder because of the Olympics beginning that day.

Faced with the prospect that the overflow room would be disconnected from the meeting, I contacted Hearings-On-The-Line, a private firm that was already at the meeting and providing the audio services of the meeting to its subscribers. I learned that the firm could arrange for the audio to be sent to the overflow room beginning at 6:00 p.m. or at any time we wished. The estimated cost given was about $100 but could have been more, depending on how long the meeting lasted. I then spoke to [redacted], Office of Facilities, Acquisitions and Central Services. [redacted] was at the meeting to oversee the technical support and to respond to any last minute problems. I explained the situation to [redacted] and asked if it would be acceptable to request Hearings-On-the-Line to provide audio services to the overflow room. [redacted] indicated that would be fine and we preceded.

During the afternoon of the meeting there was a severe thunderstorm which interrupted the satellite transmission. During the interruption of the transmission, we utilized the audio provided by Hearings-On-The-Line until the satellite transmission was restored. Again, at 6:00 p.m., the audio services were used until the end of the meeting. The total cost of the audio service provided was $143.50.

[redacted]

[redacted]

NATIONAL
NARROWCAST
NETWORK℠
FRIENDSHIP STATION. P.O. BOX 9597. WASHINGTON. D.C. 20016
PHONE: (202) 966-2211 FAX: (202) 966-1770

Invoice Date: August 26, 1996

ACS/ORM,CDER
FDA
5600 Fishers Lane -- HFD-21
Rockville, MD 20857

INVOICE #: 6082609
(156BA5N)

NAME	DATE	HEARING(S)	UNITS	FEE
	7/19/96	FDA/Reproductive Health Drugs	8	$
			5	$

SUBTOTAL

SUBTOTAL $143.50
DC SALES TAX $ 00.00

****
$143.50
****

PLEASE REFERENCE INVOICE NUMBER WITH PAYMENT

** PAYABLE UPON RECEIPT

** INTEREST ON OVERDUE BILLS 1.25% PER MONTH

... we thank you for your patronage. Please call us whenever there's a Washington event you'd like to hear on Hearings-On-The-Line®.

REGULATORY TV/VIDEO SERVICE

Preliminary Telecast Order Form

1. ***Bill To:*** Name and Title

Company FDA, ORM, ACS, HFD-21

Address 5600 Fishers Lane

City, State, Zip, Country Rockville MD 20857-1000

Phone FAX

2. ***Site Receiving Telecast***

Company FDA c/o Gaithersburg Hilton

Address 620 Perry Parkway

City, State, Country Gaithersburg MD

Transmission options: (Check one) ☒ KU-band satellite ☐ Videoconference

Contact(s) *(Only individuals named herein will be provided coordinates for accessing the satellite or videoconference transmission.)*

Phone FAX

After Hours Phone (Office and/or Home) N/A

3. ***Request***

A. Advisory Committee Reproductive Health

Meeting Date 19 July 96

B. Coverage Desired [X] One Day [ ] Two Days [ ] Three Days

4. ***Payment*** (U.S. Dollars Only. Payable to F-D-C Reports, Inc. Maryland residents add 5% sales tax)

[X] Invoice me (purchase order # optional) # 7560600

[ ] American Express [ ] Mastercard [ ] Visa

(Account Number) (Exp. Date)

(Signature) 7-5-96 (Date)

(more)

5. Agreement

I have reviewed and understand the "Conditions of Sale" below and the various charges described in the Regulatory TV price list. I agree to abide by the "conditions of sale" herein and to pay the applicable charges incurred in response to this order.

(Signature) 7-5-96 (Date)

Conditions of Sale

Regulatory TV telecasts (Telecasts) of FDA advisory committee meetings are sold by F-D-C Reports, Inc. (Seller) under the following conditions:

1. Telecasts may contain copyrighted material. Federal law [Title 17 USC, Sections 501 and 506] provides severe civil and criminal penalties for unauthorized reproduction, distribution and exhibition of copyrighted works. Criminal copyright infringement is investigated by the FBI and may constitute a felony with a maximum penalty of up to five years in prison and/or a $250,000 fine. In addition, state law provides severe civil penalties for the misappropriation of Seller's Telecasts, including monetary damages.

2. Telecasts are for the internal viewing by the purchasing organization at the site specified on the order form. Viewing at unauthorized sites is strictly prohibited. Viewing by any non-employee of the purchasing organization is prohibited without the permission of the Seller.

Videotape Duplication Rules

3. Telecasts are not to be recorded or duplicated in any manner by the Purchaser, except under the following terms: a) Purchaser is authorized to make one video recording of the Telecast for internal use only by the purchasing organization; b) additional copies of the recording can be purchased from the Seller under the prices and terms specified in the F-D-C Regulatory TV/Video Service price list ("Additional-copy Rates") and "Conditions of Sale;" or c) Purchaser obtains written authorization from the Seller to make additional copies directly at a charge specified by the Seller. Resale or an exchange of any kind of these recordings with organizations or individuals outside the purchasing organization is strictly prohibited.

4. In the event of a complete disruption of the Telecast, or cancellation by the Seller, Seller is liable only for the refund of paid orders.

Purchaser can also choose to receive videotape recordings of such meetings within five business days after the meeting. Purchaser will be billed at the current prices for F-D-C Regulatory TV/Video Service recordings of FDA advisory committee meetings.

5. In the event of a partial interruption of the Telecast, Seller will make every effort to provide Purchaser with a videotape recording of the interrupted portions of the Telecast to be available within two business days after the date of the Telecast. Seller will also, at its sole discretion, consider adjustments to the Purchaser's charges for the Telecast.

Seller is not responsible for problems with Purchaser's reception of the Telecasts (Contact Seller for procedures for assistance with reception problems.)

6. Although the Seller believes that the information contained in the Telecasts are an accurate and complete record of the public portions of the FDA advisory committee meetings, no guarantee is offered to that effect. The Seller does not assume any liability for the accuracy and comprehensiveness of the information presented.

7. Prices are subject to change without notice, including due to satellite availability.

8. Purchaser's Preliminary Order is valid until ten business days prior to the Telecast date. Purchaser can cancel a Preliminary Order at any time during the valid period. After that date, Purchaser can convert the Preliminary Order to a Firm Order for the Telecast. Cancellation of a Firm Order is at the sole discretion of the Seller.

Mail or FAX form to:
Lori Hardin, F-D-C Reports, Inc.

CANCELLED Thank You.

Date: July 3, 1996

From: Advisors and Consultants Staff, HFD-9

Subject: Scheduling of Meeting Rooms

To: Conference Control Office
Parklawn Building, Room 3B-55

OK 7-3-96 D+E
CANCEL CONF ROOM

Would you please schedule meeting rooms to accommodate the following needs:

DATE: July 19, 1996 TIME: 8 a.m. - 5:30 p.m. ROOM(s) D & E

DATE: _____ TIME: _____ ROOM(s) _____

NAME OF MEETING: Advisory Committee for Reproductive Health Drugs

ADVISORY: X STAFF: _____ NUMBER OF PEOPLE: 250

EXECUTIVE SECRETARY: _____ PHONE: _____

REQUESTED BY: _____ PHONE: _____

REMARKS: Will need table with microphones to seat 15 to 16 people, lectern with microphone and light, electronic pointer, 2x2 carousel projector, overhead projector, podium with microphone and (2) floor microphones.

(Diagram attached). Please cancel.

Setup instructions: Put tables in "U" shaped position. (in front of screen)

PLEASE RETURN FORM TO CONFIRM RESERVATION, BY FAX _____ OR MAIL, THANK YOU.

Please cancel. Thanks

_____ _____

Date Conference Control Office

Signs

DATE: 7/2/96

TO: _____

_____

_____

_____

_____

FROM: _____

Food and Drug Administration
Advisors and Consultants Staff
5600 Fishers Lane
HFD-9, Room 8B-45
Rockville, MD 20857

Facsimile no: _____

Phone number: _____

Phone number: _____

Facsimile no: _____

No. of pages 1
(not including cover)

PLEASE CALL IMMEDIATELY IF RE-TRANSMISSION IS NECESSARY.

Thank You!

☆U.S. GOVERNMENT PRINTING OFFICE:1993—357-864

FDA REQUEST FOR GRAPHIC SERVICES

VISUAL INFORMATION SERVICES BRANCH
5600 Fishers Lane Rm. 9-67, Rockville, MD 20857
PHONE # —— FAX # ——

YOUR NAME: [redacted] PHONE # [redacted] FAX # [redacted]

OTHER CONTACT:

DATE IN: 7/2/96 DATE DUE: ASAP 7/10/96

CENTER/OFFICE: CDER/ACS MAIL CODE: HFD-21

PLEASE, If submitting a Disk, you Must:
- Submit a 3½" **HD** (High Density) **copy** of your original disk
- **Label** your disk (your name, file name & program job was created in)
- Submit **only the necessary file(s)**
- **Include paper copies** of all enclosed files

PLEASE LABEL
HD

PROJECT TITLE: Adv. Cmte. for Reproductive Health Drugs — July 19, 1996

CAN #: 6-6992304

Authorized Signature for Approval/Title:

TO BE FILLED OUT BY VISB STAFF WITH REQUESTER

GENI JOB # _____ DISK # _____ MAC DISK # _____ RECEIVED BY _____ ARTIST _____

SLIDES

	Quantity	Set(s)
☐ PHOTO		
☐ GENI		
☐ MAC		
☐ VENDOR CREATES		
☐ *DISK IMAGING		

VUGRAPHS

	Quantity	Set(s)
☐ PHOTO		
☐ GENI		
☐ MAC		
☐ VENDOR CREATES		
☐ *DISK IMAGING		

PHOTOGRAPHY

☐ **35mm PROCESSING**
_____ Roll(s)

☐ **B/W PRINT(S)**
Quantity: Size:

☐ **COLOR PRINT(S)**
Quantity: Size:

GRAPHICS

Quantity	Size	
2	easel	☒ Poster(s)
		☐ Cover Design
		☐ Brochure
		☐ Lino - Paper Pos.
		☐ Lino - Film Pos.
		☐ Lino - Film Neg.
		☐ Other: *See Special Instructions

ART/FRAMING SERVICES

Quantity	
	☐ Nameplate(s)
	☐ Name Tags/Badges
	☐ 8½ x 11 Canon Copies
	☐ 11 x 17 Canon Copies
	☐ *Framing (Custom)
	☐ *Framing (In-House)

GERBER GRAPHICS

Quantity	Size	
		☐ Banner(s)
		☐ Sign(s)
		☐ Flip Chart(s)
		☐ Other: _____

*SPECIAL INSTRUCTIONS: Hi —— ., the signs you made were great. I need a duplicate of the same signs.

Signs should read:

All personal belongings and packages are subject to inspection.

be shown before entering meeting.

DEPARTMENT OF
HEALTH AND HUMAN SERVICES
PURCHASE/SERVICE/STOCK REQUISITION

BPA and Call No. BPA 90243
CALL #17

REQUISITION NUMBER: F08008
OFFICE CODE/SYMBOL: ACS:HFD-21

TO: DHHS/FDA/ACS/DAN/PROC (Rm 5101)

REQUEST FOR: ☐ PURCHASE ☒ SERVICE ☐ STOCK ISSUE ☐ RENTAL/LEASE

REQUESTING ORGANIZATION	CUSTODIAL AREA	DATE	OBJECT CLASS
Food and Drug Administration	CDER	07/12/96	25.2P

FOR REFERENCE CALL	EXTENSION	APPROPRIATION
	443-4090	7560600 223200 20

DELIVER TO:
FDA/CDER/ACS
1901 Chapman Avenue, Rm 200, HFD-21
Rockville, MD 20852

CAN: 6-6992862 D-51764

DATE REQUIRED: 07/19/96

ITEM NO.	DESCRIPTION (INCLUDE STOCK NUMBER, MODEL/PART NO., ETC.)	QUANTITY REQUIRED	UNIT OF ISSUE	COST UNIT	COST TOTAL
	Transcription services for a meeting of an FDA/CDER Advisory Committee meeting, Rquest is made for: (1) An original-4 per page, ONE SIDE (2) A hard copy-1 per page, doublespaced, ONE SIDE (3) 3-1/2" diskett-1 per page with WP60 Compatibility, KEY WORD INDEX (4) Tapes EIGHT DAY DELIVERY!!! DELIVER TO ATTENTION VENDOR: PLEASE PROVIDE INVOICE WITH TRANSCRIPT MEETING: Reproductive Health Drugs Advisory Committee. PLACE: FDA Technical Center 16071 Industrial Drive Gaithersburg, MD DATE: July 19,1996 TIME: July 19;9:00am-5:00pm OPEN The contractor must have been approved by FDA for access to "Priveleged Information" and must be certified as being capable to receive and protect such information according to the requirements set forth in 21 CFR 20.90 (Disclosure to Contractor). SOURCE: C.A.S.E.T. ASSOCIATES 10201 Old Lee Highway Suite 180 Fairfax, VA 22030 Contact: Phone:	1	EA	2000.00	2000.00

350/PAGE
12.50/DISK
3.50/MASTER TAPE

RECEIVED
JUN 24 2 47 PM '96
OD-DIV. OF ACQUISITION MANAGEMENT, ASO

RECEIVED
JUN 24
DIVISION OF CONTRACTS MANAGEMENT

6/24
ENTERED

NOT TO EXCE

TOTAL: 2000.00

I certify that the property/services requested are required for Government business, and are not available from excess or current assets.*

FUNDS AVAILABLE (Signature/Title): SGE Programs Officer

DATE: 6/21/96

REQUESTED BY (Signature/Title)*: Cmte. Mgmt. Asst.

DATE: 6/21/96

RECOMMEND APPROVAL (Signature/Title)* | DATE

APPROVED BY (Signature/Title)*: SGE Programs Officer

DATE: 6/21/96

PROPERTY MANAGEMENT OFFICER (Signature)* | DATE

RECEIVING OFFICIAL - I certify that the quantities indicated in the "Quantity Required" column above have been received in total or as annotated.

RECEIVING OFFICIAL (Signature/Title) | DATE

ORDER NO. (PO, DO, FEDSTRIP, ETC.) | ORDER DATE

VOUCHER NO. | VOUCHER DATE

National Narrowcast Network, L.P.

Box 9597, Friendship Station
Washington, D.C. 20016
(202)966-2211 or Fax (202)966-1770

Hearings-On-The-Line® Service Agreement {Separate form should be submitted for each authorized user.}

NAME: _____

POSITION: ACS, ORA, CDER, FDA

ORGANIZATION: HFD-21

ADDRESS: 5600 FISHERS LANE

CITY: ROCKVILLE STATE: MD ZIP: 20857

PHONE: _____ FAX: _____

I DO want to use National Narrowcast Network's Hearings-On-The-Line®. Please provide me with my personal H-O-T-Line℠ authorization code, and instructions on how to tune in to Congressional hearings live at my desk or from any phone. I understand that the regular charge for each hearing is $20 for the first 10 minutes or part and $15 for each additional 10 minutes or part, plus any additional taxes, and that I personally and my organization will be responsible for any charges to this code. If I do not pay the bills for my usage promptly, I authorize National Narrowcast Network, L.P., or its agents, after notice to me, to charge my VISA account for the overdue amounts, Acct. Name MASTER CHARGE Acct. _____ Exp. Date: _____ {if I do not have a VISA account I will make other arrangements with NNN}. Interest on overdue bills will be 1.25% per month. I understand that the cost of the Hearings-On-The-Line®. service does not include the cost of the calls I make to connect to H-O-T-Line℠.

I understand that while Hearings-On-The-Line®. will do its best to provide coverage of scheduled hearings, this service is necessarily subject to last minute changes in schedules, locations, availability for coverage, and witnesses, and to other technical interruptions or last minute circumstances which may cause non-transmission of a particular hearing, and that National Narrowcast Network, L.P. does not guarantee that a particular hearing will occur, will be available for transmission, or will in fact be transmitted to subscribers. I agree that neither National Narrowcast Network, L.P., nor its agents or affiliates, will have any liability whatsoever, except for refund of any amount paid in advance, for any failure to carry any hearing.

I also understand that the charges above are for direct use of the Hearings-On-The-Line®. service by the authorized person and do not authorize re-transmission in any manner, other than listening on an existing telephone extension at the same location as the authorized person. I understand that any other use, including re-transmission or re-broadcast in any manner, will entail substantial additional charges, for which I and my organization will be responsible. I am authorized to bind my organization to this agreement.

Date: 7/19/96 Signed: _____ _____

{Mother's full birth name for identification verification:

First..... Middle..... Last.....

Send to: ***Hearings-On-The-Line®***., Box 9597, Friendship Station, Washington, D.C. 20016; or FAX to 202-966-1770

Center for Drug Evaluation and Research
Executive Operations
Correspondence Control Tracking Form

Log Number 2000- 2185 | Received Date 10/4/00 | Due Date

FDA Number | Document Date 10/3/00

From [redacted] | Affiliation U.S. Senate (several)

To [redacted] | Is this a Congressional Request? Yes

Is this a FDA Exsec Request? No

Is this a 10 Day Turnaround? No

Subject Writes about the approval of RU486.

EOS Team Leader [redacted] | EOS Project Manager [redacted]

Status: closed | Status Date 10/4/00

Incoming (filename) y:\correspondence\incoming\00-2185.pdf

Outgoing (filename) y:\correspondence\outgoing\

ACTION REQUESTED FROM:

Mailcode	Office Name	Requested Action	Date Sent	Due Date	Returned

FYI COPIES SENT TO:

Mailcode	Name
HFD-005	[redacted]
HFD-103	ODE III
HFD-001	[redacted]
HFD-006	[redacted]

Mailcode	Name

Comments

Please send all responses and inquiries to CDER Executive Operations Staff, HFD-006
(Email: CDEREXSEC or Phone 301-594-6779)

Friday, October 06, 2000

* * * * * * * CONGRESSIONAL * * * * * * *
* * * DOCUMENT/INFORMATION REQUEST * * *

Date: October 3, 2000

From: James M. Jeffords
Chairman
Committee on Health, Education,
Labor and Pensions

Subj: Approval of Mifepristone,
better known as RU-486.

FOR YOUR INFORMATION

TO: Dr. Henney

[redacted]

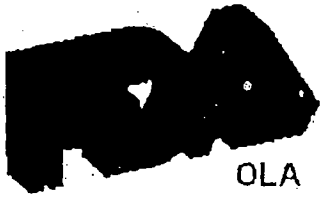
[redacted] via fax)

[redacted] (Exec. Sec.)

From: [redacted] Room No: [redacted]
Phone No: [redacted]

Copies

TELEFAX TRANSMITTAL SHEET



FOOD AND DRUG ADMINISTRATION
Office of Legislation
5600 Fishers Lane
Parklawn Bldg. / Room 15-55
Rockville, MD 20850
TEL: [redacted]
FAX: (301) 443-2567. (301) 443-5897
(301) 594-6778

PLEASE DELIVER THE FOLLOWING PAGES

TO: [redacted] DATE: 10/03/2000

TELEPHONE #: FAX#: [redacted]

FROM: [redacted]

COMMENTS:

NUMBER OF PAGES, INCLUDING COVER: 3

IF YOU DO NOT RECEIVE THE NUMBER OF PAGES INDICATED ABOVE, PLEASE CALL IMMEDIATELY

TO _____

DATE _____ TIME _____

PHONE CALLS

"WHILE OUT" RECORD

M. _____

OF _____

PHONE _____
AREA CODE NUMBER EXTENSION

TELEPHONED		PLEASE CALL	
CALLED TO SEE YOU		RETURNED CALL	
WILL CALL AGAIN		URGENT	

MESSAGE Needs to see you for 1 minute before your 4pm mtg re: RU4Ko bill to be introduced tomorrow

TAKEN BY: _____

SEARLE

08/31/00

August 21, 2000

SEARLE
4901 SEARLE PARKWAY
SKOKIE, ILLINOIS 60077

Division of Gastrointestinal and Coagulation Drug Products
Center for Drug Evaluation and Research (HFD-180)
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

SUPPL NEW CORRESP

Re: NDA 19-268/S-031
Cytotec® (misoprostol)

Dear ——

SLR-031-C

Please refer to our supplemental New Drug Application (S-031) dated October 13, 1998, to your letters relating to this supplement dated March 17, April 2, April 9, 1999 and to your approvable letter dated December 17, 1999 to which we responded on March 9, 2000.

We acknowledge receipt of your letter dated May 23, 2000, recommending changes to our draft "Dear Health Care Practitioner" ("HCP") letter. These recommendations have been incorporated into a final version with the exception of the suggested placement of the phrase "maternal and fetal death." We have left that phrase as it appears in our draft version since not all cases of maternal and fetal death, as reported to FDA, resulted from amniotic fluid embolism. A final version of our letter is enclosed for your records.

Our defined audience for the HCP letter is a comprehensive list of practitioners most likely to be associated with misoprostol use for the off-label indications addressed in our HCP letter. Please note that, in response to the agency's suggestion, we have expanded our distribution to include both family and general practitioners who are likely prescribers of misoprostol and may assist in labor and delivery, and emergency room physicians, because they may assess patients who have been administered misoprostol for induction of labor or abortion.

If you have any questions or concerns, please address to the undersigned,

Sincerely,

Mary Jo Pritza, MPH, PharmD.
Regulatory Affairs Associate
Ph: 847-982-7831
Fax: 847-982-8090

cc: MEDWATCH-HF2

SEARLE

SEARLE
5200 OLD ORCHARD ROAD
SKOKIE, ILLINOIS 60077
PHONE (847) 982-7000
FAX (847) 470-1480

IMPORTANT DRUG WARNING
CONCERNING UNAPPROVED USE OF INTRAVAGINAL OR ORAL MISOPROSTOL IN PREGNANT WOMEN FOR INDUCTION OF LABOR OR ABORTION

August 23, 2000

Re: Cytotec® (misoprostol)

Dear Health Care Practitioner:

The purpose of this letter is to remind you that Cytotec administration by any route is contraindicated in women who are pregnant because it can cause abortion. Cytotec is not approved for the induction of labor or abortion.

Cytotec is indicated for the prevention of NSAID (nonsteroidal anti-inflammatory drugs, including aspirin)-induced gastric ulcers in patients at high risk of complications from gastric ulcer, e.g., the elderly and patients with concomitant debilitating disease, as well as patients at high risk of developing gastric ulceration, such as patients with a history of ulcer.

The uterotonic effect of Cytotec is an inherent property of prostaglandin E_1 (PGE_1), of which Cytotec is a stable, orally active, synthetic analog. Searle has become aware of some instances where Cytotec, outside of its approved indication, was used as a cervical ripening agent prior to termination of pregnancy, or for induction of labor, in spite of the specific contraindications to its use during pregnancy.

Serious adverse events reported following off-label use of Cytotec in pregnant women include maternal or fetal death; uterine hyperstimulation, rupture or perforation requiring uterine surgical repair, hysterectomy or salpingo-oophorectomy; amniotic fluid embolism; severe vaginal bleeding, retained placenta, shock, fetal bradycardia and pelvic pain.

Searle has not conducted research concerning the use of Cytotec for cervical ripening prior to termination of pregnancy or for induction of labor, nor does Searle intend to study or support these uses. Therefore, Searle is unable to provide complete risk information for Cytotec when it is used for such purposes. In addition to the known and unknown acute risks to the mother and fetus, the effect of Cytotec on the later growth, development and functional maturation of the child when Cytotec is used for induction of labor or cervical ripening has not been established.

Searle promotes the use of Cytotec only for its approved indication. Please read the enclosed updated complete Prescribing Information for Cytotec.

Further information may be obtained by calling 1-800-323-4204.

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ACOG PRACTICE BULLETIN

CLINICAL MANAGEMENT GUIDELINES FOR OBSTETRICIAN–GYNECOLOGISTS

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This Practice Bulletin was developed by the ACOG Committee on Practice Bulletins—Obstetrics with the assistance of Susan M. Ramin, MD. The information is designed to aid practitioners in making decisions about appropriate obstetric and gynecologic care. These guidelines should not be construed as dictating an exclusive course of treatment or procedure. Variations in practice may be warranted based on the needs of the individual patient, resources, and limitations unique to the institution or type of practice.

Induction of Labor

The goal of induction of labor is to achieve vaginal delivery by stimulating uterine contractions before the spontaneous onset of labor. According to the National Center for Health Statistics, the overall rate of induction of labor in the United States has increased from 90 per 1,000 live births in 1989 to 184 per 1,000 live births in 1997 (1). Generally, induction of labor has merit as a therapeutic option when the benefits of expeditious delivery outweigh the risks of continuing the pregnancy. The benefits of labor induction must be weighed against the potential maternal or fetal risks associated with this procedure. The purpose of this bulletin is to review current methods for cervical ripening and induction of labor and to summarize the effectiveness of these approaches based on appropriately conducted outcomes-based research. These practice guidelines classify the indications for and contraindications to induction of labor, describe the various agents used for cervical ripening, cite methods used to induce labor, and outline the requirements for the safe clinical use of the various methods of inducing labor.

Background

In 1948, Theobald and associates described their use of the posterior pituitary extract, oxytocin, by intravenous drip for labor induction (2). Five years later, oxytocin was the first polypeptide hormone synthesized by du Vigneaud and associates (3). This synthetic polypeptide hormone has since been used to stimulate uterine contractions. Other methods used for induction of labor include membrane stripping, amniotomy, and administering prostaglandin E (PGE) analogues.

Cervical Ripening

If induction is indicated and the status of the cervix is unfavorable, agents for cervical ripening may be used. The status of the cervix can be determined by the Bishop pelvic scoring system (Table 1) (4). If the total score is more than 8,

Table 1. Bishop Scoring System

Score	Factor				
	Dilation (cm)	Effacement (%)	Station*	Cervical Consistency	Position of Cervix
0	Closed	0–30	–3	Firm	Posterior
1	1–2	40–50	–2	Medium	Midposition
2	3–4	60–70	–1, 0	Soft	Anterior
3	5–6	80	+1, +2	—	—

*Station reflects a –3 to +3 scale.

Modified from Bishop EH. Pelvic scoring for elective induction. Obstet Gynecol 1964;24:267

the probability of vaginal delivery after labor induction is similar to that after spontaneous labor.

Acceptable methods for cervical ripening include mechanical cervical dilators and administration of synthetic prostaglandin E_1 (PGE_1) and prostaglandin E_2 (PGE_2) (5-9). Mechanical dilation methods are effective in ripening the cervix and include hygroscopic dilators, osmotic dilators (*Laminaria japonicum*), the 24-French Foley balloon, and the double balloon device (Atad Ripener Device) (10-15). Laminaria ripen the cervix but may be associated with increased peripartum infections (6, 16).

Misoprostol, a synthetic PGE_1 analogue, can be administered intravaginally or orally and is used for both cervical ripening and induction. It currently is available as a 100-mcg or 200-mcg tablet, and can be broken to provide 25-mcg or 50-mcg doses. Misoprostol currently is approved by the U.S. Food and Drug Administration (FDA) for the prevention of peptic ulcers, but not for cervical ripening or induction of labor.

Two PGE_2 preparations are commercially available: a gel available in a 2.5-mL syringe containing 0.5 mg of dinoprostone and a vaginal insert containing 10 mg of dinoprostone. Both are approved by the FDA for cervical ripening in women at or near term. The vaginal insert releases prostaglandin (PG) at a slower rate (0.3 mg/h) than the gel. Both the gel and the vaginal insert have been reported to increase the probability of successful initial induction, shorten the interval from induction to delivery, and decrease the total and maximal doses of oxytocin needed to induce contractions (17).

Other pharmacologic methods for cervical ripening include continuous intravenous oxytocin drip, extraamniotic saline infusion, vaginal recombinant human relaxin, and intracervical purified porcine relaxin. The safety and efficacy of these latter methods are unclear.

Methods of Labor Induction

In addition to oxytocin and misoprostol, other agents can be used for induction of labor. The progesterone antagonist mifepristone (RU 486) is one such suitable and effective induction agent (18). Nonpharmacologic methods of labor induction include stripping the amniotic membranes, amniotomy, and nipple stimulation.

Oxytocin

Oxytocin, an octapeptide, is one of the most commonly used drugs in the United States. The physiology of oxytocin-stimulated labor is similar to that of spontaneous labor, although individual patients vary in sensitivity and response to oxytocin. Based on pharmacokinetic studies of synthetic oxytocin, uterine response ensues after 3–5 minutes of infusion, and a steady state of oxytocin is achieved in plasma by 40 minutes (19). The uterine response to oxytocin depends on the duration of the pregnancy; there is a gradual increase in response from 20 to 30 weeks of gestation, followed by a plateau from 34 weeks of gestation until term, when sensitivity increases (20). Cervical dilation, parity, and gestational age are predictors of the dose response to oxytocin for labor stimulation (21).

Membrane Stripping

Stripping the amniotic membranes is commonly practiced to induce labor. However, several studies have yielded conflicting results regarding the efficacy of membrane stripping (22–24). Significant increases in phospholipase A_2 activity and prostaglandin $F_{2\alpha}$ ($PGF_{2\alpha}$) levels occur from membrane stripping (25). Stripping membranes appears to be associated with a greater frequency of spontaneous labor and fewer inductions for postterm pregnancy. In a randomized trial of 195 normal pregnancies beyond 40 weeks of gestation, two thirds of the patients who underwent membrane stripping labored spontaneously within 72 hours, compared with one third of the patients who underwent examination only (26).

Amniotomy

Artificial rupture of the membranes may be used as a method of labor induction, especially if the condition of

the cervix is favorable. Used alone for inducing labor, amniotomy can be associated with unpredictable and sometimes long intervals before the onset of contractions. However, in a trial of amniotomy combined with early oxytocin infusion compared with amniotomy alone, the induction-to-delivery interval was shorter with the amniotomy-plus-oxytocin method (27).

Clinical Considerations and Recommendations

▶ *What are the indications and contraindications to induction of labor?*

Indications for induction of labor are not absolute but should take into account maternal and fetal conditions, gestational age, cervical status, and other factors. Following are examples of maternal or fetal conditions that may be indications for induction of labor:

- Abruptio placentae
- Chorioamnionitis
- Fetal demise
- Pregnancy-induced hypertension
- Premature rupture of membranes
- Postterm pregnancy
- Maternal medical conditions (eg, diabetes mellitus, renal disease, chronic pulmonary disease, chronic hypertension)
- Fetal compromise (eg, severe fetal growth restriction, isoimmunization)
- Preeclampsia, eclampsia

Labor also may be induced for logistic reasons, for example, risk of rapid labor, distance from hospital, or psychosocial indications. In such circumstances, at least one of the criteria in the box should be met or fetal lung maturity should be established (28).

Generally, the contraindications to labor induction are the same as those for spontaneous labor and vaginal delivery. They include, but are not limited to, the following situations:

- Vasa previa or complete placenta previa
- Transverse fetal lie
- Umbilical cord prolapse
- Previous transfundal uterine surgery

Confirmation of Term Gestation

- Fetal heart tones have been documented for 20 weeks by nonelectronic fetoscope or for 30 weeks by Doppler.
- It has been 36 weeks since a positive serum or urine human chorionic gonadotropin pregnancy test was performed by a reliable laboratory.
- An ultrasound measurement of the crown–rump length, obtained at 6–12 weeks, supports a gestational age of at least 39 weeks.
- An ultrasound obtained at 13–20 weeks confirms the gestational age of at least 39 weeks determined by clinical history and physical examination.

However, the individual patient and clinical situation should be considered in determining when induction of labor is contraindicated. Several obstetric situations are not contraindications to the induction of labor but do necessitate special attention. These include, but are not limited to, the following:

- One or more previous low-transverse cesarean deliveries
- Breech presentation
- Maternal heart disease
- Multifetal pregnancy
- Polyhydramnios
- Presenting part above the pelvic inlet
- Severe hypertension
- Abnormal fetal heart rate patterns not necessitating emergent delivery

▶ *What criteria should be met before the cervix is ripened or labor is induced?*

Assessment of gestational age and consideration of any potential risks to the mother or fetus are of paramount importance for appropriate evaluation and counseling before initiating cervical ripening or labor induction. The patient should be counseled regarding the indications for induction, the agents and methods of labor stimulation, and the possible need for repeat induction or cesarean delivery.

Additional requirements for cervical ripening and induction of labor include cervical assessment, pelvic assessment, assessment of fetal size and presentation, and personnel familiar with the effects of uterine stimu-

lants on the mother and fetus because uterine hyperstimulation may occur with induction of labor. Monitoring fetal heart rate and uterine contractions is recommended as for any high-risk patient in active labor. Although trained nursing personnel can monitor labor induction, a physician capable of performing a cesarean delivery should be readily available.

▶ *What is the relative effectiveness of available pharmacologic methods for cervical ripening?*

Intracervical or intravaginal PGE_2 (dinoprostone) commonly is used and is superior to placebo or no therapy in promoting cervical ripening (29). Several prospective randomized clinical trials and a meta-analysis have demonstrated that PGE_1 (misoprostol) is an effective method for cervical ripening (30-34). Misoprostol administered intravaginally has been reported to be either superior to or as efficacious as dinoprostone gel (9, 32, 34, 35). It is difficult, however, to compare the results of studies on misoprostol because of differences in endpoints, including Bishop score, duration of labor, total oxytocin use, successful induction, and cesarean delivery rate. The rates of operative vaginal delivery and cesarean delivery are inconsistent between trials. The cesarean delivery rate has been reported to be higher with dinoprostone compared with misoprostol (31); however, further studies are needed. The results of cesarean delivery rate with dinoprostone use are inconsistent; some have shown a reduction but most have not shown a significant decrease.

▶ *How should prostaglandin be administered?*

If there is inadequate cervical change with minimal uterine activity after one dose of intracervical PGE_2, a second dose may be given 6–12 hours later. The manufacturers recommend a maximum cumulative dose of 1.5 mg of dinoprostone (three doses or 7.5 mL of gel) within a 24-hour period. A minimum safe time interval between PG administration and initiation of oxytocin has not been determined. According to the manufacturers' guidelines, after use of 1.5 mg of dinoprostone in the cervix or 2.5 mg in the vagina, oxytocin induction should be delayed for 6–12 hours because the effect of PG may be heightened with oxytocin. After use of dinoprostone in sustained-release form, delaying oxytocin induction for 30–60 minutes after removal is sufficient. One quarter of one 100-mcg tablet (approximately 25-mcg) of misoprostol should be considered for cervical ripening and labor induction.

▶ *What are the potential complications with each method of cervical ripening, and how are they managed?*

Hyperstimulation may occur with the use of the PGE analogues. There is no uniform definition of uterine hyperstimulation. In some studies hyperstimulation is never defined. In others, uterine hyperstimulation has been defined as either a series of single contractions lasting 2 minutes or more or a contraction frequency of five or more in 10 minutes (36). Another definition of hyperstimulation is uterine contractions lasting 2 minutes or more or a contraction frequency of 5 or more in 10 minutes with evidence that the fetus is not tolerating this contraction pattern, as demonstrated by late deceleration, or fetal bradycardia (37). Fortunately, most women and their fetuses tolerate uterine hyperstimulation without adverse outcome.

The intracervical PGE_2 gel (0.5 mg) has a 1% rate of uterine hyperstimulation, while the intravaginal PGE_2 gel (2–5 mg) or vaginal insert is associated with a 5% rate (29, 36–38). Uterine hyperstimulation typically begins within 1 hour after the gel or insert is placed but may occur up to 9 1/2 hours after the vaginal insert has been placed (36–38).

Removing the PGE_2 vaginal insert usually will help reverse the effect of hyperstimulation. Irrigation of the cervix and vagina is not beneficial. Maternal side effects from low-dose PGE_2 (fever, vomiting, and diarrhea) are quite uncommon (17). Prophylactic antiemetics, antipyretics, and antidiarrheal agents usually are not needed. The manufacturers recommend that caution be exercised when using PGE_2 in patients with glaucoma, severe hepatic or renal dysfunction, or asthma. However, PGE_2 is a bronchodilator, and there are no reports of bronchoconstriction or significant blood pressure changes after the administration of the low-dose gel.

In several studies of misoprostol, the term tachysystole was used to define hyperstimulation without corresponding fetal heart rate abnormalities in order to distinguish this complication from hyperstimulation with fetal heart rate changes. Data indicate that both tachysystole (defined in some studies as six or more uterine contractions in 10 minutes in consecutive 10-minute intervals) and hyperstimulation (with and without fetal heart rate changes) are increased with a 50-mcg or greater dose of misoprostol (9, 30, 39, 40). There seems to be a trend toward lower rates of uterine hyperstimulation with fetal heart rate changes with lower dosages of misoprostol (25 mcg every 6 hours versus every 3 hours) (40). Although in studies of misoprostol there were no differences in perinatal outcome, the studies have been insufficient in

size to exclude the possibility of uncommon serious adverse effects (40). The use of misoprostol in women with prior cesarean birth has been associated with an increase in uterine rupture (41). Misoprostol use for second-trimester pregnancy termination also has been associated with uterine rupture, especially when used with oxytocin infusion (40). An increase in meconium-stained amniotic fluid also has been reported with misoprostol use (34). Although misoprostol appears to be safe and effective in inducing labor in women with unfavorable cervices, further studies are needed to determine the optimal dosage, timing interval, and pharmacokinetics of misoprostol. Moreover, data are needed on the management of complications related to misoprostol and when it should be discontinued. If uterine hyperstimulation and a nonreassuring fetal heart rate pattern occur with misoprostol use and there is no response to routine corrective measures (maternal repositioning and supplemental oxygen administration), cesarean delivery should be considered. Subcutaneous terbutaline also can be used in an attempt to correct the nonreassuring fetal heart rate tracing or the abnormal contraction pattern or both.

Increased maternal and neonatal infection have been reported in connection with the use of laminaria and hygroscopic dilators when compared with the PGE_2 analogues (6, 12, 16).

▶ *What are the recommended guidelines for fetal surveillance for each type of prostaglandin preparation?*

The PG preparations should be administered at or near the labor and delivery suite, where uterine activity and fetal heart rate can be monitored continuously. The patient should remain recumbent for at least 30 minutes. The fetal heart rate and uterine activity should be monitored continuously for a period of 30 minutes to 2 hours after administration of the PGE_2 gel (42). The patient may be transferred elsewhere if there is no increase in uterine activity and the fetal heart rate is unchanged after this period of observation. Uterine contractions usually are evident in the first hour and exhibit peak activity in the first 4 hours (42, 43). Fetal heart rate monitoring should be continued if regular uterine contractions persist; maternal vital signs should be recorded as well.

Because uterine hyperstimulation can occur as late as 9 1/2 hours after placement of the PGE_2 vaginal insert, fetal heart rate and uterine activity should be monitored electronically from the time the device is placed until at least 15 minutes after it is removed (44). This controlled-release PGE_2 vaginal pessary should be removed at the onset of labor (37).

Patients treated with misoprostol should receive fetal heart rate and uterine activity monitoring in a hospital setting until further studies evaluate the safety of outpatient therapy.

▶ *Are cervical ripening methods restricted to inpatient use only?*

One small, randomized trial found that sequential outpatient administration of low-dose (2-mg) PGE_2 gel was no better than placebo in ripening the cervix in postterm patients (45). Larger controlled studies are needed to establish an effective and safe dose and vehicle for PGE_2 before application on an outpatient basis can be recommended. However, outpatient use may be appropriate in carefully selected patients.

▶ *What are the potential complications of various methods of induction?*

The side effects of oxytocin use are principally dose related; uterine hyperstimulation and subsequent fetal heart rate deceleration are the most common side effects. Hyperstimulation may result in abruptio placentae or uterine rupture. Fortunately, uterine rupture secondary to oxytocin use is rare even in parous women (46). Water intoxication can occur with high concentrations of oxytocin infused with large quantities of hypotonic solutions. The antidiuretic effect usually is observed only after prolonged administration with at least 40mU of oxytocin per minute (47).

Misoprostol appears to be safe and beneficial for inducing labor in a woman with an unfavorable cervix. Although the exact incidence of uterine tachysystole is unknown and the criteria used to define this complication are not always clear in the various reports, there are reports of uterine tachysystole occurring more frequently in women given misoprostol (30–32). There does not appear to be a significant increase in adverse fetal outcomes from tachysystole (31, 35); however, one also must consider the possibility of uterine rupture as a rare complication of induction of labor with misoprostol (40). The occurrence of complications does appear to be dose-dependent (9, 40). Oral misoprostol administration is associated with fewer abnormal fetal heart rate patterns and episodes of uterine hyperstimulation when compared with vaginal administration (48), but there are not yet enough data to support oral administration as an alternative method.

The potential risks associated with amniotomy include prolapse of the umbilical cord, chorioamnionitis, significant umbilical cord compression, and rupture of vasa previa. The physician should palpate for an umbili-

Table 2. Labor Stimulation with Oxytocin: Examples of Low- and High-Dose Oxytocin

Regimen	Starting Dose	Incremental Increase (mU/min)	Dosage Interval (min)
Low-Dose	0.5–1	1	30–40
	1–2	2	15
High-Dose	~6	~6	15
	6	6*, 3, 1	20–40

*The incremental increase is reduced to 3 mU/min in presence of hyperstimulation and reduced to 1 mU/min with recurrent hyperstimulation.

cal cord and avoid dislodging the fetal head. The fetal heart rate should be assessed before and immediately after amniotomy.

Stripping the amniotic membranes is associated with bleeding from undiagnosed placenta previa or low-lying placenta, and accidental amniotomy. Uterine hyperactivity and fetal heart rate decelerations have been reported in association with nipple stimulation (49).

▶ ***When oxytocin is used for induction of labor, what dosage should be used and what precautions should be taken?***

Any of the low- or high-dose oxytocin regimens outlined in Table 2 are appropriate for labor induction (50–56). Most women attain normal progression of labor with 150–350 Montevideo units of uterine activity (50). Low-dose regimens and less frequent increases in dose are associated with decreased uterine hyperstimulation (52). High-dose regimens and more frequent dose increases are associated with shorter labor and less frequent cases of chorioamnionitis and cesarean delivery for dystocia, but increased rates of uterine hyperstimulation (52).

Each hospital's obstetrics and gynecology department should develop guidelines for the preparation and administration of oxytocin. Synthetic oxytocin generally is diluted 10 U in 1,000 mL of an isotonic solution for an oxytocin concentration of 10 mU/mL. Oxytocin should be administered by infusion using a pump that allows precise control of the flow rate and permits accurate minute-to-minute control. Bolus administration of oxytocin can be avoided by piggybacking the infusion into the main intravenous line near the venipuncture site. Oxytocin also can be administered by pulsatile infusion, which may better simulate spontaneous labor (53). The total amount of oxytocin given may be decreased by administering oxytocin in 10-minute pulse infusions (53, 57).

A numeric value for the maximum dose of oxytocin has not been established. The fetal heart rate and uterine contractions should be monitored closely. Oxytocin should be administered by trained personnel who are familiar with its effects.

▶ ***How should complications associated with oxytocin use be managed?***

If hyperstimulation with a nonreassuring fetal heart rate occurs, intravenous infusion of oxytocin should be decreased or discontinued to correct the pattern. Additional measures may include turning the woman on her side and administering oxygen or more intravenous fluid. If hyperstimulation persists, use of terbutaline or other tocolytics may be considered.

Hypotension may occur following a rapid intravenous injection of oxytocin; therefore, it is imperative that a dilute oxytocin infusion be used even in the immediate puerperium. Although amniotic fluid embolism was once thought to be associated with oxytocin-induced labor, there is no causal relationship between oxytocin use or antecedent hyperstimulation and amniotic fluid embolism (58, 59).

▶ ***Are the various methods of labor induction equally applicable to patients with intact or ruptured membranes?***

The same precautions should be exercised when prostaglandins are used for induction of labor with ruptured membranes as for intact membranes. Intravaginal PGE_2 for induction of labor in women with premature rupture of membranes appears to be safe and effective, although it has not been approved by the FDA for this indication (60). In a meta-analysis of labor induction in women with premature rupture of membranes at term, only one dose of intravaginal misoprostol was necessary

for successful labor induction in 86% of the patients (61). There is no evidence that use of either of these prostaglandins increases the risk of infection in women with ruptured membranes (60, 61).

▶ ***What methods can be used for induction of labor with intrauterine fetal demise in the late second or third trimester?***

Intravenous oxytocin usually is a safe and effective method of inducing labor for a fetal death near term but is less effective remote from term (62). Laminaria or hygroscopic cervical dilators may be beneficial before the use of oxytocin or PGE for induction (63, 64). High-dose PGE_2 vaginal suppositories and more concentrated intravenous oxytocin are effective for achieving delivery, particularly when the gestational age is 28 weeks or less (62, 65, 66). Reported side-effects associated with higher doses of PGE_2 include nausea, vomiting, and diarrhea, which may be ameliorated with pretreatment medications. Although PGE_2 vaginal suppositories have been used safely in the third trimester (67), the risk of uterine rupture is increased. Vaginal misoprostol, intramuscular or extraamniotic infusion of $PGF_{2\alpha}$ and mifepristone also have been used safely and effectively; however, studies are few. In one study, mifepristone (600 mg per day for 48 hours) was effective in achieving delivery within 72 hours after the initial dose in 63% of women (68). In another study using intravaginal misoprostol, the mean time from induction to delivery was 12.6 hours, and all women delivered by 48 hours (69).

▶ ***What is the cost effectiveness of these agents?***

There is a significant cost difference for induction of labor between misoprostol and dinoprostone. The approximate cost of a 100-mcg tablet of misoprostol ranges from $0.36 to $1.20, whereas a dinoprostone gel kit ranges from $65 to $75, and the dinoprostone vaginal insert is $165 (34, 35, 39, 70). The cost would be increased further if oxytocin augmentation were needed. Moreover, dinoprostone is an unstable compound that requires refrigeration to maintain its potency, whereas misoprostol is stable at room temperature.

Summary

The following recommendations are based on good and consistent scientific evidence (Level A):

- Prostaglandin E analogues are effective in promoting cervical ripening and inducing labor.
- Women in whom induction of labor is indicated may be appropriately managed with either a low- or high-dose oxytocin regimen.
- Fetal heart rate and uterine activity should be continuously monitored from the time the PGE_2 vaginal insert is placed until at least 15 minutes after it is removed.
- High-dose PGE_2 vaginal suppositories may be used in the management of intrauterine fetal demise in the second trimester of pregnancy.
- Although the optimal dose and timing interval of misoprostol is unknown, lower doses (25 mcg every 3–6 hours) are effective for cervical ripening and induction of labor.
- With term premature rupture of membranes, labor may be induced with prostaglandins.

The following recommendations are based on evidence that may be limited or inconsistent (Level B):

- Misoprostol use in women with prior cesarean birth should be avoided because of the possibility of uterine rupture.
- The use of higher doses of misoprostol (50 mcg every 6 hours) to induce labor may be appropriate in some situations, although there are reports of increased risk of complications, including uterine hyperstimulation.

The following recommendations are based primarily on consensus and expert opinion (Level C):

- For women with third-trimester intrauterine fetal demise, intravaginal misoprostol can be used to induce labor.
- Fetal heart rate and uterine activity should be continuously monitored from 30 minutes to 2 hours after administration of PGE_2 gel.

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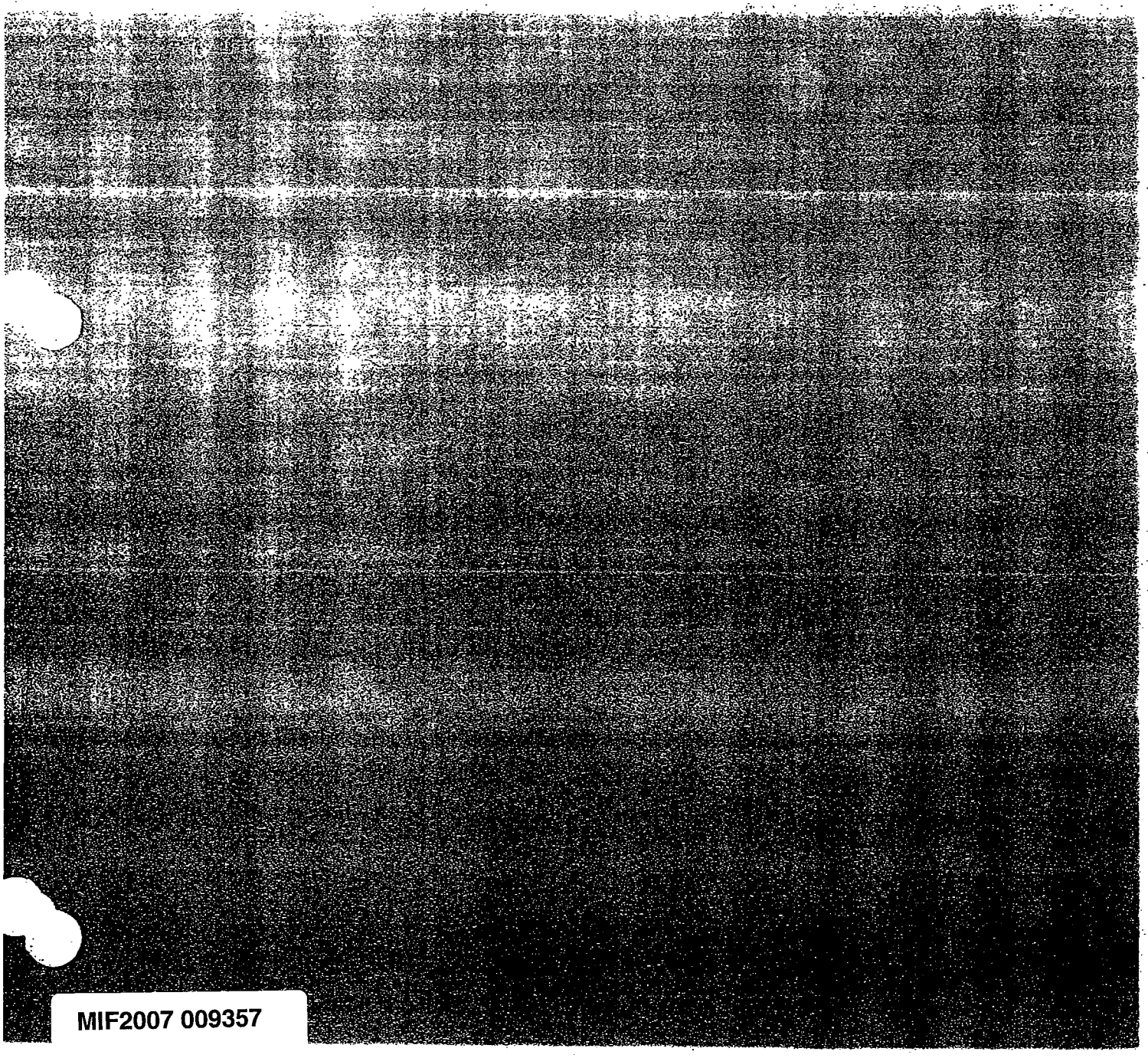

NDA 20-687

FEB 18 2000

Population Council
Attention: Sandra P. Arnold
1230 York Avenue
New York, NY 10021

Dear Ms. Arnold:

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

We acknowledge receipt of your submissions dated September 18 and 26, 1996; January 30, March 6 and 31, July 28, August 5, September 3 and 24, November 26, 1997; January 30, February 19, April 27, June 25, October 26, December 7 and 8, 1998; February 8, 22, March 31, April 28, May 10, 20, June 3 (2), 15, 25, 30, July 14, 22, August 3, 13, 18, 30, September 3, 8, 13, 30, October 5, 26, 28, November 16, 29 (2), December 6, 7, 23, 1999; January 21, 28 (2), and February 16, 2000. Your submission of August 18, 1999 constituted a complete response to our September 18, 1996 action letter.

We have completed the review of this application, as amended, and it is approvable. Before this application may be approved, however, it will be necessary for you to address the following:

Chemistry

Drug Substance

Drug Product

Labeling

Address the recommendations in the enclosed draft labeling for the Physician Insert and Patient Package Insert.
It will be necessary for you to submit revised draft labeling for the drug. We recommend that the

labeling be identical in content to the enclosed draft labeling (text for the Physician Package Insert and Patient Package Insert).

If additional information relating to the safety or effectiveness of this drug becomes available, revision of the labeling may be required.

Phase 4 Commitments

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

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

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

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

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

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

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

Distribution Plan

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

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

Promotional Activities

Please note that promotional activities for this NDA are subject to 21 CFR 314.550. As such, please submit three copies of the introductory promotional materials that you propose to use for this product. All proposed materials should be submitted in draft or mock-up form, not final print. Please send one copy to the [redacted], and two copies of both the promotional materials and the package insert directly to:

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

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

listed below. The update should cover all studies and uses of the drug including: (1) those involving indications not being sought in the present submission, (2) other dosage forms, and (3) other dose levels, etc.

1. Retabulation of all safety data including results of trials that were still ongoing at the time of NDA submission. The tabulation can take the same form as in your initial submission. Tables comparing adverse reactions at the time the NDA was submitted versus now will certainly facilitate review.
2. Retabulation of drop-outs with new drop-outs identified. Discuss, if appropriate.
3. Details of any significant changes or findings.
4. Summary of worldwide experience on the safety of this drug.

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

6. English translations of any approved foreign labeling not previously submitted.

7. Information suggesting a substantial difference in the rate of occurrence of common, but less serious, adverse events.

Within 10 days after the date of this letter, you are required to amend the application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. In the absence of any such action FDA may proceed to withdraw the application. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

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

If you have any questions, call [redacted]

Sincerely,

Enclosure

cc:
Archival NDA 20-687
Div. Files

(with labeling)

DISTRICT OFFICE

Drafted by: February 14, 2000
Initialed by: 2.15.00 2.15.00 2.15.00 2.15.00 2.15.00
2.15.00 2.15.00 2.15.00 2.15.00 2.15.00
final: February 18, 2000
filename: 20687AE.WPD

APPROVABLE (AE)

arm
ABORTION RIGHTS MOBILIZATION
175 Fifth Avenue (Suite 814)
New York, N.Y. 10010
212/673-2040

FAX No. [redacted]

November 18, 1994

[redacted]

Dear [redacted]

Following our phone talk this morning, I am outlining ARM's approach (along with our allies, NOW, Feminist Majority, etc.) The political situation, the possibility of a bill to ban RU 486, and a change in the Presidency all intensify the need to get RU 486 to women quickly. RU 486 must be generally available to prove how essential it is at least a year before 1996 elections.

I have had long meetings with Margaret Catley-Carson, president of Population Council, the last on Nov. 15. Pop.

All the best,

Larry Lader (Pres.)

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

December 15, 1992

Representative Ron Wyden
Chairman
Subcommittee on Regulation,
Business Opportunities, and Energy
House of Representatives
B-363 Rayburn House Office Building
Washington, D.C. 20515-6318

Dear Mr. Wyden:

This is in response to your letter of December 10, 1992, regarding the drug mifepristone (RU-486) manufactured by Roussel-Uclaf, in which you ask several questions.

You asked first whether the Food and Drug Administration would consider clinical trials in Europe as adequate evidence of the drug's safety and efficacy for purposes of approval in the United States for interruption of early pregnancy and whether additional human testing might be necessary to fulfill United States requirements. As with any other drug, the FDA is willing to consider foreign clinical trials as evidence of safety and efficacy, although we always reserve the right to audit the data according to our usual procedures. We recently approved an oral contraceptive (Desogen) based entirely on clinical studies conducted in the United Kingdom. Other drugs have also been approved on the basis of foreign trials alone. Agency staff who will be responsible for reviewing any mifepristone application report that, based on publicly available information and literature reports, the available data may well be sufficient to permit an adequate review. Therefore, further clinical trials may not be required. However, without an application submitted to the Agency for review, we cannot give a definitive answer on this question.

You also ask for an estimate of the length of time and the costs involved for a company seeking to obtain approval of mifepristone in the United States. While we are not experts on cost issues, the costs of preparing a new drug application for this product should not be excessive because much of the necessary information is already available. The Pharmaceutical Manufacturers Association, or its member companies, may be able to be more helpful on this issue. Based on our current knowledge regarding the data on the drug's safety and effectiveness, we estimate that the review process at the FDA would take approximately four to six months, which would include the involvement of a public advisory committee.

In response to your last question, an unresolved issue would be obtaining access in this country to a prostaglandin which, as you know, under the terms of the foreign approvals, must be taken in conjunction with mifepristone. In addition, as you are aware, distribution of mifepristone is closely controlled under the terms of the foreign approvals. The appropriate distribution system for mifepristone in this country would also need to be resolved.

Sincerely yours,

Carol R. Scheman
Deputy Commissioner
for External Affairs

102d Congress

United States House of Representatives
Committee on Small Business

Subcommittee on Regulation, Business Opportunities, and Energy

2-363 Rayburn House Office Building
Washington, DC 20515-6318

December 10, 1992

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

Via Fax: (301) 443-3100

Dear Dr. Kessler,

This subcommittee is investigating several issues relating to the U.S. regulation of, and marketplace opportunities for the French drug RU 486, manufactured by Roussel Uclaf. Key to this inquiry is the current view of the U.S. Food and Drug Administration regarding the safety and efficacy proofs which will be required should the manufacturer decide to market this drug in the United States, and the time burden likely to face the company should it seek a new drug approval from your agency.

While the agency should not -- and does not -- intend to in any way lessen the normal burden of proof required for any new drug, in the case (prospectively) of RU 486, we are interested in whether scientists within the FDA's new drug approval section have any views regarding the breadth and quality of experience with this drug in France, and in other foreign markets.

In this context, I have several questions for the agency:

-- To what extent does the agency deem European experience with this drug, including more than 100,000 clinical medical cases in France since 1988, as evidence of the drug's safety and efficacy for purposes of approval in the United States?

-- If European experience with RU 486 is directly applicable to requirements demanded within the FDA standard drug approval process, is it possible to attach some comparative value to that which is already known about the drug?

Specifically, can you give a rough estimate as to the percentage or portion of the usual U.S. drug approval process, including demands for extensive human testing, which may already be satisfied by the European experience?

-- Similarly, can you provide any estimate as to how long a U.S. drug approval process would take in light of the extensive evidence of safety and effectiveness already available for RU 486? Perhaps the agency can point to the case of another foreign drug used extensively, and safely, overseas prior to the manufacturer's application for a U.S. drug approval?

-- Subcommittee staff have spoken with a number of U.S. pharmaceutical companies which have an interest in licensing and distributing RU 486, or a similar drug, in the U.S. These companies have suggested that U.S. approval of this drug, for the reasons mentioned above, would be relatively swift and inexpensive.

The representative of one firm interviewed by subcommittee staff estimated that the total cost would be well under $5 million -- a marked difference from the average cost of a full-scale, full-phase, drug approval process estimated by Tufts University at more than $200 million.

While this estimate of the possible cost of taking RU 486 through the U.S. drug approval process obviously is very speculative, would you say that this forecast still could be in the ballpark given what we know of the European experience with RU 486 in terms of safety and effectiveness, and whatever additional proofs may be demanded by the agency?

-- Finally, are you aware of any unusual or unique circumstances involving this drug which could delay, jeopardize or otherwise seriously impede its review in the FDA's drug approval process, should the company come forward with an application?

Thank you for your attention to these questions. I would very much appreciate your earliest possible response. Should you have any questions, please don't hesitate to contact me, or Steve Jenning of the subcommittee staff at (202) 225-7797.

Sincerely,

RON WYDEN
Chairman

cc. Congressional Affairs, FDA.

The Honorable Ron Wyden
Chairman, Subcommittee on Regulation,
Business Opportunity, and Energy
Committee on Small Business
House of Representatives
Washington, D.C. 20515

Dear Mr. Wyden:

We are writing because we are concerned about statements made at your December 5, 1991, hearing on RU-486.

Specifically, on page 147, lines 3357-3361, of the transcript, you attribute to Dr. Solomon Sobel a statement regarding the Administration's position on abortion research. You stated: "He said that there was no problem with abortion research as far as the Bush Administration is concerned." We believe that you may be referring to Dr. Sobel's comments at your Subcommittee's November 19, 1990, hearing on RU-486. I refer specifically to page 40 of the printed record of that hearing, where Dr. Sobel is discussing the RU-486 import alert and its impact on research on potential uses of this drug. He said: "Even in regard to abortion, the agency has not taken a position of stopping investigational use." This is a correct statement of the FDA policy. Because we believe this statement is not in accord with your characterization at the December 5 hearing, we respectfully request that this hearing record be corrected.

In addition, you stated at the December 5 hearing (page 141, lines 3236-3242) that "now we checked with the FDA as of yesterday, there were two compassionate use approvals, no new investigational drug applications for research within the last three years." I would like to clarify for the record conversations between our staffs just prior to the December 5 hearing regarding investigational new drug applications (INDs). Specifically, your staff was informed that while we could (and did) share with the Subcommittee information on the existence of new INDs, our regulations prohibit public discussion of such new applications. Further, we advised your staff that because a number of the previously disclosed studies (applications) had been either completed or discontinued, the number of active ongoing studies had declined. We did not characterize the status of current research as "moribund.

BUC & BEARDSLEY
919 Eighteenth Street, N.W.
Suite 600
Washington, D.C. 20006-5503
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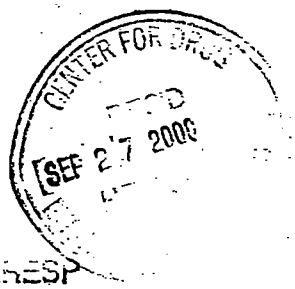

FACSIMILE TRANSMISSION

September 22, 2000

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WRITER'S TELEPHONE
202-736-3610

TELEPHONE
202-736-3600
FACSIMILE
202-736-3608

September 21, 2000

Re: NDA 20-687, Mifeprex (mifepristone) Oral Tablets
MACMIS #9342

Dear ———

In the rush last night, I included a draft page 2 instead of a corrected page 2 in my letter. I am attaching a complete copy of the letter, including the correct page 2.

Sincerely,

Nancy L. Buc

Printed by [redacted]

Electronic Mail Message

Sensitivity: COMPANY CONFIDENTIAL

Date: 23-Jul-1999 10:05am
From: [redacted]

Dept: [redacted]
Tel No: [redacted] , FAX 301-443-9285

TO: [redacted]

Subject: FWD: Re: Call from Searle--heads up

[redacted]

As you can see, others are becoming interested in the Cytotec - uterine perforation/rupture issue. I need to consult DRUDP. Any progress on the labeling review? Thanks.

APPEARS THIS WAY
ON ORIGINAL

Electronic Mail Message

Date: 4/14/00 4:00:52 PM
From: [redacted]
To: [redacted]
Cc: [redacted]
Cc: [redacted]
Subject: Cytotec "Dear Health Care Practitioner" letter

[redacted]

I tried to call you this afternoon, but were told you were out of the office. I am on leave, or I wouldn't be bugging you this late on Friday. I am trying to get out of here for vacation, but something ALWAYS comes up.

Searle has submitted (3/9/00)a draft Dear Health Care Practitioner letter that they would like to issue ASAP. What else is new, huh?? Anyway, we transferred a drug group from one PM [redacted], to another [redacted], and this sort of fell thru the cracks. [redacted] is on leave next week also. The letter is about the "unapproved use of intravaginal or oral misoprostol in pregnant women for induction of labor or abortion".

As you may know, misoprostol is used with mifepristone (??? spelling) to induce abortions, which I hear is back in the FDA for review with a FDAMA goal date of sometime in September. I would like DDMAC to look at this letter, but because it previously fell thru the cracks, we need someone to look at it ASAP.

I would like to consult it up to you, and if it needs to be turfed to someone else, that is fine. I will contact you when I return from leave on 4/24.

Sorry for the babbling.

[redacted]

TOM A. COBURN, M.D.
2D DISTRICT, OKLAHOMA

COMMITTEE ON COMMERCE
SUBCOMMITTEES:
HEALTH AND ENVIRONMENT
ENERGY AND POWER

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

215 STATE STREET, SUITE 515
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(918) 341-9437 (FAX)

34 "A" STREET N.E., ROOM 202
MIAMI, OK 74354
(918) 542-5337
(918) 542-5367 (FAX)

October 16, 2000

Ralph W. Hale, MD, FACOG
Executive Vice President
American College of Obstetricians and Gynecologists
409 12th St. SW
Washington DC 20024-2188

Dear Dr. Hale,

Thank you for your letter stating ACOG's opposition to H.R. 5385 and S. 3157, the RU-486 Patient Health and Safety Act. Of course, I am not surprised by ACOG's opposition to this legislation because I am familiar with July 27, 2000 communication from ACOG to the FDA regarding the patient protection guidelines the FDA was reportedly considering. As you can see, my bill is nothing other than an attempt to codify most of those very same guidelines.

Each one of those guidelines has but one purpose: the protection of patient health and safety. It was a sad day when the FDA approved RU-486 — the first drug ever approved for the specific purpose of ending a human life. But that was made even worse by the fact that the FDA succumbed to the political pressure brought by ACOG and other elements of the abortion lobby by dropping most of the proposed patient protections, and thereby recklessly exposing women to avoidable risk.

Let us review the patient protection standards to which you objected and which the FDA dropped under that pressure, evidently in response to those objections.

1) Limit distribution of the drug only to licenced physicians. The point of this, obviously, is to ensure that mifepristone is administered only under a doctor's direct supervision. The FDA actually retained this standard, but your objection to it raises very troubling concerns about ACOG's commitment to patient protection.

2) Require the physician to be "trained and authorized by law" to provide surgical abortions. I am surprised that ACOG would object either to training or legal authorization for a physician. The legal authorization is a matter of state law. As for training in abortion procedures, the real issue in connection with a mifepristone/misoprostol abortion is the ability to handle complications, and especially the ability to perform a dilatation and curettage in the event of an incomplete abortion — a rather common complication, according to the clinical trials. I have dealt with this in my bill by adding to the original FDA proposal a distinct requirement that the prescribing physician be qualified to handle the complications of an incomplete abortion or an ectopic pregnancy.

429 CANNON HOUSE OFFICE BUILDING
WASHINGTON, DC 20515
(202) 225-2701 FAX: (202) 225-3038

E-MAIL: rep.coburn@mail.house.g
WEB SITE: www.house.gov/cobur

My bill does not address the paradox that the FDA has approved a drug which, used by itself, is not efficacious in achieving the intended purpose of a completed abortion, and which becomes effective only when used in combination with another drug whose manufacturer has warned is unsafe in that application. The FDA cannot escape the logical dilemma of having approved a drug that is either ineffective (when used without misoprostol) or unsafe (when used with misoprostol).

Your justification for authorizing the use of misoprostol for chemically inducing abortion is that without misoprostol, mifepristone is ineffective. That is what is known as circular reasoning.

The evidence that we have from the clinical trials about the safety of the mifepristone/ misoprosol combination for abortion is not entirely encouraging. There were no deaths among the sample population, but the rate of incomplete abortions was nearly 8 percent and the incidence of hemorrhaging was 5 percent. These are both potentially serious complications with rates of occurrence that are too high to be dismissed as "rare." In France, where far more stringent safety precautions are in effect, one death and two near-fatal cardiac arrests were recorded within the first two years of availability. In 1991, in response to concerns about such complications, France banned the use of mifepristone by women over 35 and by smokers. The U.S. clinical trials reportedly did not include smokers or women over 35 among the subjects, but neither of these conditions is listed in the label, the prescriber's agreement, the patient agreement, or the medication guide as a contraindication. Undoubtedly, some women from both of those risk categories will be likely to receive the drug combination because neither they nor their doctors have any way of knowing these factors pose an additional risk.

You will note that my legislation does not at all address the question of the use of misoprostol to induce labor. As a practitioner, I am grateful to Searle for calling attention to the risks and contraindications of induction with misoprostol. But I am also cognizant of the benefits of using misoprostol for induction in some cases. The freedom of doctors to weigh the risks and benefits and then to act in the best interest of their patients is not at all affected by my legislation and is irrelevant to the conditions under which mifepristone was approved.

I have no doubt that if women were asked whether their doctor should have to be able to read a sonogram, handle complications, and get them admitted to a hospital in case of emergency, they would not hesitate to demand those levels of competence. Nor do I have any doubt that women would expect their doctors to be trained in the use of a potentially risky drug. In light of the very real and very serious risks to maternal health associated with this method of abortion, I remain amazed and dismayed that ACOG opposes the elementary patient protection standards that I have proposed. I encourage you to reconsider your position.

Sincerely,

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

Electronic Mail Message

Date: 10/17/00 9:14:42 AM
From: [redacted]
To: [redacted]
To: [redacted]
Cc: [redacted]
Subject: FWD: - no subject (01JVEW7I77ZE8Y52Z0) -

[redacted] had a few calls last month from the American College of OB GYN and they were saying the new cytotec letter was scaring some institutions about using this for Abortions, or at the least causing reevaluation of its use at institutions. The college was planning to hold a meeting on whether it should change its guidelines for use because of this letter.

[redacted], can you follow up with the OBGYN contact on their conference they had earlier this month and see if they are changing the college's recommendation for its use. Let us know. Thanks.

[redacted]

APPEARS THIS WAY
ON ORIGINAL

From:
Sent: Tuesday, October 03, 2000 5:54 PM
To:
Cc:
Subject: FW: Secret manufacturers

Sensitivity: Confidential

Secret manufacturers

Let's discuss.

----Original Message----
From:
[mailto: @cder.fda.gov]
Sent: Tuesday, October 03, 2000 5:21 PM
To: (OC)
Subject: FWD: Secret manufacturers
Sensitivity: Confidential

Would OCC be interested in responding to him??

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

Date: 03-Oct-2000 05:24pm EDT
From: [redacted]

Dept: [redacted]
Tel No: [redacted] FAX [redacted]

TO: [redacted] ([redacted])

CC: [redacted] ([redacted])

Subject: Final Footnote - Mifeprex 20687

[redacted]

Below is the final footnote that will appear (per [redacted] concurrence) on the CY Grid Line Listing for Mifeprex, NDA 20-687.

Total approval time for NDA 20-687, Mifeprex was adjusted. The time period (9/18/96-8/19/99) was excluded because the sponsor had to find a new manufacturer, the final study report for the US Clinical trial was completed an submitted late in the review and stability issues had to be addressed before th sponsor could resubmit the application for review. The time period (2/18/00-3/31/00) was excluded while the sponsor prepared for a facilities inspection.

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

ensitivity: COMPANY CONFIDENTIAL

Date: 02-Oct-2000 09:41am EDT
From:

Dept: HFD-023
Tel No: 301 — FAX 301-827-1540

O:

ubject: FWD: Re: Adjusted Time 20687 Mifeprex

i

am in the process of sending you a new e-mail. Give me a few more minutes efore I forward it. Yes, I was just getting ready to address comments in my new e-mail. I will send it as soon as I pass it through —.

hanks.

Electronic Mail Message

Date: 10/2/00 1:26:54 PM
From: [redacted]
To: See Below
Subject: Document Requests

In follow up to our meeting of last week and in anticipation of any major document requests concerning a recent major approval, here is the plan we worked out at the meeting. We'll be scheduling a followup meeting for this week. Comments are welcome. Please send to anyone I may have missed.

[redacted]

To: [redacted]
To:
To:
To:
To:
To:
To:
To:
To:
To:
To:
To:
Cc:

Mifepristone Outstanding Issues 8-11-00

- Chemistry and Manufacturing
  - 483 issued 7/28/00 with minor deficiencies to be corrected by 8/30/00
  - Analytic and stability data outstanding

- Labeling
  - Black Box
    - Surgical intervention may be necessary; prescribers should determine in advance whether they will provide such care or refer. Patients should be given clear instructions on whom to call and what to do. Patients should receive Med Guide, read and discuss it and Patient Agreement
  - Day 3 return for misoprostol
    - FDA: Return on Day 3 for misoprostol

Mifepristone Outstanding Issues 8-11-00/ cont.'

- Distribution System: Physician Qualifications
  - [redacted] distribution of drug to physicians do not possess surgical intervention skills, but must be able to date pregnancies, diagnose ectopics, and assure referral to physician with surgical skills, if needed.
  - For safety reasons, we need to ensure quality of outcomes [redacted] those patients treated by physicians who possess surgical intervention skills (as in the clinical trials) and by physicians who refer patients for surgical intervention.
    - Four of six Phase 4 commitments become part of risk management/monitoring system to ensure quality:
      - To monitor the adequacy of distribution system and credentialing
      - To follow up on medical failure outcomes [redacted]
      - To ascertain completion of regimen
      - To study outcomes of children born after treatment failure
        - » Audit patient agreement? 2% chart audit versus confidentiality issues
        - » Study of referral/non-referral practices on rates of med failure, return rates for day 14, transfusion, hospitalization, surgical intervention for bleeding, infection rates
        - » Return rates for day 14 collected above. Consider nested case-control study with data collection on patient variables who don't return versus who do.
        - » Study of a sample of above practices supplemented with spontaneous reports on pregnancy outcomes of infants exposed

Mifepristone Outstanding Issues 8-11-00/ cont.'

- Remaining Phase 4 Studies
  - Two other studies
    - Assess long term effects in multiple use (European data)
    - Assess S/E in women under age 18, over 35, and in smokers
- Medication Guide
  -
  -
  - Ensure distribution of Guide through unit of use packaging, attestation of distribution by physician when signing to receive drug
- Subpart H
  - Pop Council requests language

Mifepristone Outstanding Issues 8-11-00/ cont.'

- Administrative Issues
  - [redacted]

MIFEPRISTONE NDA

STATUS

Brief Summary of Publicly Available Information

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

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

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

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

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

Brief Summary of Non-Public Information

Review Issues

Printed by [redacted]

Electronic Mail Message

Date: 20-Jul-2000 01:00pm
From: [redacted]
Dept: [redacted]
Tel No: [redacted] FAX [redacted]

Subject: FWD: mifepristone INDs in 150, 120, and 510.... info request

[redacted]

Per note on copy of this e-mail I dropped on your desk.

[redacted]

Electronic Mail Message

Date: 02/07/2000 1:19:52 PM
From: [redacted] ([redacted])
To: [redacted] ([redacted])
Subject: Re: Mifepristone

[redacted]

attached is the info sheet I send out to physicians requesting mifepristone on a single-patient IND basis. Note, the info you're looking for is on page 4 of the document. The rest of the pages are likely irrelevant, but it was easier to attach the whole document.

you can reach met @ [redacted]

[redacted]

>
>
> [redacted]
>
>I am a medical officer reviewing an IND on mifepristone. In my effort to
>obtain safety/tox. info on this drug, a Med Officer in your division, [redacted] suggested I request from you a copy of information
>you provide for patients taking mifepristone regarding side
>effects/risks of mifepristone treatment understand [redacted]
>
>compassionate use of mifepristone). Could you fax me the info, as soon
>as you are able, at fax no. [redacted] Could you also call me at
>[redacted] when you have a few minutes? I greatly appreciate your
>assistance.
>
>Sincerely,
>
> [redacted]
>[redacted]

Electronic Mail Message

Date: 2/1/00 4:55:44 AM
From: [redacted]
Subject: ? about registry

Hi [redacted]

I sometimes feel like a detective...
The registry you spoke about yesterday was for the Pop Council.
No one would discuss the drug or anything about it in yesterday's open forum.
Was told to contact [redacted] for further information.
Hope that last night's meeting was informative, but uneventful!

Thanks,
[redacted]

Printed by [redacted]

Electronic Mail Message

Sensitivity: COMPANY CONFIDENTIAL

Date: 15-Oct-1999 03:08pm
From: [redacted]
Dept: [redacted]
Tel No: [redacted] FAX [redacted]

TO: [redacted] ([redacted])

CC: [redacted] ([redacted])

Subject: User Fee Date Approaching

I was looking at the list of user fee dates that are approaching and the following application(s)that contain foreign facilities are getting close to deadline:

20687 - will miss the date because the inspection of Shanghai Hualian Pharmaceutical is scheduled for 10/25-27/99, [redacted] will be the investigator. The user fee date is 10/19/99. The application was submitted by HFD-530.

These are the only two application that contain foreign facilities that I have come across.

Thank you,

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 [redacted], 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

Date: 10-May-1999 03:51pm
From: [redacted]
Dept: [redacted]
Tel No: [redacted] FAX [redacted]

Subject: FWD: Re: Mifepristone

This is the information that I am getting from oncology. Please let me know what I should do or who I should be talking to. It seems as though there is more to this than I thought.

[redacted]

MEDICATION/DEVICE INVENTORY

STUDY INITIATION

SPONSOR: Population Council

PROJECT: Mifepristone / Misoprostol

PROTOCOL: 166A

PRIMARY INVESTIGATOR: Dr Suzanne T Poppema

CO-INVESTIGATOR(S):

ADDRESS: Aurora Medical Services
1207 N. 200th, Suite 214
Seattle, WA. 98133

PATIENT NUMBERS	BOTTLE/CARD/KIT NUMBERS	CONTENTS
—	3 bottles	51 tablets per bottle.
		153 total tablets.

Suzanne T. Poppema, M.D.
Seattle, WA CFN 3032921
EI: 11/01/99-11/05/99
Exhibit 29 Page 1 of 5

SIGNATURE OF INVESTIGATOR

11-8-94
DATE

SIGNATURE OF MONITOR

11-8-94
DATE

MEDICATION/DEVICE INVENTORY

SPONSOR: Population Council

PROJECT: Mifepristone / Misoprostol

PROTOCOL: 166A

PRIMARY INVESTIGATOR: Dr. Poppema

CO-INVESTIGATOR(S):

ADDRESS: Aurora Medical Services, Inc
1207 N. 200th, Suite 214
Seattle, WA 98133

PATIENT NUMBERS	BOTTLE/CARD/KIT NUMBERS	CONTENTS
—	4 Bottles	51 tablets each.
		(204 tablets)

Suzanne T. Poppema, M.D.
Seattle, WA CFN 3032921
EI: 11/01/99-11/05/99
Exhibit 29 Page 2 of 5

SIGNATURE OF INVESTIGATOR — DATE: 1/19/95

SIGNATURE OF MONITOR — DATE: 1/9/95

MEDICATION/DEVICE INVENTORY

Additional Supply

SPONSOR: Population Council

PROJECT: 166A (Mifepristone)

PROTOCOL: 166A

PRIMARY INVESTIGATOR: Dr. Poppema

CO-INVESTIGATOR(S):

ADDRESS: Aurora Medical Services, Inc
1207 N. 200th, Suite 214
Seattle, WA 98133

PATIENT NUMBERS	BOTTLE/CARD/KIT NUMBERS	CONTENTS
	4 Bottles of Mifepristone (51 tablets each bottle)	204 tablets.
	Lot #: TMP 2552A-109 Expiration Date: 7/97	

Suzanne T. Poppema, M.D.
Seattle, WA CFN 3032921
EI: 11/01/99-11/05/99
Exhibit 29 Page 3 of 5

SIGNATURE OF INVESTIGATOR — DATE: 3/21/95

SIGNATURE OF MONITOR — DATE: 3/16/95

MIF2007 009679

MEDICATION/DEVICE INVENTORY

SPONSOR: Population Council

PROJECT: Mifepristone/M.301-0501

PROTOCOL: 166A

PRIMARY INVESTIGATOR: Suzanne Poppema

CO-INVESTIGATOR(S):

ADDRESS: Aurora Med. Serv., Inc
1207 N. 200th., Suite 214
Seattle, WA 98133

PATIENT NUMBERS	BOTTLE/CARD/KIT NUMBERS	CONTENTS
	3 bott. x 51 tabs	200mg tablets
	= 153 tabs	Mifepristone
		Lot# JMP2524-105
		Exp. 7/97

Suzanne T. Poppema, M.D.
Seattle, WA CFN 3032921
EI: 11/01/99-11/05/99
Exhibit 29 Page 4 of 5

Suzanne Poppema
SIGNATURE OF INVESTIGATOR

5-3-95
DATE

SIGNATURE OF MONITOR

4/29/95
DATE

MEDICATION/DEVICE INVENTORY

SPONSOR: Population Council

PROJECT: mifepristone/misoprostol

PROTOCOL: 166A

PRIMARY INVESTIGATOR: Suzanne Poppema

CO-INVESTIGATOR(S):

ADDRESS: Aurora Medical Center
1207 N. 200th, Suite 214
Seattle, WA 98133

PATIENT NUMBERS	BOTTLE/CARD/KIT NUMBERS	CONTENTS
		15 tablets
	Lot #JMP2552A-109	200 mg mifepristone
	Exp 7/97	

Suzanne T. Poppema, M.D.
Seattle, WA CFN 3032921
EI: 11/01/99-11/05/99
Exhibit 29 Page 5 of 5

Suzanne Poppema MD
SIGNATURE OF INVESTIGATOR

9/29/95
DATE

SIGNATURE OF MONITOR

9/30/95
DATE

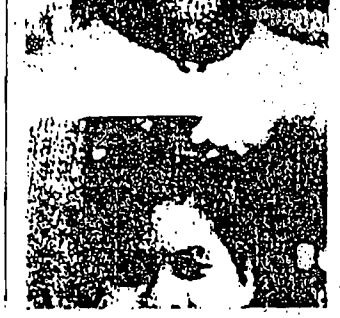
Proposal #948057
REVIEW CATEGORY: C

Date: 09/15/94
To: Daniel R. Mishell, Jr., M.D.
Professor and Chairman
Dept of Obstetrics and Gynecology
Women's Hospital, #L-1009
(213)226-3416

FROM: [redacted]

TITLE OF PROPOSAL:
EVALUATION OF THE EFFICACY, SAFETY AND ACCEPTABILITY OF MIFEPRISTONE AND MISOPROSTOL IN INDUCING ABORTION IN PREGNANCY WOMEN WITH AMENORRHEA OF UP TO 63 DAYS

Action Date: 09/15/94 Action Taken: Approved
Committee : [redacted] SECRETARY
Note:
The press release to be used for this study was reviewed and APPROVED by [redacted], Secretary [redacted] on September 13. 1994. The study was assigned Review Category C. ([redacted] Office [redacted])



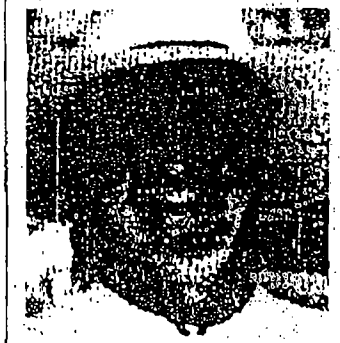
Trojan on the street

"What do you consider to be safe sex?"

Reporting and photos by Kensaka Okada

"There's no such thing. Safe sex is an illusion."

Carlos Romero
sophomore
psychology



"With a condom. It's the safest way to go."

Ian Aler
graduate student
business

"Abstinence."

Joy Ho
sophomore

ABORTION PILL STUDY

Women wishing early pregnancy termination are invited to participate in a Food and Drug Administration approved study of the Abortion Pill at no cost to the participant. For information please contact:

WOMEN'S HOSPITAL CONTRACEPTION CLINIC

at

213/226-3104

Daily 49er Ad - Cal State LB.

BLUE

CDER OC FOREIGN INSPECTION TRACKING SYSTEM
DATA FORM

RECORD: 3418 CONTROL : 322-00-08-0181 DATE ENTERED: 8/18/00

CFN: 9615606 FEI: 3002914652 FIRM LOOKUP FIRM TYPE: MA TYPE EI: 4

FIRM: SHANGHAI HUA LIAN PHARMACEUTICAL CO LTD - XIN LIAN PHAR

STREET: 217 MING LE ROAD

CITY: PUDONG ST-PROV: SHANGHAI COUNTRY: CH

APPLICATION DATA

TYPE	NUMBER	SUPPLEMENT	USER FEE DATE	STATUS
N	20-687		9/30/00	A

FIRST DATE EI:	7/24/00	LAST DATE EI:	7/28/00	DATE ENDORSED:	8/15/00	DATE OF RECOMM:	8/15/00
INITIAL CLASS:	AE	DATE REC'D:	8/18/00	ACTION TYPE:	EIR	PRIORITY:	HIGH
DATE DUE:	8/25/00	DATE ASSIGNED:	8/21/00	ASSIGNED TO:	—	CSO COMP. DATE:	8/21/00
FINAL CLASS:	AE	RESC DATE:	05/2003	COMP. ACTION:	CON	COMP. DATE:	8/21/00

COMMENTS: This was a compliance reinspection of this API manufactured scheduled following the previous PAI in 10/99 which found several GMP deficiencies and laboratory procedures which were not the same as described in the application. This firm does not have a DMF and the API mfg & testing procedures were submitted in the NDA, An untitled leter was issued 12/99.

This inspection verified corrections following the previous inspection and untitled letter. Additional deficiencies re. Methods validation, laboratory standards, and HEPA filter & pressure differentials qualifications were noted. On 8/10, the firm's US agent submitted an interim response to these deficiencies. The firm has corrected or is in the process of correcting all deficiencies, and will be completed by Aug 31. Based on the previous verified corrections, and nature of deficiencies,this commitment appears satisfactory. CDER concurs with approval recommendation.

PROFILES	STATUS
CSN	A

GMP PROBLEMS
07
17

Final Response OK

9/11/00

CDER OC FOREIGN INSPECTION TRACKING SYSTEM
DATA FORM

RECORD: 3418 CONTROL : 322-00-08-0181 DATE ENTERED: 8/18/2000

CFN: 9615606 FEI: 3002914652 FIRM LOOKUP FIRM TYPE: MA TYPE EI: 4

FIRM: SHANGHAI HUA LIAN PHARMACEUTICAL CO LTD - XIN LIAN PHAR

STREET: 217 MING LE ROAD

CITY: PUDONG ST-PROV: SHANGHAI COUNTRY: CH

APPLICATION DATA

TYPE	NUMBER	SUPPLEMENT	USER FEE DATE	STATUS
N	20-687		9/30/2000	A

FIRST DATE EI:	7/24/2000	LAST DATE EI:	7/28/2000	DATE ENDORSED:	8/15/2000	DATE OF RECOMM:	8/15/2000
INITIAL CLASS:	AE	DATE REC'D:	8/18/2000	ACTION TYPE:	EIR	PRIORITY:	HIGH
DATE DUE:	8/25/2000	DATE ASSIGNED:	8/21/2000	ASSIGNED TO:	[redacted]	CSO COMP. DATE:	8/21/2000
FINAL CLASS:	AE	RESC DATE:	05/2003	COMP. ACTION:	CON	COMP. DATE:	8/21/2000

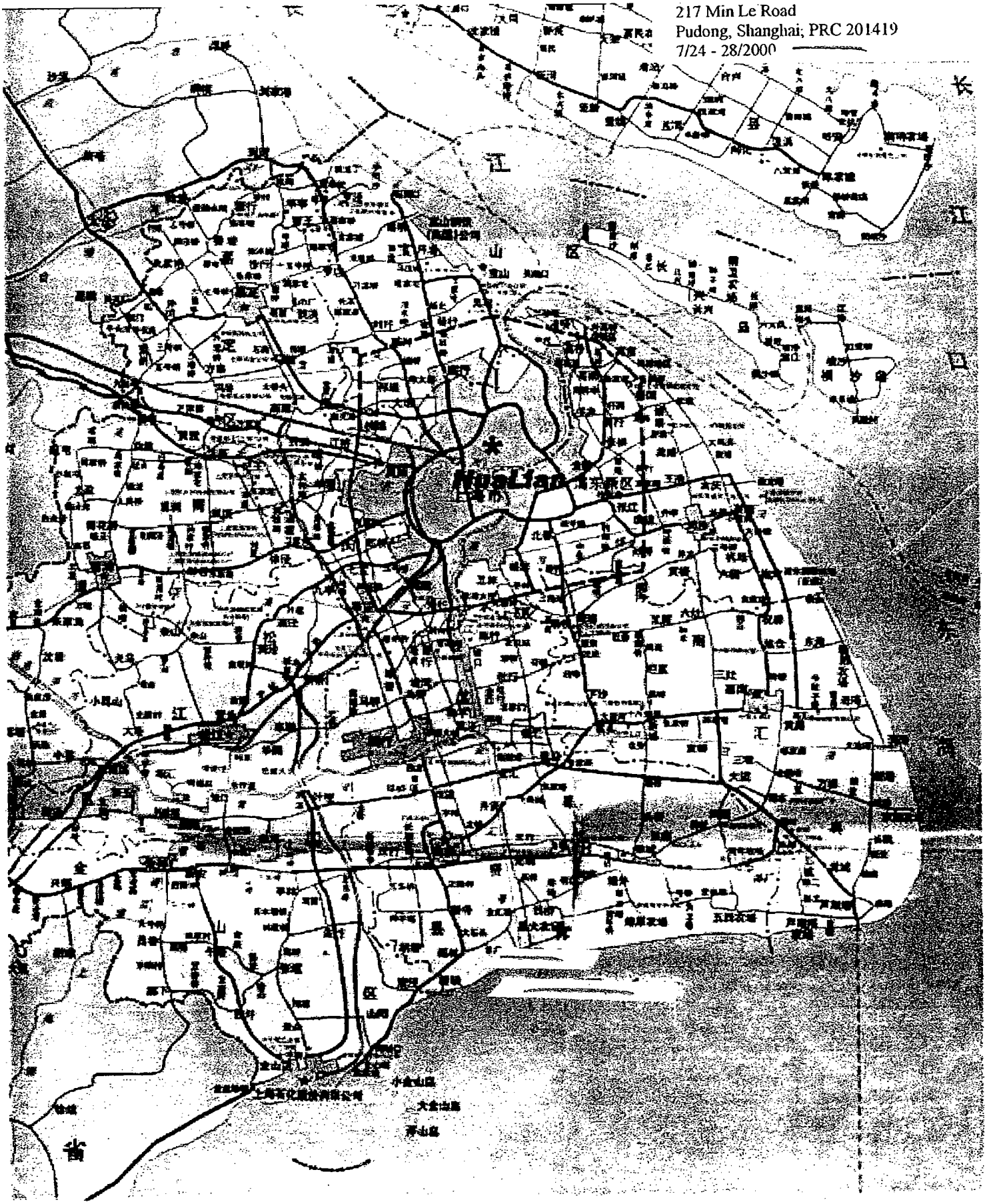
COMMENTS: This was a compliance reinspection of this API manufactured scheduled following the previous PAI in 10/99 which found several GMP deficiencies and laboratory procedures which were not the same as described in the application. This firm does not have a DMF and the API mfg & testing procedures were submitted in the NDA, An untitled leter was issued 12/99. This inspection verified corrections following the previous inspection and untitled letter. Additional deficiencies re. Methods validation, laboratory standards, and HEPA filter & pressure differentials qualifications were noted. On 8/10, the firm's US agent submitted an interim response to these deficiencies. The firm has corrected or is in the process of correcting all deficiencies, and will be completed by Aug 31. Based on the previous verified corrections, and nature of deficiencies,this commitment appears satisfactory, CDER concurs with approval recommendation. Firm Response 8/18/00 satisfactory

PROFILES	STATUS
CSN	A

GMP PROBLEMS
07
17

APPEARS THIS WAY
ON ORIGINAL

Exh. 1 Pg. 1 of 1 Pg.
Shanghai Hua Lian Pharm. Co., Ltd.
Xin Lian Pharm. Factory
217 Min Le Road
Pudong, Shanghai; PRC 201419
7/24 - 28/2000



MIF2007 010705

CDER OC FOREIGN INSPECTION TRACKING SYSTEM
DATA ENTRY/CONTROL FORM

TYPE	NUM	SUPPL	RECOM
N	20-687		W

CONTROL: 322-99-12-04 CFN : 9615606 NEW CFN FIRM TYPE : M TYPE EI : 1

FIRM: SHANGHAI HUA LIAN PHARMACEUTICAL CO LTD - XIN LIAN PHAR

STREET: 217 MING LE ROAD

CITY: PUDONG ST-PROV: SHANGHAI COUNTRY: CH

FIRST DATE EI: 10/25/99 LAST DATE EI: 10/28/99 DATE ENDORSED: 12/3/99 DATE OF RECOMM: 12/3/99

INITIAL CLASS: AA DATE REC'D: 12/14/99 ACTION TYPE: EIR USER FEE DATE: 10/19/99

PRIORITY: HIGH DATE DUE: 12/18/99 DATE ASSIGNED: 12/14/99 CSO: ———

COMPLETED: 12/15/99 FINAL CLASS: AA COMP. ACTION: ——— RESC DATE: 10/00

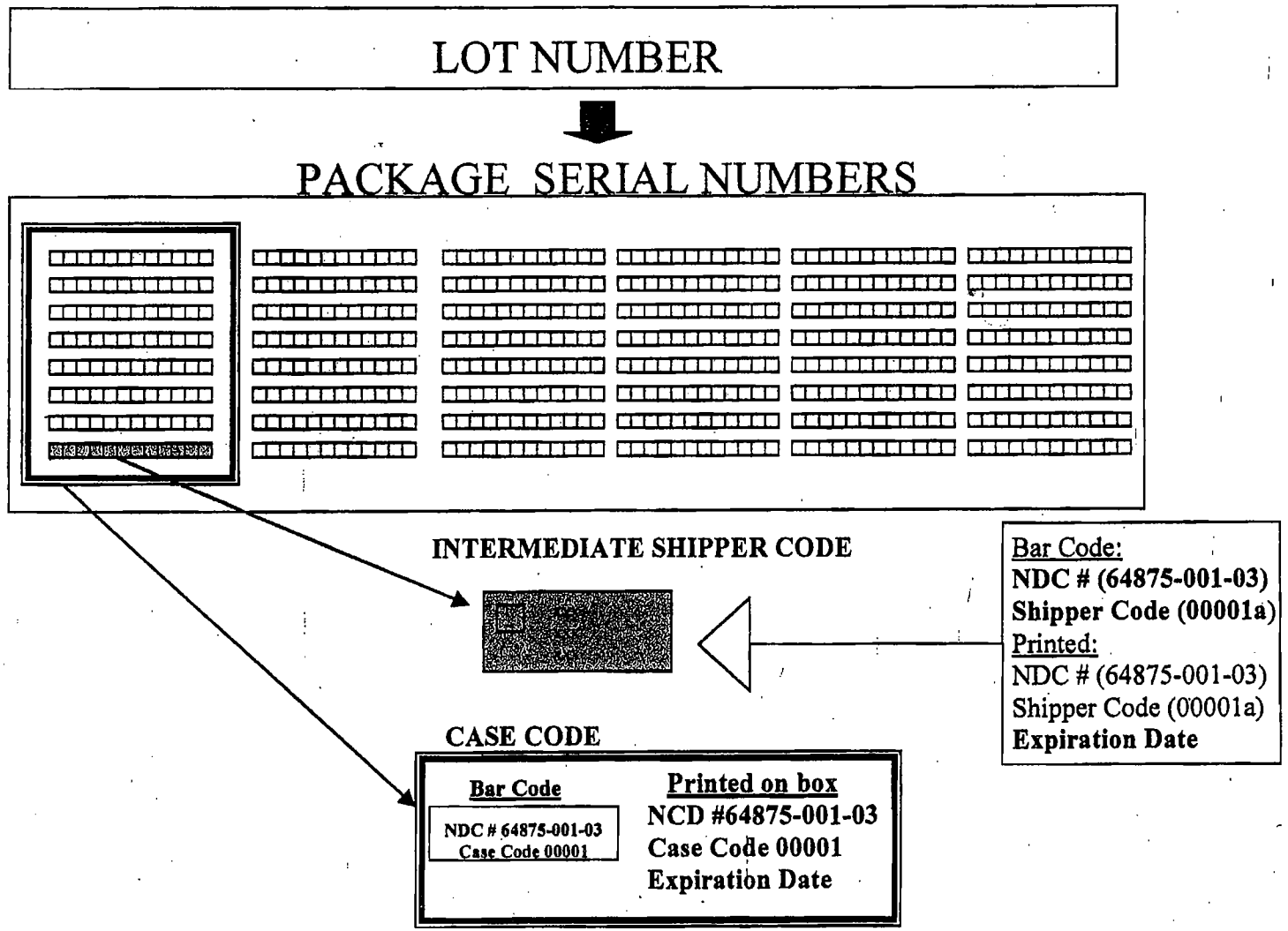
COMMENTS :

This was the initial inspection of this API manufacturer, covering mifepristone. The facility als manufactures betamethasone on separate equipment. CGMP deficiencies regarding labeling and handling of recycled solvent containers and calibration of a ———; analyzer were noted, but the firms written response provides satisfactory corrections. The district recommends withholding approval because the laboratory procedures, (raw material, in-process, and finished product) described in the NDA are not the same as used in this laboratory, and the in-process ———tests used to monitor critical reactions have not yet been finalized or validated. The firm's response states that an ammendment has been submitted to correct the NDA errors.. We concur in the withold recommendation re failure to follow NDA commitments. Untitled letter re. NDA deficiencies.

PROFILE	STATUS
CSN	N

TYPE PROBLEM
3
9

DATA TRACKING HIERARCHY



DEPARTMENT OF HEALTH AND HUMAN SERVICES

PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

STATEMENT OF INVESTIGATOR

(TITLE 21, CODE OF FEDERAL REGULATIONS (CFR) Part 312)
(See instructions on reverse side.)

Form Approved: OMB No. 0910-0014.
Expiration Date: November 30, 1995.
See OMB Statement on Reverse.

NOTE: No investigator may participate in an investigation until he/she provides the sponsor with a completed, signed Statement of Investigator, Form FDA 1572 (21 CFR 312.53(c)).

1. NAME AND ADDRESS OF INVESTIGATOR

Judy Tyson, M.D.
Planned Parenthood of Northern New England
51 Talcott Rd., #1
Williston, Vermont 05495

2. EDUCATION, TRAINING, AND EXPERIENCE THAT QUALIFIES THE INVESTIGATOR AS AN EXPERT IN THE CLINICAL INVESTIGATION OF THE DRUG FOR THE USE UNDER INVESTIGATION. ONE OF THE FOLLOWING IS ATTACHED:

☒ CURRICULUM VITAE ☐ OTHER STATEMENT OF QUALIFICATIONS

3. NAME AND ADDRESS OF ANY MEDICAL SCHOOL, HOSPITAL, OR OTHER RESEARCH FACILITY WHERE THE CLINICAL INVESTIGATION(S) WILL BE CONDUCTED.

Planned Parenthood of Northern New England
51 Talcott Rd., #1
Williston, Vermont 05495

4. NAME AND ADDRESS OF ANY CLINICAL LABORATORY FACILITIES TO BE USED IN THE STUDY.

5. NAME AND ADDRESS OF THE INSTITUTIONAL REVIEW BOARD (IRB) THAT IS RESPONSIBLE FOR REVIEW AND APPROVAL OF THE STUDY(IES).

Institutional Review Board
Under the Auspices of

6. NAMES OF THE SUBINVESTIGATORS (*e.g., research fellows, residents, associates*) WHO WILL BE ASSISTING THE INVESTIGATOR IN THE CONDUCT OF THE INVESTIGATION(S).

7. NAME AND CODE NUMBER, IF ANY, OF THE PROTOCOL(S) IN THE IND FOR THE STUDY(IES) TO BE CONDUCTED BY THE INVESTIGATOR.

Evaluation of the Efficacy, Safety and Acceptability of Mifepristone and Misoprostol in Inducing Abortion in Pregnant Women with Amenorrhea of up to 63 Days

Protocol #166A

Med. Lic. # Vermont # 42.0004438

CURRICULUM VITAE

NAME: Judith Tyson

DATE OF BIRTH: [redacted]

BIRTHPLACE: [redacted]

CITIZENSHIP: U.S.A.

MARITAL STATUS: [redacted]

FAMILY: [redacted]

LANGUAGES: English, German, Spanish, French

EDUCATIONAL RECORD:

Secondary: George School, Newtown, Pennsylvania.
Gertraudenschule, Berlin, Germany

College: Bryn Mawr College, Bryn Mawr, Pennsylvania. B.A. Political Science 1957

Graduate: University of Madrid, Spain-Middlebury College. M.A. Hispanic Studies 1958

Dartmouth College, Hanover, New Hampshire. Premedical Sciences 1963-1965

University of Vermont, Burlington, Vermont. Premedical Sciences 1965 (Summer)

Dartmouth Medical School, Hanover, New Hampshire. Research Assistant, Dept. of Pharmacology 1965-1966

University of Vermont College of Medicine, Burlington, Vermont. 1966-1970. M.D.

INTERNSHIP:

Roosevelt Hospital, New York City, Rotating Ob/Gyn, under Drs. Ezra Davidson and Thomas Dillon, 1970-1971

RESIDENCIES:

University of Vermont College of Medicine, Burlington, Vermont (Medical Center Hospital of Vermont), Anesthesiology, under Dr. John Abajian, 1971-1972

Roosevelt Hospital, New York City, Ob/Gyn, under Dr. Thomas Dillon, July-September 1974

The Western Pennsylvania Hospital, Pittsburgh, Pennsylvania, Ob/Gyn, under Drs. Leonard Laufe and John Walker, 1975-1978

FELLOWSHIPS:

American College of Obstetricians and Gynecologists, Junior Fellow, 1975

American College of Obstetricians and Gynecologists, Fellow, 1982

ACADEMIC APPOINTMENTS:

Dartmouth Medical School, Hanover, New Hampshire, Assistant Professor, Maternal and Child Health, 1979-

HOSPITAL APPOINTMENTS:

Dartmouth-Hitchcock Medical Center, Hanover, New Hampshire, Staff obstetrician/gynecologist, 1979-

OTHER APPOINTMENTS:

Physician to Planned Parenthood of Vermont, 1971-1975
Founder of and Physician to Vermont Women's Health Center, Burlington, Vermont, 1972-1975
Medical Advisory Committee, Vermont Women's Health Center, 1972-1973, 1980-
Board of Trustees, Vermont Women's Health Center, 1972-1973

Consultant, International Fertility Research Program, Chapel Hill, N.C. IFRP delegate to First International Conference on Menstrual Regulation, Honolulu, Hawaii, 1973

Consultant, International Pregnancy Advisory Services, Chapel Hill, N.C., 1973-

Medical Advisory Committee, Planned Parenthood of Northern New England, 1973-1975, 1978-

Medical Advisory Board, National Women's Health Coalition, 1974-1980

Consultant, Advanced Techniques in Fertility Management, University of Pittsburgh, Population Division, Graduate School of Public Health, 1975-1978

Publications Committee, Association of Planned Parenthood Physicians, 1975-1978

Medical Director, Planned Parenthood of Pittsburgh, Pittsburgh, Pennsylvania, 1976-1977

Medical Advisory Committee, Planned Parenthood of Pittsburgh, 1976-1977

Consultant, Bangladesh Fertility Research Program and Government of Bangladesh. Minilap Tubal Banding (Female Sterilization) Orientation Program, Bangladesh, September 1976

Medical Director, Planned Parenthood of Northern New England, July 1978-

Member, Birth Planning Observer Group to Peoples Republic of China, November 1978

Consultant, Population Crisis Committee, Washington, D.C., 1978-

Consultant, Center for Population Activities, Washington, D.C., 1978-

Medical Advisory Committee, International Women's Health Coalition, 1978-

National Medical Committee, Planned Parenthood Federation of America, 1980-1983; 1988

Membership Committee, Assn. Planned Parenthood Professionals, 1981-1984

Medical Standards Advisory Team, Planned Parenthood Federation of America, 1982-1984

Guest Faculty: First U.S.-Nicaragua Colloquium on Health, Managua, Nicaragua, November 1983

Consultant, Division of Maternal and Child Health, N.H. State Health Dept. 1983-

Consultancy to Philippines, Indonesia, Bangladesh, India, for Population Crisis Committee, September-October, 1984

Consultancy to Philippines, Indonesia, India, for Population Crisis Committee, International Women's Health Coalition, July 1985

Consultancy: Association for Voluntary Sterilization, New York, NY, 1985

Consultancy: International Projects Assistance Services: Zaire, Nigeria, Kenya, Zambia, March 1987

Consultancy: International Projects Assistance Services: Turkey, December 1987
Consultancy: International Projects Assistance Services: Brazil, October 1988
Delegate Trainee: Norplant Training: Santo Domingo, December 1989
Consultancy to Egypt for Pathfinder International, January 1992

PROFESSIONAL ORGANIZATIONS:

Founding Member, Vermont Chapter, Medical Committee for Human Rights, Advisor, Women's Health Section, 1972-1975
Association of Planned Parenthood Professionals, 1973-1987
Association of Professors of Gynecology and Obstetrics, 1983-
Association of Reproductive Health Professionals, 1987- (President 1988-1989)
Medical Directors Council of the Planned Parenthood Federation of America, 1987- (Northeast Region Representitative, 1987-1988)

PUBLICATIONS:

1. Co-author: "The Evolution of a Woman's Clinic: An Alternate System of Medical Care". Presented at the Annual Meeting of American Gynecological Society, 1976, and published in the American Journal of Obstetrics and Gynecology, Vol. 126, No. 7, Dec. 1, 1976.

2. Contributing Editor: "Serve the People: The Expanding Role of the Non-M.D. Practitioner", paper presented before the Association of Planned Parenthood Physicians Annual Meeting, October 1977, Atlanta, Georgia.

3. Editorial Boards: American Journal of Gynecologic Health.

HONORS:

Vermont Susan B. Anthony Award, 1986

Vermont NARAL Freedom of Choice Award, 1988

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IND/NDA SUBSEQUENT SUBMISSIONS REVIEW TRANSMITTAL

1. IND/NDA NUMBER	2. CORRESPONDENCE DATE	3. DATE RECEIVED	4. DOCUMENT IDENTIFICATION
022047	01-08-01	01-09-01	N21-PN,PT-FC

DELIVER TO LAST ADDRESSEE INDICATED BELOW:

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		1/8/01

REVIEWER - If this decision is incorrect, notify Group Consumer Safety Officer at once.

	TYPE OF ACTION		
MEDICAL OFFICER	REVIEW	INFO	NAI
CHEMIST	REVIEW	INFO	NAI
	✓		
PHARMACOLOGIST	REVIEW	INFO	NAI
		✓	
STATISTICIAN	REVIEW	INFO	NAI
MICROBIOLOGIST	REVIEW	INFO	NAI
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01-09-01

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POST AND DESTROY.

Mifepristone Outstanding Issues 8-11-00/ cont.'

- Distribution System: Physician Qualifications
  - [redacted] distribution of drug to physicians do not possess surgical intervention skills, but must be able to date pregnancies, diagnose ectopics, and assure referral to physician with surgical skills, if needed.
  - For safety reasons, we need to ensure quality of outcomes [redacted] those patients treated by physicians who possess surgical intervention skills (as in the clinical trials) and by physicians who refer patients for surgical intervention.
    - Four of six Phase 4 commitments become part of risk management/monitoring system to ensure quality:
      - To monitor the adequacy of distribution system and credentialing
      - To follow up on medical failure outcomes [redacted]
      - To ascertain completion of regimen
      - To study outcomes of children born after treatment failure
        - » Audit patient agreement? 2% chart audit versus confidentiality issues
        - » Study of referral/non-referral practices on rates of med failure, return rates for day 14, transfusion, hospitalization, surgical intervention for bleeding, infection rates
        - » Return rates for day 14 collected above. Consider nested case-control study with data collection on patient variables who don't return versus who do.
        - » Study of a sample of above practices supplemented with spontaneous reports on pregnancy outcomes of infants exposed

Mifepristone Outstanding Issues 8-11-00/ cont.'

- Remaining Phase 4 Studies
  - Two other studies
    - Assess long term effects in multiple use (European data)
    - Assess S/E in women under age 18, over 35, and in smokers

- Medication Guide

  - Ensure distribution of Guide through unit of use packaging, attestation of distribution by physician when signing to receive drug

- Subpart H
  - Pop Council requests language

Pop Council 9/7/00 3pm

What Do We Know about Induced Abortion in the United States

Induced Abortion Data:

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

Who Seeks Abortion Service:

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

Who Provides Abortion Service:

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

Access to Abortion Service:

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

Safety of Abortion Service:

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

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Efficacy and Safety of Mifepristone:

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

Safe and Effective Use of Mifepristone:

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

Reference

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

Table 1. Number of Abortion, Abortion Rate and Number of Providers by Census Divisions and States

Census Divisions and States	Number of Abortions	Abortion Rate	Number of Providers
Total	**1,365,730**	**22.9**	**2,042**
New England	**71,280**	**23.5**	**141**
Connecticut	16,230	22.5	40
Maine	2,700	9.7	16
Massachusetts	41,160	29.3	51
New Hampshire	3,470	12.7	16
Rhode Island	5,420	24.4	5
Vermont	2,300	17.1	13
Middle Atlantic	**270,220**	**32.0**	**421**
New Jersey	63,100	35.8	94
New York	167,600	41.1	266
Pennsylvania	39,520	15.2	61
East North Central	**190,050**	**19.3**	**161**
Illinois	69,390	26.1	38
Indiana	14,850	11.2	16
Michigan	48,780	22.3	59
Ohio	42,870	17.0	37
Wisconsin	14,160	12.3	11
West North Central	**48,660**	**11.9**	**51**
Iowa	5,780	9.4	8
Kansas	10,630	18.9	10
Minnesota	14,660	13.9	13
Missouri	10,810	9.1	10
Nebraska	4,460	12.3	8
North Dakota	1,290	9.4	1
South Dakota	1,030	6.5	1
South Atlantic	**263,600**	**24.7**	**361**
Delaware	4,090	24.1	7
District of Columbia	20,790	154.5	18
Florida	94,050	32.0	114
Georgia	37,320	21.1	41
Maryland	31,310	26.3	47
North Carolina	33,550	20.2	59
South Carolina	9,940	11.6	14
Virginia	29,940	18.9	57
West Virginia	2,610	6.6	4

Census Divisions and States	Number of Abortions	Abortion Rate	Number of Service Providers
East South Central	**46,100**	**12.5**	**48**
Alabama	15,150	15.6	14
Kentucky	8,470	9.6	8
Mississippi	4,490	7.2	6
Tennessee	17,990	14.8	20
West South Central	**120,610**	**18.1**	**96**
Arkansas	6,200	11.4	6
Louisiana	14,740	14.7	15
Oklahoma	8,400	11.8	11
Texas	91,270	20.7	64
Mountain	**67,020**	**18.6**	**127**
Arizona	19,310	19.8	24
Colorado	18,310	20.9	47
Idaho	1,600	6.1	7
Montana	2,900	15.6	11
Nevada	15,450	44.6	14
New Mexico	5,470	14.4	13
Utah	3,700	7.8	7
Wyoming	280	2.7	4
Pacific	**288,190**	**30.1**	**636**
Alaska	2,040	14.6	8
California	237,830	33.0	492
Hawaii	6,930	27.3	44
Oregon	15,050	21.6	35
Washington	26,340	20.9	57

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

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

1 Cullen MR. Chrysotile asbestos: enough is enough. *Lancet* 1998; 351: 1377–78
2 Selikoff IJ, Seidman H. Asbestos-associated deaths among insulation workers in the United States and Canada, 1967–1987. *Ann N Y Acad Sci* 1991; 1643: 1–14.
3 Landrigan PJ. Asbestos—still a carcinogen. *N Engl J Med* 1998; 338: 1618–19.
4 Rohl AN, Langer AM, Moncure G, Selikoff IJ, Fischbein A. Endemic pleural disease associated with exposure to mixed fibrous dust in Turkey. *Science* 1982; 216: 518–20.
5 Artvinli M, Bariş YI. Environmental fiber-induced pleuro-pulmonary diseases in an Anatolian village: an epidemiologic study. *Arch Environ Health* 1982; 37: 177–81.

Fetal malformation and failed medical termination of pregnancy

Sir—Claudette Gonzalez and colleagues (May 30, p 1624)[1] describe birth defects after failed illegal abortion in 42 infants who were exposed to misoprostol at doses of 200–1600 µg during the first 3 months of gestation. This report underscores both the risk of misuse of misoprostol used as a sole agent to procure abortion and the social consequences of the restrictive laws on abortion in Brazil.

Misoprostol is registered for use in association with mifepristone for legal termination of early pregnancy (up to 49 days of gestation) in France. The licensed regimen has proved over 95% effective in inducing complete abortion.[2] In the UK and Sweden, the prostaglandin PgE1 analogue gemeprost is registered for use in association with mifepristone for termination of early pregnancy of up to 63 days' gestation, and efficacy has been shown to be about 95%.[3] The regimens of oral misoprostol or vaginal gemeprost in association with mifepristone are associated with a complete failure rate of between 1·5% and 0·3%, respectively.[2,3]

The Exelgyn (the French company set up by ES to further develop and market Mifegyne [mifepristone] outside the USA) datasheet indicates that it is essential that termination of pregnancy by another method be undertaken in the event of failure. Nevertheless, if a woman changes her mind or the clinician fails to follow-up or make a diagnosis, some pregnancies will continue.

We reviewed 71 cases of continuing pregnancy after failed early medical termination of pregnancy. The cases occurred between 1987 and 1998, and in that time we estimate that about 405 000 early medical terminations of pregnancy had been done in the UK, France, and Sweden. In 21 of these cases mifepristone was used alone, in the remaining cases mifepristone was associated with a prostaglandin analogue: misoprostol 400 µg orally (22), sulprostone 0·25–0·5 mg intramuscularly (four), gemeprost 1 mg vaginally (ten), and an unspecified prostaglandin (14). In eight of the 71 cases, malformation of the fetus or baby was reported. The table shows details of the drug regimen used, age of pregnancy, and outcome in those for whom abnormality was reported. There were no reported cases of malformation associated with use of misoprostol when used with mifepristone.

Our findings show the safety of legal, early, medical termination of pregnancy in association with mifepristone and prostaglandin, but also provide information on the risk associated with continuing a pregnancy to term after a failure of the method. The apparent risk should be viewed with respect to the rate of spontaneous fetal malformation or non-viability, which might be as high as 34% at the stage of gestation appropriate for early medical termination of pregnancy.[4] We emphasise the need for rigorous adherence of the recommended procedure and counselling of women who change their minds about termination after a failed medical procedure should be undertaken to explain the possible risks to the fetus and the high rate of naturally occurring abnormalities that may lead to later miscarriage or non-viability.

Case	Gestation	Mif dose (mg)	PG type	Outcome	Defect
1	7 weeks	400	None	TToP	Sirenomelia, cleft palate
2	8 weeks	600	Gemeprost	ABN	Bilateral talipes equinovares
3	9 weeks 2 days	600	Gemeprost	ABN	Fingernail defect 3
4	8 weeks	600	Gemeprost	TToP	Talipes equinovares
5	9 weeks	600	Gemeprost	TToP	Acheiria, talipes equinovares
6	7–8 weeks	600	Gemeprost	TToP	Anencephalia, talipes equinovares
7	8 weeks 4 days	600	Gemeprost	ABN	Heart malformation
8	6–7 weeks	200	Gemeprost	TToP	Cerebrellum atrophy

Mif=mifepristone, Pg=prostaglandin, TToP=therapeutic termination of pregnancy, ABN=abnormality at term.

Fetal malformation associated with failed medical termination of pregnancy

*Regine Sitruk-Ware, *Angela Davey, Edouard Sakiz*
Exelgyn SA, 6 Rue Christophe Colomb, 75008 Paris, France

1 Gonzalez CH, Marques-Dias MJ, Kim CA, et al. Congenital abnormalities in Brazilian children associated with misoprostol misuse in first trimester of pregnancy. *Lancet* 1998; 351: 1624–27.
2 Peyron R, Aubeny E, Targosz V, et al. Early termination of pregnancy with mifepristone (RU486) and the orally active prostaglandin misoprostol. *N Engl J Med* 1993; 328: 1509–13.
3 UK multicentre study group. The efficacy and tolerance of mifepristone and prostaglandin in termination of pregnancy of less than 63 days gestation; UK multicentre study—final results. *Contraception* 1997; 55: 1–5.
4 Blanch G, Quenby S, Ballantyne ES, et al. Embryonic abnormalities at medical termination of pregnancy with mifepristone and misoprostol during first trimester: observational study. *BMJ* 1998; 316: 1712–13.

Conceptions and terminations after the 1995 warning about oral contraceptives

Sir—Susan Jick and colleagues (May 9, p 1404)[1] report that the General Practice Research Database showed no change in the frequency of pregnancies or terminations in women using Third-generation oral contraception after the warning letter from the Committee on Safety on Medicines in October, 1995, or in the database as a whole. This finding seems to contradict claims that the 1995 so-called pill scare led to an increase in unplanned pregnancy and abortion. By contrast, national data suggest a strong association between the scare and a substantial increase in conceptions and legal abortions in 1996. Quarterly conception figures recorded by the Office for National Statistics show an increase of 1% in the last quarter of 1995, and of 7%, 4%, and 2%, respectively, in the first three quarters of 1996, compared with the same quarters in 1995.[2] There were 26 000 more conceptions in England and Wales in 1996 than in 1995. The notification of 13 601 additional abortions in 1996 suggests that at least half of the additional conceptions did not result in a birth.

One reason why Jick and co-workers did not detect an increase in pregnancies is that those that resulted in births would not appear in their

	MIF ALONE	MIF+ MIS	MIF+ SUL	MIF+ UNK	MIF+ PG	MIF+ GEM	TOTAL
Normal Babies	12	13	2	4	2	4	37
Malformation at Term	0	0	0	0	0	3	3
MALF / TToP	1	0	0	0	0	5	6
Delayed Spont. Abortion	3	1	0	0	0	0	4
TToP UNK	4	3	0	0	2	0	9
TToP Normal Foetus	2	6	1	1	1	0	11
UNK/USNL	3	4	0	2	3	0	12
UNK	13	9	1	2	0	0	25
TOTAL	38	36	4	9	8	12	107

Update 30 November 1999

LEGENDS

MIF= mifepristone
MIS= misoprostol
SUL= sulprostone
GEM= gemeprost
PG= prostaglandin (unspecified)
UNK= unknown
TToP= Therapeutic Termination of Pregnancy
USNL= Ultrasound Normal (at second or third trimester)
Delayed Spont Abortion= Delayed Spontaneous Abortion
MALF/TToP=Malformation with therapeutic termination of pregnancy

OFFICE OF THE COMMISSIONER MEETING
EXECUTIVE SUMMARY

Date: August 11, 2000
Time: 11:00 a.m. – 12:00 noon
Location: Rm. 14-68, PKLN

Subject: Mifepristone

Attendees: Jane Henney.

Meeting Purpose: To provide an update on the review of mifepristone.

Meeting Agenda: [redacted] will lead the briefing.

Background: [redacted] s talking points are attached.

Executive Secretariat Contact: [redacted]

Mifepristone Outstanding Issues 8-11-00

- Chemistry and Manufacturing
  - 483 issued 7/28/00 with minor deficiencies to be corrected by 8/30/00
  - Analytic and stability data outstanding

- Labeling
  - Black Box
    - Surgical intervention may be necessary; prescribers should determine in advance whether they will provide such care or refer. Patients should be given clear instructions on whom to call and what to do. Patients should receive Med Guide, read and discuss it and Patient Agreement
  - Day 3 return for misoprostol
    - FDA: Return on Day 3 for misoprostol;

Mifepristone Outstanding Issues 8-11-00/ cont.'

- Distribution System: Physician Qualifications
  - distribution of drug to physicians who do not possess surgical intervention skills, but must be able to date pregnancies, diagnose ectopics, and assure referral to physician with surgical skills, if needed.
  - For safety reasons, we need to ensure quality of outcomes those patients treated by physicians who possess surgical intervention skills (as in the clinical trials) and by physicians who refer patients for surgical intervention.
    - Four of six Phase 4 commitments become part of risk management/monitoring system to ensure quality:
      - To monitor the adequacy of distribution system and credentialing
      - To follow up on medical failure outcomes
      - To ascertain completion of regimen
      - To study outcomes of children born after treatment failure
        - » Audit patient agreement? 2% chart audit versus confidentiality issues
        - » Study of referral/non-referral practices on rates of med failure, return rates for day 14, transfusion, hospitalization, surgical intervention for bleeding, infection rates
        - » Return rates for day 14 collected above. Consider nested case-control study with data collection on patient variables who don't return versus who do.
        - » Study of a sample of above practices supplemented with spontaneous reports on pregnancy outcomes of infants exposed

Mifepristone Outstanding Issues 8-11-00/ cont.'

- Remaining Phase 4 Studies
  - Two other studies
    - Assess long term effects in multiple use (European data)
    - Assess S/E in women under age 18, over 35, and in smokers
- Medication Guide
  - T
  - Ensure distribution of Guide through unit of use packaging, attestation of distribution by physician when signing to receive drug
- Subpart H
  - Pop Council requests language

APPOINTMENT DETAILED
19-Jul-2000 to 19-Jul-2000

Date: Wednesday, 19-Jul-2000 Time: 09:00am Length: 01:30 Hrs:Min

Subject: Pop Council mtg-N 20-687 Loc: potomac room

Attendees

Agenda

Pop Council/ Danco mtg.

Agenda:

Restricted Distribution System (with Subpart H provisions)

Labeling

Confidentiality requst from sponsor (possible item to discuss)

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Key to Attendee Status

Bold = Confirmed Underline = Rejected All Others = Pending

Calendar Manager 6-Jul-2000

OFFICE OF THE COMMISSIONER MEETING
EXECUTIVE SUMMARY

Date: July 14, 2000
Time: 11:30 – 12:00 PM
Location: Rm. 14-68, PKLN

Subject: Mifepristone

Attendees: Jane Henney

Meeting Purpose: To provide an update on the review of mifepristone.

Meeting Agenda: will lead the briefing.

Background: Mifepristone, also know as RU 486, is an abortifacient to be used with misoprostol for medical abortion. Mifepristone is being reviewed by CDER with a PDUFA date of September 30, 2000. The drug's sponsor, The Population Council (PC), has three areas to address from the last approvable action of February 18, 2000: chemistry/manufacturing, distribution system, and labeling.

Chemistry/manufacturing - In May 2000, FDA was informed that the manufacturing processes for the drug substance have been changed from how the NDA described the process. These changes are significant and require pre- and post-change comparative physical, analytical, and stability data to demonstrate that quality is maintained. The sponsor is responsible for supplying physical and analytical data by mid-July and stability data sometime in September.

The inspection of the Chinese drug substance maker is scheduled for July 27 and 28.

Distribution System - On July 5, 2000, the sponsor proposed that mifepristone be directly distributed to health care providers who self-attest to specific qualifications. PC proposes that the drug be provided by or under the supervision of a physician who has the ability to assess the duration of pregnancy accurately, to diagnose ectopic pregnancies, and to assure patient access to medical facilities equipped to provide emergency treatment of incomplete abortion, blood transfusions and emergency resuscitation. The sponsor does not believe it is necessary for prescribers to possess all the qualifications needed to perform every step in the patient's care. PC believes the prescriber can be advised to plan for care such as handling of incomplete abortions and the need for surgery and to give patient information about how to obtain these types of care. The sponsor does not propose health care providers who are distributing this drug be trained in the use of this drug, but the sponsor is making available educational programs. The sponsor also objects to approving this drug under Subpart H's provision for restricted distribution

Labeling - The sponsor

Executive Secretariat Contact:

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2/24/93 Senior representatives of FDA and Roussel Uclaf met to discuss [redacted]

N

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.

Talking Points for Press Interviews
Internal Use Only

With the encouragement of the United Sates government, Roussel-Uclaf today agreed to license the drug RU-486 to the Population Council for distribution in the United States.

Hoechst-Roussel/Uclaf is not willing to be involved in the distribution or production of RU-486 in the United States.

The Population Council will identify a manufacturer for RU-486 in the U.S. market.

The Population Council will begin a clinical trial to test the drug in the U.S. This trial would include a minimum of 2,000 women.

The Population Council will move as soon as possible to submit an NDA.

The FDA will begin the review of the existing toxicology and chemistry data upon receipt from Roussel. Once a New Drug Application is submitted for RU-486, the Food and Drug Administration will complete its formal review of the data concerning the safety and efficacy of the drug.

Funds for these activities will be sought from private sources, including foundations.

The Population Council is a non-profit scientific and technical organization which seeks to apply science to assist developing countries to find solutions to population issues and improved human reproductive health.

From: [redacted]
Sent: Wednesday, October 04, 2000 7:07 PM
To: Hennev, Jane; [redacted]

Cc: [redacted]
Subject: Proposed Legislation on Mifepristone

Importance: High

Introduced 10/4
HR 5385

Please find attached what we believe to be the legislation proposed by Rep. Coburn on limiting access to mifepristone. We have been told this is the proposal, however, we are not certain it has been filed yet and will not know until Thursday. Also below is language said to have been circulated by Rep. Coburn's office in suport of the legislation. If these versions change we will circulate new versions as soon as available.

[redacted]
coburn_095.pdf

> "COBURN OFFICE Summary of
> RU-486 Patient Health and Safety Protection Act
>
> The purpose of this bill is to protect mothers from the irresponsible and
> politically motivated malpractice of the Food and Drug Administration in
> approving this drug without safeguards. It is to ensure that RU-486 kills
> only one person at a time instead of two at a time.
>
> This bill simply codifies the patient protection standards that were
> reportedly considered by the FDA prior to approval of RU-486, but which
> were evidently dropped under political pressure from the abortion lobby.
>
> 1) The prescribing physician must be qualified to handle
> complication of an incomplete abortion. Basically, the prescribing
> physician must be able to do a dilation and curettage (d & c) in the event
> of an incomplete abortion. According to the clinical trials in the US,
> approximately 5% of the women who used this method of abortion prior to
> seven weeks LMP experienced an incomplete abortion. (Among the entire
> clinical trial population, which included those who had been pregnant
> longer, it was about 15%.) An incomplete abortion left untreated is a
> very serious, potentially fatal, complication.
>
> 2) The prescribing physician must be legally empowered to commit an
> abortion and trained to do so. The training standard is essentially the
> same as point 1; the legal standard is just current law.
>
> 3) The prescribing physician must be qualified to read a sonogram in
> order to date the pregnancy and identify an ectopic pregnancy. The
> effectiveness of RU-486 in killing the baby is sharply reduced after seven
> weeks, while the rate of complications is much higher. The use of RU-486
> in the case of an ectopic pregnancy is not recommended at all for the sake
> of the mother.
>
> 4) The prescribing physician must be properly trained in the
> administration of this drug. Doctors who don't know what they are doing
> are likely to hurt their patients.
>
> 5) The physician must have admitting privileges at a nearby

> hospital. Complications requiring emergency care, such as heavy bleeding,
> are relatively common with the use of this drug combination, and the
> prescribing physician must take responsibility for the care of his/her
> patients. If complications do arise, and the attending doctor is out of
> range or unavailable to care for his/her patient, other doctors who may
> have moral and ethical objections to abortion are then put in a position
> of having to perform the surgical abortion.
>
> The Coburn bill simply enacts these provision into law except for the
> provision creating a national registry of RU-486 providers and the
> provision calling for a follow-up study. Coburn believes these provisions
> should be left to the discretion of the Secretary of the Department of
> Health and Human Services."

Thanks

APPEARS THIS WAY
ON ORIGINAL

DOCUMENT LISTING -- RU-486

DATE	FROM	TO	SUBJECT
11/03/88	Dr. Irving M. Spitz Population Council	[redacted]	Letter (and enclosures) in response to FDA's request for adverse reaction reports (ADRs) for IND 22-047.
11/17/88	Dr. Irving M. Spitz	[redacted]	Letter (and enclosures) regarding ADRs.
11/19/90	Dr. Irving M. Spitz	[redacted]	Letter (and enclosures) regarding ADRs.
11/18/94	Dr. Irving M. Spitz	FDA	IND Safety Report
11/21/94	Dr. C. Wayne Bardin	[redacted]	Letter (and enclosures) regarding ADRs.
12/01/94	Dr. C. Wayne Bardin Population Council	[redacted]	Letter (and enclosures) regarding ADRs.
12/02/94	Dr. Irving Spitz	FDA	IND Safety Report
12/07/94	Dr. C. Wayne Bardin	[redacted]	Letter (and enclosures) regarding ADRs.
12/14/94	Dr. Fred Schmidt Population Council	FDA	IND Safety Report
12/20/94	Dr. C. Wayne Bardin	[redacted]	Letter (and enclosures) regarding ADRs.
01/18/95	Dr. C. Wayne Bardin	[redacted]	Letter (and enclosures) regarding ADRs.
01/23/95	Dr. C. Wayne Bardin	[redacted]	Letter (and enclosures) regarding ADRs.
02/07/95	Dr. C. Wayne Bardin	[redacted]	Letter (and enclosures) regarding ADRs.
02/10/95	Dr. Fred Schmidt	FDA	IND Safety Report
02/15/95	Dr. C. Wayne Bardin	[redacted]	Letter (and enclosures) regarding ADRs.
02/17/95	Dr. C. Wayne Bardin	[redacted]	Letter (and enclosures) regarding ADRs.

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

DATE	FROM	TO	SUBJECT
02/17/95	Population Council	FDA	IND Safety Report
02/17/95	Dr. Fred Schmidt	FDA	IND Safety Report
02/24/95	Dr. Fred Schmidt	FDA	IND Safety Report
03/95	[redacted]	FDA	[redacted]
03/03/95	Dr. C. Wayne Bardin	[redacted]	Letter (and enclosures) regarding ADRs.
03/06/95	Dr. C. Wayne Bardin	[redacted]	Letter (and enclosures) regarding ADRs.
03/09/95	Dr. Fred Schmidt	FDA	IND Safety Report
03/10/95	Dr. C. Wayne Bardin	[redacted]	Letter (and enclosures) regarding ADRs.
03/13/95	Dr. C. Wayne Bardin	[redacted]	Letter (and enclosures) regarding ADRs.
04/11/95	Dr. C. Wayne Bardin	[redacted]	Letter (and enclosures) regarding ADRs.
04/19/95	Dr. C. Wayne Bardin	[redacted]	Letter (and enclosures) regarding ADRs.
06/02/95	Dr. Fred Schmidt	FDA	IND Safety Report
06/07/95	Dr. C. Wayne Bardin	[redacted]	Letter (and enclosures) regarding ADRs.
06/07/95	Dr. André Ulmann	Dr. C. Wayne Bardin	Tolerance of RU-486 during U.S. Studies
06/13/95	Dr. C. Wayne Bardin	[redacted]	Letter (and enclosures) regarding ADRs.
07/95	Roussel Uclaf	FDA	International Safety Report

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

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

- In a letter dated September 21 to Secretary Donna Shall, Senators Sam Brownback (R-KS), James M. Inhofe (R-OK), Michael B. Enzi (R-WY), Mike DeWine (R-OH), Tim Hutchinson (R-AR), Bob C. Smith (R-NH), John Ashcroft (R-MO), Jeff Sessions (R-AL) and Frank A. Murkowski (R-AL) requested answers to several questions concerning mifepristone.

NEW POSTINGS CDER's WEBSITE

DRUG INFORMATION

Mifepristone (9/28/2000)
http://www.fda.gov/cder/drug/infopage/mifepristone/default.htm

***INFORMATION NOT RELEASABLE TO THE PUBLIC**

- Mifeprex (mifepristone) Tablet, Population Council, posted 9/28/2000

ITEMS OF INTEREST FROM OTHER PARTS OF THE AGENCY, INCLUDING CROSS-CUTTING ISSUES, MAY BE VIEWED ON THE FDA WEEKLY INFORMATION UPDATE POSTED BY 10AM MONDAY AT http://intranet.fda.gov/execsec

***INFORMATION NOT RELEASABLE TO THE PUBLIC**

K1.1

K1.1

N20687

N20687

NDA 20-687

1012/CV
2-25-97

Mifepristone 200 mg

Population Council
1P

PM: [redacted]

Phone: [redacted]

HFD-580

Resubmission Date: March 30, 2000
User Fee Goal Date: September 30, 2000

Administrative Information

Volume 1 of 7

MIF2007 011337

K1.2

K1.2

N20687

N20687

NDA 20-687

10/2/00
2:25 DM

Mifepristone 200 mg

Population Council
1P

PM: [redacted]

Phone: [redacted]

HFD-580

Resubmission Date: March 30, 2000
User Fee Goal Date: September 30, 2000

Administrative Information

Volume 2 of 7

K1.3

K1.3

N20687

N20687

NDA 20-687

[redacted]

10/2/00
2:25PM

Mifepristone 200 mg

Population Council
1P

PM: [redacted]

Phone: [redacted]

HFD-580

Resubmission Date: March 30, 2000
User Fee Goal Date: September 30, 2000

Administrative Information

Volume 3 of 7

K1.4

K1.4

N20687

N20687

NDA 20-687

10-2-00
2:55PM

Mifepristone 200 mg

Population Council
1P

PM: [redacted]

Phone: [redacted]

HFD-580

Resubmission Date: March 30, 2000
User Fee Goal Date: September 30, 2000

Clinical Information

Volume 4 of 7

K1.5

K1.5

N20687

N20687

NDA 20-687

10/2/00
2:25 PM

Mifepristone 200 mg

Population Council
1P

PM: [redacted]

Phone: [redacted]

HFD-580

Resubmission Date: March 30, 2000
User Fee Goal Date: September 30, 2000

Clinical Information

Volume 5 of 7

K1.6

K1.6

NDA 20-687

N20687

N20687

10/12/00
2:25 PM

Mifepristone 200 mg

Population Council
1P

PM: [redacted]

Phone: [redacted]

HFD-580

Resubmission Date: March 30, 2000
User Fee Goal Date: September 30, 2000

Chemistry Information

Volume 6 of 7

K1.7

K1.7

NDA 20-687

N20687

N20687

Mifepristone 200 mg

10/2/00
2:25 PM

Population Council
1P

PM: [redacted]

Phone: [redacted]

HFD-580

Resubmission Date: March 30, 2000
User Fee Goal Date: September 30, 2000

Pharm/tox Information

Volume 7 of 7

NDA/EFFICACY SUPPLEMENT ACTION PACKAGE CHECKLIST

NDA 20-687 /SE____ - ____

Drug Mifeprex™ (200mg.) Tablets Applicant Population Council

RPM____ Phone____

505(b)(1)
505(b)(2) Reference listed drug mifepristone

Fast Track Rolling Review Review priority: S (P)

Pivotal IND(s) ____

Application classifications:
Chem Class 1 P
Other (e.g., orphan, OTC) ____

PDUFA Goal Dates:
Primary 9-30-00
Secondary ____

Arrange package in the following order:

Indicate N/A (not applicable), X (completed), or add a comment.

GENERAL INFORMATION:

- User Fee Information: (User Fee Paid) / User Fee Waiver (attach waiver notification letter) / User Fee Exemption
- Action Letter..... (AP) AE NA
- Labeling & Labels
  - FDA revised labeling and reviews..... X
  - Original proposed labeling (package insert, patient package insert)..... X
  - Other labeling in class (most recent 3) or class labeling..... X
  - Has DDMAC reviewed the labeling?..... (Yes (include review)) No
  - Immediate container and carton labels..... N/A
  - Nomenclature review..... X
- Application Integrity Policy (AIP) Applicant is on the AIP. This application is (is not) on the AIP.
  - Exception for review (Center Director's memo)..... ____
  - OC Clearance for approval..... ____

Continued

	Materials requested in AP letter
♦ Status of advertising (if AP action) Reviewed (for Subpart H – attach review)	
♦ Post-marketing Commitments	
Agency request for Phase 4 Commitments	X
Copy of Applicant's commitments	X
	X
♦ Was Press Office notified of action (for approval action only)?	(Yes) No
Copy of Press Release or Talk Paper	
♦ Patent	
Information [505(b)(1)]	X
Patent Certification [505(b)(2)]	X
Copy of notification to patent holder [21 CFR 314.50 (i)(4)]	X
♦ Exclusivity Summary	X
♦ Debarment Statement	X
♦ Financial Disclosure	
No disclosable information	X
Disclosable information – indicate where review is located	
♦ Correspondence/Memoranda/Faxes	X
♦ Minutes of Meetings	X
Date of EOP2 Meeting	
Date of pre NDA Meeting	
Date of pre-AP Safety Conference	
♦ Advisory Committee Meeting	X
Date of Meeting	
Questions considered by the committee	
Minutes or 48-hour alert or pertinent section of transcript	
♦ Federal Register Notices, DESI documents	

CLINICAL INFORMATION:

	Indicate N/A (not applicable), X (completed), or add a comment.
♦ Summary memoranda (e.g., Office Director's memo, Division Director's memo, Group Leader's memo)	X
♦ Clinical review(s) and memoranda	X

Continued

- Safety Update review(s) X

- Pediatric Information
  Waiver/partial waiver (Indicate location of rationale for waiver) Deferred
  Pediatric Page..... _____
  Pediatric Exclusivity requested? Denied Granted Not Applicable

- Statistical review(s) and memoranda X

- Biopharmaceutical review(s) and memoranda..... X

- Abuse Liability review(s) ..... N/A
  Recommendation for scheduling ..... _____

- Microbiology (efficacy) review(s) and memoranda ..... N/A

- DSI Audits X
  (Clinical studies) bioequivalence studies X

CMC INFORMATION:

Indicate N/A (not applicable), X (completed), or add a comment.

- CMC review(s) and memoranda X

- Statistics review(s) and memoranda regarding dissolution and/or stability ..... _____

- DMF review(s) ..... _____

- Environmental Assessment review/FONSI/Categorical exemption ..... N/A

- Micro (validation of sterilization) review(s) and memoranda ..... N/A

- Facilities Inspection (include EES report)
  Date completed _____ ..... (Acceptable) Not Acceptable

- Methods Validation ..... Completed (Not Completed)

PRECLINICAL PHARM/TOX INFORMATION:

Indicate N/A (not applicable), X (completed), or add a comment.

- Pharm/Tox review(s) and memoranda X

- Memo from DSI regarding GLP inspection (if any) ..... N/A

Continued

- Statistical review(s) of carcinogenicity studies 1
- CAC/ECAC report .....

FACSIMILE TRANSMISSION RECORD

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

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

DATE: 9/26/00 NUMBER OF PAGES 13

FROM: [redacted]

TO: [redacted]

FAX#: 4-6197 PHONE #: [redacted]

COMMENTS:

Confidential

For [redacted] Only

NDCLIST_ALL QUERY

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

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

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

Count: *1 <Replace>

NDCLIST_ALL QUERY

Tradename:MIFEPRISTONE Rx/OTC:R

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

DOSAGE & ROUTE INFORMATION

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

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

Count: *1 <Replace>

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

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

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

Count: *1 <Replace>

MIF2007 0011352

09/26/00 09:59 FAX KX UKUS HFD-330 → 4017

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

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

DRUG PRODUCT LISTING

(In accordance with Public Law 92-387)

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

LABELING REVISION
CHANGE OF:
☐ SITE OF A ADMIN ☐ INDICATION
☐ NAME / DOSE / STRENGTH
☐ OTHER (Specify)

[redacted] LI 156,027

SEC	S	U	PRODUCT TRADE NAME OR CATALOG NAME	NATIONAL DRUG CODE: LABELER	PRODUCT
01			MIFEPRISTONE (A.V. Sop)	[redacted]	64877001

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

RECEIVED

DOSAGE FORM	ROUTES OF ADMINISTRATION	SEC	S	U	PKG CODE	PACKAGE SIZE	PACKAGE TYPE
31315		03				**AS ORDERED	DRM
		03					
[redacted]		03					
MO / YEAR / MO / YEAR / MO / YEAR		03					
		03					

PIMB

NOTICE: This report is required by law (21 C.F.R. 207.20). Failure to report can result in imprisonment for not more than one year or a fine of not more than $1,000, or both (FD&C Act, Section 303).

SEC	S	U	FT	ESTABLISHED NAME OF PRODUCT AND / OR INGREDIENT(S) OR BIOLOGIC PROPER NAME, TEST OBJECTIVE / EQUIPMENT / REAGENT NAME, ETC.	AMOUNT: WHOLE NUMBER	DECIMAL	UNIT
05		A		MIFEPRISTONE	100		% W/W
05							
05							
05							
05							
05							
05							
05							
05							
05							

RECEIVED
MAY 03 1999
PIMB

SEC	S	U	SITE OR FIRM ESTABLISHMENT REGISTRATION NUMBER	ACTUAL MANUFACTURING SITE OF THE ABOVE DRUG PRODUCT	STATE	FOREIGN COUNTRY	NDC LABELER CODE	SHORT NAME
07		F	CIC H 4199	SHANGHAI HUALIAN PHARMACEUTICAL CO LTD		CHINA		
07				MINLEI ROAD PUDONG DEVELOPMENT AREA				
07				SHANGHAI 201419				

FORM FDA 2657 (10/93) PREVIOUS EDITION IS OBSOLETE.

Approvable letter.

MF - Approvable letter

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Rockville

RECEIVED
MAY 03 1999
PIMB

recd Sept 96 via fax SEP 18 1996

NDA 20-687

recd orig by mail 25 Sept to

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

Dear Dr. Robbins:

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

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

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

[redacted]

Please submit a comprehensive description of the proposed distribution system.

[redacted]

Drug Substance:

Original sent under separate cover.

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

Attn: ———

April 26, 1999

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

Dear ———

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

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

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

Thank you for your attention.

Sincerely,

Encl.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

4.13.99

Shanghai Hualian Pharmaceutical

RECEIVED
MAY 03 1999
PIMB

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

Preliminary Requirements

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

Section 01

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

Section 03

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

Section 05

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

Section 07

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

See back page for additional comments.

Comments

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

Other

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

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

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

If you need assistance, please contact _____ at _____

Enclosure(s)

MIF2007 011357

09/26/00 10:01 FUH KX UKUS MTU-330 # 4017

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

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

DRUG PRODUCT LISTING

(In accordance with Public Law 92-387)

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

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

[redacted] LI 156,027

SEC	S	U	PRODUCT TRADE NAME OR CATALOG NAME	NATIONAL DRUG CODE LABELER	PRODUCT
01			MIFEPRISTONE	66497	0001

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

RECEIVED
APR 05 1999

DOSAGE FORM	ROUTES OF ADMINISTRATION 1	2	3	OTH	PT	SEC	S	U	PKG CODE	PACKAGE SIZE	PACKAGE TYPE
313135						03				KK AS ORDERED	DRM
[redacted]						03					
[redacted]						03					
MO YEAR	MO YEAR	MO YEAR				03					
.						03					

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

SEC	S	U	EST	PT	ESTABLISHED NAME OF PRODUCT AND / OR INGREDIENT(S) OR BIOLOGIC PROPER NAME, TEST OBJECTIVE / EQUIPMENT / REAGENT NAME, ETC.	[redacted]	AMOUNT WHOLE NUMBER	DECIMAL	UNIT
05				A	MIFEPRISTONE	[redacted]	100		% W/W
05									
05									
05									
05									
05									
05									
05									
05									
05									

SEC	S	U	STATE OF FOR. ESTABLISHMENT REGISTRATION NUMBER	ACTUAL MANUFACTURING SITE OF THE ABOVE DRUG PRODUCT	STATE	FOREIGN COUNTRY	NDC LABELER CODE	SHORT NAME
07			FCC HU919	SHANGHAI HUALIAN PHARMACEUTICAL CO LTD		CHINA		
07				MINLEI ROAD PUDONG DEVELOPMENT AREA				
07				SHANGHAI 201419				

FORM FDA 2657 (5/91) PREVIOUS EDITION IS OBSOLETE.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

4.27.99

Bar Code #: _____

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

Preliminary Requirements

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

Section 01

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

Section 03

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

Section 05

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

Section 07

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

See back page for additional comments.

Comments

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

Other

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

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

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

If you need assistance, please contact _____ at _____

Enclosure(s)

Original sent under separate cover.

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

Attn: [redacted]

April 26, 1999

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

Dear [redacted]

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

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

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

Thank you for your attention.

Sincerely,

Postit Fax Note 7671 | Date 4/26 | # of pages 5

Encl

Mifepristone Outstanding Issues 8-11-00

- Chemistry and Manufacturing
  - 483 issued 7/28/00 with minor deficiencies to be corrected by 8/30/00
  - Analytic and stability data outstanding
- Labeling
  - Day 3 return
- Distribution System: Physician Qualifications
  -

Mifepristone Outstanding Issues 8-11-00/ cont.

- Remaining Phase 4 Studies
  - Two other studies [redacted]
    - Assess long term effects in multiple use (European data)
    - Assess S/E in women under age 18, over 35, and in smokers
- Medication Guide [redacted]
- Subpart H

CENTER FOR DRUG EVALUATION AND RESEARCH

WEEKLY REPORT

July 6, 2000

HOT ISSUES

RU486 Correspondence

FDA has received a total of 576 E-mails and letters regarding the drug RU486 (190 urging approval of the drug and 386 against approval).

*INFORMATION NOT RELEASABLE TO THE PUBLIC

CENTER FOR DRUG EVALUATION AND RESEARCH

WEEKLY REPORT

FEBRUARY 24, 2000

HOT ITEM

FDA Issues Approvable Letter for Mifepristone

On February 18, 2000 the Food and Drug Administration issued an approvable letter to the Population Council for mifepristone, when used in combination with misoprostol. The drug regimen is being evaluated for the termination of early pregnancy. The Population Council's new drug application was filed on March 18, 1996. On July 19, 1996, an FDA Advisory committee found the data supportive of approval of the drug. The agency first acted on this application by issuing an approvable letter on September 18, 1996. The Population Council has filed a response to the outstanding issues. (Under the Prescription Drug User Fee Act, the Agency has a six-month goal for acting on information submitted in response to an original action.) FDA issues approvable letters to manufacturers when remaining questions need to be resolved before final marketing approval can be granted.

21 CFR 314.50(j) Claimed Exclusivity

(j) Claimed Exclusivity. A new drug product, upon approval, may be entitled to a period of marketing exclusivity... . If an applicant believes its drug product is entitled to a period of exclusivity, it shall submit with the new drug application prior to approval the following information:

(I) A statement that the applicant is claiming exclusivity.
(2) A reference to the appropriate paragraph under section 314.108 that supports its claim.
(3) If the applicant claims exclusivity, information to show that, to the best of its knowledge or belief, a drug has not been previously approved under section 505(b) of the act containing any active moiety in the drug for which the applicant is seeking approval.

Please refer to the attached statement.

Statement of Claimed Marketing Exclusivity

The Population Council claims a period of marketing exclusivity as described in section 314.108(b)(2). To the best of our knowledge and belief, no drug has previously been approved under section 505(b) of the act which contains any active moiety in the drug for which this application is submitted.

Ann Robbins

Signed

Ann Robbins, Ph.D / Scientist

Printed Name/Title

27 Feb 1996

Date

termination process. This rate is at a minimum for pregnancies of less than 5 weeks, and increases with increasing gestational age. The overall rate for the mifepristone in combination with misoprostol procedure for pregnancies of less than or equal to 49 days is comparable to the rate of the need for a second procedure following a surgical termination of an early pregnancy.

For women who still have viable pregnancies following the administration of mifepristone in combination with misoprostol, it is not known whether there are any continued risks to the fetus. For this reason, all women who have incomplete procedures are to be advised of this uncertainty and offered a surgical procedure to complete the failed pharmacologic procedure.

8.11.3 **Reference List** - ***Reprints Available in Appendix J***

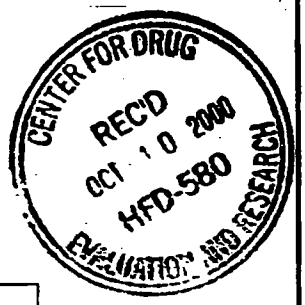
1. Edelman DA, Brenner WE, Berger GS. The Effectiveness and Complications of Abortion by Dilatation and Vacuum Aspiration Versus Dilatation and Rigid Metal Curettage. Am J Obstet Gynecol 119:473-480, 1974.

2. Edelman DA, Berger GS. Menstrual Regulation. In: Techniques of Abortion, JE Hodgson ed. Academic Press, London, 1981.

IND/NDA SUBSEQUENT SUBMISSIONS REVIEW TRANSMITTAL

1. IND/NDA NUMBER	2. CORRESPONDENCE DATE	3. DATE RECEIVED	4. DOCUMENT IDENTIFICATION
20687	9-27-00	10-2-00	NC

DELIVER TO LAST ADDRESSEE INDICATED BELOW:



TO: SUPEVISORY TECHNICIAN/CSO	INITIALS	DATE
	[ ]	10/3/00

REVIEWER - If this decision is incorrect, notify Group Consumer Safety Officer at once.

	TYPE OF ACTION		
MEDICAL OFFICER [ ]	REVIEW	INFO	NAI
			✓
CHEMIST [ ]	REVIEW	INFO	NAI
			✓
PHARMACOLOGIST [ ]	REVIEW	INFO	NAI
			✓
STATISTICIAN/MICROBIOLOGIST	REVIEW	INFO	NAI
b2 CSO	—		

Deliver to Document Control Desk when this box is checked.	When copies of all reviews have been returned, forward to the Group Consumer Safety Officer in the original Jacket.

GROUP CONSUMER SAFETY OFFICER	If follow-up is needed, complete the box at right. →	RESPONSE DUE DATE
[ ]		

Deliver to Document Control Desk when this box is checked.	**POST AND DESTROY.**

[ ] 10-2-00

MIF2007 011394

IND/NDA SUBSEQUENT SUBMISSIONS REVIEW TRANSMITTAL

1. IND/NDA NUMBER	2. CORRESPONDENCE DATE	3. DATE RECEIVED	4. DOCUMENT IDENTIFICATION
20-687	1-21-00	1-24-00	BM

DELIVER TO LAST ADDRESSEE INDICATED BELOW:

TO: SUPERVISORY TECHNICIAN/CSO	INITIALS	DATE
		1/27/00

CENTER FOR DRUG EVALUATION AND RESEARCH
REC'D
OCT 31 2000
HFD-580

REVIEWER - If this decision is incorrect, notify Group Consumer Safety Officer at once.

	TYPE OF ACTION		
MEDICAL OFFICER	REVIEW ✓	INFO	NAI
CHEMIST	REVIEW	INFO	NAI ✓
PHARMACOLOGIST		INFO	NAI
STATISTICIAN/MICROBIOLOG	REVIEW	INFO	NAI

Deliver to Document Control Desk when this box is checked.	File review. Destroy this form and attached submission.

1-24-00

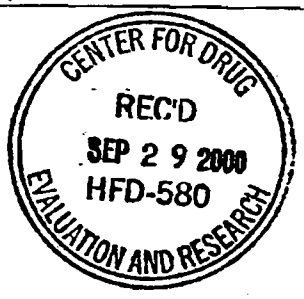
FORM FDA 2774 (7/90) PART II - CHEMIST'S COPY

MIF2007 011416

IND/NDA SUBSEQUENT SUBMISSIONS REVIEW TRANSMITTAL

1. IND/NDA NUMBER	2. CORRESPONDENCE DATE	3. DATE RECEIVED	4. DOCUMENT IDENTIFICATION
20687	9-12-00	9-13-00	BM

DELIVER TO LAST ADDRESSEE INDICATED BELOW:



TO: SUPEVISORY TECHNICIAN/CSO	INITIALS	DATE
	J	9/18/00

REVIEWER - If this decision is incorrect, notify Group Consumer Safety Officer at once.

	TYPE OF ACTION		
MEDICAL OFFICER	REVIEW	INFO	NAI
	✓		
CHEMIST	REVIEW	INFO	NAI
			✓
PHARMACOLOGIST	REVIEW	INFO	NAI
			✓
STATISTICIAN/MICROBIOLOGIST	REVIEW	INFO	NAI
	✓		

304

Deliver to Document Control Desk when this box is checked.	When copies of all reviews have been returned, forward to the Group Consumer Safety Officer in the original Jacket.

GROUP CONSUMER SAFETY OFFICER	If follow-up is needed, complete the box at right. →	RESPONSE DUE DATE

ment Control Desk when	POST AND DESTROY.

9-13-00

MIF2007 011418

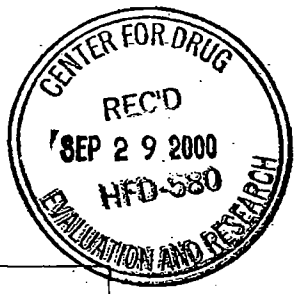
PART I - MEDICAL OFFICER'S COPY

IND/NDA SUBSEQUENT SUBMISSIONS REVIEW TRANSMITTAL

1. IND/NDA NUMBER	2. CORRESPONDENCE DATE	3. DATE RECEIVED	4. DOCUMENT IDENTIFICATION
20687	9-26-00	9-28-00	BL

DELIVER TO LAST ADDRESSEE INDICATED BELOW:

TO: SUPEVISORY TECHNICIAN/CSO	INITIALS	DATE
	—	9/27/00



REVIEWER - If this decision is incorrect, notify Group Consumer Safety Officer at once.

	TYPE OF ACTION		
MEDICAL OFFICER	REVIEW	INFO	NAI
—			—
CHEMIST	REVIEW	INFO	NAI
—			—
PHARMACOLOGIST	REVIEW	INFO	NAI
—			—
STATISTICIAN/MICROBIOLOGIST	REVIEW	INFO	NAI
CSO	—		

Deliver to Document Control Desk when this box is checked.	When copies of all reviews have been returned, forward to the Group Consumer Safety Officer in the original Jacket.

GROUP CONSUMER SAFETY OFFICER	If follow-up is needed, complete the box at right. →	RESPONSE DUE DATE
—		—

Deliver to Document Control Desk when this box is checked.	**POST AND DESTROY.**

9-26-00

MIF2007 011454

IND/NDA SUBSEQUENT SUBMISSIONS REVIEW TRANSMITTAL

1. IND/NDA NUMBER	2. CORRESPONDENCE DATE	3. DATE RECEIVED	4. DOCUMENT IDENTIFICATION
20687	9-22-00	9-25-00	NC

DELIVER TO LAST ADDRESSEE INDICATED BELOW:

TO: SUPEVISORY TECHNICIAN/CSO	INITIALS	DATE
	—	9/26/00

CENTER FOR DRUG REC'D SEP 2 9 2000 HFD-580 EVALUATION AND RESEARCH

REVIEWER - If this decision is incorrect, notify Group Consumer Safety Officer at once.

	TYPE OF ACTION		
MEDICAL OFFICER	REVIEW	INFO	NAI
			✓
CHEMIST	REVIEW	INFO	NAI
			—
PHARMACOLOGIST	REVIEW	INFO	NAI
			✓
STATISTICIAN/MICROBIOLOGIST	REVIEW	INFO	NAI
CSO	—		

Deliver to Document Control Desk when this box is checked.	When copies of all reviews have been returned, forward to the Group Consumer Safety Officer in the original Jacket.

GROUP CONSUMER SAFETY OFFICER	If follow-up is needed, complete the box at right. →	RESPONSE DUE DATE
—		—

Deliver to Document Control Desk when checked.	**POST AND DESTROY.**

9-25-00

MIF2007 011455

FORM FDA 2774 (7/90) PART I - MEDICAL OFFICER'S COPY

IND/NDA SUBSEQUENT SUBMISSIONS REVIEW TRANSMITTAL

1. IND/NDA NUMBER	2. CORRESPONDENCE DATE	3. DATE RECEIVED	4. DOCUMENT IDENTIFICATION
20687	9-21-00	9-22-00	BL

DELIVER TO LAST ADDRESSEE INDICATED BELOW:

TO: SUPEVISORY TECHNICIAN/CSO	INITIALS	DATE
		9/25/00

CENTER FOR DRUG EVALUATION AND RESEARCH
RECD
SEP 2 9 2000
HFD-960

REVIEWER - If this decision is incorrect, notify Group Consumer Safety Officer at once.

	TYPE OF ACTION		
MEDICAL OFFICER	REVIEW	INFO	NAI ✓
CHEMIST	REVIEW	INFO	NAI ✓
PHARMACOLOGIST	REVIEW	INFO	NAI ✓
STATISTICIAN/MICROBIOLOGIST	REVIEW ✓	INFO	NAI

1 of CSO

Deliver to Document Control Desk when this box is checked.	When copies of all reviews have been returned, forward to the Group Consumer Safety Officer in the original Jacket.

GROUP CONSUMER SAFETY OFFICER	If follow-up is needed, complete the box at right. →	RESPONSE DUE DATE

9-25-00

Deliver to Document Control Desk when ed.	**POST AND DESTROY.**

MIF2007 011456

FORM FDA 2774 (7/90) PART I - MEDICAL OFFICER'S COPY

IND/NDA SUBSEQUENT SUBMISSIONS REVIEW TRANSMITTAL

1. IND/NDA NUMBER	2. CORRESPONDENCE DATE	3. DATE RECEIVED	4. DOCUMENT IDENTIFICATION
20687	9-25-00	10-2-00	N/C

DELIVER TO LAST ADDRESSEE INDICATED BELOW:

TO: SUPEVISORY TECHNICIAN/CSO	INITIALS	DATE
	—	10/3/00

CENTER FOR DRUG EVALUATION AND RESEARCH
RECD
OCT 10 2000
HFD-580

REVIEWER - If this decision is incorrect, notify Group Consumer Safety Officer at once.

	TYPE OF ACTION		
MEDICAL OFFICER —	REVIEW	INFO	NAI
			—
CHEMIST —	REVIEW	INFO	NAI
			—
PHARMACOLOGIST —	REVIEW	INFO	NAI
			/
STATISTICIAN/MICROBIOLOGIST CSO	REVIEW	INFO	NAI
	—		

Deliver to Document Control Desk when this box is checked.	When copies of all reviews have been returned, forward to the Group Consumer Safety Officer in the original Jacket.

GROUP CONSUMER SAFETY OFFICER —	If follow-up is needed, complete the box at right. →	RESPONSE DUE DATE
		/ — 10-2-00

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MIF2007 011457

IND/NDA SUBSEQUENT SUBMISSIONS REVIEW TRANSMITTAL

1. IND/NDA NUMBER	2. CORRESPONDENCE DATE	3. DATE RECEIVED	4. DOCUMENT IDENTIFICATION
20687	9-26-00	9-28-00	N C

DELIVER TO LAST ADDRESSEE INDICATED BELOW:

CENTER FOR DRUG EVALUATION AND RESEARCH
REC'D
SEP 2 9 2000
HFD-580

TO: SUPEVISORY TECHNICIAN/CSO	INITIALS	DATE
	—	9/28/00

REVIEWER - If this decision is incorrect, notify Group Consumer Safety Officer at once.

	TYPE OF ACTION		
MEDICAL OFFICER	REVIEW	INFO	NAI
			—
CHEMIST	REVIEW	INFO	NAI
			—
PHARMACOLOGIST	REVIEW	INFO	NAI
			—
STATISTICIAN/MICROBIOLOGIST	REVIEW	INFO	NAI
CSO	—		

Deliver to Document Control Desk when this box is checked.	When copies of all reviews have been returned, forward to the Group Consumer Safety Officer in the original Jacket.

GROUP CONSUMER SAFETY OFFICER	If follow-up is needed, complete the box at right. →	RESPONSE DUE DATE
—		—

Deliver to Document Control Desk when ked.	**POST AND DESTROY.**

9-29-00

MIF2007 011458

FORM FDA 3774 (7/90)

IND/NDA SUBSEQUENT SUBMISSIONS REVIEW TRANSMITTAL

1. IND/NDA NUMBER	2. CORRESPONDENCE DATE	3. DATE RECEIVED	4. DOCUMENT IDENTIFICATION
20687	7/5/00	9-27-00	NC

CENTER FOR DRUG EVALUATION AND RESEARCH
RECD
SEP 29 2000
HFD-580

DELIVER TO LAST ADDRESSEE INDICATED BELOW:

TO: SUPEVISORY TECHNICIAN/CSO	INITIALS	DATE
		9/27/00

REVIEWER - If this decision is incorrect, notify Group Consumer Safety Officer at once.

	TYPE OF ACTION		
MEDICAL OFFICER	REVIEW	INFO	NAI
			✓
[redacted]			
CHEMIST	REVIEW	INFO	NAI
			✓
[redacted]			
PHARMACOLOGIST	REVIEW	INFO	NAI
			✓
[redacted]			
STATISTICIAN/MICROBIOLOGIST	REVIEW	INFO	NAI
CSO	✓		

Deliver to Document Control Desk when this box is checked.	When copies of all reviews have been returned, forward to the Group Consumer Safety Officer in the original Jacket.

GROUP CONSUMER SAFETY OFFICER	If follow-up is needed, complete the box at right. →	RESPONSE DUE DATE

Deliver to Document Control Desk when this box is checked.	**POST AND DESTROY.**

9-27-00

MIF2007 011459

Vol 28.1

IND/NDA SUBSEQUENT SUBMISSIONS REVIEW TRANSMITTAL

1. IND/NDA NUMBER	2. CORRESPONDENCE DATE	3. DATE RECEIVED	4. DOCUMENT IDENTIFICATION
20687	9-27-00	10-3-00	NC

CENTER FOR DRUG EVALUATION AND RESEARCH RECD OCT 10 2000 HFD-580

DELIVER TO LAST ADDRESSEE INDICATED BELOW:

TO: SUPEVISORY TECHNICIAN/CSO	INITIALS	DATE
		10/3/00

REVIEWER - If this decision is incorrect, notify Group Consumer Safety Officer at once.

	TYPE OF ACTION		
MEDICAL OFFICER	REVIEW	INFO	NAI
			✓
CHEMIST	REVIEW	INFO	NAI
			✓
PHARMACOLOGIST	REVIEW	INFO	NAI
			✓
STATISTICIAN/MICROBIOLOGIST	REVIEW	INFO	NAI
X CSO	✓		

Deliver to Document Control Desk when this box is checked.	When copies of all reviews have been returned, forward to the Group Consumer Safety Officer in the original Jacket.

GROUP CONSUMER SAFETY OFFICER	If follow-up is needed, complete the box at right. →	RESPONSE DUE DATE

10-20-00

Deliver to Document Control Desk when this box is checked.	**POST AND DESTROY.**

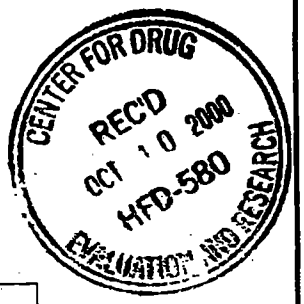
MIF2007 011460

FORM FDA 3774 (7/90) PART I - MEDICAL OFFICER'S COPY

IND/NDA SUBSEQUENT SUBMISSIONS REVIEW TRANSMITTAL

1. IND/NDA NUMBER	2. CORRESPONDENCE DATE	3. DATE RECEIVED	4. DOCUMENT IDENTIFICATION
20687	9-27-00	10-2-00	NC

DELIVER TO LAST ADDRESSEE INDICATED BELOW:



TO: SUPEVISORY TECHNICIAN/CSO	INITIALS	DATE
	—	10/3/00

REVIEWER - If this decision is incorrect, notify Group Consumer Safety Officer at once.

	TYPE OF ACTION		
MEDICAL OFFICER	REVIEW	INFO	NAI
			✓
CHEMIST	REVIEW	INFO	NAI
			✓
PHARMACOLOGIST	REVIEW	INFO	NAI
			✓
STATISTICIAN/MICROBIOLOGIST	REVIEW	INFO	NAI
✓ CSO	—		

Deliver to Document Control Desk when this box is checked.	When copies of all reviews have been returned, forward to the Group Consumer Safety Officer in the original Jacket.

GROUP CONSUMER SAFETY OFFICER	If follow-up is needed, complete the box at right. →	RESPONSE DUE DATE
—		—

Deliver to Document Control Desk when this box is checked.	**POST AND DESTROY.**

10-2-00

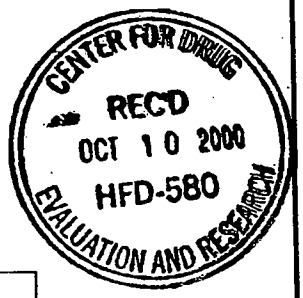
MIF2007 011461

FORM FDA 2774 (7/90) PART I - MEDICAL OFFICER'S COPY

IND/NDA SUBSEQUENT SUBMISSIONS REVIEW TRANSMITTAL

1. IND/NDA NUMBER	2. CORRESPONDENCE DATE	3. DATE RECEIVED	4. DOCUMENT IDENTIFICATION
20687	9-27-00	10-2-00	nc

DELIVER TO LAST ADDRESSEE INDICATED BELOW:



TO: SUPEVISORY TECHNICIAN/CSO	INITIALS	DATE
	—	10/3/00

REVIEWER - If this decision is incorrect, notify Group Consumer Safety Officer at once.

	TYPE OF ACTION		
MEDICAL OFFICER —	REVIEW	INFO	NAI
			—
CHEMIST —	REVIEW	INFO	NAI
			—
PHARMACOLOGIST —	REVIEW	INFO	NAI
			—
STATISTICIAN/MICROBIOLOGIST — CSO	REVIEW	INFO	NAI
	—		

Deliver to Document Control Desk when this box is checked.	When copies of all reviews have been returned, forward to the Group Consumer Safety Officer in the original Jacket.

GROUP CONSUMER SAFETY OFFICER —	If follow-up is needed, complete the box at right. →	RESPONSE DUE DATE
		—

Deliver to Document Control Desk when this box is checked.	**POST AND DESTROY.**

10-2-00

MIF2007 011462

FORM FDA 2774 (7/90) PART I - MEDICAL OFFICER'S COPY

Meeting Minutes

Date: April 24, 2000 **Time:** 12:00 – 1:00 PM **Location:** Parklawn; 17B-43

NDA 20-687 **Drug:** mifepristone, 600 mg

Indication: induction of abortion

Sponsor: Population Council

Type of Meeting: Status Meeting

Meeting Chair: [redacted]

Meeting Recorder: [redacted]

FDA Attendees:

[redacted] Office of Drug Evaluation III (ODEIII; HFD-102)
[redacted], Division of Reproductive and Urologic Drug Products (DRUDP; HFD-580)
[redacted], DRUDP (HFD-580)
[redacted], Division of New Drug Chemistry II (DNDCII) @ DRUDP (HFD-580)
[redacted] – Chemist, DNDCII @ Division of Reproductive and Urologic Drug Products (DRUDP; HFD-580)
[redacted] – Biopharmaceutics Reviewer, Office of Clinical Pharmacology and Biopharmaceutics (OCPB) @ DRUDP (FD-580)
[redacted] - Regulatory Project Manager, DRUDP (HFD-580)
[redacted] Project Management Staff, DRUDP (HFD-580)
[redacted] Office of Post Drug Review Assessment (OPDRA; HFD-
[redacted], OPDRA DDRE2 (Division 2) (HFD-440)
[redacted] – Regulatory Project Manager, DRUDP (HFD-580)

Meeting Objective: To evaluate the March 30, 2000 submission for completeness and update the team on the goal dates for this application.

Background: This NDA was originally submitted on March 14, 1996 receiving an approvable action on September 18, 1996. This application had a complete response dated August 18, 1999 and received another approvable action on February 18, 2000. This resubmission dated March 30, 2000 was submitted as a complete response by the sponsor.

Decisions made:
Chemistry

Biopharmaceutics

- the sponsor has included the metabolism information in the label, as requested by the reviewer and has accepted the dissolution specification

Action Items:

- send acknowledgement letter of complete response as a Class 2 resubmission to the sponsor (completed)
- [redacted] will be working with [redacted] on the Black Box Warning and Distribution System
- provide [redacted] with the foreign label that the sponsor provided in this submission (completed)
- send consult to the thalidamide working group (completed)
- [redacted] to provide [redacted] with copies of FDA letters sent out regarding restricted distribution programs

Minutes Preparer **Concurrence, Chair**

TELEFAX TRANSMITTAL SHEET

FOOD AND DRUG ADMINISTRATION
Office of Legislative Affairs

5600 Fishers Lane
Parklawn Bldg./Room 15-55
Rockville, MD 20857
Telephone: _____

FAX: 301-443-2567
301-227-6778

faxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx

DATE: 8/5

TO: _____

TELEFAX NUMBER: _____

FROM: _____

COMMENTS:

Per conversation

NUMBER OF PAGES, EXCLUDING COVER: _____

If you do not receive the number of pages indicated above, please call immediately.

RON WYDEN
OREGON
3D DISTRICT

1111 LONGWORTH BUILDING
WASHINGTON, DC 20515-3703
(202) 225-4811

500 NE MULTNOMAH, SUITE 250
PORTLAND, OR 97232
(503) 231-2300

Congress of the United States
House of Representatives

ENERGY AND COMMERCE COMMITTEE
SUBCOMMITTEES:
HEALTH AND THE ENVIRONMENT
TELECOMMUNICATIONS AND FINANCE
OVERSIGHT AND INVESTIGATIONS

SMALL BUSINESS COMMITTEE
CHAIRMAN
SUBCOMMITTEE ON REGULATION, BUSINESS OPPORTUNITIES AND TECHNOLOGY

JOINT ECONOMIC COMMITTEE
CO-CHAIRMAN
FORESTRY 2000 TASK FORCE
CO-CHAIRMAN
EXPORT TASK FORCE

August 3, 1993

The Honorable David A. Kessler, M.D.
Commissioner
U.S. Food and Drug Administration
5600 Fishers Lane, Room 14-90
Rockville, Maryland 20857

Dear Dr. Kessler:

I refer to you a letter from an Oregon constituent whose brother, apparently, is suffering from a highly aggressive brain tumor which may be treatable with the French drug RU 486.

For your information, I attach the constituent's letter. It includes details on the health problems of [redacted] the treatment he has had so far, and the reasoning and identity of doctors who suspect that RU 486 may be useful in his case.

This person and his doctors have had significant difficulty in obtaining from the manufacturer any quantity of this unapproved French drug, however, for compassionate use. All other therapies seem to have been exhausted in the case.

I write to you, today, to ascertain whether the Food and Drug Administration can use its good offices to assist [redacted], whose condition truly seems desperate and rapidly deteriorating at this point. I recall a similar instance two years ago involving a Georgia resident, [redacted] in which the FDA intervened on behalf of the patient. It is my understanding that in the interim, [redacted] who suffers from the same malady as [redacted] has experienced significant health improvement using the drug.

I wish to underscore that I am not suggesting or requesting that FDA exceed its usual practice, or circumvent any statutory authority or limitation in this matter. Should you have any questions regarding this request, please contact Steve Jenning of my staff at (202) 225-7797.

Sincerely,

RON WYDEN
Member of Congress

MIF2007 011588

Date

UTING AND TRANSMITTAL SLIP

ıe, office symbol, room number, 'ing, Agency/Post)	Initials	Date

Action		File		Note and Return	
Approval		For Clearance		Per Conversation	
As Requested		For Correction		Prepare Reply	
Circulate		For Your Information		See Me	
Comment		Investigate		Signature	
Coordination		Justify			

EMARKS

pt. not registered SWOG on study

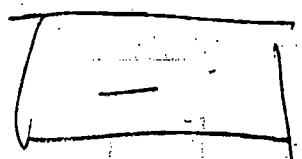
contact person [ ]

O NOT use this form as a RECORD of approvals, concurrences, disposals, clearances, and similar actions

ROM: *(Name, org. symbol, Agency/Post)*	Room No.—Bldg.
	Phone No.

041-102
U.S.G.P.O.: 1993 342-198/80007

OPTIONAL FORM 41 (Rev. 7-76)
Prescribed by GSA
FPMR (41 CFR) 101-11.206



→ recurrent meningioma

→

SWOG protocols;

→ radiation oncologists.

→ FOR MORE SURGERY
· evaluated him

w

medical oncologist
evaluated & pcal. for measurable disease & easily resectable

pt. back to — for surgery
no word yet.

IEMORANDUM
OF CALL

Previous editions usable

O:

☐ YOU WERE CALLED BY– ☐ YOU WERE VISITED BY–

F (Organization)

☐ PLEASE PHONE ▶ ☐ FTS ☐ AUTOVON

☐ WILL CALL AGAIN ☐ IS WAITING TO SEE YOU

☐ RETURNED YOUR CALL ☐ WISHES AN APPOINTMENT

IESSAGE

Will await for dlg. for SWOB protocol.

ECEIVED BY | DATE 4/28/93 | TIME

3-110 NSN 7540-00-634-4018 STANDARD FORM 63 (Rev. 8-81)
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OF CALL

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MESSAGE

Sent Copy of "Record of re" 6/16/93

RECEIVED BY | DATE | TIME

63-110 NSN 7540-00-634-4018 STANDARD FORM 63 (Rev. 8-81)
Prescribed by GSA
FPMR (41 CFR) 101—11.6

☆U.S. G.P.O. 1991: 281-781/40011

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OF CALL

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OF (Organization) Legislative Affairs

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☐ RETURNED YOUR CALL ☐ WISHES AN APPOINTMENT

MESSAGE RU 4/86

RECEI | DATE | TIME 3:30

63-110 NSN 7540-00-634-4018 STANDARD FORM 63 (Rev. 8-81)
Prescribed by GSA
FPMR (41 CFR) 101—11.6

☆U.S.G 281-781/40011

MIF2007 011596

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STAFF MEMBER
202-225-0091

102d Congress

United States House of Representatives
Committee on Small Business

Subcommittee on Regulation, Business Opportunities, and Energy

B-363 Rayburn House Office Building
Washington, DC 20515-6315

July 22, 1992

Dr. David Kessler, M.D.
Commissioner
U.S. Food and Drug Administration
5600 Fishers Lane
Bethesda, Maryland 20857
Via Fax: (301) 443-2567

Dear Dr. Kessler:

Pursuant to our on-going inquiry into the actions of your agency involving the French drug RU 486, I request the following:

-- A complete list of all investigational new drug (IND) approvals granted by your agency to persons or institutions conducting clinical trials with RU 486.

-- A brief description of those trials, individually.

-- Your understanding regarding the status of those trials, individually (Is experimentation on-going? Do researchers currently have quantities of RU 486, or are they receiving the drug from the company?).

-- The name and telephone number of a contact person for each IND.

As I believe this information is readily available, and may have been recently collated and up-dated by your staff, I request that your response be telefaxed to my subcommittee staff by close-of-business, Thursday. Their number is (202) 225-8880.

Should you have any questions regarding this request, please don't hesitate to contact me, or Steve Janning of the subcommittee staff at (202) 225-7797.

Thank you for your assistance in this matter.

Sincerely,

RON WYDEN
Chairman

1 Recent Hx. -qz agree to provide current

Dr. —

to justify administration

1. Call RU to get their protocol.
2. Pt. can be tx according to their protocol. if Dr — agrees to provide info on pts current status B4 starting tx
3. Pt. must not be pregnant + agree to use effective non-hormonal contraception if as of child-bearing potential + sexually active.

progression or stable.

Pt. —

MRI next week Mon or Tues.

Submitting a Request to Charge for the Investigational New Drug Mifepristone

The following information is provided to aid the licensed medical practitioner in submitting to the FDA a request to charge their patient(s) for the unapproved new drug mifepristone for use under an Investigational New Drug (IND) application.

Usually, the best way for a patient to be treated with an investigational drug is by being enrolled into a formal study sponsored by the drug's commercial sponsor/manufacturer. However, when there is no open clinical trial for which the patient is eligible and has access, the patient's medical practitioner may seek to obtain the drug from a pharmaceutical supplier and submit his/her own IND to the FDA. The practitioner is then the sponsor of the IND and is referred to in this document as the "physician-sponsor." The pharmaceutical supplier may charge the physician-sponsor for the drug. Consequently, the physician-sponsor may wish to recover the costs he/she incurred in obtaining the drug. Under the FDA's regulations 21 CFR 312.7(d), sponsors may not charge patients for investigational drugs except when charging is specifically authorized by the FDA. Normally, the cost of an unapproved drug is presumed to be a routine business cost of drug development. However, in certain situations, upon FDA authorization, costs associated with the manufacture, research and development, and handling of the drug may be passed on to the patient. Permission to charge will only be granted for indications for which there are data showing the activity of mifepristone against the patient's specific disease or condition.

To receive permission to recover his/her cost for the investigational drug, the physician-sponsor must submit to FDA a specific, written request to charge. **The patient may not be charged until written authorization to charge is received from the FDA**. If authorization to charge is granted, it will be for a maximum period of one year. If use of the drug is long-term, the physician-sponsor must request renewal of permission to charge in his/her annual report to the IND, which is due to the FDA within 60 days of the anniversary of the date the IND went into effect (usually 30 days after the original IND was received by the FDA; for single-patient IND's, the effective date is the date the IND number was granted).

The request to charge may be included in the original IND application and must contain the following information. If the request to charge is submitted as an amendment to an existing IND, the amendment should include all of the following information not already submitted to the IND as well as a report on the patient's clinical progress on RU-486 (mifepristone).

1. A completed form FDA 1571 (the third block in the shaded region, "CHARGE REQUEST/NOTIFICATION 21 CFR 312.7(d)" should be checked.

2. A statement as to why the physician-sponsor was not permitted to be included as an investigator under an existing IND, or was not permitted to enroll his/her patient in an ongoing trial.

The amount to be charged per unit dose and per month and an explanation of how that amount was determined (physician-sponsors may recover only their cost for the drug). A copy of the bill from the drug supplier should be provided.

RENEWAL of RU-486 Single-Patient IND Requests

If you wish to obtain RU-486 (mifepristone) for a patient who was previously treated with the product, please follow these procedures:

1. **OBTAINING DRUG SUPPLY**
   Contact Jennifer Jackman, Ph.D., at the Feminist Majority Foundation (FMF) at one of the following numbers:

   Phone: (703) 522-2214 **FAX:** (703) 522-2219

2. **INFORMATION TO BE SUBMITTED TO THE FMF**

   a. IND number.

   b. Date IND number was issued.

   c. IND Physician/Sponsor name.

   d. Patients Initials.

   e. Indication.

3. **CHARGING PATIENTS**
   If the physician intends to charge the patient for the supply of RU-486 ($5.00 per tablet), please read the attached document titled "Submitting a Request to Charge for the Investigational New Drug Mifepristone" and submit the required information to the Food & Drug Administration (FDA).

4. **REQUESTING AN INVESTIGATIONAL NEW DRUG (IND) APPLICATION NUMBER**
   Send all information required in item #3, **via facsimile**, to the attention of [redacted]

NOTE: The timeframe for approval of your request to charge for the drug is approximately 2 months. However, the drug supply may be distributed to the patient prior to the approval of a request to charge. **Under no circumstances can a physician/sponsor charge a patient for an investigational drug until written authorization to charge is received from the FDA** [21 CFR 312.7(d)].

QUESTIONS?? Call [redacted]

RU-486 (mifepristone)
Single-Patient IND Submission Checklist

Physician Name: _____ Date of Fax: _____

Patient Name/Initials: _____ Indication: _____

YES	NO		ITEM	NOTES
____	____	1.	Patient History	
____	____	2.	Statement re: Informed Consent & IRB approval	
____	____	3.	Protocol, Journal Article or Treatment Agreement	
____	____	4.	FAX commitment from supplier to provide drug	
____	____	5.	Physician/Sponsor CV	
____	____	6.	LOA from the Population Council (not needed to issue IND #)	

If physician intends to charge patient for the drug, the following should be provided:

YES	NO		ITEM	NOTES
____	____	1.	FDA Form 1571 w/ Request to Charge box checked	
____	____	2.	Statement re: exclusion from existing IND or ongoing trial.	
____	____	3.	–amount to be charged/unit dose/month –explanation of how amt was determined –copy of bill from drug supplier	
____	____			
____	____			

Request: Signature

☐ Approved _____

☐ Denied _____

IND Number: _____
Date Issued: _____
Spoke With: _____
Initials: _____
ROUTED TO:
____
____

Fax

DIVISION OF ONCOLOGY DRUG PRODUCTS
Center for Drug Evaluation and Research, HFD-150
Parklawn Building
5600 Fishers Lane, Rockville, MD 20857

To:
Fax:
Phone:
Pages (including cover): 1
Re: Single-Patient IND number for RU-486 (mifepristone)

From: [redacted]
Fax: [redacted]
Phone: [redacted]
Date:

Urgent **For Review** **Please Comment**
Please Reply **Please Recycle**

- **Comments:**

This is to confirm that an IND was issued to the following physician for single-patient use of RU-486.

IND #:
Date Issued:
IND
Physician/Sponsor:
Patient Initials:
Indication:

- **We remind you that IRB approval and informed consent should be obtained prior to initiating treatment.**
- **Additionally, you can not charge your patient for the drug until written authorization to charge is received from the FDA.**
- This FAX should be forwarded to:
  Dr. _____ of *the* FMF @ (703) _____ so that the drug may be shipped to you for your patient, and a letter of authorization can be provided on your behalf.
- Should you have any questions, my direct phone number is listed above.

Sincerely,

[redacted]

[redacted]

The ones were busy. Can you fax this to Drs. Ulmann and Silvestre for me? I think the numbers are correct

Ulman

Silvestre

Thanks.

Amendment to H.R. 4101, as Reported Offered by Mr. Coburn of Oklahoma

At the end of the bill, insert after the last section (preceding the short title) the following new section:

SEC. 739. None of the funds made available in this Act may be used by the Food and Drug Administration for the testing, development, or approval (including approval of production, manufacturing, or distribution) of any drug for the chemical inducement of abortion.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

September 27, 2000

Ms. Nancy L. Buc
Buc & Beardsley
919 Eighteenth Street, N.W.
Suite 600
Washington, D.C. 20006-5503

Re: NDA 20-687, Mifeprex (mifepristone) Oral Tablets
MACMIS #9342

Dear Ms. Buc:

This is in response to your letter of September 27, 2000 regarding the submission to the FDA of the training materials for mifepristone.

As we indicated in our phone conversations earlier today, under 21 C.F.R. 314.550, the applicant is required to submit to the agency for consideration during the preapproval review period copies of all promotional materials, including promotional labeling as well as advertisements, intended for dissemination within 120 days following marketing approval. Furthermore, after 120 days following marketing approval, unless otherwise informed by the agency, the applicant must submit promotional materials 30 days prior to the intended time of initial dissemination of the labeling or publication of the advertisement.

We believe that the training materials your clients, The Population Council and Danco Laboratories, LLC, intend to use for mifepristone, including those that they intend to reference on their WEB sites and in the Prescriber's Agreement, clearly constitute promotional labeling within the meaning of 21 C.F.R. 314.550. Furthermore, in accordance with this provision, you would normally have been required to submit and we would have reviewed these materials before approval. However, in view of your representations to us today that none of these materials

are yet completed, we are willing to defer your submission and our review until after approval.

We would, however, like to clarify that we understand your commitment to mean that you will submit these materials to FDA for review and, as contemplated by section 314.550, that you will not disseminate or use them in any manner until FDA has had an opportunity to review and comment on them. We expect to be able to do that within the 30 day period described in section 314.550.

Please confirm your agreement with our understanding of your commitment.

Sincerely,

APPEARS THIS WAY
ON ORIGINAL

20687

BUC & BEARDSLEY
919 EIGHTEENTH STREET, N.W.
SUITE 600
WASHINGTON, D.C. 20006-5503

WRITER'S TELEPHONE
202-736-3610

TELEPHONE
202-736-3600
FACSIMILE
202-736-3608

ORIGINAL

September 27, 2000

Confidential

NEW CORRESP

Food and Drug Administration
5600 Fishers Lane
Rockville, Md. 20857

Dear [redacted]

In accordance with our telephone conversation today, I am writing on behalf of my clients, The Population Council and Danco Laboratories, LLC, to request that the agency redact from materials about mifepristone the name of any clinical investigator whose work on or relationship with the drug is not already publicly available, including [redacted]

Thank you.

Sincerely,

Nancy L. Buc

REVIEWS COMPLETED

CSO ACTION:
☐ LETTER ☒ N.A.I. ☐ MEMO

CSO INITIALS DATE