CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: **20-574**

ADMINISTRATIVE DOCUMENTS

CLOTRIMAZOLE 3-DAY VAGINAL CREAM

13. Patent Information

The undersigned declares that there are no unexpired U.S. Patents which cover the drug product, or a formulation or composition containing the drug product or a method of using the drug product. The drug product is the subject of this application for which approval is being sought under Section 505 of the Federal Food, Drug and Cosmetic Act.

John M. Clayton

4/27/95

John M. Clayton, Ph.D.
Senior Vice President
Scientific & Regulatory Affairs

Date

EXCLUSIVITY SUMMARY for NDA # 20-574 SUPPL # _____

Trade Name Gyne-Lotrimin 3 ® 3-Day Vaginal Cream Generic Name Clotrimazole vaginal cream (2%)

Applicant Name Schering-Plough HealthCare Products HFD- 590

Approval Date _____

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 questions about the submission.

   a) Is it an original NDA?

   YES /X/ NO /__/

   b) Is it an effectiveness supplement?

   YES /__/ NO /X/

   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 /X/ 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:

_____

_____

Form OGD-011347 Revised 8/7/95; edited 8/8/95

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

d) Did the applicant request exclusivity?

YES / X / NO / __ /

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

3 years

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?

YES / __ / NO / X /

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 / X /

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 / X / NO / ___ /

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

NDA # 17-717 Gyne-Lotrimin Vaginal Inserts

NDA # 18-052 Gyne-Lotrimin Vaginal Cream (1%)

NDA # 20-289 Gyne-Lotrimin Combination Pack

NDA 20-525
Gyne-Lotrimin 3-3 Day
Vaginal Inserts

NDA 20-526
Gyne-Lotrimin 3-3 Day
Vaginal Inserts Plus

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.)

[Not a combination] 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 /X/ 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.

For the purposes of this section, studies comparing two products with the same ingredient(s) are considered to be bioavailability studies.

(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 /X/ 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 /X/ NO /__/

(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 /X/

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 /X/

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:

Investigation #1, Study # 93-34

Investigation #2, Study # 93-40

Investigation #3, Study # 95-50

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 / X /
Investigation #2	YES /___/	NO / X /
Investigation #3	YES /___/	NO / X /

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

NDA # _____ Study # _____
NDA # _____ Study # _____
NDA # _____ Study # _____

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 / X /
Investigation #2	YES /___/	NO / X /
Investigation #3	YES /___/	NO / X /

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

NDA # _____ Study # _____
NDA # _____ Study # _____
NDA # _____ Study # _____

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"):

Investigation #1, Study # 93-34

Investigation #2, Study # 93-40

Investigation #3, Study # 95-50

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 # [redacted] YES / X / ! NO / / Explain: _____

Investigation #2

IND # [redacted] YES / X / ! NO / / Explain: _____

Investigation #3 ! NO/ X / Conducted in Canada by Taro Pharmaceuticals

(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 / X / Explain _____

Investigation #2

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

_____ _____

_____ _____

(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 /_x_/

If yes, explain: _____

_____

_____

_____

/S/ 10/28/98

Signature Date

Title: Project Manager

/Regulatory Health Project Coordinator/

/S/ 11/10/98

Signature of Division Director Date

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

CDER LABELING AND NOMENCLATURE COMMITTEE

CONSULT # 982	HFD# 590	PROPOSED PROPRIETARY NAME:	PROPOSED ESTABLISHED NAME:
ATTENTION:	DOROTA MATECKA	GYNE-LOTRIMIN 3	CLOTRIMAZOLE VAGINAL CREAM

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:

Label should contain the statement:
3-DAY TREATMENT

D. Established Name

XXX Satisfactory

___ Unsatisfactory/Reason

Recommended Established Name

E. Proprietary Name Recommendations:

XXX ACCEPTABLE ___ UNACCEPTABLE

F. Signature of Chair/Date /S/ 5/14/98

CDER Establishment Evaluation Report
for November 05, 1998

Application: NDA 20574/000
Priority: 3S
Org Code: 590
Stamp: 27-APR-1995 Regulatory Due: 25-NOV-1998
Action Goal:
District Goal: 26-JUL-1998
Applicant: SCHERING PLOUGH HLTH
110 ALLEN RD
LIBERTY CORNER, NJ 07938
Brand Name: GYNE LOTRIMIN 3/3 DAY VAGINAL CREAM
Established Name:
Generic Name: CLOTRIMAZOLE
Dosage Form: CRM (CREAM)
Strength: 200 MG (DOSE)

FDA Contacts:

C. CHI	(HFD-590)	301-827-2127	, Project Manager
D. MATECKA	(HFD-590)	301-827-2398	, Review Chemist
N. SCHMUFF	(HFD-590)	301-827-2425	, Team Leader

Overall Recommendation:

ACCEPTABLE on 21-APR-1998 by J. D AMBROGIO (HFD-324) 301-827-0062

Establishment:
DMF No:
AADA No:
Profile: CRU OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date 11-FEB-1998
Decision: ACCEPTABLE
Reason: DISTRICT RECOMMENDATION
Responsibilities:

Establishment:
DMF No:
AADA No:
Profile: CSN OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date 10-FEB-1998
Decision: ACCEPTABLE
Reason: BASED ON PROFILE
Responsibilities:

Establishment:
DMF No:
AADA No:
Profile: CTL OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date 21-APR-1998
Responsibilities:

Decision: **ACCEPTABLE**
Reason: **DISTRICT RECOMMENDATION**

Establishment: **1031623**
SCHERING PLOUGH HEALTHCARE
9 OLD MICHIGAN AVENUE ROAD
CLEVELAND, TN 37311

DMF No:
AADA No:

Profile: **CTL** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Milestone Date **10-FEB-1998**
Decision: **ACCEPTABLE**
Reason: **BASED ON PROFILE**

Responsibilities:

Establishment: **2650149**
SCHERING PLOUGH PRODUCTS IN
CARRETERA ESTATAL NUMBER 68
MANATI, PR 00701

DMF No:
AADA No:

Profile: **OIN** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Milestone Date **17-FEB-1998**
Decision: **ACCEPTABLE**
Reason: **DISTRICT RECOMMENDATION**

Responsibilities:

APPEARS THIS WAY
ON ORIGINAL

Schering's

8.K. # Statement of Compliance

[21 CFR § 314.50(d)(5)(ix)]

All clinical studies involving human subjects were conducted in compliance with the institutional review board regulations under 21 CFR § 56 and the informed consent regulations under 21 CFR § 50.

Taro's

8.K. Statement of Compliance

Taro clinical study #95-50 involving human subjects was conducted under review and approval of an institutional review board in Canada and appropriate informed consent, as approved by the institutional review board, was obtained from all subjects.

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

LICATION 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 last page.

FOR FDA USE ONLY

APPLICATION NUMBER

APPLICANT INFORMATION

NAME OF APPLICANT	DATE OF SUBMISSION
Schering-Plough HealthCare Products	10/28/98
TELEPHONE NO. *(Include Area Code)* (908) 604-1962	**FACSIMILE (FAX) Number** *(Include Area Code)* (908) 604-1741

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

Schering-Plough HealthCare Products
110 Allen Road
PO Box 276
Liberty Corner, NJ 07938

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

Ronald J. Garutti, MD
Schering-Plough HealthCare Products
110 Allen Road
PO Box 276
Liberty Corner, NJ 07938

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER (If previously issued) 20-574

ESTABLISHED NAME *(e.g., Proper name, USP/USAN name)*	PROPRIETARY NAME *(trade name)* IF ANY
clotrimazole vaginal cream	Gyne-Lotrimin® 3-Day Vaginal Cream

CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME *(If any)*	CODE NAME *(If any)*
1 (o-chloro-alpha, alpha-diphenyl benzyl) imadazole	SCH 15335L; Bay b5097; Bay 5097

DOSAGE FORM:	STRENGTHS:	ROUTE OF ADMINISTRATION:
intravaginal cream	100 mg (2% cream)	intravaginal

(PROPOSED) INDICATION(S) FOR USE:

-atment and cure of vulvovaginal candidiasis (over-the-counter)

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: Additional APE data

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

NUMBER OF VOLUMES SUBMITTED — 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, telephone 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.

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

NDAs 17-613,17-619; 17-717;18-052;18-813;18-827;19 20-525;20-526

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
X	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 314.5 (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 product 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
Mary E. Williams for RJG	Ronald J. Garutti, MD V.P., Regulatory Affairs/Clin.Research	10/28/98
ADDRESS *(Street, City, State, and ZIP Code)*		Telephone Number
		(908) 604-1962

Please DO NOT RETURN this form to this address.

Schering-Plough HealthCare Products

To: Christina Chi

cc:

From: Joseph D. Clark

Date: April 9, 1996

Subject: FDA Meeting - Gyne-Lotrimin 3-Day Inserts and Cream

On April 3, 1996 a meeting was held at the FDA Corporate Boulevard facility with representatives of the Division of Anti-Infective Drug Products. In attendance were:

FDA - Division of Anti-Infective Drug Products: (DAIDP)

Brad Leissa, M.D.	Team Leader
Joseph Winfield, M.D.	Review Officer
Julius Piver, M.D., J.D.	Review Officer (Consultant)
Christina Chi, Ph.D.	Project Manager

Schering-Plough Healthcare Products: (SPHCP)

Joseph Clark, Ph.D.	Vice President, Regulatory Affairs
Richard Paul, M.D.	Vice President, Clinical Research

Dr. Winfield began discussion by explaining their new organization. DAIDP has been structured into four teams with Dr. Leissa heading the Vaginal Team. Dr. Renata Albrecht has returned and is now Deputy Director of the Division reporting to Dr. Mary Fanning. Holly Hamilton is also on the team and we may interact with her in the future on labeling.

Discussions were divided into two major topics; revised guidelines for future clinical studies (on the 3-Day Cream) and the status of the review of the 3-Day Insert NDAs [redacted]

A. Guidance on Clinical Protocol Design for a 3-Day Cream Study:

1. General

- Two well-controlled clinical trials are required unless the same product was previously marketed Rx, then one additional study will suffice.

- A product does not have to have been Rx to be approved for OTC use, therefore, the 2% cream can be OTC if two well-controlled clinical trials (which meet the acceptance criteria) are conducted. FDA agreed to confirm this position with the OTC Division and get back to us. — OK

- It was recommended that we choose either 1% or 2% cream but not study both. The Agency was concerned over the numbers of patients needed for a three arm study (including the 7-Day control arm).

- The new guidelines recommend investigator blinding. Therefore, the 14 and 28 day follow-up visits will be calculated from the day of entry into the study. The day 28 visit can be 28 (-3) or (+7) days (i.e., 25-35 days after the start of treatment).

- SPHCP recommended that the requirement for a KOH test be deleted as it was redundant since cultures were being conducted. The Agency disagreed. However, it was agreed that if there is a discordance between the KOH and culture results at any test period, the culture would be the defining result.

- Trials should not exclude diabetics, pregnant women, oral contraceptive users and other groups known to experience recurrent infections. The study should be open but it is not necessary to recruit separate cohorts for these groups.

- Patient population should be "approximately 100 to 130 evaluable patients per arm."

- Criteria for success will be:

a. 3-day treatment results will not be statistically different from the results of a 7-day treatment in the same study.

b. Therapeutic cure rates for both 3-day and 7-day treatments must be greater than 50%

2. <u>Specific Criteria</u>

a. <u>Day 14</u>

- It was suggested that the 14 day evaluation was unnecessary since the 28 day evaluation would be used to determine ultimate success. The Agency wants the 14 day test to determine treatment failure early on so patients can be referred for specific treatment. Patients will not be dropped at day 14 if they are improving. If the culture is positive on Day 14 the patient is a failure and is dropped from the study no matter what is happening clinically.

b. Day 28

- If the patient is evaluated on Day 14 but not on Day 28 the patient is considered "non-evaluable" (LOCF cannot be used).

-If at Day 28 the culture is negative but clinical symptoms are still present the patient will be included but will be the subject of a separate evaluation with more detailed discussion.

c. Signs and Symptoms

- Discharge will be eliminated as a sign as it is too prevalent and difficult to subjectively quantitate.

- Symptoms will include itching/irritation (one symptom) and burning and will be scored as 0-3 (i.e., none, mild, moderate, severe).

- Signs will include erythema, edema and excoriation and will be scored as 0 (absent) or 1 (present).

It was agreed that Dr. Paul will prepare investigator's instructions to describe how to score signs, symptoms and a global assessment. Also a short summary of the protocol design will be forwarded to Dr. Winfield for review.

B. 3-Day Insert

The status of the 3-Day Insert NDA was discussed.

- Dr. Clark reviewed the history of the reanalysis which was submitted and the withdrawal of the 3-Day Cream NDA which had been described as competing with the review of the 3-Day Insert. The urgency of a completed review was emphasized.

- Dr. Winfield agreed to move on the review as rapidly as he could.

- There was agreement on the following items which will speed the ultimate approval:

- Labeling will be essentially the same as for the approved 7-Day Insert, except "3-Day" will replace "7-Day" and there could be minor warning changes. The Agency did not anticipate major revision.

- Dr. Winfield indicated that their intention is to deem the NDA as "approved" rather than "approvable."

- It was agreed that when the 3-Day Insert is approved the 7-Day product does not have to be removed from the market. (It was anticipated that market forces would result in its removal in the normal process.)

Dr. Winfield agreed to our calling him in two weeks to follow-up on our protocol and to check on the status of the review with the OTC Division. At that time we can also check on his progress on the review of the 3-Day insert and review any questions he may have on the re-analysis.

PRE-NDA MEETING
TARO & SCHERING-PLOUGH

MEMORANDUM OF MEETING MINUTES

Meeting Date: June 18, 1997

Time: 11:30 AM - 1:00 PM

Location: 9201 Corporate Blvd., Rockville, MD 20850

Application: Taro: Pre-NDA Clotrimazole 2% Vaginal Cream (No IND)
Schering: NDA 20-574 GyneLotrimin 3, Clotrimazole 2% Cream

Type of Meeting: Pre-NDA meeting; possibility of an NDA joint submission between the two companies for a product which is going to be marketed OTC.

Meeting Chair & Recorder: Christina H. Chi, Ph.D., Project Manager

FDA Attendees:

Division of Over The Counter Drug Products:
Linda Katz, M.D., M.P.H., Deputy Division Director
Helen Cothran, Team Leader
Sakineh Walther, R.N., Project Manager

Division of Special Pathogens And Immunologic Drug Products:
Mark Goldberger, M.D., Acting Division Director
Renata Albrecht, M.D. Deputy Division Director
Christina Chi, Ph.D., Project Manager
Philip Colangelo, Ph.D., Biopharmaceutics Reviewer
Daniel Davis, M.D., Medical Officer
Carmen DeBellas, Acting Supervisor Regulatory Health Manager
Linda Gosey, Microbiologist
Sheryl Lard, Ph.D., Acting Microbiology Team Leader
Brad Leissa, M.D., Medical Team Leader
Dorota Matecka, Ph.D., Chemistry Reviewer
Owen McMaster, Ph.D., Pharmacology Reviewer
Frank Pelsor, Ph.D., Biopharmaceutics Team Leader
Norman Schmuff, Ph.D., Chemistry Acting Team Leader
Nancy Silliman, Ph.D., Acting Supervisor Statistician
Joseph Winfield, M.D., Medical Officer

Office of Generic Drug:
Donald Hare, Special Assistant to the Director

PRE-NDA MEETING
TARO & SCHERING-PLOUGH

Sponsor Attendees: **Taro Pharmaceuticals, USA, INC.**
Avraham Yacobi, Ph.D., Chief E.O. President.
Daniel Moros, M.D., Vice Chairman, Med. Dir.
Terry Feldman, Ph.D., V.P., Res. & Development.

Schering-Plough HealthCare Products
Joseph Clark, Ph.D., V.P., Reg. Affairs
Mary Williams, Assoc. Dir, Reg. Affairs

Background:

April 27, 1995: Schering-Plough submitted NDA 20-574 for GyneLotrimin 3 (clotrimazole) Vaginal Cream 2%. This was a 3-day therapy for vaginal yeast infections (candidiasis). Both had 3-arm studies, comparing the 3-day to the 7-day treatments and the 1-day to the 7-day treatments. The results indicated that the 7-day 1% was equivalent to the 3-day 2% cream in one study. In the other study, the 7-day 1% was equivalent to the 3-day 1%. Because two studies were required, the data submitted did not support approval for either the 1-day or the 3-day as equivalent to the 7-day product.

January 29, 1996: The applicant chose to withdraw the application.

September 12, 1996: The Agency met with Taro to discuss evaluability criteria and clinical trial design for a proposed clotrimazole 2% vaginal cream for a one or three day therapy to treat vaginal yeast infections (Candidiasis). Based on this meeting, it was concluded that this study would support the 3-day treatment, because efficacy was generally better in the 3-day treatment group (vs. the 1-day arm).

January 10, 1997: Schering-Plough and Taro entered into a joint venture (based on an earlier business agreement of October 22, 1993, between Schering-Plough and Taro) for both parties to provide data needed to support the approval of a 3-day clotrimazole 2% vaginal cream.

Meeting Objectives:

1. To seek FDA's comment on their pooling the data from two clinical trials done by Schering-Plough into one study.

2. To seek FDA's comment on the use of Taro's data with their 3-day 2% vaginal cream as the second study to support Schering's direct-OTC NDA.

3. To seek the reactivation of Schering's NDA with Schering as the manufacturer and Taro as the distributor.

Discussion points and agreements reached:

1. The FDA agreed that it appears reasonable to pool the two Schering clinical studies (93-34 and 93-40) as a single study.

2. The FDA suggests that the pooled data from these two studies be reanalyzed using the FDA's current evaluability criteria.

3. Pending the results of Taro's study (95-50 – an on-going study), a determination will be made as to whether the pooled study from Schering can be used in conjunction with Taro's study to support approval of Schering's NDA.

4. The FDA cannot assume that the two different formulations have identical activity. The sponsors must demonstrate that the activity of the two different products are the same (do a clinical study of 2 arms to bridge the difference). Therefore, the FDA recommended that the two companies perform a "bridging" study demonstrating therapeutic equivalence between their respective formulations of the two products.

5. The FDA will not accept *in-vitro* data alone as the "bridging" study.

6. Linda Katz, OTC, stated that over 5 years of marketing experience is desired for a product to receive direct OTC marketing approval.

7. Taro has a 3-day 2% cream currently marketed in Canada (over 5 years since approval) while Schering doesn't have this experience with their product. The FDA has difficulty extrapolating Taro's safety experience to support Schering's product, because the formulations are different. In light of Taro's postmarketing experience, it may be easier for Schering's data to support Taro's product – rather than the reverse.

Unresolved issues or issues requiring further discussion:

1. The sponsors will consider a new clinical study to bridge the two formulations. They

stated that they will provide the FDA with a response on this issue within 1-2 weeks.

2. If the sponsors do not want to conduct a bridging study, they may request that FDA seek General Counsel's opinion on whether the data from two different formulations can be used (with no direct comparison between the two) to support approval.

3. The sponsors will decide which of the two formulations (Schering's or Taro's) to market.

Projected submission date: uncertain at this time.

Action Items: None.

/S/

Minutes Preparer: Christina Chi, Ph.D. 7/7/97

Chair Concurrence: Carmen DeBellas 6/20/'97

Attachments:

meeting request:	2 pages
pre-meeting package:	10 pages
meeting transparencies:	2 pages
summary of NDA 20-574 clinical studies:	1 page
Total:	15 pages

APPEARS THIS WAY
ON ORIGINAL

To Distribution

From Mary Williams MW

Date 7/8/97

Subject **Minutes of 6/18/97 FDA Meeting on Clotrimazole 2% Cream NDA**

On June 18, 1997 representatives from the FDA, Schering-Plough HealthCare Products (SPHCP) and Taro Pharmaceuticals (see Attachment 1 for list of attendees) met at the FDA Corporate Boulevard facility to discuss the proposed joint strategy for a 2% clotrimazole cream NDA. (See Attachment 2 for overheads.)

PROPOSAL AND RATIONALE

Dr. Daniel Moros (Taro) opened the discussion with a brief history on the use of antifungals to treat vaginal yeast infections, including a list of the critical studies SPHCP and Taro have conducted to demonstrate bioequivalence of various dosing regimens of clotrimazole to the 1% / 7 day "gold standard". Noting that SPHCP and Taro each have one pivotal study which supports a 2% / 3-day cream product, Dr. Moros informed the group that SPHCP and Taro would like to combine their work and jointly pursue approval of a single NDA. The purpose of this meeting was to outline the strategy and gain FDA feedback on the proposal.

Dr. Joseph Clark (SPHCP) then reviewed SPHCP's history of 3-day vaginal yeast products, i.e., insert, combination pack, and cream. Early in his review of the data for the pending 3-day cream NDA, Dr. Winfield (FDA Medical Officer) had concluded that one of the pivotal studies supported the 2% / 3-day treatment while the other pivotal study supported a 1% / 3-day treatment, resulting in the need for an additional study. This led SPHCP to withdraw the 3-day cream NDA (1/26/96) so that the FDA could focus their attention on the insert and combination pack pending NDAs (subsequently approved 7/29/96). At SPHCP's request, a meeting was held with the FDA on April 4, 1996 where agreement was reached on revised pass/ fail criteria for a future cream study and on the decision that only the 2% clotrimazole cream should be pursued for direct OTC marketing.

Since that meeting, SPHCP and Taro have decided to explore joint development of a 2% clotrimazole cream NDA, but are seeking the Agency's counsel before preceding. Specifically, guidance is requested on whether or not the data from SPHCP's two

studies are "poolable", and whether or not (given the minor differences in formulation excipients) SPHCP and Taro can combine their two studies as the pivotal clinical trials in support of a single NDA. Assuming this proposal is acceptable to the Agency, the strategy would be for SPHCP to reactivate its withdrawn NDA, amend it with a re-analysis of the SPHCP combined data using the revised criteria, and add Taro's clinical study as the second pivotal study. SPHCP would manufacture the product using its formula and include Taro in the NDA as a distributor.

Dr. Terry Feldman (Taro) presented a detailed comparison of the formulas used in SPHCP's and Taro's clinical studies which are qualitatively and quantitatively very similar. To demonstrate formula equivalence and support the use of these two formulas for a single NDA (which will seek approval of only one formula), in-vitro studies were conducted to compare the release rates of both formulas. A summary of the data was presented which demonstrated that the release rates are essentially the same for the two formulas.

Dr. Clark then gave an overview of the clinical protocols used in both SPHCP's and Taro's studies. Since both protocols were based on the FDA's guidelines, they were also essentially the same.

Finally, Dr. Clark and Dr. Moros each presented a brief review of the clinical and mycological results for their respective company's clinical studies.

QUESTION AND ANSWER PERIOD HIGHLIGHTS

- Dr. Winfield suggested that the same statistical and evaluation criteria be applied to the Taro study as that used in the SPHCP study analysis.

- Drs. Winfield and Albrecht asked if any studies had been done to demonstrate bioequivalency of the two formulas. Dr. Moros said that they had not but that both formulas had been tested against the same standard. Dr. Albrecht responded that just because A=B and C=B, that is no guarantee that A=C. In addition the FDA felt that in-vitro data by itself is not sufficient to demonstrate equivalency. When Dr. Clark pointed out that a product could go through several formulations during its development phase, Dr. Albrecht responded that this is true for oral dosage forms which are then subjected to a bioavailability study to tie all the formulations together. The outcome of this discussion was that the FDA wants a bridging study to allow the use of two different formulas to support one formula for an NDA.

- Dr. Katz advised that the OTC division's position would be that the Taro formula which is currently marketed OTC in Canada would be the preferred OTC product since it could provide an OTC safety data base. She further noted that if the SPHCP formula were used it might need to be marketed first as an Rx product. There was a brief discussion of how we might satisfy the Agency's safety concerns with the SPHCP product since it's active ingredient is the same as Taro's and it's vehicle is the same as that which has been marketed by SPHCP, both Rx and OTC, for many years with an excellent safety experience among millions of consumers.

- There was no foreseeable problem with SPHCP pooling their two clinical studies into one pivotal study for purpose of the proposed NDA.

- Dr. Albrecht indicated that if the bridging study was begun and was progressing adequately, they may begin their review of the resubmitted NDA to try to meet a six month deadline for an action. They would try to work with us to accelerate the review.

NDA 20-574

MEMORANDUM OF TELECON

DATE: September 29, 1997

APPLICATION NUMBER: NDA 20-574 clotrimazole 2% cream

BETWEEN SPONSOR:

Schering-Plough HealthCare Products:
Ronald J. Garutti, M.D., Vice President, Clinical Research/Regulatory Affairs
Walt Chambliss, Ph.D., Vice President, Research & Development
Joseph Clark, Ph.D., Consultant
Mary Williams, Associate Director, Regulatory Affairs

Taro Pharmaceuticals, USA, Inc.
Daniel Moros, M.D., Vice Chairman, Medical Director
Lorraine Sachs, RAC, Senior Regulatory Affairs Scientist

Taro Pharmaceuticals, CANADA, Inc.
Terry Feldman, Ph.D., V.P., Research & Development.

AND FDA:

Division of Over the Counter Drug Products, HFD-560:
Ling Chin, M.D., Medical Officer
Helen Cothran, Team Leader
Cheryl Turner, R.N., Interdisciplinary Scientist
Sakineh Walther, R.N., Project Manager

Division of Special Pathogens and Immunologic Drug Products, HFD-590:
Renata Albrecht, M.D., Dep. Div. Dir.
Christina Chi, Ph.D., Project Manager
Daniel Davis, M.D., Medical Officer
Brad Leissa, M.D., Medical Team Leader
Joseph Winfield, M.D., Medical Officer

SUBJECT: The possibility of reopening of Schering's withdrawn NDA 20-574 Vaginal Cream clotrimazole 2% for OTC marketing with the support of Taro's 2% Vaginal Cream. Reconfirmation of the FDA opinion and understanding.

NDA 20-574

DISCUSSION POINTS:

* Reactivation of the withdrawn NDA 20-574 with the following new information and data:
  - one study will be a combination of the 2 Schering clinical studies (previously submitted as part of an original NDA 20-574 which was withdrawn later on) which are currently being pooled and reanalyzed.
  - one ongoing clinical study of Taro will fulfill the second study requirement.
  - one clinical "bridging" study has just been started.

  The FDA agreed to the plan provided that the bridging study can demonstrate comparability between the Taro and Schering formulations.

* FDA's guidance on the appropriateness in using the 2% Schering cream formulation:
  The FDA explained that based on the earlier faxed communication supplied by the sponsor which contained a table comparing the 4 different cream formulations (1% and 2%) of Taro and Schering, it appears that both the creams of Taro and Schering could be considered similar. Therefore there is no objection in using the Schering (2%) cream formulation for marketing. The sponsor will have to send a collated safety information to the FDA on all 1% and 2% cream products, including data from Canada.

* Sponsor stated that they would be marketing the Schering product under NDA 20-574.
  They expressed their gratitude over this brief yet very productive telecon.

/S/ Ph.D 12/12/97

Christina Chi, Ph.D.

cc: Original NDA 20-574
HFD-560/Div.File
HFD-560/TL/HCothran
HFD-560/ClinRev/LChin 12/11/97
HFD-560/PM/SWalther
HFD-590/Div. File
HFD-590/DepDivDir/RAlbrecht
HFD-590/ClinTL/BLeissa 10/6/97 BL 12/12/97
HFD-590/ClinRev/JWinfield
HFD-590/ClinRev/DDavis
HFD-590/PM/Christina Chi

Concurrence only: HFD-590/ClinTL/BLeissa

Drafted and prepared by: CChi 9/29/97 Final: 12/12/97.
TELECON, Schering-Plough Health Care and Taro Pharmaceuticals.

NDA 20-574
Review time and filing requirements.

JAN 23 1998

MEMORANDUM OF TELECON

DATE: January 12, 1998

APPLICATION NUMBER: NDA 20-574 clotrimazole 2% cream

BETWEEN SPONSOR:

Schering-Plough HealthCare Products, Inc.:
Ronald J. Garutti, M.D., Vice President, Clinical Research/Regulatory Affairs
Joseph Clark, Ph.D., Consultant
Mary Williams, Associate Director, Regulatory Affairs

AND FDA:

Division of Special Pathogens and Immunologic Drug Products, HFD-590:
Renata Albrecht, M.D., Dep. Div. Dir.
Christina Chi, Ph.D., Project Manager
Brad Leissa, M.D., Medical Team Leader
Joseph Winfield, M.D., Medical Officer

SUBJECT: 1. The sponsor's request for a 6-month review time for the reactivated NDA 20-574 Vaginal Cream clotrimazole 2% for OTC marketing.
2. Reiteration of the FDA request that complete information of the bridging study (between Schering's Cream and Taro's cream) as well as pertinent data from the study, including the outcome and analyses, be officially submitted before Friday, January 23, 1998, to NDA 20-574.

DISCUSSION POINTS:

* According to the FDA's understanding and opinion, this submission cannot be called a resubmission, since the NDA was withdrawn prior to the issuance of an action letter. The submission is merely a reactivation of the withdrawn NDA 20-574 with new information, data, and analyses.

* The FDA firmly stated that the PDUFA review time for the reactivated NDA 20-574 Vaginal Cream clotrimazole 2% is and will remain as 12 months. However, the Division will review the application as expeditiously as possible. The Division has reviewed its meeting

minutes and cannot identify any previous commitment on our part to review the application in 6 months.

* The FDA expressed a concern that this submission is incomplete at face value and therefore is unable to begin its review. The information still needed prior to January 23, 1998, are:

1. The two studies previously submitted (studies 93-34 & 93-40), which should be pooled as one study as recommended by the FDA on June 18, 1997, are not included in the package as one study in a complete format for review. Since the original application was previously withdrawn on January 29, 1996, administratively they do not exist. To date, only the new analyses have been submitted, but the reasons for patient exclusion from the studies has to be stated.

2. Information on the bridging study (Taro's clinical study # 95-50) is incomplete since it only contains summary data. Additional documents to be submitted include: the number of qualified patients, the reasons for exclusion, the number of evaluable patients, the reason for the nonevaluability, the patient's line listing, and the final outcome. The typical appendiceal data analysis tables should be submitted.

3. Biometrics requirements were communicated by telephone earlier today and will be explained further in a separate telecon tomorrow. These documents also must be submitted prior to the filing date.

4. Taro's Canadian postmarketing experience, which will be evaluated from only the report of adverse events, was limited to "no serious adverse event" without more specific explanation or any detailed marketing information. This makes it harder to assess the safety of the product for OTC marketing. Therefore, a document explaining the product's use history (Rx and OTC) should be submitted as soon as possible.

The sponsor expressed their understanding and commitment in supplying the necessary documents as soon as possible. The FDA reiterated that the goal is to file the submission, but in order to do so, the sponsor has to complete the submission with documents needed for review before the 60-day filing date, which is January 23, 1998. The FDA firmly stated that the PDUFA goal date is and will remain as 12 months. The telecon was adjourned amicably.

/S/ 1/23/98
Christina Chi, Ph.D.

Concurrence only: HFD-590/ClinTL/BLeissa 1/23/98

To: Distribution

From: Mary Williams

Date: 1/21/98

Subject: **Minutes of 1/12/98 FDA Teleconference on Review Clock for Gyne-Lotrimin3™ 3-Day Vaginal Cream NDA #20-574**

FDA Participants: **Division of Special Pathogens and Immunologic Drug Products:**
Renata Albrecht, M.D.
Christina Chi, Ph.D
Brad Leissa, M.D.
Joseph Winfield, M.D.

Sponsor Participants: **Schering-Plough HealthCare Products (SPHCP):**
Joseph Clark, Ph.D.
Ronald Garutti, M.D.
Mary Williams

Teleconference Objective: SPHCP had requested to speak informally with FDA's Dr. Renata Albrecht to gain a better understanding of the one-year review clock assigned to the resubmission of the subject NDA. This teleconference was in response to that request.

Background Information: The original NDA had been submitted on April 27, 1995 and subsequently withdrawn on January 26, 1996 (by mutual agreement with the Division prior to an action letter), after SPHCP was informed by the medical reviewer that we did not have two adequate studies to support the NDA. (Note: nine months of the twelve month review period had already elapsed and a significant amount of the review had commenced or had been completed, including the successful pre-approval inspection of the manufacturing facility in Puerto Rico, prior to withdrawal of the NDA.)

At a June 18, 1997, joint SPHCP/Taro meeting with FDA to discuss the "resubmission" of the subject NDA, it was communicated to Schering and Taro that if the bridging study the FDA had requested at that meeting was well underway, the sponsors could resubmit the NDA and the Agency would work with them toward a six-month action letter. This communication was reflected in the SPHCP minutes submitted to the FDA on July 8,1997, but did not appear in FDA's minutes which were faxed to SPHCP on September 9, 1997.

Prior to the resubmission, SPHCP submitted the proposed format of its contents in a letter to the FDA Project Manager. This letter outlined the strategy to "reactivate" the NDA and would shortly thereafter be followed by an amendment to include the pooling and reanalysis of our two clinical trials and to add the Taro clinical study. However, just prior to the submission, the FDA Project Manager instructed SPHCP to provide the letter to reopen the file and the amendment in one submission which *must* be clearly labeled as a "Resubmission."

The application therefore designated as a "Resubmission" was sent to the FDA on November 24, 1997. On December 4, 1997 SPHCP received notification of FDA receipt of the Resubmission which established November 25, 1998 (12 month review clock) as the date for an action letter. SPHCP questioned this review period and attempted to contact Dr. Albrecht to discuss.

Discussion and agreements reached:

Drs. Garutti and Clark opened the meeting with a brief discussion of the background including the discrepancy in the respective minutes of the June meeting. Dr. Leissa then stated that a 6 month review clock was only for priority submissions and for resubmissions. He noted that according to 21CFR section 314, the SPHCP submission was technically ***not*** a resubmission and should not have been designated as such. In addition, at the 45-day review meeting for acceptability of filing which had been held that morning, it was noted that FDA had not yet received the entire final report for the bridge study. (Note: extensive results had been submitted informally on 1/8/98 and the full clinical study report was subsequently submitted on 1/15/98.) Dr. Leissa indicated that FDA had decided to accept the submission for filing.

Dr. Leissa noted several items that needed further input or clarification as follows: the medical reviewer, Dr. Winfield, and the Biometrics reviewer had several comments/questions - it was agreed that these would be handled directly with the reviewers; the Agency needed the full bridge study report - this would be submitted before the end of the week (Post-teleconference note: the final bridge study report was sent January 15, 1998); also the Agency needed the adverse event data, including the quantities distributed, both Rx and OTC, for the Taro Canadian marketed cream product - this would be submitted as soon as possible.

Dr. Leissa indicated that they understood our desire for an expedited review. He suggested that we get the remaining information to them as soon as possible so they could commence their review.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

Date: July 13, 1998

To: Schering-Plough HealthCare Products
Att: Ronald Garutti, Ph.D.

From: Dorota Matecka, Ph.D., Chemistry Reviewer DM 7/13/98

Through: Norman R. Schmuff, Ph.D., Chemistry Team Leader NRS 7/13/98
Division of Special Pathogens and Immunologic Drug Products, HFD-590

Re: CMC Comments/NDA 20-574 (Clotrimazole 2% Vaginal Cream)

Please address the following CMC comments regarding the Gyne-Lotrimin 3 Vaginal Cream (NDA 20-574):

1. Please describe in-process controls for the manufacturing process of the drug product. For bulk product testing, samples should be taken not only from the top, but also from the middle and bottom of the compounder.

2. Please include a viscosity specification for the drug product. Viscosity should also be monitored on stability.

3. Please specify the dose of the cream delivered by both the reusable and the disposable applicators. Please provide any available data from the applicator dosage evaluation studies. Please specify which applicators were used in the clinical trials.

4. Please provide batch analysis data for all the manufactured batches of the drug product.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

Date: July 14, 1998

To: Bayer AG/Miles Inc. Pharmaceutical Division
Att: Carl Calcagni, R.Ph.

From: Dorota Matecka, Ph.D., Chemistry Reviewer

Through: Norman R. Schmuff, Ph.D., Chemistry Team Leader NRS 7/14/98
Division of Special Pathogens and Immunologic Drug Products, HFD-590

Re: CMC Comments/Type II DMF [redacted] (Clotrimazole, Drug Substance)

Please address the following CMC comments regarding the 7/2/95 update of your Type II DMF (Clotrimazole, Drug Substance):

1. Please submit an updated list of companies authorized to reference DMF [redacted]

2. Please describe the method(s) used to characterize the two polymorphic forms of clotrimazole [redacted]

3. Please specify at which step of the manufacturing process the described in-process controls occur. Please explain how [redacted] (7/2/95 DMF Update, p. 25) serves as an in-process control in the production of clotrimazole.

DEPARTMENT OF HEALTH AND HUMAN SERVICES Public Health Service

MEMORANDUM Center for Drug Evaluation and Research

Date: 10/7/98

From: Jose Carreras, M.D.
CIB/HFD 344

To: Christina Chi - Project Manager
Joseph Winfield - Medical Officer

Subject: NDA 20-574
Sponsor - Schering Plough
Product - GyneLotrimin 3 Cream 2%

Name of Investigator	Classification
Daniel Wiener, M.D. Montreal, Quebec	VAI
Melvin Guralnick, M.D. Montreal, Quebec	VAI

No objectionable conditions were found which would preclude the use of the data submitted in support of pending NDA.

Note:

VAI = Minor deviation(s) from
regulations - Data Acceptable

Jose A Carreras, M.D.

To: Distribution

From: Mary Williams

Date: 11/20/98

Subject: **Minutes of 10/21/98 Meeting with FDA To Discuss Labeling for Gyne-Lotrimin3® 3-Day Vaginal Cream**

FDA Participants: **Office of Compliance - OTC Compliance Team**
Robert Eshelman
William Nychis

Division of Over The Counter Drug Products:
Ling Chin, M.D.
Linda Katz, M.D.
Cheryl Turner, R.N.
Sakineh Walther, R.N.
Elizabeth Yuan

Division of Special Pathogens and Immunologic Drug Products:
Christina Chi, Ph.D.
Edward Cox, M.D.
Brad Leissa, M.D.
Dorota Matecka
Owen McMaster
Joseph Winfield, M.D.

Division of Drug Marketing, Advertising, and Communications
Karen Lechter

Sponsor Participants: **Schering-Plough HealthCare Products (SPHCP):**
Joseph Clark, Ph.D. (consultant)
Ronald Garutti, M.D.
Mary Williams

Meeting Objective:

- An internal Agency meeting of the four FDA divisions (DSPIDP, DDMAC, DOTCDP, and Office of Compliance) responsible for review and approval of the OTC labeling for the subject product had been scheduled for October 21, 1998. SPHCP requested the opportunity to attend this meeting to discuss the possibility of marketing the subject product with the original SPHCP tube label for the first six months following approval of the NDA.

Discussion and agreements reached at 10/21/98 meeting:

- Prior to SPHCP joining them, the four FDA reviewing divisions had discussed the pre-meeting information submitted by SPHCP to support the use of the original SPHCP tube label, as well as the colored mock-up labeling for the carton and educational brochure which SPHCP had provided on 10/16/98 at the Agency's request. (Note: this colored mock-up labeling was based on the final version of labeling as reviewed by DOTCDP and sent to SPHCP on 10/6/98. A copy of the mock-up labeling is attached.)

  Following Dr. Garutti's presentation of a side-by-side comparison of the SPHCP tube labeling and the FDA proposed tube labeling, making the point that they were comparable in their message to the consumer (supported by the results of a recent market research study to that effect), the Agency informed SPHCP that they would allow the use of the original SPHCP tube label for the first six months of marketing, following approval of the NDA. (Post Meeting Note: in an 11/6/98 Phase IV Commitment letter, SPHCP formally committed to revise "the 21 gram tube of cream label according to the Agency's labeling review and addendum faxed on October 29, 1998, at the next printing or six months after the approval of the NDA, whichever comes first.")

  The Agency then questioned the status of SPHCP's efforts to revise the carton and educational brochure labeling according to the 10/6/98 comments from DOTCDP. SPHCP responded that the artwork process was completed and the order had been placed for these pieces with the vendors. The Agency stated that they would be recommending additional minor changes to both of these pieces which should be implemented prior to launch of the product if possible, or no later than six months following approval. SPHCP agreed that they would consider incorporating the changes prior to launch, depending on the extent of the Agency's comments and when they were received. If it were determined to be not feasible to incorporate prior to launch, both the FDA and SPHCP agreed that incorporating within six months of the NDA approval would be acceptable.

  The Agency concluded the meeting with the following comments/ recommendations:

  • SPHCP should work towards revising the subject labeling according to the February 27, 1997 (62 FR 9024) proposed standardized format labeling for OTC drug products. The revised labeling should be submitted to the Agency for approval prior to implementation.

  • SPHCP should work towards incorporating a Toll-Free Number in the carton and educational brochure labeling within the next year.

  • Other minor changes to be made on the carton and educational brochure will not be considered conditions for approval of the NDA.

Additional Post Meeting Note:

On October 29, 1998, SPHCP received the Agency's addendum to the labeling review which stated that the "revisions should be done within 6 months or at the next printing, whichever occurs first." Given the long lead time needed to obtain these packaging components, SPHCP is unable to incorporate these labeling changes for launch but has committed to implementing them within the timeframe allowed by the Agency. In fact, the artwork process for the first post-launch revision of labeling has been initiated to incorporate these changes and a mock-up version was provided to the Agency on November 17, 1998 for their final approval.

APPEARS THIS WAY
ON ORIGINAL

MEMORANDUM TO THE RECORD

NOV 2 4 1998

Date: November 24, 1998

From: Christina H. Chi, Ph.D.
Regulatory Health Manager
Division of Special Pathogen and Immunologic Drug Products, HFD-590

To: NDA 20-574 File

Subject: **GyneLotrimin-3 ™ Vaginal Cream, NDA 20-574: a list of all the reviews of the original NDA and the Summary Basis of Approval.**

On April 27, 1995, Schering-Plough HealthCare Products (SPHCP) submitted a New Drug Application, NDA 20-574, for the over-the-counter (OTC) marketing of GyneLotrimin-3® Vaginal Cream which contain a 21 gram tube of intravaginal cream and 3 disposable applicators.

SCHCP withdrew the application on January 29, 1996, because they believed that the Agency would be sending a nonapproval letter which stated that the application failed to meet the requirements of two adequate and well controlled studies demonstrating equivalence or superiority of the three day regimen versus the established seven day regimen.

On November 25, 1997, the sponsor resubmitted the application providing the requested information acquired from Taro Pharmaceuticals. On January 8, 1998, a bridging study summary report was submitted.

The following are the reviews of the original NDA:

Medical Officer's Review: November 4, 1998.

Safety Update and Worldwide Post Marketing Review (OTC): October 27, 1998.
Statistical Review and Evaluation: October 26, 1998.

Chemist's Reviews: October 30, 1998.
Trade Mark: May 14, 1998, September 14, 1998.
EER: April 21, 1998.
Product Quality Microbiology (ONDC): July 16, 1998, August 27, 1998, November 11, 1998.

Pharmacologist's memorandum: June 29, 1995, November 5, 1998.
Microbiologist's Review: November 12, 1998.
BioPharmaceutic's Review: August 3, 1995, April 16, 1998.

NDA 20-574
List of original NDA reviews and
the Summary Basis of Approval

Labeling Review and Addendum (OTC): October 29, 1998.
Labeling Review (DDMAC): August 21, 1998.

/S/

Christina H. Chi, Ph.D. 11/24/98
Project Manager.

cc: Orig NDA 20-574

HFD-590/Div. files
HFD-560/DivDir/MGoldberger(signed:11/9/1998)
HFD-560/DepDivDir/RAlbrecht(signed:11/9/1998)
HFD-590/MTL/BLeissa(signed:11/4/1998)
HFD-590/MO/JWinfield(signed:11/4/1998)
HFD-590/PharmTL/KHastings
HFD-590/ChemTL/NSchmuff
HFD-590/MicroTL/SLard
HFD-590/BioPharm.TL/FAjayi(signed: 11/6/1998)
HFD-590/StatRev/AChakravarty(signed:11/9/1998)
HFD-590/SPM/EFrank(signed:11/4/1998)
HFD-590/PM/CChi

HFD-560/Div. files
HFD-560/ActDivDir/DBowen
HFD-560/DepDivDir/LKatz
HFD-560/TL/HCothran
HFD-560/ClinRev/LChin
HFD-560/LabelRev/CTurner

HFD-40/DDMACRev/KLechter(signed:11/9/1998)

HFD-160/ONDC/MicroTL/PCooney
HFD-160/ONDC/MicroRev/PHughes

Drafted by: CHC/November 4, 1998

LIST OF REVIEWS ON THE ORIGINAL NDA AND
THE SUMMARY BASIS OF APPROVAL