

NDA 20-827
45-day Meeting Minutes
Page 4

6. Foreign labeling Rx & OTC Chi Aug. 1, 1997
7. Costa Rican population info. Dr. Davis Sept. 1, 1997

Minutes Preparer:

Christina Chi, Ph.D.

*Ph.D.
8/15/97*

cc: Original NDA 20-827

HFD-540/Div. Files
HFD-590/Div. Files
HFD-590/Meeting Minutes files
HFD-40/DDMAC/KLechter
HFD-40/DDMAC/JSpearmon
HFD-560/DivDir/DBowen8/6/97
HFD-560/MO/LChin7/22/97
HFD-560/MO/HCothran5/29/97,7/22/97
HFD-560/SPM/RCook
HFD-560/PM/SWalther7/72/97
HFD-590/ActDivDir/MGoldberger
HFD-590/MTL/BLeissa7/17/97
HFD-590/MO/JWinfield
HFD-590/MO/DDavis7/18/97
HFD-590/SupMicro/SLard
HFD-590/Micro/LGosey 5/27/97
HFD-590/Chem/NSchmuff
HFD-590/Chem/DMatecka
HFD-590/Pharm/OMcMaster
HFD-590/SupBioPharm/CSahajwalla
HFD-590/BioPharm/PColangelo
HFD-590/PM/CChi
HFD-725/ActSupStat/NSilliman
HFD-725/Stat/CDixon
HFD- 344/DSL/MThomas

Concurrence:

Carmen DeBellas, SPM., DSPIDP5/28/97
Brad Leissa, M.O. T.L., DSPIDP7/17/97

Initialed by: CChi
final: 8/15/97

MEETING MINUTES

MAY 23 1997

45-Day Filing Meeting**CLINICAL PHARMACOLOGY / BIOPHARMACEUTICS**

NDA: 20-827**Submission Date:** March 31, 1997**Drug Product:** Miconazole Nitrate 4% Vaginal Cream
Trade Name: MONISTAT® 3**Sponsor:** Advanced Care Products
New Brunswick, NJ**Category:** S**OCPB Reviewer:** Philip M. Colangelo, Pharm.D., Ph.D.
OCPB Log-In: April 21, 1997

I. BACKGROUND

Miconazole nitrate is a synthetic imidazole-derivative antifungal agent. The product, MONISTAT®, has been approved in several dosage forms for use in the U.S. and several other countries worldwide for the treatment of vulvovaginal candidiasis. MONISTAT® has been on the U.S. market for prescription use since 1974, and is currently available as a 2% (100 mg) vaginal cream, 100 and 200 mg vaginal suppositories, 100 mg tampon, and combination packs of suppositories (100 or 200 mg) and external vulvar cream for 3 to 7-day treatment of vaginal candidiasis. The 2% cream and 100 mg vaginal suppositories have been approved from prescription to over the counter (OTC) use for 7-day treatment since 1991; the combination packs have been approved for 3 or 7-day OTC use since 1993.

In this current submission, the sponsor is seeking approval to market a higher strength 4% miconazole nitrate cream for OTC use as a 3-day treatment for vaginal candidiasis under the tradename MONISTAT® 3 Vaginal Cream. It will be specifically indicated for the treatment of vaginal candidiasis in women who have been previously diagnosed with vaginal yeast infections by their doctor and recognize the same condition/symptoms again. The proposed dosage regimen is a single 200 mg dose (one full applicator) of the 4% cream intravaginally for 3 days. This regimen is identical to that of the currently marketed OTC MONISTAT® 3 Combination Pack containing the 200 mg suppositories and external vulvar cream. The rationale for development of this

newer product appeared to be driven by consumer preference, which according to the sponsor, was for a 3-day, cream-based treatment over the OTC products currently available (i.e., MONISTAT® 7 Vaginal Cream or Suppositories; MONISTAT® 3 or 7 Combination Packs). Thus, the 4% cream was developed using an improved base which is purported to retain viscosity at body temperature, and thereby reduce drip from the vagina.

II. SYNOPSIS

A copy of the proposed OTC labeling, including an educational brochure for the patient, is provided as **Attachment 1**. **Item 6: Human Pharmacokinetics and Bioavailability** of this NDA submission contained one study to compare the absorption and systemic exposure to miconazole resulting from single and repeated intravaginal dose administration of the proposed 4% miconazole cream in the new more viscous base formulation (i.e., 200 mg MONISTAT® 3 Vaginal Cream x 3 days) to that of a 2% cream in the same new base formulation (i.e., 100 mg MONISTAT® 7 Vaginal Cream x 7 days), and to that of the 2% cream in the currently marketed less viscous base formulation (i.e., 100 mg MONISTAT® 7 Vaginal Cream x 7 days). The intent of this study was not to establish the *in vivo* bioequivalence of the proposed 4% cream, but rather to assess the safety of this proposed new base formulation by comparison with the currently marketed product and a historical control formulation. Application for market approval of the 2% cream in the new more viscous base formulation was submitted to NDA 17-450, Supplement SCF-043. Although this NDA was recently approved, this new cream has apparently not yet been marketed.

No outstanding deficiencies were noted upon initial review of this study to the current NDA.

In addition to the PK study in Item 6, two Phase III efficacy and safety protocols in patients with vaginal candidiasis were included in **Item 8: Clinical Data** of this submission to evaluate the therapeutic equivalence between the 3-day regimen with the proposed 4% miconazole cream in the new more viscous base formulation to the 7-day regimen with the currently marketed less viscous product.

III. RECOMMENDATION

Item 6 (Human Pharmacokinetics and Bioavailability) of NDA 20-827 for miconazole nitrate 4% vaginal cream is fileable.

/S/

5/23/97

Philip M. Colangelo, Pharm.D., Ph.D.
Office Clinical Pharmacology/Biopharmaceutics,
Division of Pharmaceutical Evaluation III

RD/FT signed by Chandra Sahajwalla, Ph.D, (Acting TL) /S/ 5/23/97

cc:

Div. File: NDA 20-827

HFD-590 (C. Chi, CSO)

//

//

HFD-340 (Viswanathan)

HFD-205 (FOI)

✓HFD-880 (Division File)

✓HFD-880 (C. Sahajwalla, TL; P. Colangelo)

✓EDR (Barbara Murphy)

APPROVED FOR SIGNATURE
CR. [unclear]

STATISTICAL REVIEW AND EVALUATION: 45 DAY MEETING REVIEW
(COMPLETED REVIEW FOR INTERNAL DISTRIBUTION ONLY)

21 1997

NDA: 20-827
DRUG CLASS: 1S
NAME OF DRUG: Monistat 3 (miconazole nitrate 4.0%)
APPLICANT: Advanced Care Products
SUBMISSION DATE: March 31, 1997

INDICATION(S): 3 day treatment of vaginal yeast infections (candidiasis)
NUMBER AND TYPE OF CONTROLLED CLINICAL STUDIES: 2 double-blind,
randomized, controlled, parallel group, comparative, multicenter Phase III studies

STATISTICAL REVIEWER: Dixon
CLINICAL REVIEWER: Davis
PROJECT MANAGER: Chi

45 DAY MEETING DATE: May 21, 1997
WAS THE NDA FILED: Yes
IF YES, DUE DATE: December 1, 1997
USER FEE DATE: March 31, 1998

I. ORGANIZATION AND DATA PRESENTATION

	YES	NO	N/A
A. Is there a comprehensive table of contents with adequate indexing and pagination?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
B. Are the original protocols, protocol amendments and proposed label provided?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
C. Adverse event listings by center and time of occurrence relative to enrollment date.	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
1. Are adverse events from cited sources (foreign and domestic) provided?	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>
D. Is a CANDAR or an electronic submission of the data necessary? <i>Data has been submitted on diskette with documentation</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>
E. If the data have been submitted electronically, has adequate documentation of the data sets been provided?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
F. Are inclusion/exclusion (evaluability) criteria adequately coded and described.	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

- G. Are there discrepancies between CRF information and CANDAR/Jacket data?
- H. If the data have been submitted electronically, can laboratory data be easily merged across studies and indications?
1. If not, can you estimate the time required to correct problems?

II. STATISTICAL METHODOLOGY

YES NO N/A

- A. Are all primary efficacy studies of appropriate design to meet basic approvability requirements, within current Divisional policy statements or to the extent agreed upon previously with the sponsor by the Division?
Sponsor has followed the FDA draft guideline "Performance of a Bioequivalence Study for Vaginal Antifungal Products", Feb 1990.
- B. For each study, is there a comprehensive statistical summary of the efficacy analyses which covers the intent-to-treat population, evaluable subject population and other applicable sub populations (age, gender, race/ethnicity, etc.)?
No efficacy analyses by age or race.
 1. If subset analyses were not done, was an acceptable explanation of why given?
No mention of subset analyses.
Subset analyses have been requested from the sponsor. Request made at the 21 day review assignment meeting on April 21, 1997.
**Received subset analyses in Amendment dated May 9, 1997.*
- C. Based on the summary analyses of each study, do you believe:
1. The analyses are appropriate for the type data collected, the study design, and the study objectives (based on protocol and proposed label claims)?
2. If there are multiple endpoints, has this been adequately addressed?
Clinical cure and microbiological cure are combined to form therapeutic cure.
3. Intent-to-treat (ITT and MITT) analyses are properly performed?
4. Sufficient and appropriate references were included for novel statistical approaches?

- | | | | | |
|----|---|---|---|---|
| D. | If interim analyses were performed, were they planned in the protocol and were appropriate significance level adjustments made? | — | — | ✓ |
| E. | Are there studies which are incomplete or ongoing? | — | ✓ | — |
| F. | Is there a comprehensive, adequate analysis of safety data as recommended in the Clinical/Statistical Guideline? | ✓ | — | — |
| | 1. Is there anything significant yet regarding safety or AE evaluations? | — | ✓ | — |

III. FILEABILITY CONCLUSIONS

From a statistical perspective, this submission is reviewable with only minor further input from the sponsor.

/S/ 5/21/97
 Cheryl Dixon, Ph.D.
 Biostatistician, DOB IV

/S/ 5/21/97

Concur: Nancy Silliman, Ph.D.
 Acting Team Leader, DOB IV

- cc:
 Archival: NDA 20-827
 HFD-590
 HFD-590/Dr. Goldberger
 HFD-590/Dr. Albrecht
 HFD-590/Dr. Leissa
 HFD-590/Dr. Davis
 HFD-590/Ms. Chi
 HFD-725/Dr. Harkins
 HFD-725/Dr. Silliman
 HFD-725/Dr. Dixon
 Chron.

MAY 12 1997

45 DAY MEETING CHECKLIST

FILE ABILITY:

on initial overview of the NDA application:

YES NO

BIOPHARMACEUTICAL:

- (1) On its face, is the biopharmaceutics section of the NDA organized in a manner to allow substantive review to begin? ✓
- (2) Is the biopharmaceutical section of the NDA indexed and paginated in a manner to allow substantive review to begin? ✓
- (3) On its face, is the biopharmaceutics section of the NDA legible so that substantive review can begin? ✓
- (4) Are the Phase 1 studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product? ✓
- (5) If several formulations of the product were used in the clinical development of the product, has the sponsor submitted biopharmaceutics data to allow comparison between the product to be marketed and the product(s) used in the clinical development? N/A
- (6) From a biopharmaceutic perspective, is the NDA fileable? If "no", please state below why it is not? ✓

/S/

5/12/97

Reviewing Biopharmaceutics Officer

/S/

5/25/97

Advisory Biopharmaceutics Officer

45 DAY MEETING CHECKLIST

NDA 20-827
 Monistat 3
 Vaginal Cream 4%
 YES NO

FILEABILITY:

-On initial overview of the NDA application:

MANUFACTURING AND CONTROLS:

- (1) On its face, is the M&C section of the NDA organized in a manner to allow substantive review to begin? X
- (2) Is the M&C section of the NDA indexed and paginated in a manner to allow substantive review to begin? X
- (3) On its face, is the M&C section of the NDA legible so that substantive review can begin? X
- (4) Are all of the facilities (manufacturing, packaging, testing, sterilization, etc.) appropriately delineated with full addresses? X
- (5) Has the applicant submitted a complete environmental impact assessment? X
- (6) Has the applicant developed appropriate controls assessment procedures that are presently ready for FDA verification? X
- (7) For an antibiotic, has the applicant submitted an appropriate validation package and committed to the readiness of exhibit samples? X
- (8) Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions with the sponsor? X
- (9) Has the applicant submitted draft labeling consistent with 201.56 and 201.57, current divisional labeling policies, and the design of the development package? X
- (10) Has the applicant submitted stability data to support and justify the proposed expiry? X
- (11) Has the applicant stated that they are ready now (Priority Drugs) for inspections of the facilities or that they will be ready within the next 6 months (Standard Drugs)? X

(12) From a manufacturing and controls perspective,
is this NDA fileable? If "no", please state
on reverse why it is not.

X

/S/

4/18/97

Reviewing Chemistry Officer

/S/

5/8/97

Supervisory Chemistry Officer

NDA 20827 Monistat nitrate cream (4%, 3 day treatment)

draft

45 day filing meeting 5-21-97

The following microbiology questions should be addressed by the sponsor regarding the microbiology data from clinical trials 95-005-P and 95-007-P.

1. Please supply the following information regarding the BiGGY test:

List the components and how the media is made

What criteria were used to identify yeasts. Are all *Candida* species brown on BiGGY agar? If so how can *C. albicans* isolates be differentiated from other *Candida* species? Will other yeasts (i.e. *T. glabrata*) grow on BiGGY agar if so what color would they be. Were all yeasts identified?

2. Are there data showing that the correct identification of *C. albicans* using the BiGGY method is comparable to that found with cornmeal agar or germ tube production. If so, these data should be sent to the Division for review.

3. Please clarify what fungal isolates were sent to the reference laboratory for species identification. Please provide in appendix 14 the species identification of all patient isolates.

4. What biochemical tests were used to speciate the fungi?

5. Please send the following information regarding fungal cultures:

How were vaginal samples collected and transported to the laboratory?

How were vaginal samples inoculated onto fungal medium?

Which fungal medium were used to culture yeasts?

Was fungal growth on fungal medium quantitated or semi-quantitated?

6. What criteria were used to interpret KOH preps (i.e. budding yeasts, hyphae, pseudo hyphae or positive /negative)?

7. Where yeast forms quantitated on the KOH preparations?

Linda L. Gosey
Microbiologist

45 DAY MEETING CHECKLIST

FILEABILITY:

On initial overview of the NDA application: 20 - 827

YES NO

CLINICAL:

- (1) On its face, is the clinical section of the NDA organized in a manner to allow substantive review to begin? ✓
- (2) Is the clinical section of the NDA indexed and paginated in a manner to allow substantive review to begin? ✓
- (3) On its face, is the clinical section of the NDA legible so that substantive review can begin? ✓
- (4) If needed, has the sponsor made an appropriate attempt to determine the most appropriate dosage and schedule for this product (i.e., appropriately designed dose-ranging studies)? ✓
- (5) On its face, do there appear to be the requisite number of adequate and well-controlled studies in the application? ✓
- (6) Are the pivotal efficacy studies of appropriate design to meet basic requirements for approvability of this product based on proposed draft labeling? ✓
- (6) Are all data sets for pivotal efficacy studies complete for all indications (infections) requested? ✓
- (7) Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling? ✓
- (8) Has the applicant submitted line listings in a format to allow reasonable review of the patient data? Has the applicant submitted line listings in the format agreed to previously by the Division? ✓

NDA 20-827

YES

NO

- (9) Has the application submitted a rationale for assuming the applicability of foreign data (disease specific microbiologic specific) in the submission to the US population? *Yes*
- (10) Has the applicant submitted all additional required case record forms (beyond deaths and drop-outs) previously requested by the Division? *N. A.*
- (11) Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously agreed to by the Division? *✓*
- (12) Has the applicant presented a safety assessment based on all current world-wide knowledge regarding this product? *✓**
- (13) Has the applicant submitted draft labeling consistent with 201.56 and 201.57, current divisional policies, and the design of the development package? *✓*
- (14) Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions with the sponsor? *N. A.*
- (15) From a clinical perspective, is this NDA fileable? If "no", please state below why it is not. *✓*

If certain claims are not filable, please state which claims they are and why they are not filable.

Potential concerns: ① Label states "this convenient 3-day treatment cures most vaginal yeast infections." How many is MOST? ② Label does not contain the usual Rindon warning (see p. 02-02, Vol 1.1). ③ 1 of 25 investigators was in San Jose, Costa Rica; this investigator had a total of 20 patients (282 at entry; 211 were evaluable at V2; 198 were evaluable at V3).

/S/ , MD, MPH

Reviewing Medical Officer

/S/ , MD

Supervisory Medical Officer

5/16/97

Monostat 3

45 DAY MEETING CHECKLIST

FILEABILITY:

On initial overview of the NDA application:

YES

NO

CLINICAL:

*NAC:
OTC has a
partial set of
volumes and
no electronic
data.*

- (1) On its face, is the clinical section of the NDA organized in a manner to allow substantive review to begin? ✓
- (2) Is the clinical section of the NDA indexed and paginated in a manner to allow substantive review to begin? ✓
- (3) On its face, is the clinical section of the NDA legible so that substantive review can begin? ✓
- (4) If needed, has the sponsor made an appropriate attempt to determine the most appropriate dosage and schedule for this product (i.e., appropriately designed dose-ranging studies)? ✓
- (5) On its face, do there appear to be the requisite number of adequate and well-controlled studies in the application? ✓
- (6) Are the pivotal efficacy studies of appropriate design to meet basic requirements for approvability of this product based on proposed draft labeling? ✓
- (6) Are all data sets for pivotal efficacy studies complete for all indications (infections) requested? ✓
- (7) Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling? ✓

OTC does not have the full set

(8) Has the applicant submitted line listings in a format to allow reasonable review of the patient data? Has the applicant submitted line listings in the format agreed to previously by the division?

depr

- (9) Has the application submitted a rationale for assuming the applicability of foreign data (disease specific microbiologic specific) in the submission to the US population?
- (10) Has the applicant submitted all additional required case record forms (beyond deaths and drop-outs) previously requested by the Division?
- (11) Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously agreed to by the Division?
- (12) Has the applicant presented a safety assessment based on all current world-wide knowledge regarding this product?
- (13) Has the applicant submitted draft labeling consistent with 201.56 and 201.57, current divisional policies, and the design of the development package?
- (14) Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions with the sponsor?
- (15) From a clinical perspective, is this NDA fileable? If "no", please state below why it is not.

defer

defer

defer

Summary provided for all formulations of miconazole nitrate on the market. This product however is direct to OTC

OTC draft labeling submitted

defer

yes

If certain claims are not filable, please state which claims they are and why they are not filable.

Note: Checklist discussed with Dr. Dan Davis and all the Yes answers checked were in concurrence with him

Remaining OTC Concerns: Since this is direct to OTC marketing, ~~and~~ the actual experience of this formulation 4% miconazole nitrate cream (200mg) is unknown. Issues:

① Chemistry: How is this final formulation different from currently available products, specifically the 100mg cream used for 7 days, or the 200mg suppository for 3 days.

Reviewing Medical Officer

Safety: If the final formulation is substantially different from current products, the adverse event profile strictly from the clinical trials may not have adequate exposure

Supervisory Medical Officer

45 DAY MEETING CHECKLIST

FILEABILITY:

initial overview of the NDA application: YES NO

PROJECT MANAGEMENT:

(1) Do any of the following apply to this application (i.e., if YES, the application MUST BE REFUSED TO FILE under 314.100(e) and there is no filing over protest):

(a) Is the drug product already covered by an approved application? ✓

(b) Does the submission purport to be an abbreviated application under 314.55; however the drug product is not one for which FDA has made a finding that an abbreviated application is acceptable under 314.55(b)? ✓

(c) Is the drug product subject to licensing by FDA under the Public Service Act and Subchapter F of Chapter I of Title 21 of the CFR? ✓

(2) Do any of the following apply to this application (i.e., if NO, the application MAY BE REFUSED TO FILE under 314.100(d) and there is the potential for filing over protest):

(a) Does the application contain a completed application form as required under 314.50 or 314.55? ✓

(b) On its face, does the application contain the sections of an application required by regulation and Center guidelines? ✓

(c) Has the applicant submitted a complete environmental assessment which addresses each of the items specified in the applicable format under 25.31 or has the applicant submitted evidence to establish that the product is subject to categorical exclusion under 25.24 of the CFR? ✓

- (d) On its face, is the NDA formatted in compliance with Center guidelines including integrated efficacy and safety summaries? ✓
- (e) Is the NDA indexed and paginated? ✓
- (f) On its face, is the NDA legible? ✓
- (g) Has the applicant submitted all required copies of the submission and various sections of the submission? ✓
- (h) Has the sponsor submitted all special studies/data requested by the Division during pre-submission discussions with the sponsor? ✓
- (i) Does the application contain a statement that all nonclinical laboratory studies was conducted in compliance with the requirements set forth in Part 58 or a statement why a study was not conducted in compliance with those requirements? ✓
- (j) If required, has the applicant submitted carcinogenicity studies? ✓
- (k) On its face, does the application contain at least two adequate and well-controlled clinical trials? ✓
- (l) Does the application contain a statement that all clinical trials were conducted in accord with the IRB/Declaration of Helsinki provisions of the CFR? ✓
- (m) Have all articles/study reports been submitted either in English or translated into English? ✓
- (n) Has the applicant submitted draft labeling in compliance with 210.56 and 210.57 of the CFR? ✓
- (o) Has the applicant submitted the required FRAUD POLICY notice? *Debarment.* ✓

(p) Has the applicant submitted copies of all package inserts (or their equivalent) from all countries in which this product has been previously approved for marketing? Have all non-English package inserts been translated?

NA
(4% formulation not approved yet in foreign country)

(g) Has the applicant stated that the integrated summary of safety includes all safety data for this product of which they are aware from all sources, domestic and foreign? What is the cut-off date for the preparation of the ISS?

yes

(r) If this is a CANDA submission, has the applicant submitted a statement to the archival NDA that the text, tables, and data in the CANDA and the archival hardcopy NDA are identical? If they are not identical, is there a letter to the archival NDA that specifies distinctly ALL of the differences in the two submissions?

NO CANDA

(3) From a project management perspective, is this NDA fileable? If "no", please state on reverse why it is not.

/S/

Project Manager

Ph.D.
May 20, 1997

/S/

Supervisory Project Manager



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration

Memorandum

Date: March 25, 1998

From: J. Michael Kuchinski, Microbiologist
Obstetrics-Gynecology Devices Branch (HFZ-470)

Subject: NDA 20-827: Monistat® 3 Vaginal Cream (Miconazole Nitrate 4.0%, formula #AV-03-02-0077)
Compatibility and Use with Latex Condoms - Monistat® 3 Vaginal Cream Labeling Change

Through: Colin M. Pollard, Chief *CMP 3/27/98*
Obstetrics-Gynecology Devices Branch (HFZ-470)

To: Norman Schmuff (HFD-590)
cc: Dorota M. Matecka (HFD-590)
Christina Chi (HFD-590)

Manufacturer: Advanced Care Products
691 Highway 1, P.O. Box 6024
North Brunswick, New Jersey 08902-0724

Devices: Latex Barrier Contraceptives (Condoms and Diaphragms)

Background

The Center for Drug Evaluation and Research (CDER) has forwarded this portion of NDA 20-827 for consultation review. Monistat® 3 Vaginal Cream, manufactured by Advanced Care Products (formally by Ortho Pharmaceuticals), is a 4% (four percent) miconazole nitrate cream intended for the treatment of vulvovaginal candidiasis (vaginal yeast infection).

In 1994 Ortho Pharmaceutical submitted a supplement to NDA 17-450 to delete the following warning from the labeling:

"Mineral oil weakens latex condoms or diaphragms. This cream contains mineral oil. Do not rely on condoms or diaphragms to prevent sexually transmitted diseases or pregnancy while using Monistat® 7 Vaginal Cream."

The original formulation for the Monistat® 7 Cream contained a small quantity of mineral oil. As demonstrated *in vitro*, even very small quantities of oils decrease the physical properties of latex condoms and diaphragms (Voeller et al., 1989¹; and Bureau of Radiation and Medical Devices, 1986²).

Review NDA 20-827

The chemical formulation is presented below and in Section II of the NDA. Dr. Matecka also provided a table comparing this and other formulations. (See below.)

¹ Voeller, et al., (1989). Mineral Oil Lubricants Cause Rapid Deterioration of Latex Condoms. *Contraception* 39:95.

² Bureau of Radiation and Medical Devices, Canada. Spermicide Damage to Mechanical Contraceptives, 1986.

As presently configured, the Monistat® 3 Vaginal Cream does not contain mineral oil. However, of the remaining constituents of the formula, there are some components that may affect, or influence, latex integrity through their chemistry. The components where their effects are not known, include: Isopropyl Myristate, NF; Polysorbate 60, Stearyl Alcohol, NF; and, Cetyl Alcohol, NF.

% W/W and Batch Formula Monistat® 3 Vaginal Cream

Ingredient	% w/w	2200 Kg Batch	Function/Property
Isopropyl Myristate, NF			
Polysorbate 60			
Stearyl Alcohol, NF			
Cetyl Alcohol, NF			
Propylene Glycol, USP			
Potassium Hydroxide, NF			
Miconazole Nitrate, USP			
Benzoic Acid, USP			
Purified Water, USP			

To demonstrate that the Monistat® 3 Vaginal Cream will not adversely affect the physical properties and integrity of latex contraceptive barriers, the manufacturer conducted compatibility testing. The compatibility of Miconazole Nitrate (4%) Vaginal Cream, Formula Designation [redacted] with latex condoms was ascertained using Protocol PD-P-0349-1, titled, "Compatibility of ACP Formulation with Commercial Latex Condoms." This condom compatibility study [redacted] The results are described below.

Condom Compatibility (Report # PD-R-0420-1)

- Title:** Compatibility of Miconazole Nitrate (4%) Vaginal Cream (Formula Designation # [redacted]) With Commercial Latex Condoms.
- Objective:**
To determine the compatibility of Monistat® 3 Vaginal Cream (Miconazole Nitrate 4%) with commercial latex condoms.
- Protocol:**
The study was conducted to determine the compatibility of a number of Advanced Care Products new products with commercial latex. The testing included three latex condom brands, Trojan-Enz Lubricated, Trojan-Enz Non-Lubricated, and Lifestyles Ultra Sensitive Non-Lubricated. Each test condom was compared with non-treated condoms. The Miconazole Nitrate 4% preparation was applied directly to the treated condoms. Testing was carried out pursuant to ASTM D 3492 methods for both airburst and tensile properties testing. The number of condoms tested are identified in the following table:

TEST	NUMBER OF CONDOM BRANDS (A)	NUMBER OF REPLICATES/BRAND (B)	TOTAL NUMBER OF CONDOMS/FORMULATION (C)=(A)x(B)
Original Airburst	3	80	240
Airburst	3	80	240
Original Tensile	3	13	39
Tensile	3	13	39

The condoms were exposed directly to the Miconazole Nitrate (4%) test formulation [redacted] Batch # PE 1281) and brushed lightly to spread the test material and expose approximately half (1/2) of each condom (closed end) for 5 seconds. The condoms were then placed on cheese cloth for 30 minutes in a humidity chamber. Following the 30 minute exposure the condoms were pat dry with the cheese cloth and the specific test conducted.

4. Results:

The average tensile strength and ultimate elongation of the condoms were measured after exposure, and are summarized below. Mean values, standard deviation and 95% confidence intervals were reported for each physical property. The 95% confidence level on the difference was calculated and reported.

Table 1: Air Inflation Testing Results

PARAMETER STUDIED	MEAN ± STANDARD DEVIATION (95% CONFIDENCE INTERVAL)			
	PRODUCT N = 80	TROJAN ENZ	LIFESTYLES	TROJAN ENZ NON-LUBRICATED
Airburst Pressure Kpa	Untreated	23.0 ± 0.1 (2.28, 2.32)	1.8 ± 0.1 (1.78, 1.82)	2.3 ± 0.2 (2.26, 2.34)
	Miconazole Nitrate (4.0%) Vaginal Cream	23.0 ± 0.2 (2.26, 2.34)	1.6 ± 0.2 (1.56, 1.64)	2.1 ± 0.2 (2.06, 2.14)
	95% C.I. on Difference	0 ± 0.05 [†] (ns)	0.2 ± 0.05 ^{**}	0.2 ± 0.06 ^{**}
Airburst Volume (L)	Untreated	37.6 ± 2.3 (37.10, 38.10)	40.6 ± 4.3 (39.66, 41.54)	43.0 ± 3.0 (42.34, 43.66)
	Miconazole Nitrate (4.0%) Vaginal Cream	33.6 ± 2.9 (32.96, 34.24)	43.4 ± 5.5 (42.19, 44.61)	39.8 ± 7.0 (38.27, 41.33)
	95% C.I. on Difference	-4.0 ± 0.81 ^{**}	2.8 ± 1.53 ^{**}	-3.2 ± 1.67 ^{**}

** significant at the 0.001 level

Table 2: Tensile Properties Testing Results

PARAMETER STUDIED	MEAN ± STANDARD DEVIATION (95% CONFIDENCE INTERVAL)			
	PRODUCT N = 13	TROJAN ENZ	LIFESTYLES	TROJAN ENZ NON-LUBRICATED
Mean Thickness mm	Untreated	0.074 ± 0.004	0.061 ± 0.005	0.73 ± 0.005
	Miconazole Nitrate (4.0%) Vaginal Cream	0.072 ± 0.003	0.058 ± 0.002	0.075 ± 0.004
Break Force N	Untreated	77.91 ± 17.96 (68.15, 87.67)	70.58 ± 6.71 (66.93, 74.23)	73.62 ± 13.43 (66.32, 80.92)
	Miconazole Nitrate (4.0%) Vaginal Cream	66.69 ± 8.54 (62.05, 71.33)	48.56 ± 10.64 (42.78, 54.34)	70.07 ± 11.49 (63.82, 76.32)
	95% C.I. on Difference	11.22 ± 12.02	22.22 ± 7.61 ^{**}	3.55 ± 10.6
Break Strength (MPa)	Untreated	26.43 ± 5.86 (23.24, 29.62)	29.18 ± 2.8 (27.66, 30.70)	25.13 ± 4.43 (22.72, 27.54)
	Miconazole Nitrate (4.0%) Vaginal Cream	23.29 ± 3.66 (21.30, 25.28)	21.07 ± 4.85 (18.43, 23.71)	23.37 ± 3.64 (21.39, 25.35)
	95% C.I. on Difference	3.14 ± 2.18	8.09 ± 5.39 ^{**}	1.76 ± 3.45
Elongation, %	Untreated	769 ± 43 (745, 792)	815 ± 13 (808, 823)	804 ± 36 (785, 824)
	Miconazole Nitrate (4.0%) Vaginal Cream	770 ± 25 (757, 784)	778 ± 34 (759, 796)	821 ± 29 (805, 837)
	95% C.I. on Difference	-10 ± 30	37 ± 22 ^{**}	-17 ± 25

** significant at the 0.001 level

* significant at the 0.01 level

95% confidence interval on the differences based on Cochran's solution to the Behren's-Fishers problem.

NOTE: The 95% confidence interval on the difference was calculated to determine the significance at the 0.001 level for the airburst pressure and volume measurements. The 95% confidence interval on the differences for the tensile properties was calculated using the Cochran's solution to the Behren's-Fishers problem.

Analysis and Observations:

- *Validation of the air burst test machine is a difficult and complex undertaking and considered to be critical for air burst testing. Now, having stated this, the issue is not that important because the condom products are being compared to a untreated control that has undergone testing using the same equipment.*
- *Although three types/styles of condoms were tested, only one lot of each type were included in the testing. In addition, only one lot of vaginal cream was involved in the test.*
- *The results from testing comparative brands indicate that there is apparently little difference between the treated and untreated samples for the Carter-Wallace Trojan brands, however, there is a general trend toward a decrease in the measured property. This may be due to the manipulation of the treated condoms vs. the untreated control.*
- *Nevertheless, there appears to be some interaction between the Lifestyles brand condom and the vaginal preparation. There is a statistically significant decrease in airburst pressure, and the tension properties of force to break, tensile strength, elongation. The general trend is for the treated product's physical property (above) to be lower than the lower bound of the confidence interval of the control. The burst volume is the only property that is not affected but there is a slight increase in the volume which may indicate a softening of the material with treatment with the Miconazole Nitrate (4%).*

The statistically significant decrease in the stress and strain properties of the Lifestyles latex condom may represent a detrimental finding with this condom formulation. However, the results show that following treatment with the Miconazole Nitrate (4%) and under the conditions of the test, that the Lifestyles condoms would pass the current voluntary standard (minimum values) for latex condoms for each test measure.

5. Comments:

In the 1994 consult request regarding a labeling change for the original formulation (Monistat® 7 Vaginal Cream (NDA 17-450)), ten condoms of each brand were unrolled and had 25 grams (5 doses) of the cream or 5 suppositories (5 doses) placed inside the condom. These were then rubbed to assure adequate surface contact. The condoms were then exposed to either the Monistat® cream, suppositories, or untreated for four hours at 37 °C. After 4 hours, each condom was tested for tensile strength and ultimate elongation according to ASTM standards.

- **Environment** - The above environmental conditions, although somewhat extreme, would provide for a worst case situation for the test of compatibility between the Monistat® Cream and a latex condom. The present study does not provide for this type of worst case stress on the condom.
- **Test Methods** - Condoms in the present study were exposed to a normal dose for a period of 30 minutes. This is not an extended period of time and the test was conducted under optimum conditions of temperature and humidity. (See section 3 - protocol.)
- **Samples** - The manufacturer tested only 3 types of condoms, and only one lot of each brand. Because two of these condoms were the same brand, the Trojan® ENZ condoms, they have the same latex formulation with the only difference being the lubricant. Because a condom's susceptibility is likely to be dependent upon its formulation, it may be extremely difficult to

extrapolate the testing of these two brands of condoms to all legally marketed condoms. The effect on a differing formulation of latex may be seen in the test with the Lifestyles condom compared to the Trojan™ Brands.

- Control Group and Sample Size - The sample size of eighty condoms per lot for air burst testing and thirteen condoms per lot is appropriate and corresponds with the Military Standard: Sampling Procedures and Tables for Inspection by Attributes (MIL-STD 105E). Nevertheless, only one lot of condoms of each type were tested, without justification.
- Tests to determine whether or not the Monistat® 3 Vaginal Cream will adversely affect the physical properties of other latex devices such as a Latex Diaphragm were not conducted in these trials but, may be even more critical because of the long term exposure of the medicament to the relatively thin walled diaphragm.
- Permeability - NO data were provided on whether or not the new formulation cream may affect the barrier or permeability properties of the device. Because small changes in physical properties may be present, it may be even more important to examine the barrier properties of the device. However, given the short exposure times, it is probably not reasonable to expect the applicant to conduct testing for permeability of the latex material following exposure. (This would be a reasonable request for other devices that are expected to undergo longer exposures.)

Conclusion

The manufacturer has not provided sufficient data to demonstrate that the Monistat® Cream will not adversely affect the physical integrity of latex contraceptive condoms. This application has not presented data on the effects of the cream on other latex barrier devices, such as contraceptive diaphragms. It is quite possible - given the results - that the manufacturer will not be able to support any labeling change from the original. See conclusions below.

The physical properties of the latex condom exposed to Monistat® 3 Vaginal Cream appeared to decrease for both brands of latex condoms. Most significantly, the one lot of Lifestyles Condoms compared to controls showed statistically significant decreases in strength characteristics. Nevertheless, the results under the conditions of the testing found that the condoms physical properties were above the minimum values for the latex condoms (i.e., following exposure to the Monistat® 3 Cream and under conditions of the test, the condoms met the minimum requirements for latex condoms ((ISO) 4074-1:1996 (E)- Rubber Condoms Part 1: Requirements). Whether or not these differences are real and have clinical significance cannot be determined. Nevertheless, Monistat® 3 Vaginal Cream does have some as yet to be explained effect on latex condoms under the conditions tested, and there remains some doubt that the new formulation is safe for use with all latex condoms.

In addition, being thicker than condoms the wall of a diaphragm or other latex barrier devices would resist short term attack by a chemical agent. Nevertheless, as most barrier contraceptives (i.e., diaphragms, cervical caps) are intended for repeat use and as such would be exposed for a greater period of time, extensive testing of this formulation is suggested.

Given the extensive testing required (which may well prove inconclusive) to support a minor labeling change, we recommend that the device continue to include a caution about reliance on condoms, diaphragms and other contraceptives made of latex for prevention of pregnancy or other STDs:

"Do not rely on condoms or diaphragms to prevent sexually transmitted diseases or pregnancy while using Monistat® 3 Vaginal Cream."

Recommendation

If the manufacturer insists on pursuing a change in the labeling, the following information should be requested:

However, the
many purpose
the diaphragm
to hold the
g, not act
a physical
barrier to the
erm.

- The physical properties of the latex condom exposed to Monistat® 3 Vaginal Cream appeared to decrease for both brands of latex condoms. In particular, its effect on the Lifestyles Condoms compared to controls showed statistically significant decreases in strength characteristics. Because a condom's susceptibility to any vaginal preparation could be dependent upon its formulation, it is difficult to extrapolate the testing of these two brands of condoms to all legally marketed condoms. Therefore, following should be requested from Advanced Care Products:

- a) Discussion of the adverse test results specifically the statistically significant decrease in the strength properties of the test condoms compared to the control.
- b) Additional testing of other manufacturers condoms or justification by the applicant for not testing other brands and types of condoms.
- c) Justification for selecting only one lot of product (both the Monistat® and the condoms).

If you have any questions please call me

/S/

J. Michael Kuchinski

APR 10 1998
ON SENIOR

Prepared by, JMK
C:\JMK\CONDOM\NDA20-827 Monistat 3 Vaginal Cream
cc: (HFZ-470)
(HFD-590) Norman Schmuff
(HFD-590) Dorota M. Matecka
(HFD-590) Christina Chi

Draft: jmk 02/24/98
Revised: jmk/rmk 03/11/98
Revised: jmk/cmp:03/24/98
Revised: jmk:03/25/98 03/25/98 2:51 PM
FINAL:

 **Advanced Care Products**

Personal Products Company
691 Highway 1, P.O. Box 6024
North Brunswick, New Jersey 08902-0724

March 26, 1998

Minutes from March 23, 1998 ACP/FDA Teleconference

Meeting Date: March 23, 1998 Time: 8:30am Location: Teleconference

NDA #: NDA 20-827, MONISTAT 3 (miconazole nitrate vaginal cream 4%) Vaginal Cream

External participant: Advanced Care Products, Personal Products Company (ACP)

Meeting Chair: Brad Leissa, MD
Medical Team Leader
DSPIDP

ACP Participant Lead: Diane Herron
Director
Regulatory Affairs

Meeting Recorder: Christina Chi, Ph.D.
Project Manager

Type of Meeting: Draft Labeling

FDA Attendees: See Attached FDA Attendees List Fax of 3/24/98, (Attachment 1)

ACP Participants: Diane Herron, Director, Regulatory Affairs
Rhea Williams, Associate, Regulatory Affairs
David Upmalis, MD, Executive Director, Clinical Affairs

Meeting Objective: Finalize draft labeling for NDA 20-827

Discussion Points: (Note: New wording is Italicized for ease of review)

1. Clarification of F.P.O. found on the fifth panel of the folding carton in the mock-up labeling. The will be nothing additional placed in this section, F.P.O. indicates that the clarity and coloring of the picture in not final.
2. Explanation of how the 800# automated response system. The consumer can speak with a nurse between the hours of 8am and 5pm. After these hours, the automated response system provides helpful information but for medical questions, the system suggests the consumer consult their doctor. ACP also requested to shorten the "Questions" statement on the Top and Bottom panel of the folding carton, and replace with the statement, "If you have questions or comments please call 1-888-MONISTAT."

Minutes from 3/23/98 Teleconference
Between Advanced Care Products and FDA
NDA 20-827, MONISTAT 3 Vaginal Cream
Proposed Labeling
March 26, 1998

3. Discussion of USP requirement for established name used on product labeling. ACP requested to include the word "Vaginal" as part of the established name on our product labeling while submitting a request to amend the miconazole nitrate cream monograph in the United States Pharmacopoeia (USP). ACP requested this to remain consistent with the other MONISTAT line of products. Additionally, other NDA approved competitive products have been approved which have been inconsistent with the established name listed in the USP monograph.
4. Discussion about inserting an active ingredient statement on the overwrap which illustrates the dose per applicator. The new wording is "*Active Ingredient: 200 mg miconazole nitrate per applicator*". ACP indicated that they had already printed the overwrap and packaged the three validation batches. The overwrap was identical to MONISTAT 7 Vaginal Cream which is already FDA approved. ACP requested to launch the packaged product with the overwrap printing as previously submitted and committed to changing to the approved format by the next printing which will occur two months following launch. FDA agreed that this would be acceptable as long as ACP placed a sticker with the active ingredient statement onto each overwrapped applicator.
5. Addition of a statement regarding the MONISTAT website to the Medical Questions paragraph found on the back panel of the Folding Carton and Educational Brochure, "*You can visit our website at www.monistat.com*". The www.monistat.com will be deleted from the address section on the back panel of the Folding Carton and the Educational Brochure.
6. Discussion of rewording of the Adverse Reaction (Side Effects) paragraph found on page two of the Educational Brochure. This was done to clarify that an increase in burning, itching and/or irritation may not only be experienced the first time of use. In addition, the wording was revised to clarify which reactions are recognized as a result of clinical trials and which reactions a consumer should stop taking the product and consult their doctor. The new paragraph says, "*A mild increase in vaginal burning, itching, or irritation may occur when MONISTAT 3 Vaginal Cream is inserted. Abdominal cramping has also been reported. Stop using MONISTAT 3 Vaginal Cream and consult your doctor if you have abdominal pain, hives, or skin rash, or if you have severe vaginal burning, itching, or irritation.*"
7. We discussed the application of the cream with the standing or lying down directions and illustrations. ACP requested to include both directions because their consumer information shows that women do not only apply this product while lying down. They generally apply the product in the bathroom while squatting. ACP would work on rewriting the wording that would include both directions for use but only include an illustration in the recumbent position.
8. ACP chose to provide the recumbent illustration with the label for vagina, uterus, and rectum.

Minutes from 3/23/98 Teleconference
Between Advanced Care Products and FDA
NDA 20-827, MONISTAT 3 Vaginal Cream
Proposed Labeling
March 26, 1998

Decisions reached:

See attached fax dated 3/23/98 from Christina Chi, FDA (Attachment 2)

Unresolved issues:

1. Use of "Vaginal" in the established name on the product labeling.
2. Wording of the directions for inserting the product while lying down or standing.

Post meeting agreement: ACP and FDA agreed upon the wording "Gently insert the applicator into the vagina as far back as it will go comfortably. This can be done while lying on your back with your knees bent (as shown in the picture), or while standing with your feet apart and your knees bent."

Diane Herron 3/26/98
Diane Herron
Director, Regulatory Affairs
Advanced Care Products, Personal Products Company

APPEARS THIS WAY
ON ORIGINAL

Food and Drug Administration
Fertility and Maternal Health Drugs Advisory Committee
Center for Drug Evaluation and Research.

14-15 June 1990

SUMMARY MINUTES

Members Present

Barbara S. Hulka, MD (Chair)
Dorothy M. Barbo, MD
Ezra C. Davidson, Jr, MD
Elizabeth R. McAnarney, MD
Susan A. R. McKay, PhD
Jennifer R. Niebyl, MD
E. Albert Reece, MD
Subir Roy, MD
James J. Schlesselman, PhD
Anne Colston Wentz, MD

Member Absent

Arthur F. Haney, MD

Executive Secretary

Philip A. Corfman, MD

Invited Speaker (14 June)

John C. LaRosa, MD

Invited Speakers (15 June)

Gary D. Friedman, MD
Jack D. Sobel, MD

"We certify that we attended the 14-15 June 1990 meeting of the Fertility and Maternal Health Drugs Advisory Committee and that these Summary Minutes accurately reflect what transpired."

/S/

Philip A. Corfman, MD
Executive Secretary

22 June 90

Date

/S/

Barbara S. Hulka, MD
Chair

6/22/90

Date

SUMMARY MINUTES

The Fertility and Maternal Health Drugs Advisory Committee of the Food and Drug Administration met on 14-15 June 1990 at the Galthersburg Marriott Hotel in Galthersburg, Maryland. A complete transcript of the meeting is available from the Dockets Management Branch of the FDA.

The following documents are annexed to these minutes:

1. The meeting agenda.
2. The questions put to the Committee(s).
3. Lists of Committee members, invited speakers and other participants.

During its two day meeting the Committee reviewed three topics and derived answers to amended versions of the questions listed in annex 2. The topics were: 1) recommendations of the National Academy of Sciences Committee on Contraceptive Development concerning the FDA review of contraceptive drugs and devices, 2) the request by Wyeth-Ayerst for the FDA to permit the label of Premarin be amended to state that Premarin may provide cardioprotection, and 3) proposals that vaginal fungicides be sold without prescriptions.

1. RECOMMENDATIONS CONCERNING THE FOOD AND DRUG ADMINISTRATION PROPOSED BY THE COMMITTEE ON CONTRACEPTIVE DEVELOPMENT OF THE NATIONAL ACADEMY OF SCIENCES (NAS)

Insofar as the NAS Report concerns both contraceptive drugs and devices, this portion of the meeting was held jointly with the Obstetrics and Gynecology Panel of the Center for Devices and Radiological Health, and the Chairs of the Committee and the Panel co-chaired the meeting. (The membership of the Panel is provided in Document 3; all members of the panel attended the meeting except Drs. Grimes and Wager.)

After announcements, Dr. Connell opened the meeting for public comment. Presentations were provided during this period by Dr. Sidney Wolf for the Public Citizen Health Research Group, Ms. Patty Morris for Public Voice, Dr. Richard D. Glasow for National Right to Life, Inc, and Ms. Lisa Kaeser for the Alan Guttmacher Institute. Since no other participants expressed a wish to speak during this period, the Chair closed the open public hearing.

The NAS Report was then presented in some detail by three members of the Committee on Contraceptive Development: Dr. Luigi Mastrolanni (the Committee Chair), Ms. Judy Norsigian, and Mr. Richard Cooper.

Dr. Hulka assumed the chair of the session and, following discussion of the Report with staff of the Food and Drug Administration, the joint committees addressed the questions put to them. The questions were directed to the six recommendations of the report (provided on pages 114-116 of the Report).

RECOMMENDATION 1. "The committee recommends that the FDA increase the weight it assigns to contraceptive effectiveness and convenience of use".

Question 1.1.: Do the advisory committees agree with this recommendation in principle?

Question 1.2.: If no, please provide the reasons.

Question 1.3.: If yes, can the advisory committees identify contraceptives whose FDA review would have been facilitated by the application of this policy? What new contraceptives yet to be reviewed by the FDA might benefit from the application of this policy?

Answer 1.1.: The advisory committees response was "yes". (There were two abstentions to the motion for concurrence.)

Answer 1.2.: (Moot.)

Answer 1.3.: The committees agreed unanimously with a motion that the committees did not have sufficient information to address to these questions.

RECOMMENDATION 2. "The FDA should also be prepared to approve, in some circumstances, a new contraceptive drug or device that presents a risk if it is shown that the new contraceptive offers a safety advantage for an identifiable group of users when compared with that group's current actual contraceptive practice (including nonuse)."

Question 2.1.: Do the advisory committees agree with this recommendation in principle?

Question 2.2.: If no, please provide the reasons.

Question 2.3.: If yes, can the advisory committees identify contraceptives whose FDA review would have been facilitated by the application of this policy? What new contraceptives yet to be reviewed by the FDA might benefit from the application of this policy?

Answer 2.: The joint committees voted that they could not address these questions because they felt that the statement lent itself to different interpretations. (There were three abstentions.)

RECOMMENDATION 3. "The committee also recommends that a comprehensive postmarketing surveillance system be established to provide systematic and timely feedback about positive and negative health effects of contraceptive products."

- Question 3.1.: Do the advisory committees agree with this recommendation in principle?
- Question 3.2.: Do the advisory committees believe that current practices by the FDA in this regard are sufficient?
- Question 3.3.: If no, what additional efforts should be undertaken?
- Question 3.4.: How do the advisory committees view the mandate of the National Institutes of Health Contraceptive Evaluation Branch in this regard?

- Answer 3.1.: The joint committees voted unanimously to agree with this recommendation.
- Answer 3.2.: The joint committees agreed with a motion that the current FDA post-marketing surveillance resources are insufficient. (There was one abstention.)
- Answer 3.3.: The joint committees unanimously recommended the establishment of an outside, exemplary, scientific group, such as a committee of the Institute of Medicine, to review the entire issue of post-marketing surveillance for the FDA. This group would be expected to involve relevant agencies and to recommend possible funding mechanisms for the work to be undertaken.
- Answer 3.4.: The joint committees felt that they had insufficient information to respond to this question.

RECOMMENDATION 4. "The committee recommends that an international conference of drug regulatory officials be held to increase the priority that such officials give to contraceptive development, to harmonize the regulatory requirements of different countries to such extent possible, to discuss the need for greater postmarketing surveillance of new contraceptives, and to clarify the basis for regulatory decisions in individual countries."

- Question 4.1.: Do the advisory committees agree that such an international meeting would be helpful?
- Question 4.2.: If yes, what entities should organize and underwrite such a meeting?
- Answer 4.1.: The advisory committees voted to agree that an international meeting would be helpful. (There was one vote against this motion.)
- Answer 4.2.: The committees voted to recommend that the following entities might be involved: the World Health Organization, other United Nations agencies, and European and Pacific rim countries. (Four committee members abstained from the vote or

RECOMMENDATION 5. "The Food and Drug Administration should complete its review of its toxicological requirements for the evaluation of contraceptive products, especially its continued use of the beagle dog."

-----Question 5.1.: Do the advisory committees believe that the Agency's current requirements for animal toxicological studies for contraceptive steroids should be amended?

Question 5.2.: If yes, what changes are recommended?

The Joint committees elected not to address these questions but voted unanimously that they agreed with the recommendation of the NAS committee.

RECOMMENDATION 6. "A report should be prepared by an independent body three to five years hence to assess FDA requirements with respect to contraceptives."

Question 6.1.: Do the advisory committees agree?

Question 6.2.: If yes, what entities should organize and underwrite such a review?

Answer 6.1.: The Joint committees voted to agree with the recommendation. (There was one vote against the motion to agree and two abstentions.)

Answer 6.2.: The Joint committees voted in favor of a motion to suggest a mechanism similar to the mechanism suggested for Recommendation 3. (There were three abstentions to the vote on this motion.)

2. Concerning a proposed cardioprotective indication for Premarin in women without a uterus

After a break the Fertility and Maternal Health Advisory Committee reconvened without participation of the Obstetrics-Gynecology Panel. After Dr. Corfman read the conflict of interest statement, three presentations were given during the open public session: Dr. Sidney Wolfe for the Public Citizen Health Research Group, Dr. Malcolm Whitehead for Ciba-Geigy, and Ms. Cynthia Pearson for the National Women's Health Network.

Since no one else expressed a wish to present during the open hearing portion of the meeting, the Chair closed this portion, and introduced the formal sessions. During the session entitled "Biomedical Studies", presentations were given by Drs. Marc Deltch, Roger Lobo, and Jay M. Sullivan speaking for the sponsor, Wyeth-Ayerst, by Dr. John C. LaRosa, a speaker invited by the FDA, and by Dr. Linda Golden, an FDA scientist. During the session entitled "Epidemiological Studies", presentations were given by Drs. Elizabeth Barrett-Connor, Melr J. Stampfer, Roger Lobo, and Marc Deltch, speaking for the sponsor, by Dr. Gary Friedman, a speaker invited by the FDA, and by Dr. Bruce Stadel, an FDA scientist.

During the discussion period, Dr. Corfman noted that the title of the session, ("A proposed cardioprotective indication for Premarin in women without a uterus"), didn't imply that such use, if advised, would necessarily appear in the "indication" section of the label; such a finding could appear elsewhere in the label, for information purposes. The final decision on how the finding might be employed in labeling will be negotiated by the FDA with the sponsor, taking into consideration the recommendations of the committee.

The committee then addressed the questions put to it as follows:

Question 1. Does the Committee believe that the epidemiological evidence provided is sufficient to conclude that estrogen replacement therapy with Premarin alone prevents cardio-vascular disease in women? (Is the employment of an meta-analysis useful in this regard?)

The Committee elected to change the question as follows:

"Does the Committee believe that the evidence provided is sufficient to conclude that estrogen replacement therapy with Premarin alone lowers the risk of cardio-vascular disease in women?"

Answer Nine members voted in favor of this amended question, and one member abstained. (At the conclusion of the meeting the abstainer elected to change the vote from abstention to a vote against the amended question.)

Question 2. If the Committee does not believe that there is sufficient evidence, what further studies does it recommend be undertaken to provide such evidence?

Question 3. If the Committee believes that there is sufficient evidence, does it also believe that the cardiovascular benefits of estrogen replacement therapy with Premarin in women without a uterus outweigh the possible risks?

The Committee elected to change the order and wording of questions 2 and 3 as follows:

Question 2. "Does the Committee believe that the cardiovascular benefits of estrogen replacement therapy with Premarin alone in women without a uterus outweigh the possible risks?"

Answer The Committee voted unanimously that the benefits of estrogen replacement therapy with Premarin in women without a uterus may outweigh the risks depending on the individual patient's risk profile for various estrogen-related diseases and conditions.

Question 3. "What further studies does the Committee recommend be undertaken?"

Answer The Committee recommended two categories of studies: 1) secondary prevention trials, which would be randomized clinical trials in high-risk women, such as women with atherosclerosis and/or a history of myocardial infarction, and 2) large cohort studies designed to ascertain risk in specific sub-groups, such as groups at high risk of cardiovascular disease in which estrogen may be of benefit, or groups at low risk, in which estrogens would be expected to be of little benefit.

3. Concerning the proposal that vaginal fungicides may be sold without prescription

This portion of the meeting was opened by the Chair for open public comment and during this period there were presentations by Ms. Judy Norsigian for the National Women's Health Network, Ms. Kara Anderson for the Planned Parenthood Federation of America, and Mr. Mark K. Taylor for Combe Inc.

There being no one else in the meeting expressing interest in commenting, the Chair closed the open comment period and introduced the formal portion of the program. Presentations were given by Dr. Joseph K. Winfield of the FDA, by Dr. Douglass B. Given, speaking for the sponsor, the Schering-Plough Corporation, by Drs. Carol Sampson Landers and Sebastian Faro, speaking for the sponsor, Advanced Care Products, and by Dr. Jack D. Sobel, a speaker invited by the FDA.

After these presentations and further discussion, the Committee addressed the questions as follows:

Question 1. Does the Committee believe that the most frequent cause of vaginal discharge, vulvovaginal itching, and burning is due to *Candida albicans* infections?

Question 2. Does the Committee believe that the cure rates presently obtained with clotrimazole and micronazole for the treatment of vulvovaginal candidiasis are sufficient to allow the over-the-counter (OTC) use of these products?

Questions 1 and 2 were withdrawn by the Agency.

Food and Drug Administration
Center for Devices and Radiological Health
OBSTETRICS-GYNECOLOGY DEVICES PANEL

Chair

Elizabeth B. Connell, MD
Emory University School of
Medicine
Atlanta GA

Voting Members

Constance J. Bohon, MD
Women's Physician Association
Washington DC

Elwyn M. Grimes, MD
Reproductive, Endocrine, and
Fertility Consultants, Inc
Kansas City MO

Gael P. Wager, MD
Abbott-Northwestern Hospital
Minneapolis, MN

Non-Voting Members

Sheryl Ruzek, PhD
(Consumer Representative)
Temple University
Philadelphia PA

John E. Mordock
(Industry Representative)
Cabot Medical Corporation
Langhorne PA

Executive Secretary

Colin M. Pollard
Food and Drug Administration

Washington C. Hill, MD
Creighton University School
of Medicine
Omaha NE

Johanna F. Perimutter, MD
Beth Israel Hospital
Boston MA

Gary S. Eglinton, MD
Georgetown University School
of Medicine
Washington DC

Non-Voting Consultants

Thomas D. Downs, PhD
University of Texas
Houston TX

Herbert B. Peterson, MD
Centers for Disease Control
Atlanta GA

Food and Drug Administration
Center for Drug Evaluation and Research
FERTILITY AND MATERNAL HEALTH DRUGS ADVISORY COMMITTEE

Chair

Barbara S. Hulka, MD
Department of Epidemiology
University of North Carolina
School of Public Health
Chapel Hill NC 27514

Dorothy Barbo, MD
Department of Obstetrics and
Gynecology
Medical College of Pennsylvania
Philadelphia PA 19129

Ezra C. Davidson, Jr, MD
Department of Obstetrics and
Gynecology
Charles R. Drew Postgraduate
Medical School
Los Angeles CA 90059

Arthur F. Haney, MD
Department of Obstetrics and
Gynecology
Duke University Medical School
Durham NC 27710

Elizabeth R. McAnarney, MD
Department of Pediatrics
University of Rochester Medical
School
Rochester NY 14642

Susan A. R. McKay, PhD
University of Wyoming School of
Nursing
University Station Box 3065
Laramie WY 82071

Executive Secretary

Philip A. Corlman, MD
Fertility and Maternal Health
Drugs Group
Division of Metabolism and
Endocrine Drug Products

Jenifer R. Niebyl, MD
Department of Obstetrics and
Gynecology
University of Iowa
School of Medicine
Iowa City IA 52242

E. Albert Reece, MD
Department of Obstetrics and
Gynecology
Yale University
School of Medicine
New Haven CT 06510

Subir Roy, MD, MSPH
Department of Obstetrics and
Gynecology
University of Southern
California School of Medicine
Women's Hospital
Los Angeles CA 90033

James Schlesselman, PhD
Department of Preventive
Medicine and Biometrics
Uniformed Services University
of the Health Sciences
Bethesda MD 20814

Anne Colston Wentz, MD
Department of Obstetrics
and Gynecology
Northwestern University
School of Medicine
Chicago IL 60611

Food and Drug Administration
Fertility and Maternal Health Drugs Advisory Committee
Center for Drug Evaluation and Research
Galthersburg Marriott
14-15 June, 1990

PARTICIPANTS

14 June 0830-1230

SPEAKERS FOR THE NATIONAL ACADEMY OF SCIENCES
COMMITTEE ON CONTRACEPTIVE DEVELOPMENT

Luigi Mastrolanni, MD (Committee Chair)
Director
Division of Human Reproduction
University of Pennsylvania Medical Center
Philadelphia PA

Judy Norsigian
Co-Director
Boston Women's Health Book Collective
West Somerville MA

Richard M. Cooper, JD
Washington DC

14 June 1330-1700 and 15 June 0800-1230

INVITED SPEAKERS

Gary D. Friedman, MD
Assistant Director of Epidemiological and Biostatistics
Division of Research
Kaiser-Permanente Medical Care Program
Oakland CA

John C. LaRosa, MD
Dean for Clinical Affairs
George Washington University Medical Center
Washington DC

FDA STAFF SCIENTIST ,

Linda Golden, MD
Medical Officer, Fertility and Maternal Health Drugs Group
Division of Metabolism and Endocrine Drug Products

15 June 1330-1530

INVITED SPEAKER

Jack D. Sobel, MD
Professor
Department of Medicine
Wayne State University Medical School
Detroit MI

FDA STAFF SCIENTIST

Joseph K. Winfield, MD
Medical Officer
Division of Anti-Infective Drug Products

14 June 13-1700 and 15 June 0800-1230

Concerning a proposed cardioprotective indication for Premarin in women without a uterus

- QUESTION 1. Does the Committee believe that the epidemiological evidence provided is sufficient to conclude that estrogen replacement therapy with Premarin alone prevents cardio-vascular disease in women? (Is the employment of a meta-analysis useful in this regard?)
- QUESTION 2. If the Committee does not believe that there is sufficient evidence, what further studies does it recommend be undertaken to provide such evidence?
- QUESTION 3. If the Committee believes that there is sufficient evidence, does it also believe that the cardiovascular benefits of estrogen replacement therapy with Premarin in women without a uterus outweigh the possible risks?

15 June 1230-1530

Concerning the proposal that vaginal fungicides may be sold without prescription

- QUESTION 1. Does the Committee believe that the most frequent cause of vaginal discharge, vulvovaginal itching, and burning is due to *Candida albicans* infections?
- QUESTION 2. Does the Committee believe that the cure rates presently obtained with clotrimazole and micronazole for the treatment of vulvovaginal candidiasis are sufficient to allow the over-the-counter (OTC) use of these products?
- QUESTION 3. Does the Committee believe that vulvovaginal candidiasis can be safely and adequately self-diagnosed and treated by the consumer?
- QUESTION 4. If approved for OTC use, does the Committee recommend that certain patient populations be identified in the labeling (i.e., those with first infections or recurrent infections)?

Food and Drug Administration
Fertility and Maternal Health Drugs Advisory Committee
Center for Drug Evaluation and Research
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14-15 June 1990

QUESTIONS TO THE COMMITTEE(S)

14 June 0830-1230

Joint Meeting
of the
Fertility and Maternal Health Drugs Advisory Committee
Obstetrics-Gynecology Devices Panel

Concerning recommendations for the Food and Drug Administration
proposed by the Committee on Contraceptive Development of the
National Academy of Sciences

The questions are directed to the six recommendations of the report
(provided on pages 114-116) as follows:

1. "The committee recommends that the FDA increase the weight it assigns to contraceptive effectiveness and convenience of use".

Question 1.1.: Do the advisory committees agree with this recommendation in principle?

Question 1.2.: If no, please provide the reasons.

Question 1.3.: If yes, can the advisory committees identify contraceptives whose FDA review would have been facilitated by the application of this policy? What new contraceptives yet to be reviewed by the FDA might benefit from the application of this policy?

2. "The FDA should also be prepared to approve, in some circumstances, a new contraceptive drug or device that presents a risk if it is shown that the new contraceptive offers a safety advantage for an identifiable group of users when compared with that group's current actual contraceptive practice (including nonuse)."

Question 2.1.: Do the advisory committees agree with this recommendation in principle?

Question 2.2.: If no, please provide the reasons.

Question 2.2.: If yes, can the advisory committees identify contraceptives whose FDA review would have been facilitated by the application of this policy? What new contraceptives yet to be reviewed by the FDA might benefit from the application of this policy?

3. "The committee also recommends that a comprehensive postmarketing surveillance system be established to provide systematic and timely feedback about positive and negative health effects of contraceptive products."

Question 3.1.: Do the advisory committees agree with this recommendation in principle?

Question 3.2.: Do the advisory committees believe that current practices by the FDA in this regard are sufficient?

Question 3.3.: If no, what additional efforts should be undertaken?

Question 3.4.: How do the advisory committees view the mandate of the National Institutes of Health Contraceptive Evaluation Branch in this regard?

4. "The committee recommends that an international conference of drug regulatory officials be held to increase the priority that such officials give to contraceptive development, to harmonize the regulatory requirements of different countries to such extent possible, to discuss the need for greater postmarketing surveillance of new contraceptives, and to clarify the basis for regulatory decisions in individual countries."

Question 4.1.: Do the advisory committees agree that such an international meeting would be helpful?

Question 4.2.: If yes, what entities should organize and underwrite such a meeting?

5. "The Food and Drug Administration should complete its review of its toxicological requirements for the evaluation of contraceptive products, especially its continued use of the beagle dog."

Question 5.1.: Do the advisory committees believe that the Agency's current requirements for animal toxicological studies for contraceptive steroids should be amended?

Question 5.2.: If yes, what changes are recommended?

6. "A report should be prepared by an independent body three to five years hence to assess FDA requirements with respect to contraceptives."

Question 6.1.: Do the advisory committees agree?

Question 6.2.: If yes, what entities should organize and underwrite such a review?

Food and Drug Administration
Fertility and Maternal Health Drugs Advisory Committee
Center for Drug Evaluation and Research
Gaithersburg Marriott
14-15 June 1990

AGENDA

14 June 0830-1230

0830-0930 Open public hearing

Joint Meeting
with the
Obstetrics-Gynecology Devices Panel
of the
Center for Devices and Radiological Health

RECOMMENDATIONS CONCERNING THE FOOD AND DRUG ADMINISTRATION
PROPOSED BY
THE COMMITTEE ON CONTRACEPTIVE DEVELOPMENT
OF THE
NATIONAL ACADEMY OF SCIENCES (NAS)

0930-1030 Presentations by NAS Committee Members

Luigi Mastrolanni, Jr, MD
Judy Norsigian
Richard M. Cooper, JD

1030-1100 Break

1100-1230 Discussion with FDA staff and response to questions

1230-1330 Lunch

14 June 1330-1700

PROPOSED CARDIOPROTECTIVE INDICATION FOR PREMARIN
BIOMEDICAL STUDIES

[Time will be provided at the beginning of this session for public comment on the proposed cardioprotective indication]

1330-1400

Presentations for the sponsor

Introduction

Marc Delitch, MD
Wyeth-Ayerst Laboratories

Overview

Roger Lobo, MD
University of Southern California School of Medicine

1400-1430

Invited speaker

Cardiovascular disease, lipoproteins, and hormones

John C. LaRosa, MD
George Washington University Medical Center

1430-1500

Presentations for the sponsor

Effect of estrogen replacement therapy on coronary lesions

Jay M. Sullivan, MD
University of Tennessee Medical School

1500-1530

Break

1530-1600

Discussion by FDA staff scientist

Linda Golden, MD

1600-1700

General discussion

15 June 0800-1230

PROPOSED CARDIOPROTECTIVE INDICATION FOR PREMARIN
EPIDEMIOLOGICAL STUDIES

- 0800-0900 Presentations for the sponsor
- Nurses study results and meta-analysis
 of all published studies
- Meir J. Stampfer, MD
 Harvard School of Public Health
- Lipid research clinics study results
- Elizabeth Barrett-Connor, MD
 University of California, San Diego,
 School of Medicine
- 0900-0930 Invited speaker
- Comments on the epidemiological issues
- Gary D. Friedman, MD
 Kaiser-Permanente Medical Care Program
- 0930-1000 Discussion by FDA staff scientists
- Comments on the epidemiological issues
- 1000-1030 Break
- 1030-1230 Discussion and response to questions
- 1230-1330 Lunch

15 June 1330-1530

PROPOSAL THAT VAGINAL FUNGICIDES
MAY BE SOLD WITHOUT PRESCRIPTION

[Time will be provided at the beginning of this session for public comment on this topic]

1330-1340

Introduction to the topic

Joseph K. Winfield, MD
Food and Drug Administration,

1340-1410

Discussion by an invited speaker.

Jack D. Sobel, MD
Wayne State University School of Medicine

1410-1500

Presentations by sponsors

Douglas B. Given, MD, PhD
Schering Corporation

Carol Sampson Landers, MD
Advanced Care Products
Ortho Pharmaceutical Corporation

Sebastian Faro, MD, PhD
Baylor College of Medicine
(Speaking for Advanced Care Products)

1500-1530

Discussion and Committee response to questions

Question 3. Does the Committee believe that vulvovaginal candidiasis can be safely and adequately self-diagnosed and treated by the consumer?

The Committee elected to change the question as follows:

"Does the Committee believe that vulvovaginal candidiasis can be safely and adequately self-treated by the consumer?"

Answer The Committee voted unanimously in favor of this question.

Question 4. If approved for OTC use, does the Committee recommend that certain patient populations be identified in the labeling (i.e., those with first infections or recurrent infections)?

Answer The Committee voted unanimously in favor of this question, recommending labeling similar to that provided by Schering-Plough on pages 10-12 of the document provided the Committee and entitled "Vaginal candidiasis: a self-treatable condition".

The agenda being completed, the Chair closed the meeting. It was noted that subsequent meeting dates for the Fertility and Maternal Health Drugs Advisory Committee are:

11-12 October 1990

7-8 February 1991

13-14 June 1991