CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

50-767

ADMINISTRATIVE DOCUMENTS

PATENT INFORMATION

CLEOCIN Vaginal Ovule

1.	Active Ingredient	Clindamycin phosphate
2.	Strength	100 mg (clindamycin free base)
3.	Tradename	CLEOCIN Vaginal Ovule
4.	Dose Form and Route of Administration	Vaginal suppository for intravaginal use
5.	Applicant Firm Name	Pharmacia & Upjohn Company
6.	NDA Number	50-767
7.	Approval Date	To be determined (no previous applications)
8.	Exclusivity - date first ANDA could be approved	Three (3) years after date of approval
9.	Applicable unexpired patent numbers	None

PATENT CERTIFICATION

CLEOCIN Vaginal Ovule

Paragraph II Certification

The patents covering clindamycin phosphate were held by Pharmacia & Upjohn and have expired.

We are requesting three (3) years of exclusivity for CLEOCIN Vaginal Ovule, pursuant to 21 CFR 314.108(b)(4)(iv), based on new clinical investigations contained in this application which were conducted or sponsored by Pharmacia & Upjohn and are essential to approval of this application.

Project Manager's note:
Applicant is Not Eligible
for exclusivity.

Christina Chi, PhD
8/2/1999.

EXCLUSIVITY SUMMARY FOR NDA # 50-767 ~~SUPPL~~ ORIGINAL #_____

Trade Name Cleocin® Vaginal Ovules Generic Name Clindamycin Phosphate Vaginal Suppositories

Applicant Name Pharmacia & Upjohn HFD # 590

Approval Date If Known Aug 13, 1999 (on target)

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following question about the submission.

a) Is it an original NDA?

YES /✓/ NO /___/

b) Is it an effectiveness supplement?

YES /___/ NO /✓/

If yes, what type? (SE1, SE2, etc.) _____

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES /✓/ NO /___/

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

_____

_____

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

d) Did the applicant request exclusivity?

YES /✓/ NO /___/

If the answer to (d) is "yes," how many years of exclusivity did the applicant request? 3 years.

e) Has pediatric exclusivity been granted for this Active Moiety?

No

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule, previously been approved by FDA for the same use? (Rx to OTC switches should be answered NO-please indicate as such)

YES /___/ NO /✓/

If yes, NDA #_____. Drug Name _____.

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

3. Is this drug product or indication a DESI upgrade?

YES /___/ NO /✓/

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including

other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES /___/ NO /___/

All previous drug products were approved under section 507. See appended listing.

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# See Appended list. _____

NDA# _____ _____

NDA# _____ _____

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES /___/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# _____ _____

NDA# _____ _____

NDA# _____ _____

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. IF "YES" GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES /✓/ NO /___/

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application ~~or~~ supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES /✓/ NO /___/

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

_____

_____

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data

would not independently support approval of the application?

YES /___/ NO /✓/

APPEARS THIS WAY
ON ORIGINAL

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES /___/ NO /___/

If yes, explain: _____

_____

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES /___/ NO /___/

If yes, explain: _____

_____

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Study 0001 - Efficacy of Clind. Vag. Ovule (3 day) vs. Clind. Vag. Cr. (7 day) & in BV

Study 0002 - " " " " " (") vs. oral Metronidazole (7 day) in BV.

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES /___/ NO /✓/

Investigation #2 YES /___/ NO /✓/

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

_____ _____

_____ _____

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES /___/ NO /✓/

Investigation #2 YES /___/ NO /✓/

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

_____ _____

_____ _____

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

Study -0001 _____

" 0002 _____

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1

IND # [ ] YES /✓/ ! NO /___/ Explain: _____

Investigation #2

IND # _____ YES /___/ ! NO /___/ Explain: _____

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1

YES /___/ Explain _____ ! NO /___/ Explain _____

Investigation #2

YES /✓/ Explain _____ ! NO /___/ Explain _____

Conducted in Europe ! _____

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES /___/ NO /✓/

If yes, explain: _____

_____

/S/

Signature

Date July 14, 1999

Title: Regulatory Health Coordinator

/S/

Signature of Office/
Division Director

8/10/99

Date

cc: Original NDA 93 Division File HFD-~~85~~ Mary Ann
Holovac

Form OGD-011347 Revised 10/13/98
cc: Original NDA Division File HFD-93 Mary Ann Holovac

PEDIATRIC PAGE

(Complete for all original applications and all efficacy supplements)

NOTE: A new Pediatric Page must be completed at the time of each action even though one was prepared at the time of the last action.

NDA/BLA # 50-767 Supplement # 000 original Circle one: SE1 ~~SE2 SE3 SE4 SE5~~ SE6

HFD-590 Trade and generic names/dosage form: Cleocin Vaginal Ovule Clindamycin phosphate 100 mg Action: AP AE NA

Applicant Pharmacia&Upjohn Therapeutic Class Vaginal Antimicrobial

Indication(s) previously approved same: Bacterial Vaginosis

Pediatric information in labeling of approved indication(s) is adequate ___ inadequate ✓

Proposed indication in this application Bacterial Vaginosis

FOR SUPPLEMENTS, ANSWER THE FOLLOWING QUESTIONS IN RELATION TO THE PROPOSED INDICATION.

IS THE DRUG NEEDED IN ANY PEDIATRIC AGE GROUPS? ___ Yes (Continue with questions) ✓ No (Sign and return the form)

WHAT PEDIATRIC AGE GROUPS IS THE DRUG NEEDED? (Check all that apply)

___ Neonates (Birth-1month) ___ Infants (1month-2yrs) ___ Children (2-12yrs) ✓ Adolecents(12-16yrs) (rarely).

___ 1. **PEDIATRIC LABELING IS ADEQUATE FOR ALL PEDIATRIC AGE GROUPS.** Appropriate information has been submitted in this or previous applications and has been adequately summarized in the labeling to permit satisfactory labeling for all pediatric age groups. Further information is not required.

___ 2. **PEDIATRIC LABELING IS ADEQUATE FOR CERTAIN AGE GROUPS.** Appropriate information has been submitted in this or previous applications and has been adequately summarized in the labeling to permit satisfactory labeling for certain pediatric age groups (e.g., infants, children, and adolescents but not neonates). Further information is not required.

___ 3. **PEDIATRIC STUDIES ARE NEEDED.** There is potential for use in children, and further information is required to permit adequate labeling for this use.

___ a. A new dosing formulation is needed, and applicant has agreed to provide the appropriate formulation.

___ b. A new dosing formulation is needed, however the sponsor is either not willing to provide it or is in negotiations with FDA.

___ c. The applicant has committed to doing such studies as will be required.

___ (1) Studies are ongoing,

___ (2) Protocols were submitted and approved.

___ (3) Protocols were submitted and are under review.

___ (4) If no protocol has been submitted, attach memo describing status of discussions.

___ d. If the sponsor is not willing to do pediatric studies, attach copies of FDA's written request that such studies be done and of the sponsor's written response to that request.

✓ 4. **PEDIATRIC STUDIES ARE NOT NEEDED.** The drug/biologic product has little potential for use in pediatric patients. Attach memo explaining why pediatric studies are not needed.

___ 5. If none of the above apply, attach an explanation, as necessary.

ARE THERE ANY PEDIATRIC PHASE IV COMMITMENTS IN THE ACTION LETTER? ___ Yes ✓ No

ATTACH AN EXPLANATION FOR ANY OF THE FOREGOING ITEMS, AS NECESSARY.

This page was completed based on information from _____ (e.g., medical review, medical officer, team leader)

/S/

Signature of Preparer and Title Project Manager

July 14 1999
Date

cc: Orig NDA/~~BLA~~ # 50-767
HFD-590 /Div File
NDA/BLA Action Package
HFD-006/ KRoberts

(revised 10/20/97)

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT, KHYATI ROBERTS, HFD-6 (ROBERTSK)

DEBARMENT CERTIFICATION

Cleocin Vaginal Suppository
for Bacterial Vaginosis

Pursuant to section 306(k)(1) of the Federal Food, Drug and Cosmetic Act, the applicant certifies that, the applicant did not and will not use in any capacity the services of any person listed pursuant to section 306(e) as debarred under subsections 306(a) or (b) of the Act in connection with this application.

/S/ 5/4/98

Ed L. Patt
Manager
Regulatory Compliance

Date

5.8 Compliance Statement

CLEOCIN Vaginal Ovule

Part 314.50(d)(2)(v)

Good Laboratory Practice Compliance Statement

All nonclinical laboratory studies conducted after the GLP effective date and included with this application were conducted in compliance with the good laboratory practice (GLP) regulations set forth in 21 CFR Chapter I, Part 58, with specific exceptions that may affect the quality or integrity of the data or report, if any, detailed with each study report.

For several studies in the application, there are no differences reported between practices used in the conduct of the study and those required by the good laboratory practices regulations because these studies were preliminary or experimental in nature and were not inspected for compliance with the GLP regulations.

Item 8.11. General Compliance Statement

8.11 GENERAL COMPLIANCE STATEMENT

8.11.1 Independent Ethics Committees

Independent review committees responsible for assuring the rights and safety of research subjects reviewed and approved the clinical studies (Protocols M/1100/0283, M/1114/0001, M/1114/0002, and M/1114/0003) conducted with clindamycin phosphate vaginal ovules (clindamycin VO), as required by the Declaration of Helsinki and national and international Good Clinical Practice guidelines and ethical standards, including those of the countries in which the studies were conducted. The Pharmacia & Upjohn Company maintains copies of these documented approvals; however, in the case of M/1114/0001, copies of periodic renewals were not on file for 4 study sites.

8.11.2 Ethical Conduct of the Studies

The clindamycin VO studies were conducted in compliance with the principles of Good Clinical Practice and in accordance with the recommendations guiding physicians in biomedical research involving human subjects adopted [redacted] and later revisions.

8.11.3 Patient Information and Consent

The Clinical Quality Assurance unit of Pharmacia & Upjohn, which is independent of the study monitors and reports through separate line management, reviewed the informed consent documents used for the clindamycin VO studies. These documents were found to meet worldwide requirements for patient information, including those of the countries in which the studies were conducted, with the following exceptions:

- *M/1100/0283*. One consent form did not state that the subject was free to withdraw from the study at any time.
- *M/1114/0002*. Consent forms for 4 sites did not discuss alternative treatments available, and consent forms for 2 sites did not fully discuss the possible risks or discomforts of the study treatment.

Pharmacia & Upjohn monitoring procedures require that the subjects sign an informed consent form prior to study participation.

Item 8.11. General Compliance Statement

8.11.4 Auditing

The Clinical Quality Assurance unit of Pharmacia & Upjohn conducted audits of Protocols M/1114/0001 and M/1114/0002 at 5 of the 20 M/1114/0001 study sites and 6 of the 23 M/1114/0002 study sites that enrolled subjects. The investigators/sites audited are listed in the table below.

Protocol	Country	Investigator
M/1114/0001	Mexico	
	United States	
M/1114/0002	Denmark	
	Finland	
	Sweden	
	United Kingdom	

Compliance with applicable regulations, good clinical practice guidelines, and Pharmacia & Upjohn monitoring procedures was evaluated during these audits. Results of the audits were reported to personnel responsible for the studies.

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

APPLICATION TO MARKET A NEW DRUG, BIOLOGIC, OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations, 314 & 601)

Form Approved: OMB No. 0910-0338
Expiration Date: April 30, 2000
See OMB Statement on page 2.

FOR FDA USE ONLY

APPLICATION NUMBER
50-767

APPLICANT INFORMATION

NAME OF APPLICANT
Pharmacia & Upjohn Company

DATE OF SUBMISSION
May 12, 1999

TELEPHONE NO. *(Include Area Code)*
616-833-9164

FACSIMILE (FAX) Number *(Include Area Code)*
616-833-8237

APPLICANT ADDRESS *(Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued):*

7000 Portage Road
Kalamazoo, Michigan 49001

AUTHORIZED U.S. AGENT NAME & ADDRESS *(Number, Street, City State,ZIP Code, telephone & FAX number)* IF APPLICABLE

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER (If previously issued)

ESTABLISHED NAME *(e.g., Proper name, USP/USAN name)*
Clindamycin phosphate vaginal suppository

PROPRIETARY NAME *(trade name)* IF ANY
CLEOCIN® Vaginal Ovule

CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME *(If any)*

CODE NAME *(If any)*

DOSAGE FORM:
Vaginal suppository

STRENGTHS:
100 mg

ROUTE OF ADMINISTRATION:
Intravaginal

(PROPOSED) INDICATION(S) FOR USE: Bacterial vaginosis

APPLICATION INFORMATION

APPLICATION TYPE (check one)
☒ NEW DRUG APPLICATION (21 CFR 314.50) ☐ ABBREVIATED APPLICATION (ANDA, AADA, 21 CFR 314.94)
☐ BIOLOGICS LICENSE APPLICATION (21 CFR part 601)

IF AN NDA, IDENTIFY THE APPROPRIATE TYPE ☒ 505 (b) (1) ☐ 505 (b) (2) ☐ 507

IF AN ANDA, OR AADA, IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION
Name of Drug Holder of Approved Application

TYPE OF SUBMISSION (check one)
☐ ORIGINAL APPLICATION ☒ AMENDMENT TO A PENDING APPLICATION ☐ RESUBMISSION
☐ PRESUBMISSION ☐ ANNUAL REPORT ☐ ESTABLISHMENT DESCRIPTION SUPPLEMENT ☐ SUPAC SUPPLEMENT
☐ EFFICACY SUPPLEMENT ☐ LABELING SUPPLEMENT ☐ CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT ☒ OTHER

REASON FOR SUBMISSION
Safety Update

PROPOSED MARKETING STATUS (check one) ☒ PRESCRIPTION PRODUCT (Rx) ☐ OVER THE COUNTER PRODUCT (OTC)

NUMBER OF VOLUMES SUBMITTED 1

THIS APPLICATION IS ☒ PAPER ☐ PAPER AND ELECTRONIC ☐ ELECTRONIC

ESTABLISHMENT INFORMATION

Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telepone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g. Final dosage form, Stability testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it wi ready.

Drug Project: Pharmacia & Upjohn Company, 7000 Portage Road, Kalamazoo, MI 49001.

Cross References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMFs referenced in the current application)

NDAs 50-200, 50-613, 50-441, 50-537, 50-600, 50-615, 50-639, 50-680;

This application contains the following items: *(Check all that apply)*	
1. Index	
2. Labeling (check one)	☐ Draft Labeling ☐ Final Printed Labeling
3. Summary (21 CFR 314.50 (c))	
4. Chemistry section	
A. Chemistry, manufacturing, and controls information (e.g. 21 CFR 314.50 (d) (1), 21 CFR 601.2)	
B. Samples (21 CFR 314.50 (e) (1), 21 CFR 601.2 (a)) (Submit only upon FDA's request)	
C. Methods validation package (e.g. 21 CFR 314.50 (e) (2) (i), 21 CFR 601.2)	
5. Nonclinical pharmacology and toxicology section (e.g. 21 CFR 314.50 (d) (2), 21 CFR 601.2)	
6. Human pharmacokinetics and bioavailability section (e.g. 21 CFR 314.50 (d) (3), 21 CFR 601.2)	
7. Clinical Microbiology (e.g. 21 CFR 314.50 (d) (4))	
8. Clinical data section (e.g. 21 CFR 314.50 (d) (5), 21 CFR 601.2)	
9. Safety update report (e.g. 21 CFR 314.50 (d) (5) (vi) (b), 21 CFR 601.2)	
10. Statistical section (e.g. 21 CFR 314.50 (d) (6), 21 CFR 601.2)	
11. Case report tabulations (e.g. 21 CFR 314.50 (f) (1), 21 CFR 601.2)	
12. Case reports forms (e.g. 21 CFR 314.50 (f) (2), 21 CFR 601.2)	
13. Patent information on any patent which claims the drug (21 U.S.C. 355 (b) or (c))	
14. A patent certification with respect to any patent which claims the drug (21 U.S.C. 355 (b) (2) or (j) (2) (A))	
15. Establishment description (21 CFR Part 600, if applicable)	
16. Debarment certification (FD&C Act 306 (k)(1))	
17. Field copy certification (21 CFR 314.50 (k) (3))	
18. User Fee Cover Sheet (Form FDA 3397)	
19. OTHER (Specify)	

CERTIFICATION

I agree to update this application with new safety information about the drug that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including, but not limited to the following:

1. Good manufacturing practice regulations in 21 CFR 210 and 211, 606, and/or 820.
2. Biological establishment standards in 21 CFR Part 600.
3. Labeling regulations in 21 CFR 201, 606, 610, 660 and/or 809.
4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR 202.
5. Regulations on making changes in application in 21 CFR 314.70, 314.71, 314.72, 314.97, 314.99, and 601.12.
6. Regulations on reports in 21 CFR 314.80, 314.81, 600.80 and 600.81.
7. Local, state and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.

The data and information in this submission have been reviewed and, to the best of my knowledge are certified to be true and accurate.

Warning: a willfully false statement is a criminal offense, U.S. Code, title 18, section 1001.

SIGNATURE OF RESPONSIBLE OFFICIAL/OR AGENT	TYPED NAME AND TITLE	DATE
Carl M. De Juliis	Carl M. De Juliis, Regulatory Affairs	May 12, 1999
ADDRESS *(Street, City, State, and ZIP Code)* 7000 Portage Road, Kalamazoo, Michigan 49001		TELEPHONE NUMBER (616) 833-9164

Public reporting burden for this collection of information is estimated to average 40 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

DHHS, Reports Clearance Officer
Paperwork Reduction Project (0910-0338)
Hubert H. Humphrey Building, Room 531-H
200 Independence Avenue, S.W.
Washington, DC 20201

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

Please DO NOT RETURN this form to this address.

CDER LABELING AND NOMENCLATURE COMMITTEE

CONSULT #	HFD#	PROPOSED PROPRIETARY NAME:	PROPOSED ESTABLISHED NAME:
1129	590	Cleocin Vaginal Ovules	clindamycin phosphate vaginal suppositories
ATTENTION: Dorota Matecka			

A. Look-alike/Sound-alike

Potential for confusion:

____ Low	____ Medium	____ High
____ Low	____ Medium	____ High
____ Low	____ Medium	____ High
____ Low	____ Medium	____ High
____ Low	____ Medium	____ High

B. Misleading Aspects:

C. Other Concerns:

Define Ovule on label.

D. Established Name

____ Satisfactory

____ Unsatisfactory/Reason

Recommended Established Name

E. Proprietary Name Recommendations:

____ ACCEPTABLE XXX UNACCEPTABLE

F. Signature of Chair/Date /S/ 3/11/99

Application: NDA 50767/000
Stamp: 14-OCT-1998
Regulatory Due: 14-AUG-1999
Applicant: PHARMACIA AND UPJOHN
7000 PORTAGE RD
KALAMAZOO, MI 490010199
Priority: 3S
Org Code: 590

Action Goal:
District Goal: 15-JUN-1999
Brand Name: CLEOCIN(CLINDAMYCIN PHOSPHATE)VAGINAL OV
Estab. Name:
Generic Name: CLINDAMYCIN PHOSPHATE
Dosage Form: (SUPPOSITORY)
Strength: 100 MG PER SUPPOSITORY

Application Comment: FIELD COPY CONSISTING OF TWO VOLUMES. VOLUME 1.4 CONTAINS THE MANUFACTURING INFORMATION AND VOLUME 1.5 CONTAINS CHEMISTRY ANALYTICAL INFORMATION. THEY WERE RECEIVED IN DET-DO IN OCTOBER 1998 AND WILL BE HELD HERE UNTIL THE PAI INSPECTION IS ASSIGNED TO A SPECIFIC CSO. (on 04-DEC-1998 by M. ROBINSON (HFR-MW250) 313-226-6260)

FDA Contacts:
C. CHI (HFD-590) 301-827-2166 , Project Manager
D. MATECKA (HFD-590) 301-827-2398 , Review Chemist
N. SCHMUFF (HFD-590) 301-827-2425 , Team Leader

Overall Recommendation: ACCEPTABLE on 16-MAR-1999 by M. EGAS (HFD-322) 301-594-0095

Establishment: 2650013
PHARMACIA AND UPJOHN CARIBE INC
HIGHWAY 2 KM 60.0
BARCELONETA/ARECIBO, PR 00617
DMF No: AADA:
Responsibilities: DRUG SUBSTANCE MANUFACTURER
Profile: CSN OAI Status: NONE
Estab. Comment:

Milestone Name	Date	Req. Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	30-NOV-1998				MATECKAD
SUBMITTED TO DO	01-DEC-1998	GMP			DAMBROGIOJ
ASSIGNED INSPECTION	04-DEC-1998	PS			CROSA
DO RECOMMENDATION	08-JAN-1999			ACCEPTABLE INSPECTION	IAYALA
NO DEFICIENCIES WERE FOUND RELATED TO THIS NDA, THEREFORE, SJND-DO RECOMMENDS APPROVAL					
INSPECTION PERFORMED	08-JAN-1999		21-DEC-1998		IAYALA
THE INSPECTION DISCLOSED DEVIATIONS RELATAED TO CONTENT UNIFORMITY AND FIELD ALERTS REQUIREMENTS. THE DEVIATIONS WERE NOT RELATED TO NDA 50-767 AND THE NDA PAC (46832) WAS CLASSIFIED NAI.					
OC RECOMMENDATION	11-MAR-1999			ACCEPTABLE DISTRICT RECOMMENDATION	EGASM
MILESTONES FLIP-FLOPPED. DO RECOMMENDATION AC, AND IN MILESTONES.					

Establishment: 1810189
PHARMACIA AND UPJOHN CO
7000 & 7171 PORTAGE ROAD
KALAMAZOO, MI 49001
DMF No: AADA:
Responsibilities: DRUG SUBSTANCE MANUFACTURER
FINISHED DOSAGE MANUFACTURER
Profile: SUP OAI Status: NONE
Estab. Comment: DET-DO WATS ASSIGNMENT # 107661 IS TO COVER GMP'S FOR SEVERAL DOSE FORMS INCLUDING (SUP) SUPPOSITORIES. IT HAS AN "A" PRIORITY WITH A 28-FEB-1999 DUE DATE.
DET-DO WATS ASSIGNMENT # 107662 IS TO COVER BULK ACTIVE PHARMACEUTICAL INGREDIENTS, AND HAS AN "A" PRIORITY WITH A 30-APR-

1999 DUE DATE.
THE PAI COVERAGE OF THE CLEOCIN DOSE FORM (SUP) SHOULD BE COVERED UNDER WATS 107661 AND THE BULK DRUG CLINDAMYCIN PHOSPHATE SHOULD BE COVERED UNDER WATS 107662. (on 04-DEC-1998 by M. ROBINSON (HFR-MW250) 313-226-6260)

Milestone Name	Date	Req. Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	30-NOV-1998				MATECKAD
SUBMITTED TO DO	01-DEC-1998	GMP			DAMBROGIOJ
ASSIGNED INSPECTION	04-DEC-1998	PS			MROBINSO
INSPECTION PERFORMED	25-FEB-1999		05-FEB-1999		MROBINSO
GMP EI DATED FEB, 1-5, 1999 COVERED PROFILE CLASSES SUO, OIN, & LIQ. NO FDA-483 WAS ISSUED AND THE EIR WILL BE CLASSIFIED NAI.					
DO RECOMMENDATION	25-FEB-1999			ACCEPTABLE INSPECTION	MROBINSO
DET-DO GMP EI DATED 2/1-5/1999 COVERED PROFILE CLASSES SUP, OIN, & LIQ. NO FDA-483 WAS ISSUED AND THE EIR WILL BE CLASSIFIED NAI.					
OC RECOMMENDATION	25-FEB-1999			ACCEPTABLE DISTRICT RECOMMENDATION	EGASM

CDER LABELING AND NOMENCLATURE COMMITTEE

CONSULT #	HFD#	PROPOSED PROPRIETARY NAME:	PROPOSED ESTABLISHED NAME:
1129	590	Cleocin Vaginal Ovules	clindamycin phosphate vaginal suppositories

ATTENTION: Dorota Matecka

A. Look-alike/Sound-alike

Potential for confusion:

_____ Low _____ Medium _____ High

_____ Low _____ Medium _____ High

_____ Low _____ Medium _____ High

_____ Low _____ Medium _____ High

_____ Low _____ Medium _____ High

B. Misleading Aspects:

C. Other Concerns:

Define Ovule on label.

D. Established Name

_____ Satisfactory

_____ Unsatisfactory/Reason

Recommended Established Name

E. Proprietary Name Recommendations:

_____ ACCEPTABLE XXX UNACCEPTABLE

F. Signature of Chair/Date /S/ 3/11/99

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

APPLICATION TO MARKET A NEW DRUG, BIOLOGIC, OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations, 314 & 601)

Form Approved: OMB No. 0910-0338
Expiration Date: April 30, 2000
See OMB Statement on page 2.

FOR FDA USE ONLY

APPLICATION NUMBER
50-767

APPLICANT INFORMATION

NAME OF APPLICANT
Pharmacia & Upjohn Company

DATE OF SUBMISSION
July 27, 1999

TELEPHONE NO. *(Include Area Code)*
616-833-9164

FACSIMILE (FAX) Number *(Include Area Code)*
616-833-8237

APPLICANT ADDRESS *(Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued)*:
7000 Portage Road
Kalamazoo, Michigan 49001

AUTHORIZED U.S. AGENT NAME & ADDRESS *(Number, Street, City, State,ZIP Code, telephone & FAX number)* IF APPLICABLE

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER (If previously issued)

ESTABLISHED NAME *(e.g., Proper name, USP/USAN name)*
Clindamycin phosphate vaginal suppository

PROPRIETARY NAME *(trade name)* IF ANY
CLEOCIN® Vaginal Ovule

CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME *(If any)*

CODE NAME *(If any)*

DOSAGE FORM:
Vaginal suppository

STRENGTHS:
100 mg

ROUTE OF ADMINISTRATION:
Intravaginal

(PROPOSED) INDICATION(S) FOR USE: Bacterial vaginosis

APPLICATION INFORMATION

APPLICATION TYPE
(check one)
☒ NEW DRUG APPLICATION (21 CFR 314.50) ☐ ABBREVIATED APPLICATION (ANDA, AADA, 21 CFR 314.94)
☐ BIOLOGICS LICENSE APPLICATION (21 CFR part 601)

IF AN NDA, IDENTIFY THE APPROPRIATE TYPE ☒ 505 (b) (1) ☐ 505 (b) (2) ☐ 507

IF AN ANDA, OR AADA, IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION
Name of Drug — Holder of Approved Application

TYPE OF SUBMISSION
(check one)
☐ ORIGINAL APPLICATION ☐ AMENDMENT TO A PENDING APPLICATION ☐ RESUBMISSION
☐ PRESUBMISSION ☐ ANNUAL REPORT ☐ ESTABLISHMENT DESCRIPTION SUPPLEMENT ☐ SUPAC SUPPLEMENT
☐ EFFICACY SUPPLEMENT ☐ LABELING SUPPLEMENT ☐ CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT ☒ OTHER

REASON FOR SUBMISSION
General Correspondence - Carton Mock-up

PROPOSED MARKETING STATUS (check one) ☒ PRESCRIPTION PRODUCT (Rx) ☐ OVER THE COUNTER PRODUCT (OTC)

NUMBER OF VOLUMES SUBMITTED 1 THIS APPLICATION IS ☒ PAPER ☐ PAPER AND ELECTRONIC ☐ ELECTRONIC

ESTABLISHMENT INFORMATION

Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telepone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g. Final dosage form, Stability testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.

Drug Project: Pharmacia & Upjohn Company, 7000 Portage Road, Kalamazoo, MI 49001.

Cross References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMFs referenced in the current application)

NDAs 50-200, 50-613, 50-441, 50-537, 50-600, 50-615, 50-639, 50-680;

EF

This application contains the following items: *(Check all that apply)*	
	1. Index
	2. Labeling (check one) ☐ Draft Labeling ☐ Final Printed Labeling
	3. Summary (21 CFR 314.50 (c))
	4. Chemistry section
	A. Chemistry, manufacturing, and controls information (e.g. 21 CFR 314.50 (d) (1), 21 CFR 601.2)
	B. Samples (21 CFR 314.50 (e) (1), 21 CFR 601.2 (a)) (Submit only upon FDA's request)
	C. Methods validation package (e.g. 21 CFR 314.50 (e) (2) (i), 21 CFR 601.2)
	5. Nonclinical pharmacology and toxicology section (e.g. 21 CFR 314.50 (d) (2), 21 CFR 601.2)
	6. Human pharmacokinetics and bioavailability section (e.g. 21 CFR 314.50 (d) (3), 21 CFR 601.2)
	7. Clinical Microbiology (e.g. 21 CFR 314.50 (d) (4))
	8. Clinical data section (e.g. 21 CFR 314.50 (d) (5), 21 CFR 601.2)
	9. Safety update report (e.g. 21 CFR 314.50 (d) (5) (vi) (b), 21 CFR 601.2)
	10. Statistical section (e.g. 21 CFR 314.50 (d) (6), 21 CFR 601.2)
	11. Case report tabulations (e.g. 21 CFR 314.50 (f) (1), 21 CFR 601.2)
	12. Case reports forms (e.g. 21 CFR 314.50 (f) (2), 21 CFR 601.2)
	13. Patent information on any patent which claims the drug (21 U.S.C. 355 (b) or (c))
	14. A patent certification with respect to any patent which claims the drug (21 U.S.C. 355 (b) (2) or (j) (2) (A))
	15. Establishment description (21 CFR Part 600, if applicable)
	16. Debarment certification (FD&C Act 306 (k)(1))
	17. Field copy certification (21 CFR 314.50 (k) (3))
	18. User Fee Cover Sheet (Form FDA 3397)
	19. OTHER (Specify)

CERTIFICATION

I agree to update this application with new safety information about the drug that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including, but not limited to the following:

1. Good manufacturing practice regulations in 21 CFR 210 and 211, 606, and/or 820.
2. Biological establishment standards in 21 CFR Part 600.
3. Labeling regulations in 21 CFR 201, 606, 610, 660 and/or 809.
4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR 202.
5. Regulations on making changes in application in 21 CFR 314.70, 314.71, 314.72, 314.97, 314.99, and 601.12.
6. Regulations on reports in 21 CFR 314.80, 314.81, 600.80 and 600.81.
7. Local, state and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.

The data and information in this submission have been reviewed and, to the best of my knowledge are certified to be true and accurate.

Warning: a willfully false statement is a criminal offense, U.S. Code, title 18, section 1001.

SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT	TYPED NAME AND TITLE	DATE
Carl M. De Juliis	Carl M. De Juliis, Regulatory Affairs	July 27, 1999

ADDRESS *(Street, City, State, and ZIP Code)*	TELEPHONE NUMBER
7000 Portage Road, Kalamazoo, Michigan 49001	(616) 833-9164

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

APPLICATION TO MARKET A NEW DRUG, BIOLOGIC, OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations, 314 & 601)

Form Approved: OMB No. 0910-0338
Expiration Date: April 30, 2000
See OMB Statement on page 2.

FOR FDA USE ONLY

APPLICATION NUMBER
50-767

APPLICANT INFORMATION

NAME OF APPLICANT
Pharmacia & Upjohn Company

DATE OF SUBMISSION
July 26, 1999

TELEPHONE NO. *(Include Area Code)*
616-833-9164

FACSIMILE (FAX) Number *(Include Area Code)*
616-833-8237

APPLICANT ADDRESS *(Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued):*
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Kalamazoo, Michigan 49001

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PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER (If previously issued)

ESTABLISHED NAME *(e.g., Proper name, USP/USAN name)*
Clindamycin phosphate vaginal suppository

PROPRIETARY NAME *(trade name)* IF ANY
CLEOCIN® Vaginal Ovule

CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME *(If any)*
–

CODE NAME *(If any)*

DOSAGE FORM:
Vaginal suppository

STRENGTHS:
100 mg

ROUTE OF ADMINISTRATION:
Intravaginal

(PROPOSED) INDICATION(S) FOR USE: Bacterial vaginosis

APPLICATION INFORMATION

APPLICATION TYPE
(check one) ☒ NEW DRUG APPLICATION (21 CFR 314.50) ☐ ABBREVIATED APPLICATION (ANDA, AADA, 21 CFR 314.94)
☐ BIOLOGICS LICENSE APPLICATION (21 CFR part 501)

IF AN NDA, IDENTIFY THE APPROPRIATE TYPE ☒ 505 (b) (1) ☐ 505 (b) (2) ☐ 507

IF AN ANDA, OR AADA, IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION
Name of Drug — Holder of Approved Application

TYPE OF SUBMISSION
(check one) ☐ ORIGINAL APPLICATION ☐ AMENDMENT TO A PENDING APPLICATION ☐ RESUBMISSION
☐ PRESUBMISSION ☐ ANNUAL REPORT ☐ ESTABLISHMENT DESCRIPTION SUPPLEMENT ☐ SUPAC SUPPLEMENT
☐ EFFICACY SUPPLEMENT ☐ LABELING SUPPLEMENT ☐ CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT ☒ OTHER

REASON FOR SUBMISSION
General Correspondence - Geriatric Labeling Change

PROPOSED MARKETING STATUS (check one) ☒ PRESCRIPTION PRODUCT (Rx) ☐ OVER THE COUNTER PRODUCT (OTC)

NUMBER OF VOLUMES SUBMITTED 1 — THIS APPLICATION IS ☒ PAPER ☐ PAPER AND ELECTRONIC ☐ ELECTRONIC

ESTABLISHMENT INFORMATION

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Drug Project: Pharmacia & Upjohn Company, 7000 Portage Road, Kalamazoo, MI 49001.

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	16. Debarment certification (FD&C Act 306 (k)(1))
	17. Field copy certification (21 CFR 314.50 (k) (3))
	18. User Fee Cover Sheet (Form FDA 3397)
	19. OTHER *(Specify)*

CERTIFICATION

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2. Biological establishment standards in 21 CFR Part 600.
3. Labeling regulations in 21 CFR 201, 606, 610, 660 and/or 809.
4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR 202.
5. Regulations on making changes in application in 21 CFR 314.70, 314.71, 314.72, 314.97, 314.99, and 601.12.
6. Regulations on reports in 21 CFR 314.80, 314.81, 600.80 and 600.81.
7. Local, state and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.

The data and information in this submission have been reviewed and, to the best of my knowledge are certified to be true and accurate.

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SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT	TYPED NAME AND TITLE	DATE
Carl M. De Juliis	Carl M. De Juliis, Regulatory Affairs	July 26, 1999
ADDRESS *(Street, City, State, and ZIP Code)* 7000 Portage Road, Kalamazoo, Michigan 49001	TELEPHONE NUMBER (616) 833-9164	

Public reporting burden for this collection of information is estimated to average 40 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

DHHS, Reports Clearance Officer
Paperwork Reduction Project (0910-0338)
Hubert H. Humphrey Building, Room 531-H
200 Independence Avenue, S.W.
Washington, DC 20201

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

Please DO NOT RETURN this form to this address.

DEPARTMENT OF HEALTH & HUMAN SERVICES — Public Health Service

Memorandum

Date: August 1, 1999

From: Brad Leissa, MD 8/1/99
Medical Team Leader
Division of Special Pathogen and Immunologic Drug Products (HFD-590)

Subject: NDA 50-767; Cleocin® (clindamycin) Vaginal Ovule (100 mg)

Applicant: Pharmacia & Upjohn Co.

Cleocin® 2% intravaginal cream (100 mg x 7 days; CVC) was approved in 1992 (NDA 50-680) for the treatment of bacterial vaginosis (BV). In 1998 clinical studies demonstrated (NDA 50-680 S-002) that efficacy was maintained in the treatment of BV when only 3 days were administered (with the exception of 2nd and 3rd trimester pregnancy which weren't studied).

The applicant argues that women desire a new formulation, which is less messy than the vaginal cream. Hence, Pharmacia & Upjohn submitted NDA 50-767 on 10/14/98 requesting U.S. marketing approval for a 100 mg vaginal ovule (CVO) in the treatment of bacterial vaginosis for 3 days.

In their application, the applicant submits data from three studies:

(1) **M/1100/0283**: placebo-controlled, double-blind, study comparing 3-day CVO vs. 5-day CVO and placebo.

(2) **M/114/001**: active-controlled, observer-blind study comparing 3-day CVO to 7-day CVC.

(3) **M/114/002**: active-controlled, double-blind, double-dummy study comparing 3-day CVO to 7-day PO metronidazole 500 mg b.i.d. (Note: CDC STD treatment guidelines recommend using this dose of metronidazole.)

In the first study, CVO was shown to be superior to placebo as it relates to efficacy. For the intent-to-treat (ITT) population: 55% vs. 14%, respectively. The 95% CI around the difference was (24%, 58%).

In the second study, CVO efficacy was shown to be statistically similar to CVC. For the ITT population: 56% vs. 50%, respectively. The 95% CI around the difference was (-3%, 15%).

In the third study, CVO efficacy was shown to be statistically similar to metronidazole. For the ITT population: 58% vs. 60%, respectively. The 95% CI around the difference was (-13%, 9%).

Based on data from the clinical trial database, CVO was reasonably safe relative to other approved comparators.

Recommendation: I agree with Dr. Joseph Winfield, the reviewing medical officer, that the applicant has submitted substantial evidence from adequate and well-controlled clinical trials to show that Cleocin® vaginal ovule for 3 days is safe and effective in the treatment of bacterial vaginosis. I recommend approval of this NDA.

cc: NDA 50-767
HFD-590/MO/Winfield
HFD-590/MTL/Leissa

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

Form Approved: OMB No. 0910-0297
Expiration Date: November 30, 1996.

USER FEE COVER SHEET

See Instructions on Reverse Before Completing This Form.

1. APPLICANT'S NAME AND ADDRESS

PHARMACIA & UPJOHN COMPANY
7000 Portage Road
Kalamazoo, MI 49001

2. USER FEE BILLING NAME, ADDRESS, AND CONTACT

PHARMACIA & UPJOHN COMPANY
7000 Portage Road
Kalamazoo, MI 49001

Robert A. Paarlberg
Director, External Affairs

3. TELEPHONE NUMBER *(Include Area Code)*
616-833-8554

4. PRODUCT NAME
CLEOCIN® Vaginal Ovule

DOES THIS APPLICATION CONTAIN CLINICAL DATA? ☒ YES ☐ NO
IF YOUR RESPONSE IS "NO" AND THIS IS FOR A SUPPLEMENT, STOP HERE AND SIGN THIS FORM.

6. USER FEE I.D. NUMBER
3541

7. LICENSE NUMBER/NDA NUMBER.
NDA 50-767

8. IS THIS APPLICATION COVERED BY ANY OF THE FOLLOWING USER FEE EXCLUSIONS? IF SO, CHECK THE APPLICABLE EXCLUSION.

☐ A LARGE VOLUME PARENTERAL DRUG PRODUCT APPROVED BEFORE 9/1/92
☐ AN INSULIN PRODUCT SUBMITTED UNDER 506
☐ THE APPLICATION IS SUBMITTED UNDER 505(b)(2) *(See reverse before checking box.)*

FOR BIOLOGICAL PRODUCTS ONLY

☐ WHOLE BLOOD OR BLOOD COMPONENT FOR TRANSFUSION
☐ BOVINE BLOOD PRODUCT FOR TOPICAL APPLICATION LICENSED BEFORE 9/1/92
☐ A CRUDE ALLERGENIC EXTRACT PRODUCT
☐ AN "IN VITRO" DIAGNOSTIC BIOLOGIC PRODUCT LICENSED UNDER 351 OF THE PHS ACT

9. a. HAS THIS APPLICATION QUALIFIED FOR A SMALL BUSINESS EXCEPTION? ☐ YES *(See reverse if answered YES)* ☒ NO

b. HAS A WAIVER OF APPLICATION FEE BEEN GRANTED FOR THIS APPLICATION? ☐ YES *(See reverse if answered YES)* ☒ NO

This completed form must be signed and accompany each new drug or biologic product, original or supplement.

SIGNATURE OF AUTHORIZED COMPANY REPRESENTATIVE	TITLE	DATE
Nancy J. Busso Nancy J. Busso	Regulatory Affairs Manager	October 13, 1998

FORM FDA 3397 (12/93)

5271 Chi

NDA # 50767 DOCUMENT ID/LETTER DATE NDoc. 10.13.98

APPLICANT NAME Pharmacia & Upjohn Company

PRODUCT NAME Cleocin Vaginal Ovule (Clindamycin Phosphate) 100mg

FORM MUST BE COMPLETED ASAP

1. (YES) User Fee Cover Sheet Validated?

NOTE TO DOCUMENT ROOM:
PLEASE MAKE THE FOLLOWING CHANGES TO THE COMIS DATA ELEMENTS:

Clinical Reviewer: J. Winfield
Pharm Tox : Owen Mc Master
Chemistry : D. Mazeika
Biopharm : P. Colangelo
Micro : L. Utrup
~~Clinical~~ Statistics: Li Ji Shen
PM : C. Chi

2. (YES) NO CLINICAL DATA?
[Check YES if contains study reports or literature reports of what are explicitly or implicitly represented by the applicant to be adequate and well-controlled trials. "Clinical data do not include data used to modify the labelling to add a restriction that would improve the safe use of the drug (e.g., to add an adverse reaction, contraindication or warning to the labeling).]

REF IF NO CLINICAL DATA IN SUBMISSION, INDICATE IF CLINICAL DATA ARE *CROSS REFERENCED* IN ANOTHER SUBMISSION?

3. YES (NO) NDA BEING SPLIT FOR ADMINISTRATIVE CONVENIENCE (OTHER THAN BUNDLING)? IF YES, list ALL NDA numbers, review divisions & indicate those for which application fees apply.

NDA #	DIVISION		
N_____	_____	FEE	NO FEE
N_____	_____	FEE	NO FEE

4. YES NO BUNDLING POLICY APPLIED CORRECTLY? NO DATA ENTRY REQUIRED FOR ELEMENT
NA
[Check YES if application is properly designated as one application or is properly submitted as a supplement instead of an original application. Check NO if application should be split into more than one application or submitted as an original instead of a supplement. IF NO, list resulting NDA numbers, and review divisions.]

NDA #	DIVISION	NDA #	DIVISION
N_____	_____	N_____	_____

5. P (S) PRIORITY OR STANDARD?

/S/
CSO SIGNATURE/DATE Nov 20, 1998.

/S/
SCSO CONCURRENCE SIGNATURE/DATE

COPY DISTRIBUTION: ORIGINAL TO ARCHIVAL AFTER DATA ENTRY, ONE COPY EACH TO DIVISION FILE AND CDER, ASSOCIATE DIRECTOR FOR POLICY HFD-5

Christine Chu
NDA 50-767
3-Day Claim Overlo

45 DAY MEETING CHECKLIST

P. BILITY:

On 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?

I believe that this is no longer required

I think they still need to claim exclusion but more products are now eligible.

Yes No

(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? ✓ (one pre-submission discussion: teleconf)

(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? Pharmacia will check & let me know. Item 5 Vol 1 p 281.

(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? ✓ we are sure they complied, but they'll double check & get back. Item 8 Vol 2 p 332+333

(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 certification, Item 6

Yes No

(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? N/A

(q) 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? Vol 1 p 53 (6 p 15) of Item 8.4 ✓ Will be updated only 1 AE was since

(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? N/A

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

/S/
Project Manager

/S/
Supervisory Project Manager

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

NDA: 50-767
DRUG CLASS: 1S
NAME OF DRUG: Cleocin Vaginal Ovule
APPLICANT: Pharmacia & Upjohn
SUBMISSION DATE: Oct. 13, 1998

INDICATION(S): treatment of Bacterial Vaginosis

NUMBER AND TYPE OF CONTROLLED CLINICAL STUDIES BY INDICATION:
2 randomized, double-dummy phase III trials

STATISTICAL REVIEWER: Liji Shen
CLINICAL REVIEWER: Joe Winfield
PROJECT MANAGER: Christina Chi

45 DAY MEETING DATE: Nov. 23, 1998
WAS THE NDA FILED: yes
IF YES, DUE DATE: Aug. 13, 1999
USER FEE DATE: Oct. 13, 1999

I. ORGANIZATION AND DATA PRESENTATION	YES	NO	N/A
A. Is there a comprehensive table of contents with adequate indexing and pagination?	x		
B. Are the original protocols, protocol protocol amendments and proposed label provided?	x		
C. Adverse event listings by center and time of occurrence relative to enrollment date.	x		
1. Are adverse events from cited sources(foreign and domestic) provided?	x		
D. Is a CANDAR or an electronic submission of the data necessary?	x		
E. If the data have been submitted electronically, has adequate documentation of the data sets been provided?			x
Note: SAS data sets were not submitted with NDA.			
F. Are inclusion/exclusion (evaluability) criteria			

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

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?	__x_	____	____
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.)?	__x_	____	____
If subset analyses were not done, was an acceptable explanation of why given?	____	___	__x_
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)?	_x__	___	___
2. If there are multiple endpoints, has this been adequately addressed?	___	___	_x__
3 Intent-to-treat (ITT and MITT) analyses are properly performed?	_x__	___	___
4. Sufficient and appropriate references were included for novel statistical approaches?	__	___	__x_
D. If interim analyses were performed, were they planned in the protocol and were appropriate significance level adjustments made?	___	___	_x__
E. Are there studies which are incomplete or ongoing?	___	_x__	___

F. Is there a comprehensive, adequate analysis of safety data as recommended in the Clinical/Statistical Guideline? _x__ ___ ___

1. Is there anything significant yet regarding safety or AE evaluations? ___ __x__ ____

III. FILEABILITY CONCLUSIONS

From a statistical perspective, is this submission, or indications therein, reviewable with only minor further input from the sponsor?

Yes. The applicant was requested to submit SAS data sets to the statistical reviewer.

/S/

Liji Shen
Biomedical Statistician, DB III

/S/ 11/23/98

Concur: Nancy Silliman, Ph.D.
Team Leader, DB III

cc:
Archival:NDA #50-767
HFD-590
HFD-590/Dr. Goldberger
HFD-590/Dr. Albrecht
HFD-590/Dr. Leissa
HFD-590/Dr. Winfield
HFD-590/Ms. Chi
HFD-725/Dr. Huque
HFD-725/Dr. Silliman
HFD-725/Dr. Shen
HFD-725/Chron.

45 DAY MEETING CHECKLIST

LITY:

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?	✓	
(6) From a biopharmaceutic perspective, is the NDA fileable? If "no", please state below why it is not?	✓	

/S/ - 11/23/98
eviewing Biopharmaceutics Officer

/S/ 11/23/98
isory Biopharmaceutics Officer

Microbiology NDA 50-164

11/23/98

45 DAY MEETING CHECKLIST

BILITY:

n initial overview of the NDA application:

	YES	NO
MICROBIOLOGY:		
(1) On its face, is the microbiologic section of the NDA organized in a manner to allow substantive review to begin?	✓	
(2) Is the microbiologic section of the NDA indexed and paginated in a manner to allow substantive review to begin	✓	
(3) On its face, is the microbiologic section of the NDA legible so that substantive review can begin?	✓	
(4) On its face, has the applicant generally submitted in vitro data in necessary quantity, using necessary clinical and non-clinical strains, and using necessary numbers of approved laboratories to meet current divisional standard for approvability of the product based on the submitted draft labeling?	✓	
(5) Has the applicant submitted any required animal model studies necessary for approvability of the product based on the submitted draft labeling?	✓	
(6) Has the applicant submitted draft breakpoint and interpretive criteria in a manner consistent with contemporary standards, in a manner which attempts to correlate criteria with clinical results of NDA studies, and in a manner to allow substantive review to begin?	✓	
(7) Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?	✓	
(8) Has the applicant submitted draft labeling consistent with 201.56 and 201.57, current divisional policy, and the design of the development package?	✓	

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

Yes

/S/ 11/13/98
Reviewing Microbiology Officer

/S/ 11-13-98
Supervisory Microbiology Officer

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 Gaithersburg Marriott Hotel in Gaithersburg, 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 on this recommendation.)

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. <u>Concerning a proposed cardioprotective indication for Premarin in women without a uterus</u>

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 Deitch, 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, Meir J. Stampfer, Roger Lobo, and Marc Deitch, 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

Executive Secretary

Colin M. Pollard
Food and Drug Administration

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

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

Johannna F. Perlmutter, MD
Beth Israel Hospital
Boston MA

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

Non-Voting Members

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

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

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

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University of Rochester Medical School
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University of Wyoming School of Nursing
University Station Box 3065
Laramie WY 82071

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

Jenifer R. Niebyl, MD
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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
Gaithersburg Marriott
14-15 June 1990

PARTICIPANTS

14 June 0830-1230

SPEAKERS FOR THE NATIONAL ACADEMY OF SCIENCES
COMMITTEE ON CONTRACEPTIVE DEVELOPMENT

Luigi Mastroianni, 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 an 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 proposat 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
Gaithersburg Marriott
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 Mastroianni, 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 Deitch, 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

Douglass 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