Teleconference Minutes

Date: April 25, 2000 **Time:** 10:44 – 11:00 AM **Location:** Parklawn; 17B-45

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

Indication: induction of abortion

Sponsor: Population Council

Type of Meeting: Guidance

FDA Attendees;

Division of New Drug Chemistry II (DNDCII) @ Division of Reproductive and Urologic Drug Products (DRUDP; HFD-580)

Regulatory Project Manager, DRUDP (HFD-580)

External Attendees:

DANCO Group (CRO for Population Council)

Meeting Objective: To communicate information to the sponsor regarding their response to three of the chemistry issues raised in the approvable letter.

Decisions made:

Drug Substance:

- Item #7 regarding
  - the sponsor indicates in their response that they are trying to generate this information but are having difficulties
  - the Division would like the sponsor to amend their application to state that they agree to a Phase 4 commitment, that within one year post approval of this product, they will commit to submitting data from these tests

Drug Product:

- Item #2 regarding expiry date
  - the Division is not able to use the Roussel information for extending the expiry date because the Roussel conditions were not well controlled
  - the Division needs to establish a link to the clinical batches; if the sponsor can make that link to the clinical batches, then an month expiry can be granted provided the data are supportive
- Item #3 regarding stability commitment
  - the stability commitment is used to extend the expiry date
  - the sponsor can change the expiry date in the annual report, if they used the data from the first three post-approval batches
  - if the sponsor is using the pre-approval batches to extend the expiry date, it would be considered a prior approval supplement and must be submitted post-approval

Action Items:

- fax meeting minutes to the sponsor within 30 days

/S/

Minutes

/S/ 4/28/00

Concurrence, Chair

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ON ORIGINAL

Teleconference Minutes

MAR 6 2000

Date: February 11, 2000 **Time:** 1:15 – 2:00 PM **Location:** Parklawn; 17B-43

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

Indication: induction of abortion

Sponsor: Population Council

Type of Meeting: Guidance

Meeting Chair:

External Lead

Meeting Recorder:

FDA Attendees:

Office of Drug Evaluation II (ODEII; HFD-102)
Office of Drug Evaluation III (ODEIII; HFD-103)
ODEIII (HFD-103)
Division of Reproductive and Urologic Drug Products (DRUDP; HFD-580)
DRUDP (HFD-580)
Division of New Drug Chemistry II (DNDCII) @ DRUDP (HFD-580)
DNDCII @ DRUDP (HFD-580)
Division of Drug Marketing, Advertising and Communications (DDMAC; HFD-040)
Project Management Staff, DRUDP (HFD-580)
Regulatory Project Manager, DRUDP (HFD-580)

External Attendees:

– The Danco Group
Fred Schmidt – Population Council
The Danco Group
The Danco Group

Meeting Objective: To discuss the approaching goal date and the planned action for this application.

Decisions made:

- The Division will be issuing an approvable letter on February 18, 2000
- The approvable letter will outline the outstanding issues
  - Outstanding chemistry issues
  - Inspection of drug substance manufacturing site
  - Physician and Patient Labeling

- Conditions related to Subpart H approval, such as distribution of the drug, if and when this product is approved

- Mifeprex is not an acceptable tradename, but the tradename [redacted] was found to be acceptable by OPDRA
- If or when Danco issues a press release, they will provide a copy to DDMAC and DRUDP

Action Items:

- Fax meeting minutes to sponsor within 30 days

/S/

Minutes Preparer

/S/

Concurrence, Chair

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[redacted]

FEB 8 2000

Meeting Minutes

Date: January 18, 2000 **Time:** 4:30-5:45 PM **Location:** Parklawn; 17B-43

NDA 20-687 **Drug:** mifepristone oral tablets 200 mg

Indication: Induction of abortion

Sponsor: Population Council

Type of Meeting: CMC Guidance

Meeting Chair: [redacted]

External Lead: [redacted]

Meeting Recorder: [redacted]

FDA Attendees:

[redacted], Office of Drug Evaluation III (ODEII; HFD-103)
[redacted], Office of Drug Evaluation II (ODEIII; HFD-102)
[redacted], Division of Reproductive and Urologic Drug Products (DRUDP; HFD-580)
[redacted], Division of New Drug Chemistry II (DNDCII; HFD-820)
[redacted], DNDCII @ DRUDP (HFD-580)
[redacted], DNDCII @ DRUDP (HFD-580)
[redacted], Project Management Staff (DRUDP; HFD-580)
[redacted], Regulatory Project Manager (DRUDP; HFD-580)

External Attendees:

Sandra Arnold – Vice President – Corporate Affairs, Population Council
[redacted], President and Chief Executive Officer, The Danco Group
[redacted], Vice President Manufacturing, The Danco Group
[redacted]

Meeting Objective: To discuss the Information Request (IR) letter sent to the sponsor on December 14, 1999.

Decisions made:
Discussion Points from the IR letter (December 14, 1999)
Drug Substance (Questions):

#4 Sufficient information has not been provided to justify the qualification of [redacted] as the starting material. The following information should be provided:

a. Justify that the [redacted] starting material is commercially available in production quantities by providing representative copies of Certificates of Analysis from each commercial source, with the typical scale of manufacture indicated for each supplier.
b. Provide copies of the literature references describing the synthetic processes of the proposed starting materials. In addition, literature references describing the use of the proposed starting materials for other synthetic methodologies should be provided. The literature references should be translated if they are not written in English.

Response:
- the Division needs evidence to establish that [redacted] is commercially available
- the concern for the Division is that there could be unknown impurities introduced when this product is synthesized, and could be carried on through the manufacturing process
- the sponsor stated that mifepristone is not the only product synthesized using [redacted]
- the Division will consider [redacted] as a starting intermediate
- the sponsor will submit the information on what other products are being made using [redacted]

#5 Please explain and provide data to support the proposed [redacted] during the following steps in the synthetic process for mifepristone:

a. preparation of the [redacted]
b. preparation of [redacted]
c. preparation of [redacted]

#7 It is recommended that a [redacted] method be developed for [redacted] and submitted along with appropriate proposed specifications.

#17 It is recommended that a [redacted] assay method be developed for [redacted] and submitted along with appropriate proposed specifications.

Response to #5, 7, and 17
- the sponsor will provide a scientific rationale and literature references, in English, to assure clarity of these intermediates

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#8 For consideration of using the [redacted] as the starting material for the synthesis of [redacted] please provide the following:

d. Information about its commercial availability,
e. Literature references describing its structural characteristics,
f. Literature references describing its synthesis, and
g. Literature references describing its use in other synthetic methodologies.

Response:

- the sponsor indicated that they will be supporting the use of [redacted] as the starting material

#19 You have responded in Amendment 029, dated June 14, 1999, that the [redacted] is an adequate release test for mifepristone with regard to its [redacted]

#10 It is recommended that the [redacted] of mifepristone be monitored during stability testing.

Response to #19 and #10

- the sponsor will submit the information regarding the [redacted] in their response

#25 Please provide data and the methods used demonstrating that the following potential synthesis impurities were not produced in the manufacturing process used by Shanghai HuaLian. This should also include any [redacted] Potential impurities are: [redacted]

Response:

- the methods need to demonstrate that these impurities are not present; this also validates the method
- the sponsor will provide information regarding the method used

#11 The stability protocol needs to be revised as follows:

a. The stability samples are stored in ambient light rather than in the dark to reflect real-life conditions.
b. The term for the extension of the expiration date is as follows: Extend the expiration dating based upon full shelf-life data obtained from the three post-approval production batches covering the entire extended shelf-life and tested according to the approved stability protocol.

#4 It is recommended that a specification for hardness be included.

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#31 In the forced degradation studies please clarify the following:

a. If the samples of drug substance are soluble in 0.1 N NaOH and 35% H_2O_2.
b. If the "other degradants" have been identified in the forced degradation studies.
c. Although the results show that the drug substance has degraded there is an absence of other peaks in the chromatograms.
d. It is unclear where the [redacted]

#33 The proposed shelf-life of [redacted] for the drug substance is not acceptable. Based on the available stability data, an 18-month re-test period is granted.

Response to #11, 4, 31, and 33:

- The sponsor will initiate a specification for tablet "hardness"
- The sponsor agrees that the stability protocol will not include dark room. Sponsor clarified that the tablets are packaged in opaque material, but can be stored on shelving in normally lit rooms.
- An expiration date is not granted for a drug substance; the FDA comment only means that the drug substance has to be retested after certain storage periods
- The sponsor will conduct another forced degradation study

Expiry on the Drug Product:

- expiration dating is determined with real-time data and supportive data from the product manufactured by the sponsor
- 6-month accelerated data and 6-month realtime data would support an expiry date of 12 or up to [redacted] months, if other appropriate supporting data are available.

Unresolved decisions: None

Action Items:

- the MaPP describing the types of resubmissions needed in response to a possible second "approvable" action will be faxed to the sponsor
- fax meeting minutes to the sponsor within 30 days
- outstanding issues for sponsor to submit
  - Response to IR letter (by 1/28/00)
  - Distribution Plan (1/24/00)
  - Primary and secondary Draft Packaging Labels (1/28/00)
  - Environmental Assessment for China (1/21/00)
  - Drug Substance: 1-year stability data (by 1/28/00)
  - Drug Product: 6-month real and accelerated data (1/21/00)

/S/
Minutes Preparer

/S/ 2/11/00
Concurrence, Chair

Teleconference Minutes

Date: December 3, 1999 **Time:** 11:30-12:00 PM **Location:** Parklawn; 17B-45

NDA 20-687 **Drug:** mifepristone **Indication:** Induction of abortion

Sponsor: Population Council

Type of Meeting: Guidance

Meeting Chair:

External Lead: Fred Schmidt

Meeting Recorder:

FDA Attendees:

Division of Reproductive and Urologic Drug Products (DRUDP; HFD-580)

Project Management Staff, DRUDP (HFD-580)

Regulatory Project Manager, DRUDP (HFD-580)

External Attendees:
Fred Schmidt, Population Council
NKO
, DANKO

Meeting Objective: To discuss the current status of the application.

Decisions made:

- Informed the sponsor that the user fee date is February 19, 2000; this clarification was made because of recent press releases announcing "approval by the end of the year"
- Discussed the 483s issued by the district offices for the Chinese facility; sponsor informed the Division of the following responses to the 483s:
  - November 15, 1999
  - November 22, 1999
  - China facility - December 2, 1999
- The sponsor was informed that the inspector for the Chinese facility is recommending that the facility be reinspected before an approval can be issued for this site
- An Information Request letter is forthcoming with Chemistry and Biopharmaceutics questions
- If and when this product is approved, it will likely be approved under Subpart H approval process (restricted distribution)

Unresolved decisions: None

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Action Items:

- Fax meeting minutes to sponsor within 30 days
- Fax Information Request letter to sponsor
- Sponsor to provide further information about restricted distribution plan

/S/
Minutes Preparer

/S/ 12/7/05
Concurrence, Chair

APPEARS THIS WAY
ON ORIGINAL

Meeting Minutes

Date: April 9, 1999 **Time:** 10:00 AM - 11:30 AM **Location:** Parklawn C/R 17B-43

NDA 20-687 **Drug Name:** mifepristone tablets

External Participant: The Population Council

Type of Meeting: CMC status update

Meeting Chair: [redacted]

External Participant Lead: [redacted]

Meeting Recorder: [redacted]

FDA Attendees:

[redacted] Division of Reproductive and Urologic Drug Products (DRUDP;HFD-580)
[redacted] DRUDP (HFD-580)
[redacted] Office of New Drug Chemistry
[redacted] Division of New Drug Chemistry II (DNDC II) @ DRUDP (HFD-580)
[redacted] DNDCII @ DRUDP (HFD-580)
[redacted] DRUDP (HFD-580)
[redacted] Project Manager, DRUDP (HFD-580)

External Constituents:
Population Council
Ms. Sandra Arnold - Vice-President

Danco Laboratories/The NeoGen Group

[redacted]

Meeting Objectives:
To discuss the current status of chemistry, manufacturing and controls (CMC) development by the sponsor and anticipated dates for submission of a complete response to the approvable letter issued on September 18, 1996

Discussion Points:

- Drug Substance
  - the drug substance is manufactured at a Chinese site
  - three validation batches ([redacted] per batch) were placed on stability earlier this year
  - according to the sponsor, the drug substance has been tested and meets all of the Rousell Uclaf (RU) specifications

- the sponsor should also perform full physical and chemical characterization of their drug substance including [redacted] etc.
- the sponsor expects the Chinese site to be ready for inspection in July
- the Division can request an early site inspection; however, because the Division does not control the precise timing of inspection site visits; the sponsor takes the risk that the inspection may be scheduled by FDA before the site is truly ready
- the sponsor will reconsider whether they wish the Division to request an early inspection of the Chinese manufacturing site and will provide their decision by the end of April

- Drug Product
  - the tableting and packaging will be carried out at a [redacted]
  - the tableter is currently setting up the equipment in preparation for their first production run of tablets
  - the equipment to be used by the tableter is the same type of equipment that was used by RU
  - a demonstration batch of tablets ([redacted] batch) is planned to be produced on May 7, 1999
  - a [redacted] is located close to the tableter and will carry out all of the laboratory testing

- Submission issues
  - the sponsor intends to submit a complete response to the approvable letter in June or July 1999
  - the initial submission is expected to contain 3 months of stability data from 3 batches of the drug substance and 1 month of stability data from the demonstration batch of drug product
  - the sponsor intends to amend their application throughout the review period with additional stability data
  - the amount of stability data with justiciation for the amount proposed to be submitted initially will be sufficient for filing
  - the review time for a complete response is 6 months, no extensions are granted
  - if stability data were to be submitted close to the action date, it may not be reviewed
  - the expiration date will be determined by the amount of data submitted and reviewed at the time of the NDA action
  - responses to the approvable letter may be submitted as they are prepared, however, the review clock will not be started until the complete response is received
  - Division reviewers may be able to review early submissions before the review clock is initiated depending on workload, however they are not obligated to initiate the review until the complete information is received

- the sponsor should clearly mark the last submission as being the complete response to the approvable letter and reference any other earlier submissions that pertain to the response
- the sponsor will submit draft labeling with the complete response and compare it with the labeling submitted with the original application's
- the sponsor does not intend to pursue the [redacted] mifepristone dosage at this time; if this application is approved it may be amended through an efficacy supplement for this [redacted]
- the sponsor is currently working on registration of the tradename Mifeprex and intends to submit this and an alternative tradename for consideration to the Labeling and Nomenclature Committee (LNC)
- the Division will forward the proposed tradenames to the LNC but expects that there may be difficulties with the proposed tradename because it is too similar to the established name; the sponsor is encouraged to consider alternative tradenames
- the sponsor will fax the additional proposed tradenames as soon as possible
- the sponsor does not intend to make any public statements regarding submission of the complete response, should this decision change the sponsor will notify the Division before making any such statements
- the sponsor is concerned about public release of information concerning the manufacturers; although the names of the manufacturers are not releasable during review, the Division cannot control this information after an approval action; the sponsor intends to initiate discussion at the Center level about maintaining confidentiality after approval

Decisions Reached:

- the sponsor expects to submit a complete response to the approvable letter by June or July, some of the information may be submitted earlier than June
- the sponsor will fax a copy of their proposed tradenames for consideration by the LNC
- requests for inspection of the Chinese manufacturing site may be made prior to receipt of the complete response, the sponsor will discuss this and inform the Division of their decision by the end of April
- Division reviewers may initiate review before a complete response is received depending on workload; the Division is under no obligation to review material, however, until before the complete response is received
- the sponsor will ensure that the final submission of information completing their response to the approvable letter is clearly marked as such and ensure that there is adequate cross referencing of the earlier submissions for the reviewers to find specific information
- the 3 months of stability data for the drug substance and 1 month stability data for the drug product is sufficient for filing, however, the expiration date of the product will be based on the stability data received and reviewed by the Division
- the review clock for a complete response is 6 months, any data submitted (i.e., stability data) just prior to that action date may not be reviewed in this review cycle, no extensions of the clock are granted for a review of a complete response

Unresolved Issues: none

Action Items: see decisions reached

/S/
Minutes Preparer 4/20/99

/S/
Concurrence, Chair 4/27/99

cc:
Orig.
HFD-580
MEETING ATTENDEES
HFD-580 4.9.99/n20687.mm2
Concurrence 4.14.99 4.14.99 4.15.99 4.15.99 4.19.99
4.19.99

MEETING MINUTES

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Meeting Minutes

Date: November 2, 1998 **Time:** 2:00 PM - 3:30 PM **Location:** Parklawn C/R 17B-43

NDA 20-687 **Drug Name:** mifepristone

External Participant: The Population Council

Type of Meeting: CMC guidance

Meeting Chair: [redacted]

External Participant Lead: Sandra Arnold

Meeting Recorder: [redacted]

FDA Attendees:

[redacted] Division of Reproductive and Urologic Drug Products (DRUDP;HFD-580)

[redacted] Division of New Drug Chemistry II (DNDC II) @ DRUDP (HFD-580)

[redacted] DNDCII @ DRUDP (HFD-580)

[redacted] Project Manager, DRUDP (HFD-580)

External Constituents:

[redacted]

Ms. Sandra Arnold - Vice-President

Patricia C. Vaughn, Esq. - Legal Councel

Frederick Schmidt, Ph.D. - Scientist

[redacted]

[redacted]

Meeting Objectives:

To discuss the sponsor's CMC plans and the deficiencies identified in the partial response submitted September 1997.

Discussion Points:

- Status Report - Sponsor Presentation
  - two manufacturers have been identified and contracted for the drug substance
  - one manufacturer is located in [redacted] the other in China
  - both manufacturers will have validation batches on stability by the end of December 1998

- there are minor manufacturing differences between the two manufacturers
- neither manufacturer has been inspected by the FDA for any product or substance
- two potential tableters have been identified, both in
- one tableter is located in and has had previous experience with
- the second tableter is located in and has had previous experience with
- one of the two tableters will be contracted to tablet the product within the next few months
- once a tableter has been contracted the tableter will be provided with bulk drug substance made by Gedeon Richter for practice tableting runs, these tablets will not be used for compassionate use requests
- the first three validation batches of tablets are expected to be submitted to the Division in March 1999

- Response to approvable letter and Stability

  - the sponsor plans to submit portions of the CMC response as they become available
  - the sponsor must submit a complete response to the deficiencies detailed in the approvable letter before the user fee clock can be started; the sponsor must also declare that they have submitted all required information once the last piece of information is submitted
  - the sponsor must submit stability data from the current manufactures, they may not rely on stability data generated by former manufacturers of the drug product or drug substance
  - current ICH requirements for stability are 6 months accelerated and 12 months real time data to consider a 2 year expiration date

- September 1997 partial response

  - GR has provided the Population Council with of bulk drug substance
  - the Population Council intends to tablet the bulk drug substance made by GR to be provided for compassionate use
  - the Population Council requires a complete deficiency list from the September 1997 CMC submission including a request for a site inspection in order to go forward with their compassionate use plans for the GR bulk drug substance

- Manufacture of bulk drug substance

  - drug substance will be manufactured according to Rousell Uclaf's method
  - the starting material will be
  - can be obtained both in Europe and China, the manufacturer will obtain their supply from China
  - data on multiple batches of the starting material should be submitted in order to ensure that there is consistency between batches

- the drug substance manufacturers will ensure that all specifications of their product are in agreement with those of RU (i.e., structure, particle size, impurity profile, stability, polymorphic structure etc)
- the manufacturers should provide [redacted] of their drug substances to identify and quantify their impurity profile
- the biggest change between the RU method and method to be utilized are changes in solvent which are not expected to cause any difference in drug substance profile
- the manufacturer must be able to demonstrate that the tablets manufactured are equivalent to those made by RU, guidelines for these *in vitro* tests are found in the SUPAC guidance document
- bioequivalence testing may also be required, however, this can not be determined until comparative dissolution data has been submitted
- the sponsor requests that inspections be scheduled as soon as the manufacturers are ready for inspection

- Discussion of Dose Changes - mifepristone and misoprostol

[redacted]

Decisions Reached:

- the manufacturing plan for the bulk drug substance appears acceptable
- a complete response to the deficiency letter should include sufficient stability data to support the expiration date the sponsor intends to request
- although the Division is under no obligation to review a partial submission to an approvable letter, the Chemistry reviewer will attempt to complete the review of the September 1997 partial response submission by the end of December 1998. A detailed letter of deficiencies noted in the review will be issued based upon that review
- manufacturing site inspections can be requested before a complete response is submitted, however timing of inspections cannot be guaranteed. The sponsor should provide location and contact numbers for the inspections once they are ready to have the sites inspected

- it is unclear at this time if the sponsor can change the clinical parameters for the current NDA, the Division will discuss this request with the [redacted] The sponsor may be required to submit another NDA for these clinical changes

Unresolved Issues: how to submit clinical changes to the current NDA application

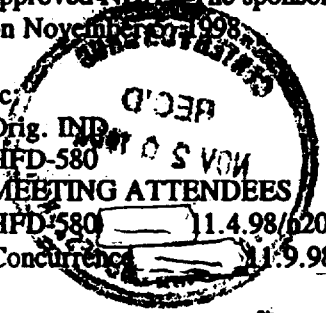
Action Items:

Item	person responsible	time frame
1. Completion of CMC partial resp. Review	[redacted]	Possibly by 1/99
2. Issue deficiency letter based on (1)		2 wks after review
3. Report results of clin. data change discussion		2 weeks

/S/ 11/19/98
Minutes Preparer

/S/ 11/19/98
Concurrence, Chair

Post-meeting note: [redacted] spoke with [redacted] regarding submission of new clinical data. The sponsor may submit the clinical data as a new NDA (referring to NDA [redacted] for non-clinical information) or they may submit the CMC data required for approval of the existing NDA, receive approval for that NDA and then submit the clinical data as an efficacy supplement to the approved NDA. The sponsor was informed of this decision by [redacted] in a telephone conversation on November [redacted] 1998.



cc:
Orig. IND
HFD-580
MEETING ATTENDEES
HFD-580 [redacted] 11.4.98/n20874.mm
Concurrence [redacted] 11.9.98, [redacted] 11.6.98, [redacted] 11.9.98

MEETING MINUTES:

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Meeting Minutes

Date: March 16, 1998 **Time:** 2:00 PM - 3:30 PM **Location:** Parklawn 17B-43

NDA 20-687 **Drug Name:** mifepristone tablets

External Participant: The Population Council

Type of Meeting: Regulatory Guidance

Meeting Chair:

External Participant Lead: Ms. Sandra Arnold

Meeting Recorder:

FDA Attendees:

Division of Reproductive and Urologic Drug Products (DRUDP;HFD-580)

, Division of New Drug Chemistry II (DNDC II) @ DRUDP (HFD-580)

DNDCII @ DRUDP (HFD-580)

Office of New Drug Chemistry (ONDC; HFD-800)

(HFD-580)

Consumer Safety Officer, DRUDP (HFD-580)

External Constituents:

Ms. Sandra Arnold - Vice-President
Patricia C. Vaughn, Esq. - Legal Councel
Frederick Schmidt, Ph.D. - Scientist

Meeting Objectives:
To discuss a proposal for responding to the Chemistry, Manufacturing, and Controls (CMC) issues delineated in the Approvable (AE) letter dated September 18, 1996.

Discussion Points:

- CMC update
  - two potential manufacturers ('A' & 'B') of bulk drug substance have been identified
  - a meeting request will be submitted for a CMC discussion with manufacturer 'A' in May

- manufacturer 'A' will initiate small scale production in their U.S. laboratory to ensure process and product consistency
- commercialized batches will be produced in an off-shore manufacturing facility owned by manufacturer 'A'
- the sponsor requests the Division schedule inspections for the fourth quarter of 1998 although they do not expect a complete CMC response to the AE letter before the first quarter of 1999
- tableting will be performed by a different manufacturer also in an off-shore facility

- Reference Standards

  - the sponsor intends to demonstrate comparability of Roussel Uclaf (RU) bulk drug substance and Gedeon Richter (GR) bulk drug substance
  - the sponsor intends to use the GR specifications as the reference for future manufacture of the drug substance
  - information regarding both GR and RU's bulk drug substance was submitted in September 1997
  - although the September submission is not a complete response to our approvable letter the Division has agreed to review the information pertaining to equivalency of standards by the end of May
  - although review of the September submission is not complete, several deficiencies have already been identified; some of these relate to the demonstration equivalence between GR and RU's drug substance lots
  - upon completion of the review those deficiencies and any others identified with regard to equivalency will be provided in a detailed information request letter
  - minor changes in process between RU and GR may be acceptable
  - the sponsor is reminded that the AE letter requested some RU specifications be tightened
  - RU used a starting material of [redacted] this is commercially available and will be fully characterized before use as a starting material by manufacturer 'A'

- Compassionate Use

  - the sponsor has depleted their supply of mifepristone tablets
  - guidance regarding the acceptability of tableting the GR bulk substance to distribute for compassionate use purposes (other than early termination of pregnancy) was requested
  - tableting may be acceptable provided the GU and RU bulk substances are found to be equivalent, without changes in component and composition of the tablets
  - the sponsor must also demonstrate equivalent dissolution profiles of the two tablets

- Additional Dosage Information

  - the sponsor is aware of an active IND in which [redacted]

- the sponsor is concerned that with a labeled dose of 600 mg (in three tablets) for their product, physicians may use only one tablet
- should this occur, the proposed distribution controls may not be effective
- this situation is currently the case in Great Britain
- the sponsor requests guidance regarding amending their dosage and administration instructions with this new information

- **Decisions Reached**

  - the Division will review the September CMC submission with respect to equivalency of bulk drug substance issues
  - upon completion of that review a detailed letter of deficiencies will be issued

  - conceptually, it may be acceptable for a manufacturer to have a starting material of commercially available [redacted] provided each batch is tested and well characterized to ensure appropriate chiral centers

  - manufacturing site inspections are not normally granted until a complete response is submitted
  - the Division will consult with the Office of Drug Evaluation II and others regarding an early site inspection

  - if the sponsor can demonstrate equivalence between the RU and GR bulk drug substances, they may tablet the substance and issue for compassionate use provided there is no change in composition or components of the tablets and the sponsor can demonstrate equivalence of tablet dissolution with the RU tablets

  - the sponsor has three routes to make a change in dosage; they may:

    - obtain right of reference to both the clinical and CMC data from the IND investigator and submit that to the Division for consideration
    - obtain information from a literature search of clinical trials in which this alternative dosage is described and submit that to the Division for consideration
    - perform their own clinical trials
    - if relying on trials performed by other investigators, the sponsor must show equivalency of drug product used in those trials

Unresolved Issues: none

Action Items: see Decisions Reached

/S/
Minutes Preparer 3/23/98

/S/ 3/23/98
Concurrence, Chair

ATTACHMENT
sponsor overheads

DF

Meeting Minutes

Date: August 11, 1997 **Time:** 3:00 PM - 4:00 PM **Location:** C/R 17B-43

NDA 20-687 **Drug Name:** mifepristone tablets

External Participant: The Population Council

Type of Meeting: Regulatory Guidance

Meeting Chair: [redacted]

External Participant Lead: Ms. Margaret Catley-Carlson

Meeting Recorder: [redacted]

FDA Attendees:

[redacted] Center for Drug Evaluation and Reseach, (CDER; HFD-002)
[redacted] Office of Drug Evaluation II,
[redacted] (GCF-1)
[redacted] Division of Reproductive and Urologic Drug Products (DRUDP;HFD-580)
[redacted] DRUDP (HFD-580)
[redacted] Division of New Drug Chemistry II (DNDC II) @ DRUDP (HFD-580)
[redacted] DNDCII @ DRUDP (HFD-580)
[redacted] Project Management Staff, DRUDP (HFD-580)
[redacted] DRUDP (HFD-580)
[redacted] DRUDP (HFD-580)

External Constituents:

[redacted]
Ms. Margaret Catley-Carlson, President
Beverly Winikoff, M.D., Director of Reproductive Health
Roger Thies, Esq., Hyman Phelps & McNamara, Regulatory Counsel
James S. Boynton, Esq. Christy & Viener, General Counsel

[redacted]
[redacted] President
[redacted] Manufacturing Consultant
[redacted]

Meeting Objectives:

The sponsor requested this meeting to discuss a proposal for responding to the Chemistry, Manufacturing, and Controls issues delineated in the Approvable letter dated September 18, 1996.

Discussion Points:

- Update of issues
  - distributorship has been restructured
  - an amendment responding to the request for labeling in the approvable letter was submitted in March of this year
  - the US clinical trial data were submitted to the IND in May of this year
- Proposal for responding to Approvable letter
  - Gedeon Richter (GR) has manufactured four pilot batches of drug substance
  - GR is prepared to submit drug master file information for the drug substance
  - GR is in possession of a Roussel Uclaf (RU) reference standard for the drug substance
  - GR is prepared to undergo an inspection of their manufacturing site
  - the sponsor will submit data to show that the drug substance manufactured by GR is comparable to the drug substance manufactured by RU (qualifies under SUPAC)
  - the sponsor will submit the GR data to support equivalency in September 1997
  - the sponsor hopes to obtain feedback regarding the adequacy of the submitted data although they understand that until a complete resubmission is made in response to all deficiencies in the Approvable letter, the resubmission review clock will not start
  - the licensee will take the bulk substance made by GR and have a to-be-named tableter make and package the final dosage form
  - the sponsor proposes to link the finished dosage form from the GR bulk substance to the RU finished dosage form by performing dissolution tests on their product and RU product purchased on the open market in Europe
  - the sponsor proposed utilizing the finished form specifications from RU as the standard if upon dissolution studies it is found that the original RU tablets used in clinical trials and the currently marketed RU tablets have changed slightly in formulation specifications
  - the sponsor will request another regulatory/chemistry meeting within the next three months to further discuss submission/development plans
  - sponsor made clear that they will use GR as bulk manufacturer and a to be named tablature as the manufacturer for the initial NDA. They will then make a corporate decision not to market product made by the approved bulk manufacturer, but will wait for further bulk manufacturers to be added via supplements to the approved NDA
- Future Plans
  - the licensee is currently negotiating with several potential bulk manufacturers (in India, China and France)
  - the sponsor ultimately intends to have more than one approved manufacturer of this substance (after approval), they are still proposing GR for the initial NDA

- GR's drug substance will be used as the reference standard for any other drug substance manufacturer (to be submitted as supplements to the Approved NDA)
- the licensee is currently negotiating with one potential tablature, packaging is expected to be carried out on site with whoever makes the final dosage form (or the licensee will build their own tableting facility); the packaged product will be shipped directly to the distributer
- neither the prospective manufacturer of the bulk drug substance nor the prospective tablature are ready for product specific GMF site inspection
- should the sponsor receive an approval letter, the sponsor will discuss their public statements with the Agency regarding lack of available product for marketing prior to making public statements

Decisions Reached:

- for the GR drug substance to be accepted as equivalent to the RU drug substance, the sponsor will have to show that it has comparable structure, impurity profile, particle size distribution, polymorphic form, and stability (per SUPAC)
- the Division will not be under any regulatory time constraint to review sponsor submissions until a complete response is made to the approvable letter
- the Division will provide comments to the sponsor on their drug substance submission before either a full submission is made, or before site inspections are completed, with the understanding that the comments will not be definitive
- inspection will not be initiated until a full submission is made
- the sponsor will submit dates for another meeting to discuss their chemistry manufacturing and control (CMC) plans in more detail within the next three months

Unresolved Issues: none

Action Items:

Item	person responsible	time frame
propose dates for FDA/Industry meeting	sponsor	ASAP
submit CMC drug substance data	sponsor	September 1997
schedule FDA/Industry meeting		upon receipt of dates from sponsor

/S/
Minutes Preparer 9/12/97

/S/ 9/12/97
Concurrence, Chair

Date: June 18, 1996 **Time:** 8:00-10:00 **Location:** Parklawn 14-56

NDA: 20-687 **Drug Name:** Mifepristone

External Participant: The Population Council

Type of Meeting: 90 day meeting

Meeting Chair: [redacted] **External Participant Lead:** Ann Robbins, Ph.D.

Meeting Recorder: [redacted]

FDA Attendees:

[redacted] Division of Reproductive and Urologic Drug Products (DRUDP; HFD-580)

[redacted] (HFD-580)
(HFD-580)
(HFD-820)
(HFD-580)
(HFD-580)
(HFD-580)
(HFD-870)

External Constituaents:

Ms. Sandra Arnold
Wayne C. Bardin, M.D.,
Mr. James Boynton
Ms. Margaret Catley-Carlson
Ann Robbins, Ph.D.

Meeting Objectives:

To discuss the status of the NDA review and the upcoming Advisory Committee Meeting.

Discussion Points: See below.

Decisions Reached:

- Change in Classification from Standard to Priority
  - The Division would like to complete the review and deliver an action letter soon after the Advisory Committee meeting (Scheduled for July 19, 1996). The target goal date will be September 14, 1996.
  - Because the target date is September, the Population Council will submit a Safety Update at the end of June. This will include some preliminary safety data from the U.S. trials.

- Starting Material

  - The Population Council acknowledged the Agency's need for more information regarding the starting material. They stated that they are currently attempting to negotiate with Roussel Uclaf on this point but have not yet received any further information. At this time they are unable to say whether they will be able to obtain more information regarding this or not.

  - The Population Council will be able to submit their new manufacturer's DMF which would contain satisfactory information on the starting material for the bulk drug early fourth quarter of this year, but will not have the rest of the data until the first quarter of next year.

  - The sponsor was told that if a new DMF were submitted by a new manufacturer, they would be required to show that the to-be-marketed formulation was identical to the clinically tested formulation with respect to identity, purity, and dosage (e.g., absorption etc.). Additionally, the sponsor would be required to show bioequivalence between the clinically tested formulation and the to-be-marketed formulation. The necessity of an in vivo bioequivalence study will be assessed with regard to changes in manufacturing site, procedure and equipment, as well as formulation composition. If a waiver of the in vivo bioequivalence study is granted, then appropriate comparative dissolution studies will be sufficient to establish the bioequivalence of the clinically tested formulation and to-be-marketed formulation. The sponsor noted that they would not be able to complete the necessary studies within the next six months.

  - It was suggested that if the sponsor was unable to supply the required information, an Approvable letter may still be a possibility.

- Status of Pending NDA issues

  - The sponsor noted that the Division of Biopharmaceutics had communicated a request for dissolution data on their drug product. They will be in France to hold discussions with Roussel Uclaf on Thursday, and request that a formal letter from the FDA outlining the Biopharmaceutic request be faxed to them prior to their meeting with Roussel, they further requested the chemistry comments also be faxed as a formal letter at the same time.

  - The sponsor noted that the U.S. trials were completed in the Fall of last year, however the 100% audit that they have elected to do on the data is not expected to be complete until July. They assert that the safety and efficacy data in the U.S. trials are similar to those in the European trail.

  - The sponsor was told that the Establishment Evaluation Request had been returned and had been found acceptable.

- The sponsor stated that the clinical trials were scheduled to be audited by DSI on June 24, 1996. The sponsor has just completed their own audit of the clinical sites and have left for the auditors a clear paper trail of what they have done, they have also included English translations of all French documents. The sponsor noted that they have not had time to see if the data from their audit might change any of the information in the NDA.

- The sponsor was told that review of the proposed labeling was not yet complete. The sponsor noted that the Division of Biopharmaceutics had given them their labeling revisions, and these revisions would be submitted as new draft labeling soon.

- Advisory Committee

  - A draft agenda was reviewed and the time allocations for presentations were discussed.

  - The Agency told the sponsor that a venue had not yet been decided upon, however there was one good prospect. It was suggested that the sponsor come the day before the meeting to view the site of the meeting.

  - The sponsor was told that the Division planned only to make opening introductions, and that we would not be discussing the concomitant use of Cytotec with their product. It was agreed that the Agency would address the fact that this NDA's safety and efficacy rests primarily on foreign data, but that there was precedence for this, the Division will discuss appropriate wording with CDER management, and obtain specific examples of other NDAs approved mainly with foreign data.

  - The sponsor stated that they would discuss preliminary safety data from their U.S. trials but would not address efficacy. Further they will make clear that the U.S. data presented have not yet been reviewed by the Agency.

  - [redacted]

  - The sponsor noted that they still have a large stock of unembossed mifepristone tablets left after the trials. They asked if they could use these for other clinical trials. The sponsor asked for clarification of the difference between compassionate use INDs and Treatment IND's. The Agency will send the appropriate sections of the CFR to the sponsor after this meeting. The sponsor noted that they do not plan to provide this drug for patients requesting it to terminate pregnancies.

  - The discussion of Cytotec and the proposed drug label was discussed. It was noted that Cytotec's label would not need to be amended. It was suggested that the label be for a combined product since Cytotec was not approved for use in pregnant women. The Division of Biopharmaceutics suggested that kinetics in pregnant women be examined post-approval.

- The sponsor was asked when they expected to be able to supply mifepristone to the U.S. population. The sponsor replied that they expected to be able to market a this produet in about twelve months.

Unresolved Issues: None

Action Items: The Agency will Fax two letters to the sponsor before 3:00 pm on June 20, 1996. These will contain the chemistry information requests, and the biopharmaceutics dissolution data request.

The sponsor will submit an updated Safety Update which will include preliminary safety data from the U.S. trials by the end of June.

/S/ 6/16/96
Signature, minutes preparer

/S/ 9/11/96
Concurrence, Chair

cc:
NDA Arch
HFD-580
HFD-580 Attendees
HFD-820
HFD-870
HFD-580 6.19,9.10.96/n20687.mm

Concurrences 8.19.96 8.26.96 8.26.96 8.26.96
8.29.96 6.19.96

No Response:

Meeting Minutes

APPEARS THIS WAY
ON ORIGINAL

MEMO OF TELEPHONE CONVERSATION

The sponsor was contacted on August 9, 1996, and the following questions were asked:

1) When will their proposed distribution system be submitted? ANS: Expect to send in next week.

2) Do you have an updated draft label? ANS: No waiting for comments from the FDA.

3) Do you have any more (new) post-marketing data from the regulatory agencies in countries in which this drug is approved for marketing (the Britain, Sweden and France)? ANS: No, we have no new data, but have yet to approach regulatory agencies. Please provide names and numbers of regulatory contacts if you have them. The sponsor was told that I would try and obtain this information for them but did not know if I would be successful.

The sponsor was also told that a letter requesting commitments to a variety of Phase IV studies would be sent within a week.

APPEARS THIS WAY
ON ORIGINAL

DATE August 9, 1996

NDA/IND NUMBER
NDA 20-687

INITIATED BY
[redacted]
HFD-580

PRODUCT NAME
Mifepristone

SPONSOR'S NAME
The Population Council

NAME AND TITLE OF PERSON WITH WHOM CONVERSATION WAS HELD
Ann Robbins, PH.D.

TELEPHONE
(212) 327-8748

FAX

cc:
Orig. NDA
HFD-580
[redacted]
8/9/96

DIVISION HFD-580

I spoke with Maggie Carlson, Director, Population Council and Ann Robins, Regulatory Affairs, Population Council today regarding their plans to submit preliminary information re: the results of the US trial of mifepristone as both part of their IND [redacted] and as part of the safety update to the NDA (20-687).

It was discussed that the Pop Council is performing a 100% audit of the data and sites (just as they did for the French data) and that therefore, the information submitted at this time would not be the final study report.

We agreed that they could submit a preliminary report to the IND and/or NDA. They acknowledge that the audit plans are there own and not a specific FDA requirement.

After submission of a preliminary report, the sponsor anticipates a brief review of the US data in their presentation to the Advisory/ Committee.

APPEARS THIS WAY
ON ORIGINAL

DATE May 24, 1996

NDA 20-687

INITIATED BY

[redacted]
HFD-510

PRODUCT NAME

Mifepristone

SPONSOR'S NAME

Population Council

NAME AND TITLE OF PERSON WITH WHOM CONVERSATION WAS HELD

Margaret Catley-Carlson
Director

TELEPHONE

(212) 339-0501

cc:
NDA 20-687
HFD-510
[redacted]

TSI

5-30-96

DIVISION HFD-510

MEMO OF TELEPHONE CONVERSATION

FEB 23 1996

[redacted] telephone conversation with [redacted] to let her know that [redacted] would be calling probably either the [redacted] week or the following week. I [redacted] CMC problem, and [redacted] have [redacted] get involved. I [redacted] that if [redacted] had not contacted [redacted] by the end of next week, that she give me a [redacted]

[redacted] said that she was going on vacation [redacted] but would be in the office on Monday. She [redacted] stated that if she had not heard from anyone by the 20th of February she would call me.

APPEARS THIS WAY
ON ORIGINAL

DATE February 12, 1996

NDA/IND NUMBER
[redacted]

INITIATED BY
[redacted]
HFD-510

PRODUCT NAME
Mifipristone

SPONSOR'S NAME
The Population Council

NAME AND TITLE OF PERSON WITH WHOM CONVERSATION WAS HELD
[redacted]

TELEPHONE
[redacted]

cc:
[redacted]
HFD-510
[redacted]

DIVISION HFD-510

BEST POSSIBLE COPY

FEB 23 1996

MEMO OF TELEPHONE CONVERSATION

[redacted] called to clarify the contact made with Dr. Euvard on February 12, 1996. I said that I had called to give Roussel the name and number of a contact that could help them determine what they would have to provide, and what they would not have to provide in their EA section. I then gave the name of [redacted] again. I [redacted] said that he had hoped that they would not have to have an EA section. I told him it had been decided in a higher level meeting that they would, but that this woman would be helping them.

[redacted] said that they only have [redacted] left of the drug substance that went into the making of the drug. I told him that I had given that question to [redacted] and he had said that it would be alright if the drug substance came from a different lot. However, [redacted] wanted to remind them that if reference standards were used in the methods of manufacture, that we would require the standards as well. I stated that I believed that this was a routine request, and should not be a surprise. [redacted] agreed that this was a standard request and that he would work on it. He also stated that Roussel was planning to respond to all the questions on our list.

I told him that I had one more concern. I noted that Roussel very obviously wanted to work through the Population Council to answer questions, and not directly with the FDA, and said that I understood this. However I requested that they think about how they wanted to answer any other chemistry questions that might come up during review if the Population Council was to be blind to the CMC section. I pointed out that the review that the reviewing chemist had done had been cursory, and meant only to cover obvious deficiencies. [redacted] said that Roussel was going to have an internal meeting to discuss these things, and that he would bring up that point.

Discussion ended at that point.

DATE February 14, 1996

NDA/IND NUMBER
IND [redacted]

INITIATED BY
[redacted]

HFD-510

PRODUCT NAME
Mifipristone

SPONSOR'S NAME
The Population Council

NAME AND TITLE OF PERSON WITH WHOM CONVERSATION WAS HELD
[redacted]

TELEPHONE
9-011-33-1-4991-4252

FAX
9-011-33-1-4991-3119

CC:
[redacted]
HFD-510

DIVISION HFD-510

Meeting Minutes

Date: September 15, 2000 **Time:** 3:00 – 4:00 PM **Location:** Parklawn; 17B-43

NDA 20-687 **Drug:** mifepristone 200 mg

Indication: induction of abortion

Sponsor: Population Council

Type of Meeting: Status

Meeting Chair:

Minutes Preparer:

External Chair: Nancy Buc

FDA Attendees:

Office of Evaluation III (ODE III; HFD-103)
Division of Reproductive and Urologic Drug Products (DRUDP; HFD-580)
DRUDP (HFD-580)
Division of Drug Marketing, Advertising, and Communications (DDMAC; HFD-042)
Project Management Staff, DRUDP (HFD-580)
Project Manager, DRUDP (HFD-580)

Meeting Objective: To discuss the Phase 4 commitments, labeling comments, Medication Guide, and the next steps for this application.

Discussion:

Medication Guide

- See attached Medication Guide with revisions.

Phase 4

- The sponsor has agreed to the studies requested in the Information Request letter dated September 13, 2000
- The sponsor is willing to conduct the study regarding the ongoing pregnancy surveillance study, but needs to finalize the study design that would meet the Agency 's objectives

DDMAC questions/timeline for submission of promotional materials

- On Monday, September 18, 2000, the sponsor will submit the following information (10 copies):
  - Press release
  - Fact sheets
  - Fast facts
  - Video script
  - Brochure for patient

- Toll free number script
- Website

- More information will be submitted to DDMAC after approval for a rolling review

Action Items:

- Sponsor will fax Physician Label, Patient Agreement, Medication Guide, Order Form, Physician Agreement and acceptance of Subpart H with a cover letter by close of business today (9-15-00)
- Sponsor will include the Phase 4 commitments in the cover letter of the submission
- Fax sponsor meeting minutes

/S/

/S/
Concurrence, Chair

APPEARS THIS WAY
ON ORIGINAL

4 **Page(s) Redacted**

Draft

Labeling

Meeting Minutes

Date: August 4, 2000 **Time:** 11 am – 12:30 pm, EST **Location:** Parklawn; Chesapeake Room

NDA 20-687 **Drug:** mifepristone **Indication:** medical abortion

Sponsor: Population Council

Type of Meeting: aprovability issues

Meeting Chair: [redacted] Office of Drug Evaluation III (ODE III, HFD-103)

Meeting Recorder: [redacted] Regulatory Affairs, ODE III

FDA Attendees:

[redacted] ODE III (HFD-103)
[redacted] Regulatory Affairs, ODE III (HFD-103)
[redacted] Project Management Staff, Division of Reproductive and Urologic Drug Products (DRUDP; HFD-580)
[redacted] DRUDP (HFD-580)
[redacted] DRUDP (HFD-580)
[redacted] Division of Drug Risk Evaluation II (DDRE II; HFD-440)
[redacted] DDRE II (HFD-440)
[redacted] Division of Drug Marketing, Advertising and Communications (DDMAC; HFD-42)
[redacted] DDMAC (HFD-42)
[redacted] DDMAC (HFD-42)
[redacted] Drug Program Review
[redacted] Center for Drug Evaluation and Research (HFD-005)
[redacted] Office of the Chief Counsel (GCF-1)
[redacted] Office of the Chief Counsel (GCF-1)

External Participants:

Sandra P. Arnold, VP, Corporate Affairs, Population Council
[redacted], President & CEO, Danco Laboratories, LLC
Beverly Winikoff, M.D., M.P.H., Program Director, Reproductive Health, International programs Division, Population Council
Richard U. Hasskn~~e~~cht, M.D., Medical Director, Danco Laboratories, LLC
Shelley D. Clark, Ph.D., Program Associate, Population Council
Heather M. O'Neill, Director of Public Affairs, Danco Laboratories, LLC
Nancy L. Buc, Buc & Beardsley, Counsel to Population Council and Danco Laboratories, LLC

Meeting Objective: To discuss approvability issues related to labeling and thedistribution plan for mifepristone, post-marketing and risk management issues that will affect the drug's life cycle (e.g., monitoring of adverse events, future generic entries into the market, drug class, further development).

Discussion:

Note: Item numbers correspond to questions and comments listed in the sponsor's July 27, 2000, submission of briefing documents for this meeting.

- The sponsor is targeting the first week of August for submitting requested chemistry, manufacturing, and controls information.
- Item 1; Boxed Warning: deferred
- Items 2 and 8; Physician training:
  - Materials and information sources proposed to support physician training will include the prescriber's letter, professional labeling, patient information sheet, patient agreement, the Danco web site, and the National Abortion Federation. The written materials will be packaged together with a cover letter.
  - FDA suggested that information regarding post-marketing studies (Phase 4 commitments) should also be included so that physicians can respond appropriately to surveillance on women who experience failure on the medical abortion regimen. The sponsor stated that information will be in the professional labeling.
  - The package of information provided to the physician needs to be complete and reasonable so that difficulty accessing information from other sources (e.g. the internet) is not an issue.
- Item 10; Incidence of need for curettage: agreement reached that the incidence was 1%.
- Item 13; Labeling revision regarding timing of dose of misoprostol: FDA requested deletion of the phrase, [redacted]
- Items 16, 17, and 33; labeling revisions: FDA agrees to sponsor's proposals.
- Items 3, 22, 23, and 31; Day 3 visit:
  - FDA renewed the assertion that the Day 3 visit should be required as it was in clinical trials. A 3-4 hour observation period following administration of misoprostol would be optional.
  - The sponsor suggested that the Guadeloupe study (retrospective study of actual use of medical abortion using mifepristone (oral) and misoprostol (vaginal administration)) supports their position that permitting women to take the misoprostol portion of the regimen at home is successful and safe. FDA noted that 4% of women in this study took the misoprostol incorrectly at home.
  - [redacted]
- Item 26; Provider qualifications:
  - FDA requested input on how the sponsor will fulfill their phase 4 commitment to monitor adequacy of provider qualifications. This may be more important if services for surgical intervention (vacuum aspiration, D&C) for complications are handled by referral.
  - Sponsor commented that monitoring qualifications is not needed because:
    - Monitoring provider self-attestation for having qualifications might give counter-intuitive results.
    - Mifepristone should not be equated with other approved drugs with significantly more serious safety issues. Therefore, mifepristone should not be held as an example for managing serious safety issues.
    - There were some physicians in the clinical trial who referred patients to other healthcare practitioners for care when complications occurred.
    - Surgical intervention following the medical abortion regimen is almost never needed immediately and, therefore, does not constitute an emergency.
  - FDA stated that consideration of approving different provider qualifications than were conditions of the clinical trials will require documentation justifying why it is appropriate to deviate from

what was discussed and agreed to earlier in the review. Monitoring performance outcomes of referring doctors will be viewed as part of a risk management program.

- Subpart H and Medication Guide:
  - FDA has determined that the application will be acted on under 21 CFR 314.520 (approval with restrictions to assure safe use- Subpart H) and is considering a requirement to provide patient information under 21 CFR 208 (Medication Guide). This will add a regulatory requirement supporting the importance of patient education since the provider will be required to give the Medication Guide to the patient. Each program is designed to address different issues.
  - FDA is in the process of reviewing the proposed patient package insert. Revisions will be sent to the sponsor in the format of a Medication Guide.
  - The sponsor requested a commitment from FDA, if they agree to approval under Subpart H and a Medication Guide, that any information FDA issues regarding the drug emphasizes that these regulations were used to ensure patient education.
- Phase 4 commitments:
  - Commitments (comments refer to the following numbers):
    - #1: Monitoring the adequacy of the distribution and credentialing system.
    - #2: Follow-up on the outcome of a representative sample of mifepristone-treated women who have surgical abortion because of the method failure.
    - #3: Ascertain the frequency with which women follow the complete treatment regimen and the outcome of those who do not.
    - #4: Assess the long-term effects of multiple use of the regimen.
    - #5: Study the safety and efficacy of the regimen in women under 18 years of age, over age 35, and in women who smoke.
    - #6: Ascertain the effect of the regimen on children born after treatment failure.
  - Prioritization of commitments:
    - Commitments # 1, 2, 3 and 6 could be incorporated into the risk management program.
    - Commitments # 4 and 5 are of lower priority than those incorporated into the risk management program.
  - Regarding commitments #1, 2, 3, and 6 to be incorporated into monitoring of the distribution system:
    - The commitments should be redesigned to evaluate the proposed physician qualifications and referral system for managing complications, for example, follow-up on treatment failures related to qualifications. Focus monitoring on the Day 14 visit rather than Day 3.
    - The commitment should also be designed to ascertain the effect of the regimen on children born after treatment failure.
  - Commitment #6 should focus on the outcome of the child at time of delivery rather than long-term effects.
  - The sponsor stated that the commitments are no longer relevant and requested re-evaluation of them because:
    - More is known now about the drug and there is more experience with medical abortion regimens than in 1996 when the commitments were made.
    - The commitments will infringe on privacy issues related to abortion.
    - The commitments were made by individuals unaware of the drug approval process or what the commitments would mean in terms of resources.

Action items

- Sponsor to consider and respond to recommendations made regarding the Day 3 visit, phase 4 commitments, and monitoring physician qualifications.
- FDA to make final determination on need for Medication Guide.

- FDA to schedule follow-up meeting.

Pending items

- Further discussions on labeling, including the Boxed Warning and Medication Guide.
- Phase 4 commitments.
- Monitoring provider qualifications.

/S/ 9/20/00
Minutes Preparer

/S/ 9/20/00
Concurrence, Chair

Note to sponsor: These minutes are the official minutes of the meeting. You are responsible for notifying us of any significant differences in understanding you may have regarding the meeting outcomes.

APPEARS THIS WAY
ON ORIGINAL

Teleconference Minutes

Date: August 25, 2000 **Time:** 3:30 – 4:00 PM **Location:** Parklawn; 17B-43

NDA 20-687 **Drug:** Mifepristone 200 mg Tablets

Indication: induction of abortion

Sponsor: Population Council

Type of Meeting: Guidance (statistics)

Meeting Chair:

Meeting Recorder:

External Lead: Nancy Buc

FDA Attendees:

Office of Drug Evaluation III (ODEIII; HFD-103)
Division of Reproductive and Urologic Drug Products (DRUDP ; HFD-580)
Division of Biometrics II (DBII) @ DRUDP (HFD-580)
Project Management Staff, DRUDP (HFD-580)

External Attendees:
Beverly Winikofi, M.D. – Population Council
Shelley Clark, Ph.D. – Population Council
Heather O'Neill – Danco Laboratories, LLC
Nancy Buc – Buc & Beardsley

Meeting Objective: The applicant requested this teleconference to clarify FDA-derived sample size calculations and to confirm the study endpoints for the referring versus non-referring physician study for post-approval (Phase 4 commitment) protocol.

Background: In teleconferences before August 23, 2000, FDA conveyed suggestions for study designs, endpoints and sample size estimates. The applicant's interpretation of the sample size calculations and endpoints are contained in their August 23 letter.

Discussion Items:

- Success rates of 92% and 95% were demonstrated in the clinical trials; rates of transfusions and hospitalizations were less than 1%
- the applicant is concerned the sample size of 120 per group is inadequate to yield a satisfactory upper limit of a confidence interval for the rate of a serious adverse event, such as transfusion, if the rate of a serious adverse event is approximately 1%

- endpoints of interest to be compared between the two groups need to include the success rate.(e.g., approximately 92 or 95%) and its converse, the failure rate (i.e., 1- success rate); most failures, if not all, will likely result in surgical termination of pregnancy
- other endpoints of interest include rates of complication, (such as transfusions, hospitalizations, etc.)
- FDA would like to exclude an absolute difference of greater than 5% in efficacy between the two groups
- FDA also would like to exclude an absolute difference of greater than 5% in complication rates between the two groups
- FDA requests complication rates estimated separately for each group, but these estimates are not the ultimate goal of the Agency
- DRUDP agreed with the applicant's concern that 120 patients per arm is inadequate to yield an acceptable upper limit of a confidence interval for an estimated complication rate *within* a group; however, 120 patients is adequate for ruling out differences in rates of greater than 5% *between* groups.
- The FDA-derived estimate of 120 patients per arm was based on the following assumptions:
    - the endpoint is rate of complications
    - the referral and non-referral groups each have an underlying rate of 1%
    - the rates for the two groups do not differ by more than 5%
    - a 95% one-sided confidence interval for the differences in rates
    - approximately 80% power
    - a randomized study
    - no adjustments for dropouts
- DRUDP indicated a sample size of 629 per group is needed to insure with 80% power that the differences in success rates are within 5% of each other, assuming
    - a 95% two-sided confidence interval
    - underlying success rate per group is 92%
    - a randomized trial
    - no adjustments for dropouts
- for patients that are referred to a physician, the sponsor will need to obtain information through the referral facility
- the sponsor may be able to plan to have fewer sites in the non-referral arm; (e.g., if a historical control is used)
- if a historical control is used, the sponsor should demonstrate the similarities between the historical control population (and clinical trial procedures) to the current population (and to procedures in the current trial); any difference in population or procedures should be evaluated for their possible impact on the outcome of the trial; ideally, FDA would like a concurrent comparison between referring and non-referring physicians
- the sponsor would like to remove the [redacted] because the [redacted] is so low
- the sponsor will maintain an audit of the physicians' compliance with the Medication Guide

APPEARS THIS WAY
ON ORIGINAL

Action Items:

- the sponsor should submit a proposal for the study described earlier including a sample size, referring physicians to get follow-up information on patients from referral facility (it built into the protocol); if the sponsor expects a lack of compliance, the sponsor can build this into the protocol
- the follow-up teleconference will be scheduled for Tuesday/Wednesday (meeting scheduled for Tuesday, August 29, 2000 @ 4:00PM if needed, for additional clarification (cancelled by sponsor)

/S/
Minutes Preparer

/S/
Concurrence, Chair

9/21/00

- Note to Sponsor: These minutes are official minutes.

APPEARS THIS WAY
ON ORIGINAL

Memorandum

Date: 10 Sep. 1996

From: [redacted] HFD-580 /S/

Subject: Labeling deficiencies

To: NDA 20-687

The draft labeling in the original NDA submission was reviewed in Chemistry Review # 1 dated 20 June 1996 and it was noted that minor labeling changes might be necessary. Labeling deficiencies were not conveyed to the Applicant because it was considered likely that an Amendment would be submitted to correct some obvious omissions (e.g. the lack of a structure for mifepristone in the Description Section). However, no Amendments pertaining to the chemistry related sections of the labeling have been submitted. The purpose of this Memorandum is to identify labeling deficiencies to be conveyed to the Applicant.
In the Description section of the draft package insert, the chemical name of mifepristone should be corrected by replacing "B" with "β". The structure of mifepristone should also be included. In addition, missing information in the 'How Supplied ' section regarding imprinting and carton contents should be provided.

CONCLUSIONS AND RECOMMENDATIONS: Labeling: The Applicant should be requested to include the structure of mifepristone in the Description section of the Package Insert and to correct the chemical name of mifepristone by replacing "B" by "β". The missing information (regarding imprinting and carton contents) in the 'How Supplied' section should also be provided. In addition, the Applicant should be informed that if a Tradename is to be used to market the product, it must be submitted and approved prior to use.

cc: Orig. NDA 20-687
HFD 580/ Div. Files
HFD 580/ [redacted]
R/D initialed by: /S/

Filename: [redacted]

APPEARS THIS WAY
ON ORIGINAL

Memorandum

To: NDA 20-687, Mifepristone Tablets, 200 mg

Through: /S/ 6/20/00

From: /S/ 6/20/00

Date: June 20, 2000

Re: Teleconference with [redacted] from Danco Laboratories, LLC

I contacted [redacted] from Danco concerning the process changes he faxed to me on June 16, 2000 and discussed at the June 19, 2000 teleconference. I requested that he provide the batch numbers and manufacturing dates of all the drug substance batches manufactured by Shanghai HuaLian prior to implementing those process changes and after implementing those changes. He informed me that the characterization data provided for the three batches (# 990101, 990102, 990103) in the NDA were manufactured prior to the process changes. I requested that the following data be provided for at least three post-change batches: 1) [redacted] 2) [redacted] 3) [redacted] and 4) [redacted]

APPEARS THIS WAY
ON ORIGINAL

cc:
Orig. NDA #20-687
HFD-580/Division File
HFD-580 [redacted]
HFD-580 [redacted]

Filename: [redacted]

SEP 11 2000

Memorandum

To: NDA 20-687, Mifeprex (mifepristone) Tablets, 200 mg

Addendum to Chemistry Review #5.

Through: /S/ 9/8/00

From: /S/ 9/8/00

Date: September 8, 2000

Re: Reference standard specifications, molecular weight calculation

---

This addendum to Chemistry Review #5 is to clarify the specifications for the mifepristone reference standard [see January 28, 2000 (#040) and September 8, 2000 (#059) amendments] and the calculation of the theoretical molecular weight used in the

As stated in Amendment #040, the mifepristone reference standard is derived through

Since the determination of the atomic weight of a molecule is based on the calculation based on is more accurate. Therefore, this is consistent with

cc:
Orig. NDA #20-687
HFD-580/Division File
HFD-580
HFD-580

HFD-820/[redacted]

Filename:[redacted]

APPEARS THIS WAY
ON ORIGINAL

NDA 20-687

INFORMATION REQUEST LETTER

Population Council
Attention: Sandra Arnold
Vice President
One Dag Hammarskjold Plaza
New York, NY 10017

Dear Ms. Arnold:

Please refer to the March 14, 1996 new drug application for Mifeprex (mifepristone) tablets, 200 mg.

We also refer to your submissions dated April 28, May 10 and 20, June 3, 15 and 30, July 14 and 22, August 13 and 18, September 13, October 26, November 16 and 29, and December 6 and 7, 1999.

We are reviewing the Biopharmaceutics and Chemistry sections of your submissions and have the following comments and information requests. We need your prompt written response to continue our evaluation of your NDA.

Biopharmaceutics

Please provide the comparison of multipoint (5, 10, 20 and 30 minutes) dissolution profiles of the clinical and the to-be-marketed formulations at [redacted]

Chemistry

Drug Substance:

[redacted]

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

JAN 18 2000

Susan Haskell, M.D.
Planned Parenthood of Greater Iowa
851 19th Street
Des Moines, Iowa 50314

Dear Dr. Haskell:

The purpose of this letter is to inform you of our conclusions concerning your conduct of the clinical study (protocol # 166A) of mifepristone that you conducted for Population Council.

Between November 16 and November 18, 1999, [redacted] representing the Food and Drug Administration (Agency), inspected the study identified above. From our evaluation of the inspection report prepared by [redacted] and copies of study records obtained during the inspection, we conclude that you conducted your study in compliance with the Federal regulations and good clinical investigational practices governing the conduct of clinical investigations and the protection of human subjects.

This inspection is part of the Agency's Bioresearch Monitoring Program. This program includes inspections to determine the validity of clinical drug studies that may provide the basis for drug marketing approval and to assure that the rights and welfare of the human subjects who participated in those studies have been protected.

We appreciate the cooperation shown Investigator [redacted] during the inspection. Should you have any questions or concerns regarding this letter or the inspection, please contact me by letter at the address given below.

Sincerely,

[redacted]

Division of Scientific Investigations
Office of Medical Policy
Center for Drug Evaluation and Research
7520 Standish Place, Suite 103
Rockville, MD 20855

APPEARS THIS WAY
ON ORIGINAL

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

JAN 12 1999
2000

Suzanne T. Poppema, M.D.
Aurora Medical Services
1207 N. Street, Suite 214
Seattle, Washington 98133

Dear Dr. Poppema:

Between November 1 and November 5, 1999, [redacted] representing the Food and Drug Administration (FDA), inspected your conduct of a clinical study (Protocol #166A) of the investigational drugs mifepristone and misoprostol. You conducted this study for The Population Council, Inc. This inspection is part of FDA's Bioresearch Monitoring Program, which includes inspections designed to validate clinical studies on which drug approval may be based and to assure that the rights and welfare of the human subjects of these studies have been protected.

From our evaluation of the inspection report and the documents submitted with that report, we conclude that you adhered to the Federal regulations and/or good clinical practices that govern the conduct of clinical studies and the protection of human subjects.

We appreciate the cooperation shown [redacted] during the inspection. Should you have any questions or concerns regarding this letter or the inspection, please contact me by letter at the address given below.

Sincerely yours,

[redacted]

Division of Scientific Investigations
Office of Medical Policy
Center for Drug Evaluation and Research,
7520 Standish Place, Suite 103
Rockville, Maryland 20855

APPEARS THIS WAY
ON ORIGINAL

Teleconference Minutes

Date: December 3, 1999 **Time:** 11:30-12:00 PM **Location:** Parklawn; 17B-45

NDA 20-687 **Drug:** mifepristone **Indication:** Induction of abortion

Sponsor: Population Council

Type of Meeting: Guidance

Meeting Chair: [redacted]

External Lead: Fred Schmidt

Meeting Recorder: [redacted]

FDA Attendees:
[redacted] Division of Reproductive and Urologic Drug Products (DRUDP; HFD-580)
[redacted] Project Management Staff, DRUDP (HFD-580)
[redacted] – Regulatory Project Manager, DRUDP (HFD-580)

External Attendees:
Fred Schmidt, Population Council
[redacted] NKO
DANKO

Meeting Objective: To discuss the current status of the application.

Decisions made:
- Informed the sponsor that the user fee date is February 19, 2000; this clarification was made because of recent press releases announcing "approval by the end of the year"
- Discussed the 483s issued by the district offices for both [redacted] the Chinese facility; sponsor informed the Division of the following responses to the 483s:
  - [redacted] November 15, 1999
  - [redacted] November 22, 1999
  - China facility - December 2, 1999
- The sponsor was informed that the inspector for the Chinese facility is recommending that the facility be reinspected before an approval can be issued for this site
- An Information Request letter is forthcoming with Chemistry and Biopharmaceutics questions
- If and when this product is approved, it will likely be approved under Subpart H approval process (restricted distribution)

Unresolved decisions: None

Action Items:

- Fax meeting minutes to sponsor within 30 days
- Fax Information Request letter to sponsor
- Sponsor to provide further information about restricted distribution plan

Minutes Preparer

Concurrence, Chair

APPEARS THIS WAY
ON ORIGINAL

Teleconference Meeting Minutes

Date: May 19, 2000 **Time:** 8:45-9:00 am **Location:** Parklawn; 18B-09

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

Indication: Medical termination of pregnancy

Sponsor: Population Council

Type of Meeting: Teleconference

Meeting Chair:

External Lead: Sandra Arnold

Meeting Recorder:

FDA Attendees:

, Division of Reproductive and Urologic Drug Products (DRUDP, HFD-580)

Regulatory Project Manager, DRUDP (HFD-580)

External Participants:
Sandra Arnold, Population Council
The Danco Group
Nancy Buc, Buc and Beardsley

Meeting Objective: To discuss proposed distribution system with the sponsor and request that sponsor present a proposal regarding provider qualifications that addresses safety concerns of patients receiving the drug product. To request Phase 4 Commitment summary protocols for review during this review cycle.

Discussion:
Distribution system:

We are actively reviewing the proposed labeling and the distribution system; final comments or decisions are pending, however, there are several issues to be addressed:

- The proposed distribution system as submitted primarily addresses security for the manufacturer and distributor; it must also include safeguards for the patient.
  - Patients must be assured that providers will be qualified physicians who are trained in the surgical abortion procedure and currently providing that service. Providers must be available to manage any emergency complications such as hemorrhage and incomplete abortions. Referral to a hospital emergency department by ambulance is not acceptable.

- Appropriate provider qualifications must be specified in the distribution plan, and the sponsor will be required to audit the distribution system to assure that providers meet appropriate qualifications.

- Provide us with acceptable, auditable criteria, e.g., that they be licensed physicians. Other criteria may include Board certification (OB/GYN or FP?), certification of training &/or experience, hospital credentials/privileges, facility certification, documentation of number of procedures performed, etc.; designate how you will audit the designated criteria.

- Indicate how you will assess compliance by providers and include a provision to discontinue from the distribution plan any provider who does not comply with the requirements.

Phase 4 commitments

The requested Phase 4 commitments are not optional and are requirements for approval. Summary protocols for these commitments, need to be submitted by August 1 to allow for review prior to approval.

Action Items:

- Sponsor to provide proposal for appropriate provider qualifications to ensure safety and appropriate follow-up care for patients
- Sponsor to submit Phase 4 summary protocols for review by August 2000

Minutes Preparer

Concurrence, Chair

APPEARS THIS WAY
ON ORIGINAL

Teleconference Minutes

Date: June 1, 2000 **Time:** 1:00 – 1:30 pm **Location:** Parklawn, 13B-45

NDA 20-687 **Drug:** mifepristone **Indication:** medical termination of pregnancy

Sponsor: Population Council

Type of Meeting: Advice

Meeting Chair: [redacted]

External Lead: [redacted]

Meeting Recorder: [redacted]

FDA Attendees:

[redacted] Office of Drug Evaluation III
[redacted] Project Management Staff, Division of Reproductive and Urologic Drug Products

External Attendees:

[redacted] The Danco Group
Sandra Arnold, Population Council
Nancy Buc, Buc and Beardsley

Meeting Objective: To convey FDA comments and recommendations regarding the proposed restricted distribution, revised labeling and requested Phase 4 protocols for this application.

Discussion:

Phase 4 protocols

- the proposed protocols to address the Phase 4 commitments described in previous regulatory letters are to be submitted to FDA by August 1; sponsor expects to submit these protocols before August 1

Restricted Distribution

- a Subpart H requirement for this drug product continues to be under discussion in the Center; feedback may be available for sponsor regarding the FDA recommendation for Subpart H by the end of June 2000; a Subpart H requirement gives FDA authority to ensure compliance with restricted distribution
- if this product is approved not under Subpart H, a voluntary restricted distribution would still be necessary to assure adequate physical tracking and audit of the product and to assure that qualified physicians are certified to receive the product; sponsor's proposed distribution for physically tracking the product was proceeding in the right direction

- the following are additional FDA recommendations for criteria to assure the adequacy of qualifications for physician recipients (these criteria apply whether Subpart H is a condition for approval or whether there would be a voluntary restricted distribution system):

Proposed Restricted Distribution System for NDA 20-687

Qualifications for Physician Recipients:

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

2. Has been trained to and is authorized by law to perform instrumental pregnancy termination (vacuum aspiration and D&C)
   - acceptable documentation:
     - sponsor to propose; self-attestation is discouraged

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

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

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

Labeling recommendations

- revisions are being made to simplify the label and make it more effective for the clinician to use; revised labeling should be available to sponsor by mid-June
- FDA is proposing to delete the specific detailed references of the French data in the physician label to include only the most relevant data for clinician's to reference; inclusion of ranges that include the French data may be acceptable
- the Black Box Warning will remain in the label
- FDA recommends that the label should include the criteria that

- the WARNINGs section will include information about changes in bleeding and the need to confirm the loss of pregnancy in a followup visit

[redacted]

- FDA recommends that the misoprostol dose be given at a Second Visit in the clinic and that the patient must be observed for 4 hours post misoprostol as was studied in the clinical trials

[redacted]

- FDA is recommending that the restricted distribution qualification requirements be listed in the HOW SUPPLIED section of the label for who would be eligible to receive the drug product
- although not a scheduled drug product, the label should emphasize the need to keep this product locked in a cabinet to assure the physical security and tracking of this product
- FDA will propose several revisions to the Patient Agreement Form; the patients will be required to initial each statement to assure an understanding and agreement of the information discussed; duplicate copies should be made so that the patient, medical record and distribution system are all assured to receive a separate copy of the Patient Agreement Form
- the labeling will refer to qualified recipients as physicians or doctors rather than "health care providers" to assure that only qualified physicians receive the drug product and assume the responsibilities under the distribution system; physician assistants and other health care professionals would not be qualified to receive this drug

Decisions made:

- further discussions between FDA and sponsor is needed before the action date for this application

Action Items:

- FDA to fax the list of Proposed Restricted Distribution System for NDA 20-687 (Qualifications for Physician Recipients) to sponsor (*NOTE: fax was sent by 2:00 pm June 1, 2000*)
- FDA to provide labeling revisions to sponsor in mid-June
- Population Council to provide responses to FDA proposed criteria for physician qualifications by mid-June
- Following reciept of FDA proposed labeling, Population Council will provide a request for a meeting and provide a package with proposed agenda, questions and any relevant information for FDA consideration prior to a meeting
- FDA to provide copy of teleconference minutes to sponsor within 30 days

Minutes Preparer

Concurrence, Chair

APPEARS THIS WAY
ON ORIGINAL

Meeting Minutes

Date: November 2, 1998 **Time:** 2:00 PM - 3:30 PM **Location:** Parklawn C/R 17B-43

NDA 20-687 **Drug Name:** mifepristone

External Participant: The Population Council

Type of Meeting: CMC guidance

Meeting Chair: [redacted]

External Participant Lead: Sandra Arnold

Meeting Recorder: [redacted]

FDA Attendees:

[redacted], Division of Reproductive and Urologic Drug Products (DRUDP;HFD-580)

[redacted], Division of New Drug Chemistry II (DNDC II) @ DRUDP (HFD-580)

[redacted] DNDCII @ DRUDP (HFD-580)

[redacted], Project Manager, DRUDP (HFD-580)

External Constituents:

Population Council
Ms. Sandra Arnold - Vice-President
Patricia C. Vaughn, Esq. - Legal Councel
Frederick Schmidt, Ph.D. - Scientist

Danco Laboratories/The NeoGen Group
[redacted], President
Manufacturing Consultant

[redacted]

Meeting Objectives:

To discuss the sponsor's CMC plans and the deficiencies identified in the partial response submitted September 1997.

Discussion Points:

- Status Report - Sponsor Presentation
  - two manufacturers have been identified and contracted for the drug substance
  - one manufacturer is located in [redacted] he other in China
  - both manufacturers will have validation batches on stability by the end of

December 1998

- there are minor manufacturing differences between the two manufacturers
- neither manufacturer has been inspected by the FDA for any product or substance
- two potential tableters have been identified, both in
- one tableter is located in and has had previous experience with
- the second tableter is located in and has had previous experience with
- one of the two tableters will be contracted to tablet the product within the next few months
- once a tableter has been contracted the tableter will be provided with bulk drug substance made by Gedeon Richter for practice tableting runs, these tablets will not be used for compassionate use requests
- the first three validation batches of tablets are expected to be submitted to the Division in March 1999

- Response to approvable letter and Stability

  - the sponsor plans to submit portions of the CMC response as they become available
  - the sponsor must submit a complete response to the deficiencies detailed in the approvable letter before the user fee clock can be started; the sponsor must also declare that they have submitted all required information once the last piece of information is submitted
  - the sponsor must submit stability data from the current manufactures, they may not rely on stability data generated by former manufacturers of the drug product or drug substance
  - current ICH requirements for stability are 6 months accelerated and 12 months real time data to consider a 2 year expiration date

- September 1997 partial response

  - GR has provided the Population Council with of bulk drug substance
  - the Population Council intends to tablet the bulk drug substance made by GR to be provided for compassionate use
  - the Population Council requires a complete deficiency list from the September 1997 CMC submission including a request for a site inspection in order to go forward with their compassionate use plans for the GR bulk drug substance

- Manufacture of bulk drug substance

  - drug substance will be manufactured according to Rousell Uclaf's method
  - the starting material will be
  - can be obtained both in Europe and China, the manufacturer will obtain their supply from China
  - data on multiple batches of the starting material should be submitted in order to ensure that there is consistency between batches

- the drug substance manufacturers will ensure that all specifications of their product are in agreement with those of RU (i.e., structure, particle size, impurity profile, stability, polymorphic structure etc)
- the manufacturers should provide [redacted] of their drug substances to identify and quantify their impurity profile
- the biggest change between the RU method and method to be utilized are changes in solvent which are not expected to cause any difference in drug substance profile
- the manufacturer must be able to demonstrate that the tablets manufactured are equivalent to those made by RU, guidelines for these *in vitro* tests are found in the SUPAC guidance document
- bioequivalence testing may also be required, however, this can not be determined until comparative dissolution data has been submitted
- the sponsor requests that inspections be scheduled as soon as the manufacturers are ready for inspection

- Discussion of Dose Changes - mifepristone and misoprostol

[redacted]

Decisions Reached:

- the manufacturing plan for the bulk drug substance appears acceptable
- a complete response to the deficiency letter should include sufficient stability data to support the expiration date the sponsor intends to request
- although the Division is under no obligation to review a partial submission to an approvable letter, the Chemistry reviewer will attempt to complete the review of the September 1997 partial response submission by the end of December 1998. A detailed letter of deficiencies noted in the review will be issued based upon that review
- manufacturing site inspections can be requested before a complete response is submitted, however timing of inspections cannot be guaranteed. The sponsor should provide

location and contact numbers for the inspections once they are ready to have the sites inspected

- it is unclear at this time if the sponsor can change the clinical parameters for the current NDA, the Division will discuss this request with the Office Director. The sponsor may be required to submit another NDA for these clinical changes

Unresolved Issues: how to submit clinical changes to the current NDA application

Action Items:

Item	person responsible	time frame
1. Completion of CMC partial resp. Review	[redacted]	Possibly by 1/99
2. Issue deficiency letter based on (1)		2 wks after review
3. Report results of clin. data change discussion		2 weeks

Minutes Preparer

Concurrence, Chair

Post-meeting note: [redacted] spoke with [redacted] regarding submission of new clinical data. The sponsor may submit the clinical data as a new NDA (referring to NDA [redacted] for non-clinical information) or they may submit the CMC data required for approval of the existing NDA, receive approval for that NDA and then submit the clinical data as an efficacy supplement to the approved NDA. The sponsor was informed of this decision by [redacted] in a telephone conversation on November 5, 1998.

cc:
Orig. IND
HFD-580
MEETING ATTENDEES
HFD-580 [redacted] 1.4.98/n20687.mm
Concurrence [redacted] 1.9.98/[redacted] 1.6.98/[redacted] 1.9.98

MEETING MINUTES

APPEARS THIS WAY
ON ORIGINAL

Meeting Minutes

Date: July 19, 2000 **Time:** 9-10:30 PM, EST **Location:** Parklawn; Potomac Room

NDA 20-687 **Drug:** mifepristone **Indication:** medical abortion

Sponsor: Population Council

Type of Meeting: aprovability issues

Meeting Chair: [redacted] Office of Drug Evaluation III (ODE III, HFD-103)

Meeting Recorder: [redacted] Regulatory Affairs, ODE III

FDA Attendees:

[redacted] Regulatory Affairs, ODE III (HFD-103)
[redacted] Division of Reproductive and Urologic Drug Products (DRUDP; HFD-580)
[redacted] ODE III (HFD-103)
[redacted] DRUDP (HFD-580)
[redacted] Center for Drug Evaluation and Research (HFD-005)
[redacted] Office of the Chief Counsel (GCF-1)
[redacted] Office of the Chief Counsel (GCF-1)

External Participants:
Sandra P. Arnold, VP, Corporate Affairs, Population Council
[redacted] President & CEO, Danco Laboratories, LLC
Beverly Winikoff, M.D., M.P.H., Program Director, Reproductive Health, International programs Division, Population Council
Richard U. Hausknecht, M.D., Medical Director, Danco Laboratories, LLC
Shelley D. Clark, Ph.D., Program Associate, Population Council
Heather M. O'Neill, Director of Public Affairs, Danco Laboratories, LLC
Nancy L. Buc, Buc & Beardsley, Counsel to Population Council and Danco Laboratories, LLC

Meeting Objective: To discuss approvability issues related to labeling and distribution plan for mifepristone.

Discussion:
Note: Item numbers correspond to questions and comments listed in the sponsor's July 5, 2000, submission of briefing documents for this meeting.

- [redacted]
- [redacted]
- Sponsor's organizational relationships were clarified. Mifepristone is the sole product handled by the licensee, Danco. Drug product manufacture is carried out in a dedicated area.

- [redacted] Danco is pursuing this for mifepristone to ensure adherence to the drug distribution plan.
- FDA agrees to the proposals made by the sponsor in items 4, 5, 6, 7, 9, 11, 12, 14, 15, 18, 19, 20, 21, 24, 25, 27, 28, 29, 30, and 32.
- Items 8, 22, 23, and 31 are repetitive of other items and were not discussed specifically.
- Item 1; Boxed Warning: Discussion of specific items to be included in a Boxed Warning was deferred until all other issues cited in the pre-meeting submission are resolved.
- Item 2; ensuring physician qualifications/training:
  - Both the sponsor and FDA agree to the importance of appropriate training for providers to ensure safe use of the drug.
  - FDA agrees to attestation by the physician to having the specified qualifications for receiving mifepristone under the distribution program.
  - FDA requests that the physician also attest to having read and understood the training materials and labeling.
  - The above constitutes the minimum amount of education necessary for safe use of the drug. Additional proposals made by the sponsor for educational materials and practices will also be beneficial.
- Item 3; Second (Day 3) visit to the clinic:
  - FDA requests that the patient be required to return to the clinic on Day 3 to receive the misoprostol portion of the drug regimen. A 3-4 hour observation period at the clinic following ingestion of misoprostol is recommended. This is similar to the practice in France and the U.K. where there is a long track record of good outcomes. Requiring the Day-3 return visit will promote patient compliance with the overall treatment regimen.
  - The sponsor is concerned that requiring the Day-3 return visit would prohibit clinics from providing medical abortion services on Thursdays or Fridays.
  - The sponsor maintains that the Day-3 visit is unnecessary because:
    - Adverse events are no more likely to occur on Day 3 as any other time.
    - Patients seeking abortions are highly motivated to complete the regimen as instructed due to the serious nature of the decision they've made.
    - Eliminating the inconvenience of a Day-3 visit is likely to increase compliance with the full regimen.
    - Since the clinics are government-run in France and the U.K., their procedures are not relevant to the U.S. situation, and, actual practice in France for individual cases is to permit certain "known" patients to take the misoprostol at home on Day 3.
  - Requiring the Day-3 visit initially and revising the requirement later based on additional data may be acceptable. The sponsor agreed to submit a proposal.
- Item 10; Rates of curettage performed for heavy bleeding: The sponsor will re-examine existing data to determine the appropriate rate and provide this to FDA.
- Item 13; Effectiveness of the regimen when misoprostol is administered more than two days after mifepristone:
  - Dr. Spitz, at the 1996 advisory committee, suggested that the uterus is most receptive to the effects of misoprostol 36-48 hours after ingestion of mifepristone and that effectiveness of the overall regimen decreases when misoprostol is given outside these parameters. However, Dr. Spitz's observations are not based on clinical data.
  - The sponsor stated there is data for vaginal misoprostol use after 48 hours of mifepristone ingestion.

- The sponsor will re-examine the data they have on patients who received oral misoprostol later than 48 hours after taking mifepristone and look in the literature for additional information regarding oral misoprostol.

- Item 16 and 33; Initiation of contraception immediately following termination of pregnancy or as soon as sexual relations resume: It was clarified that the labeling should address when to re-start contraceptive therapy following termination of pregnancy, including oral contraceptives which need to be taken for a month prior to intercourse to be effective.
- Item 17; Carcinogenesis, Mutagenesis, Impairment of Fertility sections of the labeling: The sponsor to forward comments as soon as possible.
- Item 26; Provider qualifications
  - Both the sponsor and FDA agree that the provider must be able to assess duration of pregnancy accurately and to diagnose ectopic pregnancies.
  - FDA requests that the ability to perform vacuum aspirations and/or D& Cs be added to provider qualifications. Providers also need to have access to emergency services. The need for surgical intervention is predictable unlike with other drugs. All OB/GYNs and other practitioners of women's health have these skills. The countries with experience with mifepristone have tight provision of complete services and have a long record of good outcomes.
  - The sponsor suggested that this was an unnecessary qualification because:
    - 92% of women will not need follow-up surgical abortion or D&C.
    - Services needed to address incomplete abortion or heavy bleeding after a medical abortion procedure are the same as those needed to take care of a spontaneous abortion (miscarriage). These services are well established and generally accessed through referral to the appropriate provider.
    - Educational materials about the safe application of the regimen will stress the need for providers to plan ahead for possible follow-up care. Materials will also be designed to promote understanding of the regimen, risks, and possible need for further intervention.
    - There is a large off-label practice experience with medical abortions in the U.S. that may indicate that the need for emergent treatment is rare and not usually immediate (follow-up intervention usually occurs 10 days or longer after aborting).
    - Other drugs do not have this type of qualification restriction (e.g., Viagra's cardiovascular complications are usually handled by referral).
- Item 28; Requiring the use of ultrasound to date pregnancy and confirm expulsion: FDA agrees that ultrasound need not be required. However, it is suggested that the labeling recommend ultrasound as a useful diagnostic tool to accurately date pregnancy and confirm expulsion.
- Item 34 and 35; Patient agreement (informed consent):
  - FDA requests that an introductory paragraph be added describing the indication for mifepristone and the medical abortion regimen (e.g., how many pills will be given, number of return visits).
  - FDA agrees that it is not necessary to require the patient to take the drugs in the presence of a healthcare provider.
  - FDA requests that the patient be asked to initial each bulleted item on the patient agreement. This procedure is similar to that for oral contraceptives dispensed by certain organizations, [redacted] and Norplant.
  - The sponsor maintains that initialing individual bullets is not necessary because:
    - The signature is all that is required to document informed consent.
    - Informed consent for abortion is required by state law. It is in the physician's best interest to ensure that the patient gives informed consent.
    - In actual practice, initialing individual items on consent forms is not done.
    - The level of risk for mifepristone is not commensurate with this procedure.
    - The educational materials emphasize the need to obtain informed consent.

  - Ensuring informed consent is critical. FDA requests that the sponsor propose how to monitor this procedure (e.g., sending a copy of the document to the distributor, random audits at the clinic, or other suggestions).
  - FDA requests that the consent include information about the potential teratogenic risk associated with misoprostol if the pregnancy fails to be terminated. The sponsor noted that information on this risk is already included in the labeling and educational materials.
- Additional issues:
  - Mifepristone is metabolized by the P450 system. FDA is checking on whether the route of metabolism and drug interaction with other drugs metabolized by the same route need to be mentioned in the labeling
  - Subpart H: FDA has not made a final decision as to whether Subpart H restrictions on distribution will be applied.

Agreements:

- Sponsor proposals in items 4, 5, 6, 7, 9, 11, 12, 14, 15, 18, 19, 20, 21, 24, 25, 27, 28, 29, 30, and 32 are acceptable.
- Attestation by the physician to having specified qualifications is acceptable.
- Ultrasound is not required for pregnancy dating or confirmation of expulsion.

Action Items:

- FDA to forward decision on confidentiality issue to the sponsor.
- Sponsor to submit revised Prescriber's Letter and training/educational materials for registration packet.
- Sponsor to examine the proposal for incorporating the Day 3 clinic visit into the treatment regimen initially with a plan for re-evaluating the need for it.
- Sponsor to re-examine data from clinical trials to determine the correct rate of curettage performed for heavy bleeding.
- Sponsor will re-examine the data they have on patients who received oral misoprostol later than 48 hours after taking mifepristone and look in the literature for additional information to address the question of regimen effectiveness.
- Sponsor to submit revised labeling incorporating changes discussed.
- Sponsor and FDA will consider the qualifications of providers again.
- Sponsor will consider requests to incorporate the drug indication, regimen, and initialing into the patient agreement (consent form). Sponsor to submit a revised patient agreement and plan for monitoring compliance with informed consent procedures.
- FDA to determine whether the route of drug metabolism and related potential drug interactions needs to be added to the labeling.
- FDA to determine whether the application will be approved under Subpart H requirements.
- FDA to schedule a meeting as soon as possible to continue discussion on outstanding issues.

Outstanding issues:

- [redacted]
- Contents of the Boxed Warning (labeling)
- Day-3 return visit
- Provider qualifications
- Patient agreement (consent form)- revisions, monitoring compliance with informed consent, initialing individual items
- Subpart H

Minutes Preparer

Concurrence, Chair

Note to sponsor: These minutes are the official minutes of the meeting. You are responsible for notifying us of any significant differences in understanding you may have regarding the meeting outcomes.

APPEARS THIS WAY
ON ORIGINAL

ORIGINAL

Population Council

Sandra P. Arnold
Vice President
Corporate Affairs

September 15, 2000

BL
ORIG AMENDMENT

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

Re: NDA 20-687, Mifepristone 200 mg Oral Tablets;
Amendment 060; Further response regarding
open issues

Dear

I am enclosing the prescribing information (package insert), Prescriber's Agreement, Order Form, Medication Guide, and Patient Agreement, as revised in accordance with discussions this week.

Also, although we do not believe that the application of 21 CFR Sections 314.500-560 is appropriate, we agree to its application as part of the approval of this NDA.

We commit to conduct post-approval the following studies:

I. A cohort-based study on safety outcomes of patients having medical abortion under the care of physicians with surgical intervention skills as compared to physicians who refer their patients for surgical intervention. Previous study questions about age, smoking, follow up on day 14 (compliance with return), as well as an audit of signed Patient Agreement forms, will be incorporated into this study.

II. A surveillance study on outcomes of ongoing pregnancies

Sincerely,

Sandra P. Arnold 9/18

Sandra P. Arnold

REVIEWS COMPLETED

CSO ACTION:
☐ LETTER ☐ N.A.I. ☐ MEMO

CSO INITIALS DATE

One Dag Hammarskjold Plaza, New York, New York 10017
Telephone: (212) 339-0663 Facsimile: (212) 980-3710 Email: sarnold@popcouncil.org http://www.popcouncil.org

50 Page(s) Redacted

Draft

Labeling

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

Date: 14-Aug-1996 10:04am EDT
From:

Dept: HFD-344
Tel No:

TO:

Subject: audit of studies submitted for NDA 20-687

Studies conducted by Dr. Aubeny, Paris and in Valencienes were submitted in support of NDA 20-687 were audited. No major problems were found. DSI will not recommend that these studies not be used in support of the submitted NDA.

APPEARS THIS WAY
ON ORIGINAL

Memorandum

FEB 11 2000

To: NDA 20-687, Mifepristone Tablets, 200 mg

From: /S/ 2/11/00

Date: February 11, 2000

Re: T-con with Office of Compliance/Division of Prescription Drug Compliance and Surveillance

---

I contacted to discuss whether the shipping cartons need to have the same full labeling as on the blister package and secondary carton. I described to him that the shipping configuration is as follows: unit dose blister packages are placed in secondary cardboard cartons, then 12 cartons are placed in an intermediate cardboard shipper and sealed with tamper-proof tape, and finally 8 intermediate shippers are placed in a cardboard shipping case and sealed with tamper-proof tape. The intermediate shippers and shipping cases are only labeled with the NDC number, shipper code or case code, expiration date, and bar code recommendation was that the labeling was adequate because the blister package and secondary package have the complete labeling information.

cc:
Orig. NDA #20-687
HFD-580/Division File
HFD-580
HFD-580/

APPEARS THIS WAY
ON ORIGINAL

Filename:

Electronic Mail Message

Date: 8/14/00 8:41:19 AM
From: [redacted]
Subject: Re: NDA 20-687 mifipristone

[redacted]

I've looked over the information you sent to me on consult. A claim of categorical exclusion or requirement for an EA only applies to an entire application. Therefore a request for a categorical exclusion for a part of an application (e.g., drug substance manufacture) is not appropriate. Additionally since the EA regulations were revised in 1997 environmental information for manufacturing sites is not normally required.

On July 11, 1996 we signed a finding of no significant impact (FONSI) for NDA 20-697. At that time (before regulation change) a categorical exclusion claim could not be made for NDA applications and an abbreviated EA was submitted for this NDA. The additional information (I assume for a different manufacturer of ds) does not affect the previous EA and FONSI because no ds manufacturing site was identified in the public part of the EA.

[redacted]

>Hi[redacted]
>
>Per[redacted]equest, last week I forwarded to you via office mail
>the "Environmental Assessment" for this NDA. They had refused to submit
>a request for categorical exclusion is what I understand. Our due date
>(action goal date) is September 30, 2000.
>
>Could you confirm when you recieve the consult request and if you
>anticipate any problems in returning the consult by early September?
>
>Thanks,
>
>[redacted]

APPEARS THIS WAY
ON ORIGINAL

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
Drug: (Mifepristone) Tablets
Type of Letter: Approvable

Clinical Division: HFD-580

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

APPEARS THIS WAY
ON ORIGINAL

ORIGINAL

July 24, 1997

NDA 20-687
Mifepristone
The Population Council

Questions Raised at July 21, 1997 Labeling Meeting

1. There was no mention made in the pivotal French trials of women who received mifepristone immediately after removal of an IUD.

2. Both pivotal French protocols required a hemoglobin determination before administration of mifepristone. Anemic subjects were excluded from both pivotal French studies. Draft labeling submitted March 31, 1997 mentions in the PRECAUTIONS section that, "There are no data on the safety and efficacy of mifepristone in women with ---- severe anemia." There is also a statement in the WARNINGS section that, "Vaginal bleeding occurs in almost all patients during the treatment procedure."

[redacted]

3. There were two subjects with amenorrhea of 49 days or less (the population for whom the drug is indicated) who received blood transfusions. These were patients 188 and 880. Protocol FF/92/486/24 permitted subjects with amenorrhea of 63 days or less to be studied. Subject 751 with amenorrhea of 60 days had a complete abortion and was also transfused. Subject 1117 with amenorrhea of 54 days had an ectopic pregnancy and was also transfused.

/S/

Noted: /S/ 8/7/97

APPEARS THIS WAY
ON ORIGINAL

DEPARTMENT OF HEALTH & HUMAN SERVICES

/S/
Public Health Service

Biopharm labeling

Food and Drug Administration
Rockville MD 20857

NDA 20-687

INFORMATION REQUEST LETTER

Population Council
Attention: Sandra P. Arnold,
VP Corporate Affairs
One Dag Hammarskjold Plaza
New York, New York 10017

JUL 25 2000

Dear Ms. Arnold:

Please refer to your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Mifepristone Tablets.

We also refer to our July 19, 2000, meeting with representatives from the Population Council, Danco Laboratories, LLC, and Ms. Nancy Buc. From the meeting, one of our action items was to determine whether information regarding the metabolic pathway for Mifepristone and potential drug interactions should be added to the drug labeling. We completed review of recent literature and conclude that the following revisions to the professional labeling are needed (deletions are shown with strike-out, additions are underlined):

1. CLINICAL PHARMACOLOGY; Metabolism subsection:

2. PRECAUTIONS; Drug Interactions subsection:

[redacted]

Appropriate revisions are also needed for the patient information sheet (patient package insert) to incorporate the information about potential drug/food interactions related to metabolism of mifepristone.

In addition, in a telephone conversation with Ms. Shelly Clark of the Population Council I conveyed the following revision requested for the patient agreement. The revisions are to the sixth bullet of the draft agreement (exhibit H) of the briefing materials submitted July 5, 2000, for the July 19, 2000, meeting as follows (deletions are shown with strike-out, additions are underlined):

[redacted]

Please include the above requests, with any comments you have, in the pre-meeting materials you will be submitting on July 28, 2000, in preparation for our next meeting on August 4, 2000.

If you have any questions, call me, at (301) 827-3143.

Sincerely,

[redacted] /S/ 7/25/00

[redacted] Regulatory Affairs
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Drug Product:

If you have any questions, contact [redacted] Regulatory Health Project Manager, at [redacted]

Sincerely,

[redacted]

Division of Reproductive and Urologic Drug Products
(HFD-580)
Office of Drug Evaluation III
Center for Drug Evaluation and Research

APPEARS THIS WAY
ON ORIGINAL

MAY - 9 1996

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: May 5, 1996

FROM: [redacted] 5/7/96
CSO, DMEDP

SUBJECT: NDA 20-687 Clinical Audits

TO: [redacted]
Division of Scientific Investigations, Office of Compliance, (HFD-344).

THROUGH: [redacted] 5/8/96
Division of Metabolism and Endocrine Drug Products (HFD-510),
ODE II

Attached please find the names and locations of the study sites which comprise the two pivotal trials for this NDA which is for a new molecular entity. We request that you conduct clinical audits of a selection of these sites as part of our review of this NDA.

ENCLOSURES

cc:
Orig. NDA
HFD-510
HFD-510/[redacted]
HFD-510/[redacted]/4.17.96/n20687.mem
concurrences: [redacted] 4.19.96/5.8.96

MEMORANDUM

APPEARS THIS WAY
ON ORIGINAL

Meeting Minutes

Date: August 4, 2000 **Time:** 11 am – 12:30 pm. EST **Location:** Parklawn; Chesapeake Room

NDA 20-687 **Drug:** mifepristone **Indication:** medical abortion

Sponsor: Population Council

Type of Meeting: aprovability issues

Meeting Chair: [redacted] Office of Drug Evaluation III (ODE III, HFD-103)

Meeting Recorder: [redacted] Regulatory Affairs, ODE III

FDA Attendees:

[redacted] ODE III (HFD-103)
[redacted] Regulatory Affairs, ODE III (HFD-103)
[redacted] Division of Reproductive and Urologic Drug Products (DRUDP; HFD-580)
[redacted] DRUDP (HFD-580)
[redacted] DRUDP (HFD-580)
[redacted] Division of Drug Risk Evaluation II (DDRE II; HFD-440)
[redacted] DDRE II (HFD-440)
[redacted] Division of Drug Marketing, Advertising and Communications (DDMAC; HFD-42)
[redacted] DDMAC (HFD-42)
[redacted] DDMAC (HFD-42)
[redacted] Drug Program Review
[redacted] Center for Drug Evaluation and Research (HFD-005)
[redacted] Office of the Chief Counsel (GCF-1)
[redacted] Office of the Chief Counsel (GCF-1)

External Participants:

Sandra P. Arnold, VP, Corporate Affairs, Population Council
[redacted], President & CEO, Danco Laboratories, LLC
Beverly Winikoff, M.D., M.P.H., Program Director, Reproductive Health, International programs Division, Population Council
Richard U. Hausknecht, M.D., Medical Director, Danco Laboratories, LLC
Shelley D. Clark, Ph.D., Program Associate, Population Council
Heather M. O'Neill, Director of Public Affairs, Danco Laboratories, LLC
Nancy L. Buc, Buc & Beardsley, Counsel to Population Council and Danco Laboratories, LLC

Meeting Objective: To discuss approvability issues related to labeling and thedistribution plan for mifepristone, post-marketing and risk management issues that will affect the drug's life cycle (e.g., monitoring of adverse events, future generic entries into the market, drug class, further development).

Discussion:

Note: Item numbers correspond to questions and comments listed in the sponsor's July 27, 2000, submission of briefing documents for this meeting.

- The sponsor is targeting the first week of August for submitting requested chemistry, manufacturing, and controls information.
- Item 1; Boxed Warning: deferred
- Items 2 and 8; Physician training:
  - Materials and information sources proposed to support physician training will include the prescriber's letter, professional labeling, patient information sheet, patient agreement, the Danco web site, and the National Abortion Federation. The written materials will be packaged together with a cover letter.
  - FDA suggested that information regarding post-marketing studies (Phase 4 commitments) should also be included so that physicians can respond appropriately to surveillance on women who experience failure on the medical abortion regimen. The sponsor stated that information will be in the professional labeling.
  - The package of information provided to the physician needs to be complete and reasonable so that difficulty accessing information from other sources (e.g. the internet) is not an issue.
- Item 10; Incidence of need for curettage: agreement reached that the incidence was 1%.
- Item 13; Labeling revision regarding timing of dose of misoprostol: FDA requested deletion of the phrase, [redacted]
- Items 16, 17, and 33; labeling revisions: FDA agrees to sponsor's proposals.
- Items 3, 22, 23, and 31; Day 3 visit:
  - FDA renewed the assertion that the Day 3 visit should be required as it was in clinical trials. A 3-4 hour observation period following administration of misoprostol would be optional.
  - The sponsor suggested that the Guadeloupe study (retrospective study of actual use of medical abortion using mifepristone (oral) and misoprostol (vaginal administration)) supports their position that permitting women to take the misoprostol portion of the regimen at home is successful and safe. FDA noted that 4% of women in this study took the misoprostol incorrectly at home.
  - [redacted]
- Item 26; Provider qualifications:
  - FDA requested input on how the sponsor will fulfill their phase 4 commitment to monitor adequacy of provider qualifications. This may be more important if services for surgical intervention (vacuum aspiration, D&C) for complications are handled by referral.
  - Sponsor commented that monitoring qualifications is not needed because:
    - Monitoring provider self-attestation for having qualifications might give counter-intuitive results.
    - Mifepristone should not be equated with other approved drugs with significantly more serious safety issues. Therefore, mifepristone should not be held as an example for managing serious safety issues.
    - There were some physicians in the clinical trial who referred patients to other healthcare practitioners for care when complications occurred.
    - Surgical intervention following the medical abortion regimen is almost never needed immediately and, therefore, does not constitute an emergency.
  - FDA stated that consideration of approving different provider qualifications than were conditions of the clinical trials will require documentation justifying why it is appropriate to deviate from

what was discussed and agreed to earlier in the review. Monitoring performance outcomes of referring doctors will be viewed as part of a risk management program.

- Subpart H and Medication Guide:
  - FDA has determined that the application will be acted on under 21 CFR 314.520 (approval with restrictions to assure safe use- Subpart H) and is considering a requirement to provide patient information under 21 CFR 208 (Medication Guide). This will add a regulatory requirement supporting the importance of patient education since the provider will be required to give the Medication Guide to the patient. Each program is designed to address different issues.
  - FDA is in the process of reviewing the proposed patient package insert. Revisions will be sent to the sponsor in the format of a Medication Guide.
  - The sponsor requested a commitment from FDA, if they agree to approval under Subpart H and a Medication Guide, that any information FDA issues regarding the drug emphasizes that these regulations were used to ensure patient education.
- Phase 4 commitments:
  - Commitments (comments refer to the following numbers):
    - #1: Monitoring the adequacy of the distribution and credentialing system.
    - #2: Follow-up on the outcome of a representative sample of mifepristone-treated women who have surgical abortion because of the method failure.
    - #3: Ascertain the frequency with which women follow the complete treatment regimen and the outcome of those who do not.
    - #4: Assess the long-term effects of multiple use of the regimen.
    - #5: Study the safety and efficacy of the regimen in women under 18 years of age, over age 35, and in women who smoke.
    - #6: Ascertain the effect of the regimen on children born after treatment failure.
  - Prioritization of commitments:
    - Commitments # 1, 2, 3 and 6 could be incorporated into the risk management program.
    - Commitments # 4 and 5 are of lower priority than those incorporated into the risk management program.
  - Regarding commitments #1, 2, 3, and 6 to be incorporated into monitoring of the distribution system:
    - The commitments should be redesigned to evaluate the proposed physician qualifications and referral system for managing complications, for example, follow-up on treatment failures related to qualifications. Focus monitoring on the Day 14 visit rather than Day 3.
    - The commitment should also be designed to ascertain the effect of the regimen on children born after treatment failure.
  - Commitment #6 should focus on the outcome of the child at time of delivery rather than long-term effects.
  - The sponsor stated that the commitments are no longer relevant and requested re-evaluation of them because:
    - More is known now about the drug and there is more experience with medical abortion regimens than in 1996 when the commitments were made.
    - The commitments will infringe on privacy issues related to abortion.
    - The commitments were made by individuals unaware of the drug approval process or what the commitments would mean in terms of resources.

Action items

- Sponsor to consider and respond to reco...mendations made regarding the Day 3 visit, phase 4 commitments, and monitoring physician qualifications.
- FDA to make final determination on need for Medication Guide.

- FDA to schedule follow-up meeting.

Pending items

- Further discussions on labeling, including the Boxed Warning and Medication Guide.
- Phase 4 commitments.
- Monitoring provider qualifications.

/S/ 9/20/00
Minutes Preparer

/S/ 9/20/00
Concurrence, Chair

Note to sponsor: These minutes are the official minutes of the meeting. You are responsible for notifying us of any significant differences in understanding you may have regarding the meeting outcomes.

APPEARS THIS WAY
ON ORIGINAL

Teleconference Minutes

Date: September 25, 2000 **Time:** 3:50 – 4:00 PM **Location:** Parklawn; 17B-45

NDA 20-687 **Drug:** Mifepristone 200 mg

Indication: induction of abortion

Sponsor: Population Council

Type of Meeting: Labeling

Meeting Chair:

External Lead: Nancy Buc, Buc and Beardsley

Minutes Recorder:

FDA Attendees:

Office of Evaluation III (ODEIII; HFD-103)
Project Management Staff, ORUDP (HFD-580)

Meeting Objective: To discuss the Package Insert for this product.

Discussion:

- in the last paragraph, on page 11, the sentence should be revised to read as follows
- it is acceptable to delete in the **WARNINGS** and **INDICTIONS** sections, (p. 5) and (see PRECAUTIONS, Pregnancy)." (p. 6)

Action Items:

- Nancy Buc will discuss these recommendations with Population Council and respond via fax followed by hard copy with revised labeling if acceptable

/S/
Minutes Preparer

/S/
Concurrence, Chair

APPEARS THIS WAY
ON ORIGINAL

Population Council

Sandra P. Arnold
Vice President
Corporate Affairs

September 27, 2000

[redacted]

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

Re: NDA 20-687 Mifepristone 200 mg Oral Tablets;
Amendment 067; Revisions to Package Insert and
Prescriber's Agreement/Order Form

Dear [redacted]

I am enclosing a revised package insert and a revised Prescriber's Agreement/Order Form. In accordance with telephone discussions today about training opportunities, we have deleted the penultimate paragraph (beginning [redacted] under DOSAGE AND ADMINISTRATION in the package insert, the last paragraph of text (beginning [redacted] .") in the Prescriber's Agreement, and [redacted]

Sincerely,

[redacted]

Sandra P. Arnold /mb
Sandra P. Arnold

One Dag Hammarskjold Plaza, New York, New York 10017
Telephone: (212) 339-0663 Facsimile: (212) 980-3710 Email: samold@popcouncil.org http://www.popcouncil.org

Population Council

Sandra P. Arnold
Vice President
Corporate Affairs

October 25, 1999

VIA FEDERAL EXPRESS

[redacted]

[redacted]

Dear Dr. [redacted]

This letter is in response to your inquiry concerning Roussel Uclaf's reasons for deciding not to market their product, mifepristone, originally known as RU-486, in the United States. As we believe you know, Roussel Uclaf decided in 1988 to withdraw mifepristone from the French and other markets in which it had been launched; this decision seemed to have been made on the basis of business pressures brought on the company by various constituencies in France and elsewhere in Europe. However, when the decision was announced, the French government took action to force Roussel Uclaf to continue to produce and market the product, stating that mifepristone was the moral property of French women. Roussel Uclaf reluctantly resumed providing the drug.

In the United States, there was considerable interest in the compound from reproductive rights activists and women's groups, and pressure was put on Roussel to market the product here. However, Roussel was unwilling to bring the drug into the United States, despite the fact that it held a US patent on it. Roussel, and its successor company Hoechst Marion Roussel (HMR), have for many years publicly expressed an extremely elevated level of fear as to the consequences for them of being identified as involved with mifepristone in the United States.

These concerns extend back to 1989 when clinical trials in California had to be stopped at the request of the company. They cited fear of public reaction that would be harmful to their interests. On many occasions Roussel (and subsequently HMR) executives expressed a very strong fear of adverse consequences if they were involved in bringing this product to the United States market. There is no question that this very high level of fear prompted many actions over a period extending across several years.

One Dag Hammarskjold Plaza, New York, New York 10017
Telephone: (212) 339-0663 Facsimile: (212) 980-3710 Email: samold@popcouncil.org http://www.popcouncil.org

In January 1993, the just-elected President Clinton stated that bringing mifepristone to the United States was a priority. In follow-up, in February and March 1993, Donna Shalala, the Secretary of Health and Human Services, and David Kessler, then head of the Food and Drug Administration, communicated with Roussel executives to ask them to bring the product to the United States. Roussel consistently refused to be directly involved in this manner, citing commercial and personal risk, as well as the prevalence of litigation in the U. S. as their reasons. Roussel announced in April 1993 that they would instead transfer U.S. patent rights to the Population Council; the Council would conduct clinical trials, file the New Drug Application, and arrange for the manufacture and distribution of mifepristone in the United States.

More than 14 months of negotiations among the Council, Roussel and others were needed to find the administrative and insurance arrangements that would allay Roussel's concerns. Over 20 meetings involving the principals, scientists, and counsel were held with Roussel, Health and Human Services, and the Food and Drug Administration in New York, Paris, and Washington, D.C. Roussel's demands, as communicated to all parties involved, were directly related to their concerns regarding boycott, violence inflicted on their staff and facilities, and litigation, and included demands for indemnification from prosecution and/or harassment to be offered by the U. S. government.

It was not until May 1995 that the patent transfer was concluded. Roussel tried strenuously to have the U. S. administration extend the anti abortion-violence bill to cover all those economically or functionally associated with abortion provision. Roussel did not succeed, but these matters delayed the transfer by many months.

Since the transfer of the patent was made to the Council at no cost, and since cost was never discussed, it is absolutely clear that those 14 months of negotiations with the Population Council and others were focussed on meeting the concerns and fears of Roussel. These concerns did not abate even though they were not to be involved directly in bringing the product to the U. S. market. It was their view -- a view buttressed by the disorder and disruption at U. S. abortion clinics -- that the level of violence and animosity created around this issue would be such as to harm their interests. Repeatedly in this time, there were expressions of fear of injury to plant and personnel, boycott, repercussions on other products, and litigation.

After the patent transfer, Roussel/HMR fears continued to manifest themselves in their policies. In April 1998, HMR very speedily divested itself of all remaining rights to mifepristone, giving these to Exelgyn, a French company formed by Edouard Sakiz, the former CEO of Roussel. The Council was told that the reason for this very abrupt divestiture was that certain customers had threatened to withhold major purchases from the company as long as it was still linked to mifepristone in any fashion.

There is no question that continuing, pervasive fear of commercial, civil and physical violence and harm was a motivating factor throughout for these companies. This was expressed to us on many

occasions. delayed negotiation for many months, and continued to be brought forward as the underlying rationale for most of their policy positions.

We have attached a copy of a recent article from the *Toronto Sun* that discusses many of these issues.

Very truly yours,

Sandra P. Arnold

Margaret Catley-Carlson

Oct 5/99

Enclosure

APPEARS THIS WAY
ON ORIGINAL

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE:

FROM: Statistical Reviewer (HFD-715) TST 9/27/00

THROUGH: [redacted] (HFD-715) TST 9/27/00

TO: NDA 20-687 (HFD-580)

SUBJECT: Efficacy of Mifepristone by age,
submission dated September 12, 2000

My previous review of "efficacy of mifepristone by age" includes an evaluation of the results reported by Spitz et. al[1]. I concluded the Spitz et al article cannot be used to determine if the success rate is unrelated to age, because a test of this relationship was not reported in the article.

In response, the applicant has now submitted an analysis to support the conclusion in the article by Spitz et al that outcomes are unrelated to age. This submission contains a chi-square test of independence between efficacy of mifepristone and age in the U.S. clinical trials, and the underlying contingency table used for the test.

My evaluation of this information concludes the success rate decreases as age increases. This conclusion disagrees with the applicant's conclusion that outcomes are unrelated to age. This disagreement is due to the handling of age in the analyses. My analyses consider age as an ordinal variable; the applicant's analyses consider age a nominal variable.

New analysis of the relationship between efficacy and age:
The age groupings differ from those reported in the clinical study reports. Whereas, the study reports break age into 5 categories, this submission combines the two youngest age categories into a single category (see Table 1).

Using a Pearson chi-square test, the applicant reports a p-value of 0.222. This result leads to their conclusion that age and outcome are unrelated.

---

[1] IM Spitz, CW Bardin, L Benton, A Robbins; "Early pregnancy termination with mifepristone and misoprostol in the United States," New England Journal of Medicine, 1998.

Table 1. Summary of Success Rates by Age Category – Spitz et. al

Age (years)	N	Rate of success
<25	290	93.8%
25-29	251	93.2
30-34	180	90.0
>35	106	88.7
Total	827	92.1

Source of data: submission dated September 12, 2000

Unlike the Pearson chi-square reported by the applicant, my analyses take advantage of the ordering of the age categories. I analyzed the effect of age on the efficacy of mifepristone by several methods:

1. Logistic regression with success rate as the dependent variable and age as a predictor, where age was coded as either 1, 2, 3, 4, or 5.
2. Logistic regression with success rate as the dependent variable and age as a predictor, where age was coded as the mid-point of the age categories: 20.5, 27, 32, or 37.
3. Linear regression with success rate as the dependent variables and age as a predictor, where age was coded as the mid-point of the age categories.

In each case, the results indicate efficacy decreases with increasing age with a p-value of approximately .05. This p-value is somewhat higher than the 0.03 reported in my earlier review. This is due to combining the two youngest age categories.

When the two youngest age categories (<20 years and 20-24 years) are combined, an observed increase in success rate among the youngest women is obscured:

Table 2. Summary of Success Rates by Age Category

Age (years)	N	Rate of success
<20	57	98.2%
20-24	233	92.7
25-29	251	93.2
30-34	180	90.0
>35	106	88.7

Source of data: NDA

Reviewer's conclusion

My conclusion is the efficacy of mifepristone decreases as age increases.

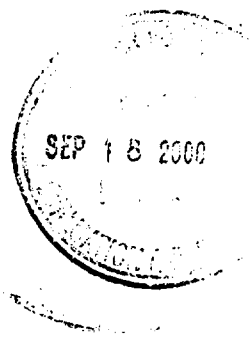
Archival NDA 20-687
HFD-580

ORIGINAL

Danco Laboratories, LLC

September 15, 2000

NEW CORRESP



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

Re: NDA 20-687, Mifepristone 200mg Oral Tablets
- Amendment 061 - Initial Promotional Materials

Dear [redacted]

I am enclosing 10 copies of our promotional materials that we wish to utilize around the NDA approval date. As agreed, could you please provide us with DDMAC's review comments as rapidly as possible, but no later than Wednesday, September 20. Please feel free to call me at any time if anything needs immediate clarification or discussion.

The materials enclosed are as follows:

- Formal announcement (press release)
- Fact sheet
- Fast Facts
- Video News Release (VNR) script
- Patient Brochure
- Tollfree Number script
- Website copy
- Provider Announcement (fax)

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Additional materials that we need to use immediately following approval will be submitted for expedited review as soon as we have received your feedback on the first batch of materials.

Thank you for your assistance.

Sincerely,

/S/

/dns
Enclosures

Cc: Sandra P. Arnold – Population Council

APPEARS THIS WAY
ON ORIGINAL

[redacted]

ORIGINAL

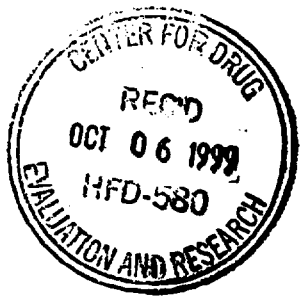
ORIG AMENDMENT

BM

Population Council

Sandra P. Arnold
Vice President
Corporate Affairs

Initial
10/7/99
/s/



October 5 1999

VIA FEDERAL EXPRESS

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

RE: NDA 20-687, Mifepristone 200 mg Oral Tablets

Dear [redacted]

Enclosed please find answers to the questions raised by [redacted] We have answered all of [redacted] questions except for the one concerning the number of subjects who had surgery for excessive, prolonged bleeding. We will provide the answer to this last question as soon as possible.

Please let us know if you need any additional information.

Very truly yours,

Sandra Arnold

Enclosures

cc: Shelly Clark
[redacted]
Dr. Frederick Schmidt
Dr. Beverly Winikoff

REVIEWS COMPLETED

CSO ACTION:
☐ LETTER ☐ E-MAIL ☐ MEMO

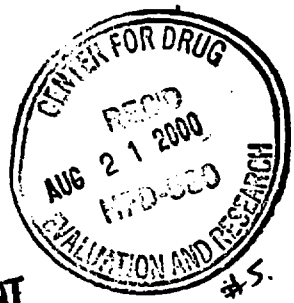
CSO INITIALS DATE

One Dag Hammarskjold Plaza, New York, New York 10017
Telephone: (212) 339-0663 Facsimile: (212) 980-3710 Email: sarnold@popcouncil.org http://www.popcouncil.org

Danco Laboratories, LLC

August 18, 2000

ORIGINAL



[redacted]

ORIG AMENDMENT

DC See Chem. Rev #5.

/S/

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

Re: NDA 20-687, Mifepristone 200mg Oral Tablets

Dear [redacted]

Per your discussion with Nancy Buc, I am enclosing our preliminary response to the Form 483 Inspectional Observations issued at the conclusion of the recent inspection of our Drug Substance plant. This response was sent initially on August 10 to [redacted]

Sincerely,

/S/

/dns
Enclosure

cc: Sandra P. Arnold – Population Council
[redacted] FDA
FDA (no enclosure)

REVIEWS COMPLETED	
CSO ACTION: ☐ LETTER ☐ N.A.I. ☐ MEMO	
CSO INITIALS	DATE

Danco Laboratories, LLC

September 8, 2000

DUPLICATE

[redacted]

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

SEP 11 2000

ORIG AMENDMENT

BC

Re: NDA 20-687, Mifepristone 200mg Oral Tablets

- Amendment 059 - Submission of Revised Mifepristone Substance Working Standard Specifications

Dear [redacted]

Following our conversations with [redacted] today, we have included [redacted] as an added specification for the mifepristone working standard.

Enclosed please find the revised Mifepristone Working Standard Specifications.

Please do not hesitate to contact me if you have any questions on the submitted material.

Sincerely,

/S/

[redacted]

/dns
Enclosure

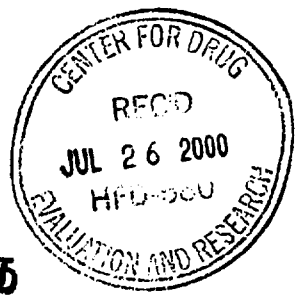
cc: Sandra P. Arnold – Population Council

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

Danco Laboratories, LLC

July 25, 2000

ORIGINAL



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

BC

Re: NDA 20-687, Mifepristone 200mg Oral Tablets
Amendment 053 - Additional Stability Data on Drug Product
- Revised Stability Commitment
- Mock-Up Sample of the Primary Package and its Blister Card

Dear

Pursuant to our telephone conversation with on July 20, 2000, we are providing the agency with the following information:

A. Additional Stability Data on Drug Product

Twelve (12) and nine (9) month long term stability data on Danco's Drug Product Lots #99005 and #99007, respectively, are enclosed (see Attachment A). Six (6) month accelerated data on these same two production-scale lots were previously supplied in Amendment 040 dated January 28, 2000 (Lot #99005) and Amendment 044 dated April 20, 2000 (Lot #99007).

These new data continue to show excellent long-term stability performance for Danco Drug Product. These results, as well as the previously provided stability data on Roussel Drug Product, demonstrate that the initial expiration dating period should be established at months.

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

B. Revised Stability Commitment

We have revised the Stability Commitment (see Attachment B) to clearly indicate that a Prior Approval Supplement will be filed with FDA if Danco wishes to use pre-approval batch data to request extension of the initial expiration dating period.

In addition, we have corrected the typographical error in the cover page to Attachment C of Amendment 047, dated May 17,2000, to read "Drug Product" rather than "Drug Substance" (see Attachment C)

C. Mock-Up Sample of the Primary Package and its Blister Card (See Enclosure)

Each blister card has a designated "print area" where the following information will be printed: (1) the Lot/ID number (2) the expiration date and (3) the "data matrix square" represented by The unique Lot/ID number is composed of

Since the original production of the mock-up of the blister card and primary package, we have made the following changes which will appear on the final packaging:

- "MIFEPREX® (Mifepristone Tablets 200mg)" that appears on the package and the blister has been changed to "MIFEPREX® (Mifepristone) Tablets, 200mg".
- The following storage statement has been added to the blister card: " Store at 25°C (77°F)" .

We believe that the trademark is prominently placed on the primary package and that a location change would not improve its prominence.

Please do not hesitate to contact me if you have any questions on the submitted material.

Sincerely,

/S/

/dns
Enclosure
cc: Sandra P. Arnold — Population Council

REVIEWS COMPLETED	
CSO ACTION: ☐ LETTER ☐ N.A.I. ☐ MEMO	
CSO INITIALS	DATE

Danco Laboratories, LLC

August 21, 2000

ORIGINAL

[redacted]

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

ORIG AMENDMENT

AUG 2 2 2000

Re: NDA 20-687, Mifepristone 200mg Oral Tablets

- Amendment 055 - Submission of Additional Testing and Stability Data on Post Process Adjustment Drug Substance

Dear [redacted]

Consistent with the commitments made in Amendment 050 dated July 5, 2000 and Amendment 052 dated July 13, 2000, this Amendment 055 provides additional information on mifepristone Drug Substance manufactured by the adjusted process, which was described in Amendment 048, dated June 22, 2000. As we have previously discussed with [redacted] this additional information is intended to establish a link between the pre process adjustment and post process adjustment Drug Substance.

A- Post Process Adjustment Drug Substance Stability Data

As per our commitment in Amendment 052, we are now providing the six-month accelerated and long-term stability data on one post process adjustment Drug Substance batch #000105 (see Attachment A-1). These data show that there are no significant changes or trends from the zero time data after six months under either accelerated or long-term storage conditions. The results continue to be consistent with the results observed in both the accelerated and long-term studies on pre process adjustment batches.

In addition, consistent with our commitment in Amendment 052, we are also providing the two-month accelerated stability data on three post process adjustment Drug Substance batches #000501, #000502 and #000503 (see Attachment A-2). Again,

these data show consistency with previously reported stability data on the pre process adjustment Drug Substance batches. As previously agreed, the three-month and six-month accelerated stability data on Drug Substance batches #000501, #000502 and #000503 will be reported to the FDA when the data becomes available.

B. Dissolution Data on Drug Product made from Post Process Adjustment Drug Substance

As per our commitment in Amendment 050, we have manufactured a production batch of Drug Product (#20001) using post process adjustment Drug Substance. Tablets from this Drug Product batch have been subjected to a [redacted] study. These data (see Attachment B-1) show that dissolution results for Drug Product batch #20001 are comparable to the results previously obtained for Drug Product batch #99007 made from pre process adjustment Drug Substance (see Attachment B-2). We have presented below a summary table of data comparing Drug Product batch #20001 to Drug Product batch #99007.

Comparison of Dissolution Studies on Drug Product Made from Pre and Post Process Adjustment Drug Substance

Drug Product Lot. No.		99007			20001		
Drug Product Manufacture Date		October 1999			August 2000		
Drug Substance Lot No. Used		990103 (pre process adjustment)			991006 (post process adjustment)		
Drug Product Dissolution Rate Profile	Time (Min)	10	20	30	10	20	30
	Mean %	97	103	105	98	101	102

Overall, the additional results reported in this amendment continue to support our conclusion in Amendment 052 that the pre and post process adjustment Drug Substance are comparable and that either is acceptable for use in manufacturing finished Drug Product.

Please do not hesitate to contact me if you have any questions on the submitted material.

Sincerely,

/S/

/dns
Enclosure

cc: Sandra P. Arnold – Population Council

The Danco Group

March 30, 2000

noted
3/31/00

151

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

ORIG AMENDMENT

Re: NDA 20-687, Mifepristone 200mg Oral Tablets
- Amendment 043 - Response To Approvable Letter Dated February 18, 2000

42

Dear

This Amendment 043 is the complete response to the Approvable Letter dated February 18, 2000. It is comprised of one volume of responses plus two volumes of Safety Update Report #3 and one volume of International Product Labeling.

Please don't hesitate to contact me if you have any questions on the submitted material.

Sincerely.

/S/

REVIEWS COMPLETED

CSO ACTION

☐ LETTER

CSO INITIALS

Enclosures

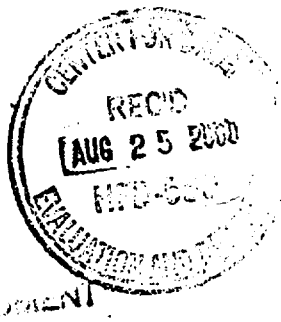
cc:
Sandra P. Arnold – Population Council
Frederick H. Schmidt – Population Council
Patricia C. Vaughan, Esq. – Population Council

FDA
Nancy L. Buc, Esq. – Buc & Beardsley

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

Danco Laboratories, LLC

August 24, 2000



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

Re: NDA 20-687, Mifepristone 200mg Oral Tablets

- Amendment 056 - Drug Substance Chemistry, Manufacturing and Controls (CMC)
  -Discontinuance of Protometric Release Method

Dear

Given the development, validation and implementation since January 1999 of a method for the Assay of Mifepristone, the original method will be discontinued as a release method for the drug substance, effective September 1, 2000. The manufacturer's Final Product Specifications for mifepristone drug substance have been revised to reflect that change (see enclosed).

Sincerely,

/dns
Enclosure

Cc: Sandra P. Arnold – Population Council

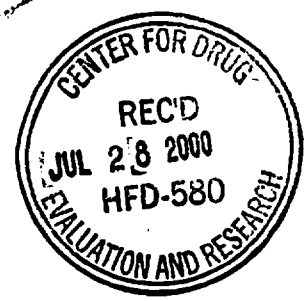
This document constitutes trade secret and confidential commercial information exempt from public disclosure under 21 C.F.R. 20.61. Should FDA tentatively determine that any portion of this document is disclosable in response to a request under the Freedom of Information Act, Danco Laboratories, LLC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

Population Council

Sandra P. Arnold
Vice President
Corporate Affairs

noted 7/29/00

ORIGINAL 1st



July 27, 2000

[redacted]

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

ORIG AMENDMENT

BL

REVIEWS COMPLETED

CSO ACTION:
☐ LETTER ☐ N.A.I. ☐ MEMO

CSO INITIALS DATE

Re: NDA 20-687, Mifepristone 200 mg Oral Tablets;
Amendment 054: Further response regarding labeling and distribution;
Follow up to July 19, 2000 Meeting

Dear [redacted]

We thought our July 19, 2000 meeting was very informative and helpful, and we appreciate your responsiveness and that of your colleagues. In this letter, we address the issues raised or left open at the July 19 meeting.

For the most part, we have used the same numbering system as we did in our July 5 letter. We have not used the captions from that letter, because many of the issues they raise have already been resolved; instead, we use new captions which capture the nature of the issue. The last issue discussed in this letter was not discussed in the July 5 letter and therefore has no number.

1. Black box warning

As you will see as you proceed through this letter, we propose two subjects for inclusion in a black box warning. First, we suggest that the physician be advised to plan for and organize

One Dag Hammarskjold Plaza, New York, New York 10017
Telephone: (212) 339-0663 Facsimile: (212) 980-3710 Email: sarnold@popcouncil.org http://www.popcouncil.org