DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

SEP 27 1996

The Honorable Joe Barton
Chairman, Subcommittee on Oversight
and Investigations
Committee on Commerce
House of Representatives
Washington, D.C. 20515

Dear Mr. Chairman:

This is in response to your letter dated July 11, 1996, seeking further information from the Food and Drug Administration (FDA) on clinical trials sponsored by the Population Council.

You raise five specific questions. We will respond to each question separately.

Question 1:

You asked for FDA's response to Dr. Bardin's December 7, 1994, letter "on whether blood transfusions constitute a 3-day telephonic report to the Agency." FDA responded by telephone to Dr. Bardin's inquiry. During that telephone conversation, we reconfirmed that he should continue to make 3-day telephonic reports to FDA whenever a blood transfusion is needed.

Question 2:

You asked to be provided with all documents relating to a report about Patient Number 042 of Submission Serial Number 109 of IND ——— These documents are enclosed (Tab A).

Question 3:

You requested a copy of Serial Number 107 of IND ——— and the typed version of FDA 3500 form. These documents are enclosed (Tab B).

Question 4:

You asked why FDA did not anticipate the need for 3-day telephonic reports to the Agency when blood transfusions were needed given that women participating in the RU-486 clinical trial may have had a small chance of excess bleeding. In fact, telephone reports are required under 21 CFR 312.32(c)(ii)(2) (Tab C). Dr. Bardin was just reconfirming that policy in his transmittal letter to ——— on December 7, 1994.

Question 5:

You asked for information regarding all adverse events related to IND ——— Based on our discussion with Mr. Alan Slobodin on July 22, 1996, we are providing you a list of all types of serious adverse events reported under the clinical trial in the United States. Enclosed is a summary table listing all the serious adverse events reported and the nature of each serious adverse event (Tab D). This summary table was prepared for FDA's Reproductive Health Drugs Advisory Committee on July 19, 1996. As I am sure you know, serious adverse events were discussed at great length at that committee meeting. In fact, Dr. Mark Louviere testified at the meeting.

As previously stated in our letter of June 27, 1996, FDA takes a careful look at all adverse event reports. As we informed you on September 18, 1996, we have issued an approvable letter for the New Drug Application (NDA) for mifepristone submitted by the Population Council; however, additional information must be submitted before a final approval decision can be made. Please be assured that, as with all drug applications, the application and the documentation from the mifepristone clinical trials are being reviewed in accordance with stringent scientific and legal standards.

This letter and the enclosed adverse event report contain confidential information and other privileged information not releasable to the public under the Freedom of Information regulations promulgated by FDA. We request that the Subcommittee not publish or otherwise make public any part of this letter or any information contained within it. In accordance with the Privacy Act, we have redacted the names of individuals associated with this clinical trial.

Thank you for your interest and concern in raising this matter to our attention. We trust that this response addresses your concerns. If you have any further questions, please let us know.

Sincerely,

/S/

———————————

for External Affairs

4 Enclosures

Adverse Event Report on Patient No.042 of Serial Number 109.
Copy of Serial Number 107 of IND ——— and the typed version of FDA 3500 form.
Summary of Serious Adverse Events Reported in IND ———
21 CFR 312.32

cc: The Honorable Thomas J. Bliley, Jr.
Chairman, Committee on Commerce

The Honorable John D. Dingell
Ranking Minority Member, Committee on Commerce

The Honorable Ron Klink
Ranking Minority Member, Subcommittee on Oversight
and Investigations

APPEARS THIS WAY
ON ORIGINAL

U.S. House of Representatives
Committee on Commerce
Room 2125, Rayburn House Office Building
Washington, DC 20515–6115
July 11, 1996

The Honorable David A. Kessler, M.D.
Commissioner of Food and Drugs
Food and Drug Administration
Room 14-71 (HF-1)
5600 Fishers Lane
Rockville, MD 20857

Dear Dr. Kessler:

I have received your June 27, 1996 letter in partial response to my letter of May 23, 1996 regarding data integrity in clinical trials sponsored by the Population Council.

Your response raises further questions and a need for additional information. Accordingly, please provide the following by July 25, 1996:

(1) Please provide FDA's response to Dr. Bardin's December 7, 1994 letter on whether blood transfusions constitute a 3-day telephonic report to the Agency.

(2) Please provide all documents relating to a report about Patient No. 042 of Submission Serial Number 109 of IND ———

(3) Please provide a copy of Serial Number 107 of IND ——— and the typed version of FDA 3500 form.

(4) The September 21, 1995 Associated Press article reported: "When asked if Louviere's patient qualifies as a serious complication, [Population Council spokesman Sandra] Waldman said it would be 'within the context of what happened before.' She said that in France, 0.1 percent of women using RU-486 bled to an extent that they needed transfusions. . . . Women participating in the test were told there was a small chance of excess bleeding." Given that history, why did the sponsor not ask the Agency about whether blood transfusions constituted a 3-day telephonic report to the Agency until after an adverse event report was submitted? Why wasn't this reporting issue anticipated?

(5) All unexpurgated books, records (including FOIA requests), correspondence, notes,

phone logs, memoranda, documents (including all drafts and without regard to whether they are on paper or recorded electronically), and electronic mail (irrespective of how stored, including but not limited to those stored on individual PCs or on file servers that are part of local area or wide area networks) mentioning or pertaining to adverse events related to IND ———

If you have any questions, please contact Mr. Alan Slobodin of the Subcommittee staff at (202) 225-2927. I appreciate your cooperation in this matter.

Sincerely,

Joe Barton

Joe Barton
Chairman
Subcommittee on Oversight
and Investigations

JB:as

cc: The Honorable Thomas J. Bliley, Jr., Chairman

The Honorable John D. Dingell, Ranking Minority Member

The Honorable Ron Klink, Ranking Minority Member
Subcommittee on Oversight and Investigations

APPEARS THIS WAY
ON ORIGINAL

TAB A

The Population Council
for
Medical Research

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

ORIGINAL

December 7, 1994

Noted
12/14/94
/S/

BY FEDEX

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

Subject: IND ——— Mifepristone Tablets, 200mg
Submission Serial Number: 109
IND Safety Report

/S/ 16 Dec 94

Dear ———

Enclosed please find information on three (3) adverse events for the above referenced study. These include: (1) an adverse event reported to Ms. of the Agency on December 1, 1994 by Dr. Irving Spitz of the Population Council (Patient ID No. 027, pp. 01-02); (2) a report of a subject hospitalized for general weakness (No. 042, pp. 03-04); and (3) a typed version of FDA 3500 Form identical to the handwritten report submitted as Serial Number 107 on November 21, 1994 (p. 05). Included in the report for adverse events (1) and (2) above is a copy of the text prepared by the physician at the site where the event occurred.

Please advise us if blood transfusions constitute a 3-day telephonic report to the Agency.

If you have require any additional information please contact me.

Sincerely,

CW Ba

C. Wayne Ba

CWB:sh

REC'D
DEC 0 9 1994

REVIEWS COMPLETED

CSO [illegible]:

☐ [illegible] /S/ ☐ N.A.I.

12/16/94

CSO INITIALS / DATE

TAB B

APPEARS THIS WAY
ON ORIGINAL

The Population Council
for
Medical Research

ORIGINAL

52

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

/S/ 12/1/94

November 21, 1994

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

/S/ 12/1/94

Subject: IND ——— Mifepristone Tablets, 200 mg
Submission Serial #107
IND Safety Report

Dear ———

Please find enclosed a copy of FDA Form 3500 in reference to the adverse event reported to you on November 18, 1994 by Dr. Irving Spitz of the Population Council in the above referenced study. In addition, we have enclosed a copy of the text prepared by the physician at the site where the adverse event occurred.

If you require any additional information please contact me.

Sincerely,

C.W. Bardin

C. Wayne Bardin, M.D.
Director

CENTER FOR DRUG EVALUATION AND RESEARCH
RECEIVED
NOV 23 1994
HFD-510

REVIEWS COMPLETED
CSO ACTION: ☐ LETTER ☒ N.A.I.
/S/ 12/1/94
CSO INITIALS DATE

TAB C

APPEARS THIS WAY
ON ORIGINAL

n that contained the proto-

he case of a new investigator, tigator's name, the qualifica- onduct the investigation, ref- the previously submitted pro- d all additional information investigator's study as is re- der §312.23(a)(6)(iii)(b).

rence, if necessary, to specific information in the IND or in ently submitted information nt to the IND that the spon- on to support any clinically t change in the new or protocol. If the reference is supporting information al- the IND, the sponsor shall by name, reference number, nd page number the location ormation.

e sponsor desires FDA to com- the submission, a request for ument and the specific ques- 's response should address.

n submitted. A sponsor shall protocol amendment for a ocol or a change in protocol s implementation. Protocol nts to add a new investigator ovide additional information vestigators may be grouped nitted at 30-day intervals. eral submissions of new proto- protocol changes are antici- ing a short period, the spon- couraged, to the extent fea- include these all in a single n.

of information requirements ap- the Office of Management and ler control number 0910-0014)

, Mar. 19, 1987, as amended at 52 June 17, 1987; 53 FR 1918, Jan. 25,

information amendments.

irement for information amend- ponsor shall report in an in- amendment essential infor- n the IND that is not within e of a protocol amendment, ty reports, or annual report. of information requiring an ion amendment include: w toxicology, chemistry, or hnical information; or port regarding the discontinu- clinical investigation.

(b) *Content and format of an information amendment.* An information amendment is required to bear prominent identification of its contents (e.g., "Information Amendment: Chemistry, Manufacturing, and Control", "Information Amendment: Pharmacology-Toxicology", "Information Amendment: Clinical"), and to contain the following:

(1) A statement of the nature and purpose of the amendment.

(2) An organized submission of the data in a format appropriate for scientific review.

(3) If the sponsor desires FDA to comment on an information amendment, a request for such comment.

(c) *When submitted.* Information amendments to the IND should be submitted as necessary but, to the extent feasible, not more than every 30 days.

(Collection of information requirements approved by the Office of Management and Budget under control number 0910-0014)

[52 FR 8831, Mar. 19, 1987, as amended at 52 FR 23031, June 17, 1987; 53 FR 1918, Jan. 25, 1988]

§312.32 IND safety reports.

(a) *Definitions.* The following definitions of terms apply to this section:

Associated with the use of the drug means that there is a reasonable possibility that the experience may have been caused by the drug.

Serious adverse experience means any experience that suggests a significant hazard, contraindication, side effect, or precaution. With respect to human clinical experience, a serious adverse drug experience includes any experience that is fatal or life-threatening, is permanently disabling, requires inpatient hospitalization, or is a congenital anomaly, cancer, or overdose. With respect to results obtained from tests in laboratory animals, a serious adverse drug experience includes any experience suggesting a significant risk for human subjects, including any finding of mutagenicity, teratogenicity, or carcinogenicity.

Unexpected adverse experience means any adverse experience that is not identified in nature, severity, or frequency in the current investigator brochure; or, if an investigator brochure is not required, that is not identified in

nature, severity, or freuquency in the risk information described in the general investigational plan or elsewhere in the current application, as amended.

(b) *Review of safety information.* The sponsor shall promptly review all information relevant to the safety of the drug obtained or otherwise received by the sponsor from any source, foreign or domestic, including information derived from clinical investigations, animal investigations, commercial marketing experience, reports in the scientific literature, and unpublished scientific papers.

(c) *IND safety reports.* (1) *Written reports.* (i) The sponsor shall notify FDA and all participating investigators in a written IND safety report of any adverse experience associated with use of the drug that is both serious and unexpected. Such notification shall be made as soon as possible and in no event later than 10 working days after the sponsor's initial receipt of the information. Each written notification shall bear prominent identification of its contents, i.e., "IND Safety Report." Each written notification to FDA shall be transmitted to the FDA division of the Center for Drug Evaluation and Research or the Center for Biologics Evaluation and Research which has responsibility for review of the IND.

(ii) In each written IND safety report, the sponsor shall identify all safety reports previously filed with the IND concerning a similar adverse experience, and shall analyse the significance of the adverse experience in light of the previous, similar reports.

(2) *Telephone report.* The sponsor shall also notify FDA by telephone of any unexpected fatal or life-threatening experience associated with use of the drug in the clinical studies conducted under the IND no later than 3 working days after receipt of the information. Each telephone call to FDA shall be transmitted to the FDA division of the Center for Drug Evaluation and Research or the Center for Biologics Evaluation and Research which has responsibility for review of the IND. For purposes of this section, life-threatening means that the patient was, in the view of the investigator, at *immediate* (emphasis added) risk of death from the reaction as it occurred, i.e., it does not include a reaction that, had it occurred in a more serious form, might have caused death. For example, drug-induced hepatitis that resolved without evidence of hepatic failure would not be considered life-threatening even though drug-induced hepatitis can be fatal.

(3) *Reporting format or frequency.* FDA may request a sponsor to submit IND safety reports in a format or at a frequency different than that required under this paragraph. The sponsor may also propose and adopt a different reporting format or frequency if the change is agreed to in advance by the director of the division in the Center for Drug Evaluation and Research or the Center for Biologics Evaluation and Research which is responsible for review of the IND.

(4) A sponsor of a clinical study of a marketed drug is not required to make a safety report for any adverse experience associated with use of the drug that is not from the clinical study itself.

(d) *Followup.* (1) The sponsor shall promptly investigate all safety information received by it.

(2) Followup information to a safety report shall be submitted as soon as the relevant information is available.

(3) If the results of a sponsor's investigation show that an adverse experience not initially determined to be reportable under paragraph (c) of this section is so reportable, the sponsor shall report such experience in a safety report as soon as possible after the determination is made, but in no event longer than 10-working days.

(4) Results of a sponsor's investigation of other safety information shall be submitted, as appropriate, in an information amendment or annual report.

(e) *Disclaimer.* A safety report or other information submitted by a sponsor under this section (and any release by FDA of that report or information) does not necessarily reflect a conclusion by the sponsor or FDA that the report or information constitutes an admission that the drug caused or contributed to an adverse experience. A sponsor need not admit, and may deny,

that the report or information submitted by the sponsor constitutes an admission that the drug caused or contributed to an adverse experience.

(Collection of information requirements approved by the Office of Management and Budget under control number 0910-0014)

[52 FR 8831, Mar. 19, 1987, as amended at 52 FR 23031, June 17, 1987; 55 FR 11579, Mar. 29, 1990]

§ 312.33 Annual reports.

A sponsor shall within 60 days of the anniversary date that the IND went into effect, submit a brief report of the progress of the investigation that includes:

(a) *Individual study information.* A brief summary of the status of each study in progress and each study completed during the previous year. The summary is required to include the following information for each study:

(1) The title of the study (with any appropriate study identifiers such as protocol number), its purpose, a brief statement identifying the patient population, and a statement as to whether the study is completed.

(2) The total number of subjects initially planned for inclusion in the study, the number entered into the study to date, the number whose participation in the study was completed as planned, and the number who dropped out of the study for any reason.

(3) If the study has been completed, or if interim results are known, a brief description of any available study results.

(b) *Summary information.* Information obtained during the previous year's clinical and nonclinical investigations, including:

(1) A narrative or tabular summary showing the most frequent and most serious adverse experiences by body system.

(2) A summary of all IND safety reports submitted during the past year.

(3) A list of subjects who died during participation in the investigation, with the cause of death for each subject.

(4) A list of subjects who dropped out during the course of the investigation in association with any adverse experience, whether or not thought to be drug related.

(5) A brief description of what, if anything, was obtained that is pertinent to an understanding of the drug's actions, including, for example, information about dose response, information from controlled trails, and information about bioavailability.

(6) A list of the preclinical studies (including animal studies) completed or in progress during the past year and a summary of the major preclinical findings.

(7) A summary of any significant manufacturing or microbiological changes made during the past year.

(c) A description of the general investigational plan for the coming year to replace that submitted 1 year earlier. The general investigational plan shall contain the information required under § 312.23(a)(3)(iv).

(d) If the investigator brochure has been revised, a description of the revision and a copy of the new brochure.

(e) A description of any significant Phase 1 protocol modifications made during the previous year and not previously reported to the IND in a protocol amendment.

(f) A brief summary of significant foreign marketing developments with the drug during the past year, such as approval of marketing in any country or withdrawal or suspension from marketing in any country.

(g) If desired by the sponsor, a log of any outstanding business with respect to the IND for which the sponsor requests or expects a reply, comment, or meeting.

(Collection of information requirements approved by the Office of Management and Budget under control number 0910-0014)

[52 FR 8831, Mar. 19, 1987, as amended at 52 FR 23031, June 17, 1987]

§ 312.34 Treatment use of an investigational new drug.

(a) *General.* A drug that is not approved for marketing may be under clinical investigation for a serious or immediately life-threatening disease condition in patients for whom no comparable or satisfactory alternative drug or other therapy is available. During the clinical investigation of the drug, it may be appropriate to use the drug in the treatment of patients not in the clinical trials, in accordance

with a treatment protocol or treatment IND. The purpose of this section is to facilitate the availability of promising new drugs to desperately ill patients as early in the drug development process as possible, before general marketing begins, and to obtain additional data on the drug's safety and effectiveness. In the case of a serious disease, a drug ordinarily may be made available for treatment use under this section during Phase 3 investigations or after all clinical trials have been completed; however, in appropriate circumstances, a drug may be made available for treatment use during Phase 2. In the case of an immediately life-threatening disease, a drug may be made available for treatment use under this section earlier than Phase 3, but ordinarily not earlier than Phase 2. For purposes of this section, the "treatment use" of a drug includes the use of a drug for diagnostic purposes. If a protocol for an investigational drug meets the criteria of this section, the protocol is to be submitted as a treatment protocol under the provisions of this section.

(b) *Criteria.* (1) FDA shall permit an investigational drug to be used for a treatment use under a treatment protocol or treatment IND if:

(i) The drug is intended to treat a serious or immediately life-threatening disease;

(ii) There is no comparable or satisfactory alternative drug or other therapy available to treat that stage of the disease in the intended patient population;

(iii) The drug is under investigation in a controlled clinical trial under an IND in effect for the trial, or all clinical trials have been completed; and

(iv) The sponsor of the controlled clinical trial is actively pursuing marketing approval of the investigational drug with due diligence.

(2) *Serious disease.* For a drug intended to treat a serious disease, the Commissioner may deny a request for treatment use under a treatment protocol or treatment IND if there is insufficient evidence of safety and effectiveness to support such use.

(3) *Immediately life-threatening disease.* (i) For a drug intended to treat an immediately life-threatening disease, the Commissioner may deny a req treatment use of an investig drug under a treatment prot treatment IND if the availat entific evidence, taken as a who to provide a reasonable basis f cluding that the drug:

(A) May be effective for its i use in its intended patient pop or

(B) Would not expose the pati whom the drug is to be adminis an unreasonable and significan tional risk of illness or injury.

(ii) For the purpose c is a an "immediately life-thr enin ease means a stage of a dis which there is a reasonable lik that death will occur within a of months or in which prematur is likely without early treatmen

(c) *Safeguards.* Treatment us investigational drug is conditio the sponsor and investigators c ing with the safeguards of t process, including the regulatio erning informed consent (21 C 50) and institutional review bo CFR part 56) and the applicabl sions of part 312, including distr of the drug through qualified maintenance of adequate manu ing facilities, and submission safety reports.

(d) *Clinical hold.* FDA may p clinical hold a proposed or treatment protocol or t me in accordance with § 312.4..

[52 FR 19476, May 22, 1987, as amen FR 13248, Apr. 15, 1993]

§ 312.35 Submissions for tr use.

(a) *Treatment protocol submi IND sponsor.* Any sponsor of a investigation of a drug who int sponsor a treatment use for t shall submit to FDA a treatm tocol under § 312.34 if the spon lieves the criteria of § 312.34 a fied. If a protocol is not su under § 312.34, but FDA believ the protocol should have been ted under this section, FDA m the protocol to be submitte § 312.34. A treatment use under ment protocol may begin 30 da FDA receives the protocol or o

TAB D

APPEARS THIS WAY
ON ORIGINAL

Table 2

IND Safety Reports (Med Watch) Submitted to IND ——

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

Table 2 (Cont'd)

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

Table 2 (Cont'd)

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

Table 2 (Cont'd)

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

Summary of Table 2

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

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

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

JUN 27 1996

The Honorable Joe Barton
Chairman
Subcommittee on Oversight and Investigations
Commerce Committee
House of Representatives
Washington, D.C. 20515

Dear Chairman Barton:

This is in response to your letter of May 23, 1996, regarding a clinical trial sponsored by the Population Council that was reported by the Associated Press in an article on September 2, 1995. You expressed concerns regarding whether public information about the clinical trial is consistent with data filed with the Food and Drug Administration (FDA) and regarding the truth in reporting clinical data.

The newspaper article referenced in your letter reported that there had been no complications among the subjects in the clinical trial. The Population Council has never represented to FDA that RU-486 (mifepristone) is without potential complications. The complications that are described in this article, while unfortunate and rare, are not unexpected complications. FDA can confirm that the specific adverse event cited by Dr. Mark Louviere was reported to FDA precisely as described by Dr. Louviere in the news article and was reported in a timely manner by the sponsor. A copy of this adverse event report is enclosed with this letter.

FDA is currently reviewing this adverse event report, and all other submitted information and data, as part of our evaluation of the new drug application submitted for mifepristone by the Population Council. Please be assured that, as with all drug applications, the application and the documentation from the mifepristone clinical trials are being reviewed in accordance with stringent scientific and legal standards.

This letter and the enclosed adverse event report contain confidential information and other privileged information not releasable to the public under the Freedom of Information regulations promulgated by FDA. We request that the Subcommittee not publish or otherwise make public any part of this letter or any information contained within it.

Thank you for your interest and concern in raising this matter to our attention. We trust that this response addresses your concerns. If you have any further questions, please let us know.

Sincerely,

/S/

for External Affairs

5 Enclosures
Adverse Event Report dated December 1, 1994
Associated Press article, September 2, 1995
Associated Press article, September 21, 1995
The Des Moines Register, September 21, 1995
Waterloo Courier, Sunday, September 23, 1995

cc: The Honorable Thomas J. Bliley, Jr.
Chairman

The Honorable John D. Dingell
Ranking Minority Member

The Honorable Ron Klink, Ranking Minority Member
Subcommittee on Oversight and Investigations

APPEARS THIS WAY
ON ORIGINAL

U.S. House of Representatives
Committee on Commerce
Room 2125, Rayburn House Office Building
Washington, DC 20515–6115

May 23, 1996

The Honorable David A. Kessler, M.D.
Commissioner
Food and Drug Administration
Room 1471
Parklawn Building
5600 Fishers Lane
Rockville, MD 20857

Dear Dr. Kessler:

Pursuant to Rules X and XI of the Rules of the U.S. House of Representatives, the Subcommittee is investigating FDA's handling of data integrity issues related to clinical trials. Under 21 CFR § 312.62(b), an investigator is required to prepare and maintain adequate and accurate case histories designed to record all observations and other data pertinent to the investigation on each individual treated with an investigational drug or employed as a control in the investigation. Under 21 CFR § 312.64(b), an investigator shall promptly report to the sponsor any adverse effect that may reasonably be regarded as caused by, or probably caused by, the drug. The Subcommittee has received credible information raising a question of whether such procedures were followed in a clinical trial.

According to an article in the September 21, 1995 Des Moines Register, Mark Louviere, M.D., of Waterloo, Iowa, stated that one of his patients who participated in a clinical trial sponsored by the Population Council lost more than half her blood, came close to death and needed surgery two weeks after taking an investigational new drug. Dr. Louviere said he saw an article in the Associated Press reporting that the clinical trial of the investigational new drug had concluded and that there had been no complications among the subjects in the clinical trial. Dr. Louviere stated: "If near-death due to the loss of half of one's blood volume, surgery and a transfusion of four units of blood do not qualify as a complication, I don't know what does." Statements from the clinical investigator and the sponsor are unclear about whether the adverse event mentioned by Dr. Louviere has been acknowledged. Dr. Louviere's statements, if accurate, raise a question about whether public information about the clinical trial is consistent with data filed with FDA. Further, his statements raise the issue of truth in reporting clinical data.

96-4062

Please provide the Subcommittee by June 6, 1996 with the following:

(1) Identities of all sponsors or subsponsors of the investigational new drug related to the adverse event referenced by Dr. Louviere.

(2) All IND applications of these sponsors or subsponsors of the investigational new drug related to the adverse event referenced by Dr. Louviere.

(3) All unexpurgated books, records (including FOIA requests), correspondence, notes, phone logs, memoranda, documents (including all drafts and without regard to whether they are on paper or recorded electronically), and electronic mail (irrespective of how stored, including but not limited to those stored on individual PCs or on file servers that are part of local area or wide area networks) mentioning or pertaining to the adverse event referred to by Dr. Louviere or any other adverse events related to the same investigational drug.

(4) If FDA confirms this was an unreported adverse event and that it was not reported to or by the sponsor, please explain how FDA plans to address this data integrity issue.

If you have any questions about this request, please contact Alan Slobodin of the Committee staff at (202) 225-2927. I appreciate your cooperation in this matter.

Sincerely,

Joe Barton
Chairman
Subcommittee on Oversight
and Investigations

cc: The Honorable Thomas J. Bliley, Jr., Chairman

The Honorable John D. Dingell, Ranking Minority Member

The Honorable Ron Klink, Ranking Minority Member
Subcommittee on Oversight and Investigations

THE COMMITTEE ON COMMERCE
UNITED STATES HOUSE OF REPRESENTATIVES
FAX TRANSMISSION

May 23, 1996

To: The Honorable David A. Kessler

FAX: (301)443-3100 and (301)443-2567

From: Congressman Joe Barton

Number of Pages (including this sheet): 3

If you receive this transmission in error, please contact the Commerce Committee immediately.

The Committee on Commerce
2125 Rayburn House Office Building
Washington DC 20515
(202) 225-2927
FAX (202) 225-1919

The Population Council
Center for
Biomedical Research

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

ORIGINAL

December 7, 1994

Noted
12/14/94
/S/

BY FEDEX

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

Subject: IND —— · Mifepristone Tablets, 200mg
Submission Serial Number: 109
IND Safety Report

Noted
/S/ 12/16/94

Dear ——

Enclosed please find information on three (3) adverse events for the above referenced study. These include: (1) an adverse event reported to —— of the Agency on December 1, 1994 by Dr. Irving Spitz of the Population Council (Patient ID No. 027, pp. 01-02); (2) a report of a subject hospitalized for general weakness (No. 042, pp. 03-04); and (3) a typed version of FDA 3500 Form identical to the handwritten report submitted as Serial Number 107 on November 21, 1994 (p. 05). Included in the report for adverse events (1) and (2) above is a copy of the text prepared by the physician at the site where the event occurred.

Please advise us if blood transfusions constitute a 3-day telephonic report to the Agency.

If you have require any additional information please contact me.

Sincerely,

CW Ba

C. Wayne Ba

CWB:sh

REVIEWS COMPLETED

CSO [illegible]:

☐ L /S/ ☐ N.A.I.

12/16/94

CSO INITIALS / DATE

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration

Memorandum

Date 12 July 1996 (Friday)

From Executive Secretary

Subject CONFIDENTIAL MATERIAL FOR JULY MEETING

To Members of the Advisory Committee for Reproductive Health Drugs

Attached is material provided by the sponsor of the NDA to be considered next Friday's meeting.

Included are a summary of the pivotal clinical trials upon which evidence for safety and efficacy primarily depend, and the draft package insert, including physician labeling, and, starting on page 10, the text of the patient information leaflet.

Since some of the discussion will involve recommendations for conditions of safe use in the United States, [redacted] asks that you read the draft package insert with particular care.

Please remember that this material is CONFIDENTIAL and should not be shared with anyone except FDA staff and other Committee members.

The dinner for Thursday remains booked for 8 pm, but we ask that you gather in the dining room at 7:30 in order for [redacted] senior FDA staff members, to discuss media and security issues.

/S/

Food and Drug Administration

APPEARS THIS WAY
ON ORIGINAL

Printed by: [redacted]

Electronic Mail Message

Date: 13-Apr-2000 05:26pm
From: [redacted]
Dept: HFD-324 MPN1 265
Tel No: [redacted]

Subject: Reinspection of Chinese facility for NDA # 20687

Good Afternoon,

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

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

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

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

/s/

[redacted]

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

[redacted]

Printed by [redacted]

Electronic Mail Message

Sensitivity: COMPANY CONFIDENTIAL

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

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

TO:

CC: [redacted]
CC:
CC:
CC

Subject: Reinspection of Chinese facility for NDA # 20687

Good Afternoon,

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

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

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

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

/s/

[redacted]

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

for your assistance. Let me know if you need more information.

Printed by [redacted]

Electronic Mail Message

Sensitivity: COMPANY CONFIDENTIAL

Date: 13-Apr-2000 11:11am
From: [redacted]
Dept: HFD-320 MPN1 272
Tel No: [redacted]

TO: [redacted]

Subject: Shanghai Hualian Reinspection

[redacted] came to me this morning with an email that [redacted] received from [redacted] regarding the reinspection of Shanghai Hualian. I called [redacted] this morning to find out if the reinspection has been scheduled. She stated at the present time it has not been scheduled. She could not give me a date for reinspection but she said that is should be scheduled sometime within the next six months.

I have the email that [redacted] was concerned about. Apparently [redacted] wants to be sure that we are on track for reinspection within the next six month review period.

I will but the email in your box.

Thanks,

[redacted]

Printed by [redacted]

Electronic Mail Message

Sensitivity: COMPANY CONFIDENTIAL

Date: 13-Apr-2000 09:14pm
From: [redacted]
Dept: HFD-103 PKLN 13B45
Tel No: [redacted]

TO: See Below
Subject: FWD: Reinspection of Chinese facility for NDA # 20687

[redacted]

Please verify what is the User Fee date for this application so that compliance will know when to conduct the inspection by...I'm assuming this is a six month review. Please reply to me and I'll reply to Compliance. Thanks.

[redacted]

Distribution:

TO:

CC:
CC:
CC:
CC:
CC:

Printed by [redacted]

Electronic Mail Message

Sensitivity: COMPANY CONFIDENTIAL

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

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

TO: [redacted]
TO: [redacted]

Subject: FWD: Reinspection Chinese Plant on Population Council Application

FYI - Please give me an update on this status.

[redacted]

Printed by [redacted]

Electronic Mail Message

Sensitivity: COMPANY CONFIDENTIAL

Date: 11-Apr-2000 07:24pm
From: [redacted]

Dept: HFD-301 MPN1 254
Tel No: [redacted]

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

Subject: FWD: Reinspection Chinese Plant on Population Council Application

Printed by [redacted]

Electronic Mail Message

Date: 11-Apr-2000 07:24pm
From: [redacted]

Dept: HFD-301 MPN1 254
Tel No: [redacted]

Subject: FWD: Reinspection Chinese Plant on Population Council Application

Printed by [redacted]

Electronic Mail Message

Date: 11-Apr-2000 07:24pm
From: [redacted]
Dept: HFD-301 MPN1 254
Tel No: [redacted]

Subject: FWD: Reinspection Chinese Plant on Population Council Application

Printed by [redacted]

Electronic Mail Message

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

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

Subject: Reinspection Chinese Plant on Population Council Application

[redacted]

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

[redacted]

Printed by

Electronic Mail Message

Date: 05-Apr-2000 03:59pm
From:

Dept: HFD-103 PKLN 13B45
Tel No:

Subject: Reinspection Chinese Plant on Population Council Application

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

Printed by [redacted]

Electronic Mail Message

Date: 05-Apr-2000 03:59pm
From: [redacted]
Dept: HFD-103 PKLN 13B45
Tel No: [redacted]

Subject: Reinspection Chinese Plant on Population Council Application

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

[redacted]

Electronic Mail Message

Date: 4/5/00 3:43:10 PM
From: [redacted]
To: [redacted]
Cc: [redacted]
Cc: [redacted]
Subject: Nancy Buc

[redacted]

[redacted] needs to know if the Pop council has sent us a letter saying that Nancy Buc, JD, represents them and we can talk to her about their application issues. Please email her and cc: us. Thanks!

[redacted]

Electronic Mail Message

Date: 3/13/00 8:11:00 AM
From: [redacted]
To: [redacted]
To: [redacted]
Cc:
Subject: NDA 20-687 Mifepristone

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

Electronic Mail Message

Date: 3/6/00 8:34:19 AM
From:
To: See Below
Subject: Response to appropriations questions on Mifepristone

The response below has been cleared through ODE 3. Please let me know if you need further information.

**********RESPONSE**********

Mifepristone is still under review at the FDA. The safety issues raised are very important to FDA and have been discussed publicly with our advisory committee as well. In particular, an adequate distribution system with proper education of health care providers and patients, as well as the presence of controls was discussed. Negotiations are ongoing with the drug sponsor to ensure that these concerns are satisfactorily addressed.

****

To:
Cc:
Cc:
Cc:
Cc:
Cc:
Cc:
Cc:

Electronic Mail Message

Date: 2/17/00 2:38:14 PM
From:
To:
To:
To:
To:
Cc:
Subject: FWD: Mifepristone

Printed by

Electronic Mail Message

Date: 16-Feb-2000 03:10pm
From:
Dept: HFD-820 PKLN 14B31

TO:
TO:

CC:
CC:
Subject: Tertiary Chemistry Review of NDA 20-687

NDA #20-687 Clinical Division: HFD-580
Drug: (Mifepristone) Tablets
Type of Letter: Approvable Drug Classification: 1P

Chemistry Tertiary Review:

EA: Submitted 03/01/96. Acceptable: 09 Jul 96.

EER: WITHHOLD per EER dated 14 Feb 2000.

MICRO: Not Required for solid oral dosage form.

Tradename: Tablets acceptable per OPDRA review dated 11 Jan 2000.

Labeling: DEFICIENT. See Item F of Chemistry Review #4 dated 11 Feb 2000.

CMC: APPROVABLE pending the selection of a commercially available starting material for the drug substance and development of an assay for

Electronic Mail Message

Date: 2/16/00 3:10:00 PM
From:
To:
To:
Cc:
Cc:
Subject: Tertiary Chemistry Review of NDA 20-687

NDA #20-687 Clinical Division: HFD-580
Drug: (Mifepristone) Tablets
Type of Letter: Approvable Drug Classification: 1P

Chemistry Tertiary Review:

EA: Submitted 03/01/96. Acceptable: 09 Jul 96.

EER: WITHHOLD per EER dated 14 Feb 2000.

MICRO: Not Required for solid oral dosage form.

Tradename: acceptable per OPDRA review dated 11 Jan 2000.

Labeling: DEFICIENT. See Item F of Chemistry Review #4 dated 11 Feb 2000.

CMC: APPROVABLE pending the selection of a commercially available starting material for the drug substance and development of an assay for

Printed by [redacted]

Electronic Mail Message

Sensitivity: COMPANY CONFIDENTIAL

Date: 16-Feb-2000 04:53pm
From: [redacted]

Dept: HFD-580 PKLN 17B45
Tel No: [redacted]

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

CC: [redacted]
Subject: Inspection request for mifepristone

It seems that we need reinspect the Chinese site in the next review cycle, however, since it will take several months to do it, I was wondering if we can request inspection before the sponsor responds to our AE letter.

Please let me know.

Thanks,

[redacted]

Printed by [redacted]

Electronic Mail Message

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

Dept:
Tel No:

TO: [redacted]
TO [redacted]

Subject: fwd: [redacted]

Comments: [redacted]
Originally T[redacted]

Originall[redacted]
Original [redacted]
Original Date: 2/14/00 7:24 AM
Comments:

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

[redacted]

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

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

[redacted]

Electronic Mail Message

Date: 2/14/00 5:25:38 PM
From:
To:
Cc:
Cc:
Cc:
Subject: Awaiting DSI Final Report for NDA 20-687 - Office action

I am following up, as agreed last week, regarding the need to get the Final DSI report for NDA 20-687.

Our due date is Friday, but this is an ODE 3, Office sign-off action and wants the Action Package by Wednesday.

Can you please let me know when we might expect your report sign-off from

You may fax or email the final report; whichever is the more timely.

Thanks in advance for your time and attention to this matter,

Printed by [redacted]

Electronic Mail Message

Date: 14-Feb-2000 07:24am
From: [redacted]

Dept: [redacted]
Tel No:

TO: [redacted]
TO: [redacted]

Subject: fwd: [redacted]

Comments [redacted]
Originally To. [redacted]
Origi[redacted]
Originally From[redacted]
Original Date: 2/14/00 7:24 AM
Comments:

Good Morning.

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

[redacted]

[redacted]

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

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

[redacted]

Printed by [redacted]

Electronic Mail Message

Sensitivity: COMPANY CONFIDENTIAL

Date: 11-Feb-2000 01:56pm
From: [redacted]

Dept:
Tel No:

TO: [redacted]
TO: [redacted]

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

[redacted]

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

[redacted] and I met with [redacted] yesterday. They have made a lot of
>corrective actions and provided much more clarification on the

>issue. Although different from what they originally explained, it seems to be
>more reasonable. [redacted] s working on confirming the other corrective actions
>and trying to determine if there are any other related issues. We briefly
>discussed a conference call on Monday if you or you [redacted] are available.
>Hopefully there will be enough information to make a final decision. So far
>things are looking good.
>
>Please advise when you might be available. Morning may be better for [redacted] in
>case he has to go out again, but I will try to find out. I will also check
>with [redacted]
>
>Thanks for your help.
>
[redacted]
>
>
>
> [redacted]
>|
>| [redacted]
>|
>| [redacted]
>|
>|
>| [redacted] Original Message Follows
>| [redacted]

>|
>|
>| I got your message that you folks were starting the
>| follow/up
>| Wednesday. Thanx
>|
>| Do you have a rough idea which way this will go at this
>| point?
>|
>| Thanx
>|
>|
>
>
>
>

Printed by [redacted]

Electronic Mail Message

Sensitivity: COMPANY CONFIDENTIAL

Date: 11-Feb-2000 09:11am
From: [redacted]

Dept:
Tel No:

TO: [redacted]

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

Hi [redacted]

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

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

Thanx [redacted]

Printed by

Electronic Mail Message

Sensitivity: COMPANY CONFIDENTIAL

Date: 10-Feb-2000 02:36pm
From:
Dept: HFD-870 PKLN 17B31
Tel No:

TO: See Below
Subject: NDA 20-687, Dissolution

Hi
Based on the review of in vitro dissolution data submitted in the amendment dated December 14, 1999 and earlier amendments, Biopharm would like to recommend the following:

Dissolution method and Specifications
Apparatus: USP 2 (paddle)
Medium: 0.01 N Hydrochloric acid
Speed: 50 RPM
Volume: 900 ml
Temperature: 37 c

Specification:
I understand that chemistry review also agrees with this recommendation.

Please convey the recommendation to the sponsor as approriate.
Please let me know if you have any questions.

Thanks,

Distribution:

TO:
TO:

CC:
CC:
CC:
CC:
CC:
CC:

Electronic Mail Message

Date: 2/10/00 2:36:11 PM
From:
To: See Below
Subject: NDA 20-687, Dissolution

Based on the review of in vitro dissolution data submitted in the amendment dated December 14, 1999 and earlier amendments, Biopharm would like to recommend the following:

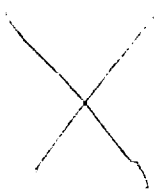
Dissolution method and Specifications
Apparatus: USP 2 (paddle)
Medium: 0.01 N Hydrochloric acid
Speed: 50 RPM
Volume: 900 ml
Temperature: 37 c

Specification:
I understand that chemistry review also agrees with this recommendation.

Please convey the recommendation to the sponsor as approriate.
Please let me know if you have any questions.

nks,

To:
To:
Cc:
Cc:
Cc:
Cc:
Cc:
Cc:



Electronic Mail Message

Date: 2/10/00 2:58:30 PM
From: [redacted]
To: [redacted]
Cc: [redacted]
Subject: Response to call

As per our discussion this morning,

We plan to issue an approvable letter on 2/18/00.

The deficiencies will include:

Chemistry: Some outstanding information request items.
CMC inspection: I'm sending the 483 and EES reports by fax as you suggested. The review division believes that the Chinese plant requires re-inspection. This is simply to confirm that what is reported for the process and testing in the NDA is truly what happens at the site. The withhold recommendation from the Compliance office states "deviation from DMF/NDA/ANDA". The division believes that it will be difficult to release this withhold without a follow-up inspection.

Labeling: changes will be laid out for the sponsor.

Subpart H: the letter will address that any approval will be under subpart H. The distribution system proposed by the sponsor will need some modifications/additions.

Let us know if you think this info will address your need. Call if needed!
Thanks

[redacted]

Electronic Mail Message

Date: 2/8/00 1:19:46 PM
From: [redacted]
To: [redacted]
Subject: NDA 20-687, Population Council

The PDUFA date on this submission is next Friday (2/18). One more letter, its compliance review, and the final Summary need to be signed off. Would you prefer to review and sign the materials or would you rather that [redacted] go over it upon his return?

Thanks,

[redacted]

Electronic Mail Message

Date: 2/8/00 12:45:00 AM
From: [redacted]
To: [redacted]
Cc: [redacted]
Subject: FWD: NDA 20-687, Population Council

Thanks for your note. If you want/need this signed off before I get back to the office on the 15th, could you bring this to [redacted] attention.

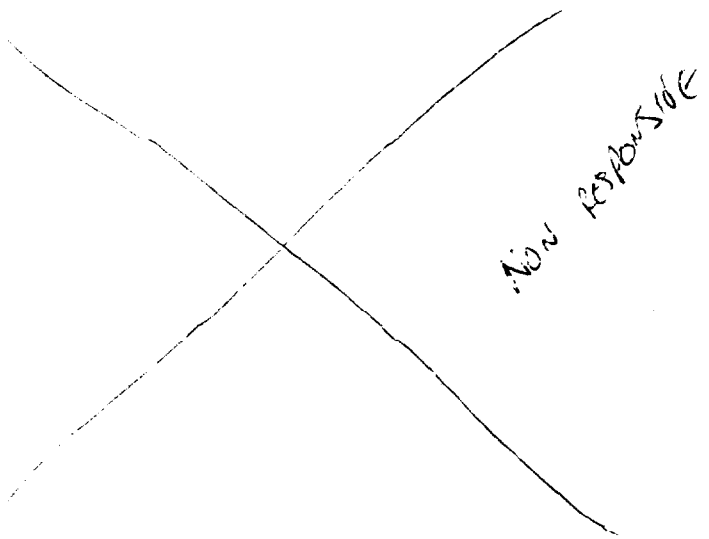
Thanks,

Electronic Mail Message

Date: 2/7/00 1:13:16 PM
From:
To: See Below
Subject: Update on DSI inspections for upcoming actions

I recieved some feedback from ——— on the DSI inspection status of our upcoming actions. (now thru the end of March)

20-687 Mife - 3/3 completed - report for sign-off with ———



To:
To:
To:
Cc:
Cc:
Cc:

Electronic Mail Message

Date: 2/7/00 5:35:59 PM
From: [redacted]
To: [redacted]
Subject: NDA 20-687, Population Council

[redacted] called from 580 and said that they would like to take an action on this NDA in the very near future. Two of the three letters are completed and signed off. The third one, from [redacted] is on the bookshelf above my name by [redacted], desk. The Compliance Review and Final Summary is with this letter. The inspections appear acceptable.

If you have the opportunity, please review this last letter and sign off as appropriate. I'd like to forward it to [redacted] prior to the Due Date.

Thanks,

Electronic Mail Message

Date: 2/7/00 5:35:59 PM
From:
Subject: NDA 20-687, Population Council

called from 580 and said that they would like to take an action on this NDA in the very near future. Two of the three letters are completed and signed off. The third one, from , is on the bookshelf above my name by desk. The Compliance Review and Final Summary is with this letter. The inspections appear acceptable.

If you have the opportunity, please review this last letter and sign off as appropriate. I'd like to forward it to prior to the Due Date.

Thanks,

Printed by [redacted]

Electronic Mail Message

Sensitivity: COMPANY CONFIDENTIAL

Date: 03-Feb-2000 01:48pm
From: [redacted]

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

TO: [redacted]
TO: [redacted]

CC: [redacted]
CC: [redacted]
Subject: NDA 20-687 reinspection at [redacted]

H: [redacted]

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

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

Thanx

Printed by [redacted]

Electronic Mail Message

Sensitivity: COMPANY CONFIDENTIAL

Date: 28-Jan-2000 11:23am
From: [redacted]

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

TO: [redacted]
TO: [redacted]

CC: [redacted]
CC: [redacted]
Subject: Re: ...no subject.

Sounds like the right thing to do.—
>
>I just read the firm's response .t seems a little more
>scientific than it was described during the inspection. However it is
>described somewhat differently than during the inspection. I think it would
>be prudent to reinspect if time (and issues) permit. The firm is "requesting
>an inspection" in the first two weeks of February. I think verification of
>this practice, the much needed method validation improvements, and other 483
>corrections would be appropriate (perhaps with a chemist if time permits).
>
>Please let me know what you think.
>
>Thanks.
>

>

>

Printed by _____

Electronic Mail Message

Sensitivity: COMPANY CONFIDENTIAL

Date: 27-Jan-2000 02:11pm
From: _____

Dept: HFD-324 MPN1 265
Tel No: _____

TO: _____
TO: _____

CC: _____)
CC: _____)
CC: _____
Subject: Re: _____ - NDA 20-687 Mifepristone

_____

Could you please Fed _____s response to the address below asap.

2/19 PDUFA date.

FDA/CDER Office of Compliance
Metro Park North I
7520 Standish Place, Room
Rockville, MD 20855
Attention _____

r

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

Printed by [redacted]

Electronic Mail Message

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

TO: [redacted]

CC: [redacted]
Subject: fwd: [redacted] - NDA 20-687 Mifepristone

Comments By [redacted]
Originally To [redacted]
Originally From: [redacted]
Original Date: 1/27/00 8:38 AM
Comments:

[redacted]

Our server is now up...I just received [redacted] evaluation o[redacted] response (FDA483 # 5). I asked him to look at it since they referred to this as an "industry practice". Their explanation is being FedEx'd to your attention...you should receive it tomorrow. Sorry for the confusion....

[redacted]

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

[redacted] esponse to [redacted] question is satisfactory. According to their response, the SOP for their method states that they are actually running standards and then using the average of the results to quantitate the samples. I was under the impression that they were not running standards very regularly and were just re-using the previous standards data. If the SOP is reflective of how the method is run, then the SOP is adequate. We can talk if what I just said is unclear.

Thanks,

[redacted]

>H
>I'm faxing you a further response fro[redacted] e: their reply to 483 Observation
># 5 - the use o[redacted] mple injections for the [redacted] ystems. I know you had some issues with their initial

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

>

Printed by [redacted]

Electronic Mail Message

Sensitivity: COMPANY CONFIDENTIAL

Date: 24-Jan-2000 04:15pm
From: [redacted]

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

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

CC: [redacted]
CC: [redacted]
Subject: NDA 20-687 - et al IR of [redacted]

Folks,

Any response from the subject company to the 483 observations on the subject applications?

If so, please FAX to the attention of [redacted]

Thanx [redacted]

Electronic Mail Message

Date: 1/12/00 11:22:55 AM
From:
To:
Subject: FWD: Re: NDA 20-687

FYI

Electronic Mail Message

Date: 1/12/00 11:21:38 AM
From:
Subject: Re: NDA 20-687

I am still awaiting word on the status of this EI and will let you know as soon as I hear. The CSO who has the assignment has not yet answered my messages and I am having management checking into this.

Electronic Mail Message

Date: 01/11/2000 10:02:47 AM
From:
To:
Subject: Re: consult

On your other item about MIFEPREX, the LNC did find the name unacceptable, but only for look-alike/sound-alike reasons (noted conflict with ____ We did not advise the division about the inappropriate use of USAN syllabels in the trademark. As a general rule (see the draft guidance), objection cannot be made about inclusion of USAN syllables in a trademark except where such use is misleading or inaccurate.

thanx,

Electronic Mail Message

Date: 1/11/00 5:42:11 PM
From: [redacted]
To: [redacted]
Subject: Status update

Please find out ASAP what the status is on [redacted] or NDA 20-687 and [redacted] These are only 2 of 7 final summaries that I am working on simultaneously.

Thanks,
[redacted]

Electronic Mail Message

Date: 1/10/00 4:29:43 PM
From: [redacted]
To: [redacted]
Cc: [redacted]
Subject: NDA 20-687

I left you a voice mail but responding back to by email might be easier. What is the status of the inspection for Dr. Daniel R. Mishell Jr on the above NDA?

Please let me know as soon as possible.

Thanks

Electronic Mail Message

Date: 1/7/00 2:53:17 PM
From:
To:
Subject: NDA 20-687, Population Council

Please contact the district and find out the status of this inspection.
We will need the report ASAP. The goal date has already been exceeded
and we are coming up on the PDUFA date (2/19/00).

Thanks,

Daniel R. Mishell, Jr., M.D.
LAC/USC Medical Center
1240 North Mission Road

Los Angeles, CA 90033
Pending

Electronic Mail Message

Date: 1/6/00 4:09:35 PM
From:
To:
Cc:
Subject: Re: FWD: Re: FWD: Advisory Committee input on Mife US Study

Great. Yes, all we need to do is mention this in the memos to the NDA.

>Here's [redacted] esponse. I don't think we need to do anything further
>except reference the mailing and non-response in our memos. Let us
know
>if you think there is anything else.
>

Electronic Mail Message

Date: 1/6/00 3:03:34 PM
From:
To:
Cc:
Subject: FWD: Re: FWD: Advisory Committee input on Mife US Study

Here's [redacted] response. I don't think we need to do anything further except reference the mailing and non-response in our memos. Let us know if you think there is anything else.

Electronic Mail Message

Date: 1/6/00 3:00:15 PM
From: [redacted]
Subject: Re: FWD: Advisory Committee input on Mife US Study

I have not received any comments from any ACRHD members regarding the mifepristone NEJM publication that was sent to them.

Let me know if there's any more that needs to be done.

[redacted]

Electronic Mail Message

Date: 1/4/00 10:54:47 AM
From: [redacted]
To: [redacted]
Cc: [redacted]
Cc: [redacted]
Subject: FWD: Advisory Committee input on Mife US Study

Hi [redacted]

As far as I am aware, none of the Ad Com folks have provided any feedback to the earlier mailing re: the mifepristone US trial results.

Let us know if you have any other info.

Thanks

[redacted]

Electronic Mail Message

Date: 12/3/99 2:21:33 PM
From: [redacted]
To: [redacted]
Subject: Re: NDA 20-687/Population Council

You are correct: acording to COMIS the inspections have still not been completed. When the sponsor says that 2 of 3 inspections are complete, they are probably saying that the investigators have concluded their on-site audits. The investigators still need to compose their reports and transmit their findings to us before anything is entered in the computer. I would assume that the investigators are still putting their findings together and will send them to us soon.

Do you have particular concerns regarding these audits? Timing, etc?

A question of my own: I noticed that the name of the drug is not mentioned in your monthly report, nor did you name it in your e-mail. Is this deliberate, and should I follow suit?

Let me know if you need any particular information regarding any of these applications.

Electronic Mail Message

Date: 12/3/99 1:16:12 PM
From: [redacted]
To: [redacted]
Cc: [redacted]
Cc: [redacted]
Subject: Re: NDA 20-687/Population Council

[redacted]

Can you inform me of the status of the DSI audits for this application? The sponsor has informed me that 2 of the 3 are complete, but I would like to know from your office because it is not yet entered in the computer.

Thanks,

[redacted]

Electronic Mail Message

Date: 11/30/99 4:44:42 PM
From: [redacted]
To: See Below
Subject: Agenda for meeting on Friday--Pop Council

Hi [redacted]

I'm hoping that at Friday's noon time meeting we can get a pretty good handle on where to go with NDA 20-687. I've cc'd all those invited to the meeting, but imagine that some may not be planning to attend. I hope all will review the following proposed agenda and comment as appropriate!

In terms of agenda, here's a proposal and others may make further suggestions:

1. Welcome, people intro
2. Quick review of NDA history- [redacted] Date submitted, due date, previous action). Do we know status of clinical audits?
3. Clinical- [redacted] eview is complete (I need to reread it, sign and submit to the document room. I'll give a copy [redacted] in advance) recommendation remains consistent with last cycle--safe and effective, approve barring deficiencies for other disciplines.
4. Chemistry--We need copies of the various 483s from the inspections. [redacted] to describe compliance issues if possible and let us know the status of the chemistry review. I understand an information request letter may need to be generated.
5. Pharm/tox- [redacted] I think all is clear here?
6. Biopharm- [redacted] -any issues?
7. Action letter--recommendation?
8. Action letter--Subpart H issues? [redacted] to provide examples. [redacted] has provided a brief list of deficiencies in the present proposed system. I will bring copy to the meeting
8. Labeling discussion--are we ready for this?
9. Action items--call to Pop Council re: chemistry/compliance and distribution system deficiencies. Add any other items raised at status meeting. Further planning for status/labeling meetings, plans for Dec. 9th meeting with Office of Public Affairs.

Let me know if you have additions, modifications, deletions, etc..

See you there!

[redacted]

All DST audits in except Dr Michel's action

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

ɔ) of this section, should be
the Associate Director for
)–5).
eld copy of an application,
ated application, amend-
lements, resubmissions, re-
waivers, and other cor-
about an application and
ated application shall be
applicant's home FDA dis-
except that a foreign appli-
end the field copy to the ap-
ddress identified in para-
) and (a)(2) of this section.
ants shall send applications
correspondence relating to
ered by this part for the
ts listed below to the Divi-
oduct Certification (HFB–
for Biologics Evaluation
h, Food and Drug Adminis-
) Rockville Pike, Bethesda,
xcept applicants shall send
r an opportunity for a hear-
§314.110 or §314.120 on the
whether there are grounds
approval of an application
ctor, Center for Biologics
and Research (HFB–1), at
dress.
dients packaged together
ners intended for the collec-
ssing, or storage of blood
mponents.
ase products.
a volume expanders and hy-
starch for leukapheresis.

Feb. 22, 1985, as amended at 50
y 23, 1985; 55 FR 11581, Mar. 29,
7997, Apr. 28, 1992; 58 FR 47352,
62 FR 43639, Aug. 15, 1997]

uidelines.

'ood and Drug Administra-
es guidelines under §10.90(b)
sons comply with require-
is part.
'enter for Drug Evaluation
ch will maintain and make
ailable a list of guidelines
to the Center's regulations.
tes how a person can obtain
ach guideline. A request for
ne list should be directed to
Executive Secretariat Staff
enter for Drug Evaluation and Research, Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857.

[50 FR 7493, Feb. 22, 1985, as amended at 55 FR 11581, Mar. 29, 1990; 56 FR 3776, Jan. 31, 1991]

Subpart H—Accelerated Approval of New Drugs for Serious or Life-Threatening Illnesses

SOURCE: 57 FR 58958, Dec. 11, 1992, unless otherwise noted.

§314.500 Scope.

This subpart applies to certain new drug products that have been studied for their safety and effectiveness in treating serious or life-threatening illnesses and that provide meaningful therapeutic benefit to patients over existing treatments (e.g., ability to treat patients unresponsive to, or intolerant of, available therapy, or improved patient response over available therapy).

[57 FR 58958, Dec. 11, 1992, as amended at 64 FR 402, Jan. 5, 1999]

EFFECTIVE DATE NOTE: At 64 FR 402, Jan. 5, 1999, §314.500 was amended by removing the phrase "and antibiotic", effective May 20, 1999.

§314.510 Approval based on a surrogate endpoint or on an effect on a clinical endpoint other than survival or irreversible morbidity.

FDA may grant marketing approval for a new drug product on the basis of adequate and well-controlled clinical trials establishing that the drug product has an effect on a surrogate endpoint that is reasonably likely, based on epidemiologic, therapeutic, pathophysiologic, or other evidence, to predict clinical benefit or on the basis of an effect on a clinical endpoint other than survival or irreversible morbidity. Approval under this section will be subject to the requirement that the applicant study the drug further, to verify and describe its clinical benefit, where there is uncertainty as to the relation of the surrogate endpoint to clinical benefit, or of the observed clinical benefit to ultimate outcome. Postmarketing studies would usually be studies already underway. When required to be conducted, such studies must also be adequate and well-controlled. The applicant shall carry out any such studies with due diligence.

§314.520 Approval with restrictions to assure safe use.

(a) If FDA concludes that a drug product shown to be effective can be safely used only if distribution or use is restricted, FDA will require such postmarketing restrictions as are needed to assure safe use of the drug product, such as:

(1) Distribution restricted to certain facilities or physicians with special training or experience; or

(2) Distribution conditioned on the performance of specified medical procedures.

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

§314.530 Withdrawal procedures.

(a) For new drugs approved under §§314.510 and 314.520, FDA may withdraw approval, following a hearing as provided in part 15 of this chapter, as modified by this section, if:

(1) A postmarketing clinical study fails to verify clinical benefit;

(2) The applicant fails to perform the required postmarketing study with due diligence;

(3) Use after marketing demonstrates that postmarketing restrictions are inadequate to assure safe use of the drug product;

(4) The applicant fails to adhere to the postmarketing restrictions agreed upon;

(5) The promotional materials are false or misleading; or

(6) Other evidence demonstrates that the drug product is not shown to be safe or effective under its conditions of use.

(b) *Notice of opportunity for a hearing.* The Director of the Center for Drug Evaluation and Research will give the applicant notice of an opportunity for a hearing on the Center's proposal to withdraw the approval of an application approved under §314.510 or §314.520. The notice, which will ordinarily be a letter, will state generally the reasons for the action and the proposed grounds for the order.

(c) *Submission of data and information.* (1) If the applicant fails to file a written request for a hearing within 15 days of receipt of the notice, the applicant waives the opportunity for a hearing.

(2) If the applicant files a timely request for a hearing, the agency will publish a notice of hearing in the FEDERAL REGISTER in accordance with §§ 12.32(e) and 15.20 of this chapter.

(3) An applicant who requests a hearing under this section must, within 30 days of receipt of the notice of opportunity for a hearing, submit the data and information upon which the applicant intends to rely at the hearing.

(d) *Separation of functions.* Separation of functions (as specified in § 10.55 of this chapter) will not apply at any point in withdrawal proceedings under this section.

(e) *Procedures for hearings.* Hearings held under this section will be conducted in accordance with the provisions of part 15 of this chapter, with the following modifications:

(1) An advisory committee duly constituted under part 14 of this chapter will be present at the hearing. The committee will be asked to review the issues involved and to provide advice and recommendations to the Commissioner of Food and Drugs.

(2) The presiding officer, the advisory committee members, up to three representatives of the applicant, and up to three representatives of the Center may question any person during or at the conclusion of the person's presentation. No other person attending the hearing may question a person making a presentation. The presiding officer may, as a matter of discretion, permit questions to be submitted to the presiding officer for response by a person making a presentation.

(f) *Judicial review.* The Commissioner's decision constitutes final agency action from which the applicant may petition for judicial review. Before requesting an order from a court for a stay of action pending review, an applicant must first submit a petition for a stay of action under § 10.35 of this chapter.

[57 FR 58958, Dec. 11, 1992, as amended at 64 FR 402, Jan. 5, 1999]

EFFECTIVE DATE NOTE: At 64 FR 402, Jan. 5, 1999, § 314.530 was amended by removing the phrase "and antibiotics" from paragraph (a), effective May 20, 1999.

§ 314.540 Postmarketing safety reporting.

Drug products approved under this program are subject to the postmarketing recordkeeping and safety reporting applicable to all approved drug products, as provided in §§ 314.80 and 314.81.

§ 314.550 Promotional materials.

For drug products being considered for approval under this subpart, unless otherwise informed by the agency, applicants must 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 or publication within 120 days following marketing approval. After 120 days following marketing approval, unless otherwise informed by the agency, the applicant must submit promotional materials at least 30 days prior to the intended time of initial dissemination of the labeling or initial publication of the advertisement.

§ 314.560 Termination of requirements.

If FDA determines after approval that the requirements established in § 314.520, § 314.530, or § 314.550 are no longer necessary for the safe and effective use of a drug product, it will so notify the applicant. Ordinarily, for drug products approved under § 314.510, these requirements will no longer apply when FDA determines that the required postmarketing study verifies and describes the drug product's clinical benefit and the drug product would be appropriate for approval under traditional procedures. For drug products approved under § 314.520, the restrictions would no longer apply when FDA determines that safe use of the drug product can be assured through appropriate labeling. FDA also retains the discretion to remove specific postapproval requirements upon review of a petition submitted by the sponsor in accordance with § 10.30.

Food and Drug Ad

PART 316—O

Subpart A—Ge

Subpart B—Written I Investigations

Subpart C—Desig

Subpart D—Or A

Subpart E— Inv

Subpart F—Av

Printed by

Electronic Mail Message

Sensitivity: COMPANY CONFIDENTIAL

Date: 05-Oct-1999 05:48pm
From:
Dept: HFD-580 PKLN 17B45
Tel No:

TO: See Below
Subject: followup re. Subpart H and restricted distribution

I have looked at the regs for the Subpart H question and they read quite clearly in regards to restriticted distribution. (I have copies for all; let me know if you want them before the next meeting.)

314.520 Approval with restrictions to assure safe use.

(a) If FDA concludes that a drug product shown to be effective can be safely used only if distribution of use is restricted, the FDA will require such postmarketing restrictions as are needed to assure safe use of the drug product, such as:

1) distribution restricted to certain facilities or physicians with special training or experience, or

2) distribution conditioned on the performance of specified medical procedures.

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

314.560 Termination of requirements.

If FDA determines after approval that the requirements established in 314.20 are no longer necessary for th esafe and effective use of a drug product, it will so notify the applicant.

For drug products approved under 314.520, the restrictions would no lonfer apply when FDA determines that safe use of the drug product can be assured through appropriate labeling. FDA also retains the descretion to remove specific post-approval requirements upon review of a petition submitted by the sponsor in accordance with 10.30.

The regs in this case are quite straightforward. We and the sponsor need to determine what those restrictions might be.

Hope this clarifies some. We can discuss more at the next meeting.

Distribution:

TO:
TO:
TO:
TO:
TO

CC:

Printed by [redacted]

Electronic Mail Message

Sensitivity: COMPANY CONFIDENTIAL

Date: 30-Nov-1999 04:44pm
From: [redacted]

Dept: HFD-580 PKLN 17B45
Tel No: [redacted]

TO: See Below
Subject: Agenda for meeting on Friday--Pop Council

[redacted]

I'm hoping that at Friday's noon time meeting we can get a pretty good handle on where to go with NDA 20-687. I've cc'd all those invited to the meeting, but imagine that some may not be planning to attend. I hope all will review the following proposed agenda and comment as appropriate!

In terms of agenda, here's a proposal and others may make further suggestions:

1. Welcome, people intro
2. Quick review of NDA history[redacted] (Date submitted, due date, previous action). Do we know status of clinical audits?
3. Clinical[redacted] review is complete (I need to reread it, sign and submit to the document room. I'll give a copy to[redacted]n advance) recommendation remains consistent with last cycle--safe and effective, approve barring deficiencies for other disciplines.
4. Chemistry--We need copies of the various 483s from the inspections. [redacted] to describe compliance issues if possible and let us know the status of the chemistry review. I understand an information request letter may need to be generated.
5. Pharm/tox--[redacted] I think all is clear here?
6. Biopharm[redacted] -any issues?
7. Action letter--recommendation?
8. Action letter--Subpart H issues?[redacted] to provide examples. [redacted] has provided a brief list of deficiencies in the present proposed system. I will bring copy to the meeting
8. Labeling discussion--are we ready for this?
9. Action items--call to Pop Council re: chemistry/compliance and distribution system deficiencies. Add any other items raised at status meeting. Further planning for status/labeling meetings, plans for Dec. 9th meeting with Office of Public Affairs.

Let me know if you have additions, modifications, deletions, etc..

See you there!

[redacted]

Distribution:

TO:

CC
CC
C
C
C
CC:
CC:
CC:
CC:
CC
C
C

CC:
CC:
CC:
CC:

Electronic Mail Message

Date: 11/24/99 11:18:57 AM
From: [redacted]
To: [redacted]
Subject: Proprietary name consult #99-085

Hello,

This is to acknowlege receipt of consult for NDA 20-687.

~~We usually~~ need 60 days to do a consult, but I have noted your December 20th date.

Thanks.

X

11/26/99 - talked with [redacted] and we revised date to 01/13/00

11/24/99 - sent e-mail requesting - no answer on phone

no labeling (carton/container) available

Electronic Mail Message

Date: 11/3/99 9:29:51 AM
From: [redacted]
To: [redacted]
Cc: [redacted]
Subject: Re: Cover letter - RU-486 publication

Hi [redacted]

Thanks for the chance to look at your draft letter. I think it is great! I'd only make one modification--removal of the comma after the word "meeting" in the middle of the first paragraph.

Thanks for your work on this!

[redacted]

Electronic Mail Message

Date: 11/1/99 8:42:22 AM
From:
To:
Cc:
Subject: Cover letter - mifepristone package

I've attached the cover I've drafted for the mifepristone publication. Please let me know if you have any comments; we'll get out this afternoon.

Electronic Mail Message

Date: 10/27/99 3:03:39 PM
From: [redacted]
To: [redacted]
Cc:
Subject: RU-486 package

Hi [redacted]

I just spoke with [redacted] regarding the RU-486 information to be sent out to the 1996 Advisory Committee members. My understanding is that now the decision has been made to send out the the publication for the clinical study rather than the clinical study report itself. If this is the case, could I please get from you a cover letter to attach to the publication. I'm not quite sure what to say to the "members" since I discussed with them that we would be sending the final report.

If you want to e:mail something to me that would be great.

Thanks

[redacted]

Electronic Mail Message

Date: 10/25/99 10:04:42 PM
From: [redacted]
To: diana.b.petitti@kp.org
Cc: [redacted]
Subject: Transcripts from July, 1996 FDA Advisory Committee for Reprod. Health Dr

Dr. Petitti,

I am the Executive Secretary for the Advisory Committee for Reproductive Health Drugs within the Center for Drugs Evaluation and Research at the FDA. As you will recall, in July of 1996 while you were a member of the committee, the committee reviewed and gave advice to the Agency on the New Drug Application for the product, RU-486. The Agency is now coming to closure on the application and we have realized that at the July, 1996 we had committed to providing the final U.S. clincical study report (when available) to the committee members. That final report is now available and therefore with this e:mail I am asking if you would be interested in receiving a copy of the final report?

Would you please call or e:mail me and let me know what if you would like this report sent to you. Our plan is to send the report to the former members for informational purposes. However, if you would care to provide comments on the report to the Reproductive Health Drugs Division I would need to know that. Because we are attempting to bring closure to the application, we would need comments within a very short turnaround time and we would need to screen for conflict-of-interest.

Thank you in advance.

[redacted]

Printed by [redacted]

Electronic Mail Message

Sensitivity: COMPANY CONFIDENTIAL

Date: [redacted]-Oct-1999 11:05am
From: [redacted]

Dept: HFD-005 WOC2 6029
Tel No: [redacted]

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

CC: [redacted]
Subject: Re: FWD: draft agenda for the RU486 meeting today.

>I noticed you weren't cc'd.
> [redacted]

Whoops, sorry I didn't copy you. Here is an additional document I just sent

Printed by [redacted]

Electronic Mail Message

Sensitivity: COMPANY CONFIDENTIAL

Date: 23-Sep-1999 11:10am
From: [redacted]
Dept: HFD-005 WOC2 6027
Tel No: [redacted]

TO: See Below
Subject: RU486 and issue of redaction of names in reviews and names of drug suppliers on 483s

Decision Meeting:

DATE: Friday, Oct. 8, 1999

TIME: 1:00 PM to 2:30 PM

LOCATION: PKLN, 13-B45

Distribution:

TO:
TO:
TO:
TO:
TO:
TO
TO:
TO:
TO:

CC:
CC
CC.