# CENTER FOR DRUG EVALUATION AND RESEARCH

# Approval Package for:

# APPLICATION NUMBER:

# 87-092

Generic Name: Methyltestosterone Tablets 10mg

Sponsor: The Lannett Company

Approval Date: November 5, 1982

# CENTER FOR DRUG EVALUATION AND RESEARCH

# APPLICATION NUMBER: 87-092

# CONTENTS

| Reviews / Information Included in this ANDA Review. | |
|---|---|
| Approval Letter | X |
| Tentative Approval Letter(s) | |
| Final Printed Labeling(s) | X |
| CSO Labeling Review(s) | |
| Chemistry Review(s) | X |
| Microbiology Review(s) | |
| Bioequivalence Review(s) | X |
| Administrative Document(s) | X |
| Correspondence | X |

# CENTER FOR DRUG EVALUATION AND RESEARCH

# APPLICATION NUMBER:

# 87-092

# APPROVAL LETTER

NDA 87-092

NOV 5 1982

The Lannett Company
Attention: Amrish R. Patel
9000 State Road
Philadelphia, Pennsylvania 19136

Gentlemen:

Reference is made to your abbreviated new drug application submitted pursuant to Section 505(b) of the Federal Food, Drug, and Cosmetic Act for Methyltestosterone Tablets, 10 mg.

Reference is also made to your amendment dated August 5, 1982.

We have completed the review of this abbreviated new drug application and have concluded that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly, the application is approved.

Any significant change in the conditions outlined in this abbreviated new drug application requires an approved supplemental application before the change may be made, except for changes made in conformance with other provisions of Section 314.8 of the new drug regulations.

This Administration should be advised of any change in the marketing status of this drug.

The requirement for adequate data to assure the biologic availability is being deferred at the present time. However, our action in approving this application is based upon an understanding that if this requirement is reinstated you will perform the appropriate procedures.

For Initial Campaigns: We request that you submit, in duplicate, any proposed advertising or promotional copy which you intend to use in your immediate advertising or promotional campaigns. Please submit all proposed materials in draft or mock-up form, not final print. Submit both copies together with a copy of the proposed or final printed labeling to the Division of Drug Advertising and Labeling (HFN-170). Also, please do not use Form FD-2253 for this submission.

For Subsequent Campaigns: We call your attention to Regulation 21 CFR 310.300(b)(3) which requires that all material for any subsequent advertising or promotional campaigns at the time of their initial use be submitted to our Division of Drug Advertising and Labeling (HFN-170) with a completed Form FD-2253. A copy of Form FD-2253 is enclosed for your convenience.

The enclosures summarize the conditions relating to the approval of this application.

Sincerely yours,

/S/ 11/5/82

Marvin Seife, M.D.
Director
Division of Generic Drug Monographs
Office of The Associate Director
for Drug Monographs
Office of Drugs
National Center for Drugs and Biologics

Enclosures:
Conditions of Approval of a New Drug Application
Records & Reports Requirements
Form FD 2253
Attachment
Class Labeling Guidelines

cc: PHI-DO
HFN-616
HFN-530
HFN-5
HFN-313
HFN-534 (H. Zell)
HZell/LDavidson
R/D INITIAL HZell/MSeife
mstephens: 11/4/82 (8652A)
Approval

/S/ 11/4/82

/S/ 11/4/82

# CENTER FOR DRUG EVALUATION AND RESEARCH

# APPLICATION NUMBER:

# 87-092

# FINAL PRINTED LABELING(S)

87-092

METHYLTESTOSTERONE TABLETS U.S.P. LAP 11/3/82

DESCRIPTION: Methyltestosterone is white or creamy white crystals or crystalline powder. It is odorless and is stable in air, but is slightly hygroscopic. It is affected by light. It has the formula $C_{20}H_{30}O_2$. Each oral tablet contains 10mg. or 25mg. of methyltestosterone.

ACTION: Methyltestosterone is effective when administered orally. Its action is similar to that of testosterone. The androgenic action of methyltestosterone is responsible for the maintenance of secondary sexual characteristics as well as for the development of accessory sexual organs in the male.

INDICATIONS:

In the Male:
1. Eunuchoidism and eunuchism.
2. Male climacteric when symptoms are secondary to androgen deficiency.
3. Impotence resulting from androgen deficiency.
4. Postpuberal cryptorchidism with evidence of hypogonadism.

In the Female:
1. Prevention of postpartum breast pain and engorgement in the nonnursing mother. There is no satisfactory evidence that this drug prevents or suppresses lactation per se.
2. Palliation of androgen-responsive, advancing, inoperable breast cancer in women who are more than 1 year, but less than 5 years, postmenopausal or who have been proven to have a hormone-dependent tumor, as shown by previous beneficial response to castration.

CONTRAINDICATIONS: Carcinoma of the male breast; know or suspected carcinoma of the prostate; cardiac, hepatic, or renal decompensation; hypercalcemia; impaired liver function; prepubescent males; patients easily stimulated; pregnancy; and breast feeding.

WARNINGS: Hypercalcemia may occur in immobilized patients and in breast cancer patients. In patients with cancer hypercalcemia may indicate progression of bony metastasis, in which case the drug should be discontinued.

Watch female patients closely for signs of virilization. Some effects such as voice change may not be reversible even when the drug is stopped.

Discontinue the drug if cholestatic hepatitis with jaundice appears or liver function tests become abnormal.

NOV 5 1982

APPROVED

PRECAUTIONS: Patients with cardiac, renal or hepatic derangement may retain sodium and water with resulting edema formation.

Males, especially the elderly, may become overly stimulated. Priapism or excessive sexual stimulation may develop.

Oligospermia and reduced ejaculatory volume may occur after prolonged administration or excessive dosage.

Hypersensitivity and gynecomastia may occur.

Alterations in liver function tests (e.g., increased BSP retention and SGOT levels) and rarely jaundice have been reported and appear to be directly related to the dose of the drug.

When any of these effects appear, the androgen should be stopped; if restarted, a lower dosage should be utilized.

Use cautiously in young boys to avoid possible premature epiphyseal closure or precocious sexual development.

The PBI may decrease during androgen therapy without clinical significance.

ADVERSE REACTIONS: Hypersensitivity, including skin manifestations and anaphylactoid reactions; acne; decreased ejaculatory volume; oligospermia; gynecomastia; edema; priapism; hypercalcemia; especially in immobile patients and those with metastatic breast carcinoma; virilization in females, cholestatic jaundice.

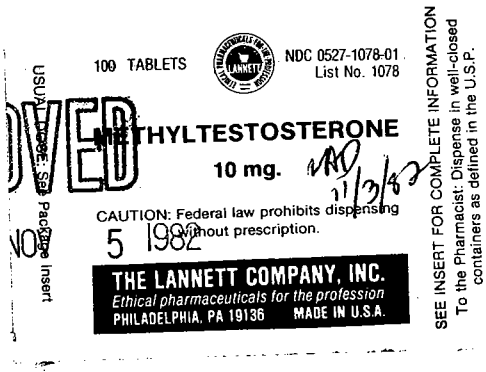
There have been rare reports of hepatocellular neoplasms and peliosis hepatis in patients who have received androgenic- anabolic steroids, usually over prolonged periods of time.

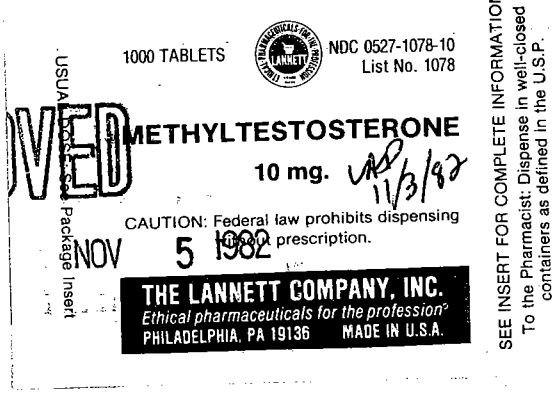
DOSAGE AND ADMINISTRATION: Dosage must be strictly individualized. Daily requirements are best administered in divided doses. The following chart is suggested as an average daily dosage guide. Duration of therapy will depend upon the response of the condition being treated and the appearance of adverse reactions.

| INDICATIONS | AVERAGE DAILY DOSAGE TABLET |
|---|---|
| In the Male: | |
| Eunuchism and eunuchoidism | 10 to 40 mg. |
| Male climacteric and male impotency | 10 to 40 mg. |
| Cryptorchidism-postpuberal | 30mg. |
| In the female: | |
| Postpartum breast pain & engorgement (3 to 5 days) | 80 mg. |
| Breast cancer | 200 mg. |

HOW SUPPLIED: Oral tablets 10mg. (white, scored) and 25mg. (yellow, scored) in bottles of 100 tablets and 1000 tablets.

June 1979


100 TABLETS
NDC 0527-1078-01
List No. 1078
METHYLTESTOSTERONE
10 mg.
CAUTION: Federal law prohibits dispensing without prescription.
THE LANNETT COMPANY, INC.
Ethical pharmaceuticals for the profession
PHILADELPHIA, PA 19136
MADE IN U.S.A.
SEE INSERT FOR COMPLETE INFORMATION
To the Pharmacist: Dispense in well-closed containers as defined in the U.S.P.
USUAL DOSE: See Package Insert
11/3/82
NOV 5 1982


1000 TABLETS
NDC 0527-1078-10
List No. 1078
METHYLTESTOSTERONE
10 mg.
CAUTION: Federal law prohibits dispensing without prescription.
THE LANNETT COMPANY, INC.
Ethical pharmaceuticals for the profession
PHILADELPHIA, PA 19136
MADE IN U.S.A.
SEE INSERT FOR COMPLETE INFORMATION
To the Pharmacist: Dispense in well-closed containers as defined in the U.S.P.
USUAL DOSE: See Package Insert
11/3/82
NOV 5 1982

# CENTER FOR DRUG EVALUATION AND RESEARCH

# APPLICATION NUMBER:

# 87-092

# CHEMISTRY REVIEW(S)

| CHEMIST's REVIEW FOR ABBREVIATED NEW DRUG APPLICATION OR SUPPLEMENT | Statement Date: DESI 3158 | NDA NUMBER: 87-092 |
|---|---|---|

NAME AND ADDRESS OF APPLICANT
The Lannett Co., Inc.
Phila, PA 19136

ORIGINAL XXXXX
AMENDMENT
SUPPLEMENT
RESUBMISSION
CORRESPONDENCE
REPORT
OTHER

PURPOSE OF AMENDMENT/SUPPLEMENT

DATE(s) of SUBM:
as per letter

| PHARMACOLOGICAL CATEGORY | NAME OF DRUG | HOW DISPENSED |
|---|---|---|
| androgen | methyltestosterone | RX XXXXX OTC_ |
| DOSAGE FORM(S) | POTENCY(IES) | RELATED IND/NDA/ |
| tablets | 10 mg. | |
| STERILIZATION | SAMPLES | |

LABELING
satisfactory per MO VVK

BIOLOGIC AVAILABILITY
required

ESTABLISHMENT INSPECTION
requested

COMPONENTS, COMPOSITION, MANUFACTURING, CONTROLS
see issued letter

PACKAGING
Amber HDPE, metal caps with ——— liners

STABILITY
**Protocol:** requested

**Exp. Date:** 2 yrs with challenge data

REMARKS AND CONCLUSION:
rev w/f CChang

reference drug 85-954, 955, 774, 776

CHEMIST'S REVIEW FOR ABBREVIATED NEW DRUG APPLICATION OR SUPPLEMENT

Statement Date: DESI 3158

NDA # 87-092

NAME AND ADDRESS OF APPLICANT:
The Lannett Company
Philadelphia, PA 19136

ORIGINAL XXX
AMENDMENT
SUPPLEMENT
RESUBMISSION
CORRESPONDENCE
REPORT
OTHER

PURPOSE OF AMENDMENT/SUPPLEMENT
Bio and control information

DATE(s) of SUBMISSION(s)
as per letter

| PHARMACOLOGICAL CATEGORY | NAME OF DRUG |
|---|---|
| Androgen | Methyltestosterone |

HOW DISPENSED
RX XXX OTC _____

| DOSAGE FORM | POTENCY(IES) |
|---|---|
| Tablets | 10 mg. |

RELATED IND/NDA/DMF

| STERILIZATION | SAMPLES |
|---|---|
| | |

LABELING
Satisfactory per MO VVK

BIOLOGIC AVAILABILITY
required

ESTABLISHMENT INSPECTION
Requested

COMPONENTS, COMPOSITION, MANUFACTURING, CONTROLS
See issued letter

PACKAGING
Amber HDPE, metal caps with ———— liners

STABILITY:
Protocol: Requested

Exp. Date: 2 years with challenge data

REMARKS & CONCLUSION: rev w/f CChang ISI - 11-14-80

Reference drug 85-954, 955, 774,776

# CHEMIST'S REVIEW NDA 87-092

3. NAME AND ADDRESS OF APPLICANT
The Lannett Company
Philadelphia, PA 19136

4. AF NUMBER
DESI 3158
FR 9/30/77

5. SUPPLEMENT(s)
Original (7/26/79)

6. NAME OF DRUG
Methyltestosterone

8. SUPPLEMENT(s) PROVIDE(s) FOR:
Original submission (amended)

9. AMENDMENTS AND OTHER DATES:
Correspondence History

| | |
|---|---|
| FIRM | |
| 8/1/79 | Original ANDA submission dated 7/26/79. |
| 6/25/80 | BIO material dated 6/10/80. |
| 6/25/80 | Amendment dated 6/20/80 - BIO, Reply to 10/14/79 letter. |
| 4/26/82 | Correspondence dated 4/22/82 - BIO |
| 8/9/82 | Amendment dated 8/5/82 - Reply to 11/17/80 letter. |
| FDA | |
| 8/9/79 | Acknowledgement of ANDA submission. |
| 8/9/79 | Request for BIO review (Seife) to Skelly. |
| 8/10/79 | Inspection Request (Chang) - Lannett, Pharmetics |
| 8/24/79 | Medical Review (Karusaitis) - Labeling acceptable. |
| 10/22/79 | Review (Chang) - Rev w/f |
| 10/24/79 | Letter sent (Chang) - Rev. w/f, Request dissolution, Certificate of Analysis, expiration dating, stability |
| 12/3/79 | BIO Review (Ise) - BIO protocol acceptable, Request samples |
| 12/3/79 | Letter sent (Seife) - BIO results |
| 11/14/80 | Review (Chang) - Rev w/f |
| 11/17/80 | Letter sent (Chang) - Rev w/f, Request dissolution profiles, stability data |
| 11/19/80 | BIO review (Mayersohn, Ise) - BIO unacceptable |
| 11/25/80 | Letter sent (Seife) - BIO results |
| | Letter sent (Seife) - Request for update |
| 4/7/82 | Letter sent (Rosen) - Request for withdrawal |
| 4/26/82 | Request for BIO review (Seife) |
| 6/17/82 | BIO review (Ise, Dighe) - BIO unacceptable |
| 6/23/82 | Letter sent (Seife) - BIO results |
| 7/6/82 | Memo from Ise (HFN-522) to Rosen (HFN-530) Re: Bio requirement deferred for 87-111 |
| 7/9/82 | Memo from Ise to Seife Re: BIO requirement deferred for 87-111 |
| 10/4/82 | BIO review (Pelsor, Ise) - Dissolution specifications, In vivo BIO study deferred |
| 10/5/82 | Letter sent (Seife) - BIO results |

CHEMIST'S REVIEW PAGE 2 -

10. PHARMACOLOGICAL CATEGORY
Androgen

11. HOW DISPENSED
RX

12. RELATED IND/NDA/DMF(s)
87-111

13. DOSAGE FORM(s)
Tablet

14. POTENCY
10 mg.

15. CHEMICAL NAME AND STRUCTURE
$C_{20}H_{30}O_2$, M.W. 302.46

17. COMMENTS
Remaining deficiencies sufficiently answered for approval. Package insert must be revised at the time of next printing in accord with 21 CFR 201.100(e) and the enclosed class labeling guidelines for androgens.

18. CONCLUSIONS AND RECOMMENDATIONS
Approval letter should issue with the condition that the package insert be revised at the time of next printing as described in review section 17 above. In vivo BIO requirements are deferred. Dissolution testing has been approved by the Division of Biopharmaceutics.

19. REVIEWER:
(S)
Jacqueline 11/4/82

DATE COMPLETED:
11/4/82

APPEARS THIS WAY
ON ORIGINAL

**Redacted** 3

**pages of**

**trade secret and/or**

**confidential**

**commercial**

**information**

# CENTER FOR DRUG EVALUATION AND RESEARCH

# APPLICATION NUMBER:

# 87-092

# BIOEQUIVALENCE REVIEW(S)

Methyltestosterone
10 mg Tablets
ANDA 87-092

Lannett Co.
Philadelphia, PA
Submission Dated:
June 20, 1980

## REVIEW OF A BIOAVAILABILITY STUDY

OBJECTIVES:

The purpose of this study was to determine the relative bioavailability of methyltestosterone tablets (10 mg) manufactured by The Lannett Co. (lot # 20676) in comparison with a solution (10 mg) of pure methyltestosterone (supplied by the Lannett Co., lot # LX-7321).

STUDY DESIGN:

The study was designed as a single-dose, two-way cross-over with random subject assignment to the sequence of product ingestion. There was a 2 week wash-out period between product ingestion. The study was performed by [redacted] All samples were assayed by [redacted] Twelve apparently healthy male subjects were employed in this study (average age and range: 24 years, 21-28 years; average weight and range: 167 lbs, 138-186 lbs). Drug and ethanol use was discontinued 2 weeks prior to and during the entire study. Subjects fasted overnight and for 4 hours following drug ingestion. On the morning of each study the subject ingested a single 10 mg tablet or 10 mg of pure drug (dissolved in [redacted]) with 8 ounces of water. On week one of the study 6 subjects ingested the tablet and 6 subjects ingested the oral solution. Two weeks later the reverse order of administration was followed. Venous blood samples were taken at the following times relative to dosing: 0, 20 and 40 minutes and 1, 1.5, 2, 3, 4, 6, 8 and 12 hours.

RESULTS:

This study provides no useful information concerning the relative bioavailability of the methyltestosterone tablet product evaluated (Table 1). This is the result of the assay that has been employed in this study. Serum samples were assayed by [redacted] using a [redacted] procedure which is reported to be specific for testosterone and dihydrotestosterone.

Table 1

Mean (+ SD) Plasma Concentration of Methyltestosterone Following Asministration of 10 mg of Methyltestosterone Tablet (Lannett) and Solution (1 mg/ml)

| Time (minutes) | Tablet 10 mg (ng/dl) | Solution 10 mg (ng/dl) |
|---|---|---|
| 0 | 599 (168) | 563 (162) |
| 20 | 555 (154) | 577 (141) |
| 40 | 586 (118) | 605 (152) |
| 60 | 641 (109) | 593 (119) |
| 90 | 595 (115) | 579 (165) |
| 120 | 605 (104) | 570 (184) |
| 180 | 606 (125) | 563 (209) |
| 240 | 603 (128) | 563 (192) |
| 360 | 435 (114) | 380 (115) |
| 480 | 391 ( 83) | 389 (106) |
| 720 | 364 ( 80) | 370 (160) |

The assay procedure was developed by and is sold commercially by _____. The assay appears sensitive to 10 pg testosterone per tube. Standard curves were prepared by spiked testosterone samples. This assay does not measure methyltestosterone concentrations. Another assay that measures only intact methyltestosterone should have been employed (e.g. J. Pharm. Sci., 61, 1746 (1972)).

Another point to be considered is that several subjects (Byers, Hemwall, Kirshner and Veale) are not within + 10% of ideal weight for their age and height. The above is a normal guideline for such studies.

Plasma concentration-time data were analyzed statistically to determine differences in: plasma concentrations at each sampling time; maximum plasma concentrations; time of maximum plasma concentration and areas under the plasma concentration-time curves. Analysis of variance was used as the method of statistical analysis. The analysis was performed by _____. There was no statistically significant differences between the two products tested for any of the measurements mentioned above.

RECOMMENDATION:

The firm should be notified that this study is not acceptable as an indication of the bioequivalence of their methyltestosterone tablet product. A study should be performed which employs a specific assay.

COMMENTS:

1. The firm should perform the bioequivalency study which employs a specific assay for the methyltestosterone.

2. The firm should determine whether enough serum samples are available to repeat the assay for specifically methyltestosterone.

3. If the above is not possible, the firm should repeat the study employing an assay method specific for methyltestosterone.

/S/

Michael Mayersohn, Expert
Biopharmaceutics Review Branch

cc: ANDA 87-092 Orig., HFD-530 (4), HFD-522 (Dr. Ise, Dr. Mayersohn), Drug File, Review File, Chron File

MMAYERSOHN/mrs/11/19/80 (8929P)
RD INITIALED BY CMISE /S/
FT INITIALED BY CMISE

APPEARS THIS WAY
ON ORIGINAL

Methyltestosterone
10 mg Tablet
ANDA 87-092

Lannett Co.
Philadelphia, PA
Submission Date
July 26, 1979

# REVIEW OF A BIOEQUIVALENCY PROTOCOL

## INTRODUCTION

Methyltestosterone is useful in the relief of eunuchordism and eunuchism, male climacteric, when symptoms are seconday to androgen deficiency, impotence resulting from androgen deficiency and post-puberal cryptochodism with evidence of hypogonadism.

## PURPOSE

The purpose of this protocol is to compare the equivalency of methyltestosterone tablets, 10 mg tablets manufactured by the Lannett Co. to an oral solution of an equivalent amount of methyltestosterone.

## RECOMMENDATION

The bioequivalency protocol submitted by the firm for methyltestosterone is acceptable. The dissolution testing data submitted by the firm has been recorded and will be reviewed following receipt of the final bioequivalency reported. This lot should be used in the bioequivalency study.

In addition a sample (_____ tablets) of this lot should be sent to :

Ms. Colleen Gresham
FDA, Bureau of Drug
Division of Biopharmaceutics (HFD-522)
5600 Fishers Lane
Rockville, Maryland 20857

## STUDY DESIGN

Healthy male volunteers (N=12) between 60-90 kg., between 5'6"-6'6" in height, and between 18-55 years old will be selected for this study. Good health will be ascertained by means of medical history physical examination and routine clinical laboratory examination. Subjects will not have any history of acute or chronic renal and/or hepatic disease, gastrointestional disease, hematologic disease, cardiac disease, hypercalcemia, carcinoma of the male breast, known or suspected carcinoma of the prostate, and chronic alcohol consumption.

After an overnight fast subjects will be administered one of the following drug treatments in a two-way crossover design.

Treatment A: Methyltestosterone, solution 10 mg (1 mg/ml) (100 mg methyltestosterone, [redacted] Lannett Co.

Treatment B: Methylteslosterone, 10 mg tablet Lannett Co.

Water (240 ml) will be administered with each drug treatment. The subjects will be fasted for 4 hours post-dosing.

Blood samples will be drawn at 0, 20, and 40 minutes, 1, 1.5, 2, 3, 4, 6, 8 and 12 hours post dosing. Serum will be harvested, frozen and stored until analysis can be conducted.

A complete analysis of variance including absorption rate (ka), peak-time (Tmax) and peak serum levels (Cmax) will be performed. Analysis of variance will be accompanied by an analysis of variance of area under the serum concentration curve with a comparison of peak time (Tmax) and peak serum levels. Also included in the statistical analysis will be mean values, standard deviation standard error and p-values.

The assay procedures will be documented as to specificity sensitivity and linearity. The firm plans to assay the serum testosterone by a [redacted] method.

This study will be conducted by the [redacted]

clinical direction of [redacted]

The firm has submitted the following dissolution data for their methyltestosterone formulation in water and 0.1N HCL.

APPEARS THIS WAY
ON ORIGINAL

Table I

Mean Dissolution of methyltestosterone tablet (12 tablets) 10 mg using the USP method II at 50 rpm in water and 0.1N HCL

| Time | Water 500 ml | 0.1N HCL 500 ml |
|---|---|---|
| 10 | 28.5± 2.6* | 26.7± 2.4 |
| 20 | 38.5 ± 2.1 | 40.2 ± 3.6 |
| 30 | 56.4 ± 5.1 | 51.8 ± 4.6 |
| 40 | 63.6 ± 3.6 | 57.2 ± 4.2 |
| 60 | 77.1 ± 2.2 | 67.5 ± 4.0 |
| 90 | 85.1 ± 2.8 | 74.9 ± 3.6 |
| 120 | 87.6 ± 2.7 | 78.5 ± 3.1 |

*Standard deviation

/S/

Charles M. Ise, Ph.D.
Biopharmaceutics Review Branch

cc: ANDA 87-092, HFD-530 (3), HFD-522 (Ise), HFD-525
Chron File, Review File

RD INITIALED BY SVDIGHE
FT INITIALED BY CMISE___ /S/

APPEARS THIS WAY
ON ORIGINAL

# CENTER FOR DRUG EVALUATION AND RESEARCH

# APPLICATION NUMBER:

# 87-092

# ADMINISTRATIVE DOCUMENTS

REVIEW OF ANDA

DATE COMPLETED

8/24/79

ANDA # 87-092
F.R. DATE: 9/30/77
(CO. NAME) The Lannett Co., Inc.

NAME OF DRUG: Trade ;

Generic; Methyltestosterone Tablets 10 mg

DATE OF SUBMISSION: 8/1/79

TYPE OF SUBMISSION: ANDA

CLINICAL EVALUATION:

1. Review of Studies:

Pertinent Data is to be Reviewed by the Chemist

Bioavailability Requirement: *Required

* Protocol for a Bio availability study submitted for comment and evaluation

2. Review of Labels:

(a) Container Labels: Satisfactory

10 mg Tablets Bottles of 100; 1000

(b) Insert Labeling: Satisfactory

June 1979 HFD-130 is Completing Revised Labeling Guidelines for Insert

CONCLUSION: Insert Labeling is Satisfactory

Container Labels are satisfactory

RECOMMENDATIONS: The firm is to be so notified

/S/
V. V. Karusaitis, M.D.

cc:
ANDA 87-092
Dup
VVKarusaitis:ih/8/24/79

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
5600 FISHERS LANE
ROCKVILLE, MARYLAND 20852

Form Approved
OMB No. 57-R0003

# NEW DRUG APPLICATION *(DRUGS FOR HUMAN USE)*

*(Title 21, Code of Federal Regulations, § 314.1)*

Name of applicant The Lannett Company, Inc.

Address 9000 State Road, Philadelphia, Pa. 19136

Date July 26, 1979

Name of new drug Methyltestosterone Tablets, 10mg.

☐ Original application (regulation § 314.1).

☐ Amendment to original, unapproved application (regulation § 314.6)

☒ Abbreviated application (regulation § 314.1(f)).

☐ Amendment to abbreviated, unapproved application (regulation § 314.6).

☐ Supplement to an approved application (regulation § 314.8).

☐ Amendment to supplement to an approved application.

The undersigned submits this application for a new drug pursuant to section 505(b) of the Federal Food, Drug, and Cosmetic Act. It is understood that when this application is approved, the labeling and advertising for the drug will prescribe, recommend, or suggest its use only under the conditions stated in the labeling which is part of this application; and if the article is a prescription drug, it is understood that any labeling which furnishes or purports to furnish information for use or which prescribes, recommends, or suggests a dosage for use of the drug will contain the same information for its use, including indications, effects, dosages, routes, methods, and frequency and duration of administration, any relevant warnings, hazards, contraindications, side effects, and precautions, as that contained in the labeling which is part of this application in accord with §201.100 (21 CFR 201.100). It is understood that all representations in this application apply to the drug produced until an approved supplement to the application provides for a change or the change is made in conformance with other provisions of §314.8 of the new-drug regulations.

Attached hereto, submitted in the form described in §314.1(e) of the new-drug regulations, and constituting a part of this application are the following:

**1. Table of contents.** The table of contents should specify the volume number and the page number in which the complete and detailed item is located and the volume number and the page number in which the summary of that item is located (if any).

**2. Summary.** A summary demonstrating that the application is well-organized, adequately tabulated, statistically analyzed (where appropriate), and coherent and that it presents a sound basis for the approval requested. The summary should include the following information: (In lieu of the outline described below and the evaluation described in Item 3, and expanded summary and evaluation as outlined in §314.1(d) of the new-drug regulations may be submitted to facilitate the review of this application.)

*a.* Chemistry.

*i.* Chemical structural formula or description for any new-drug substance.

*ii.* Relationship to other chemically or pharmacologically related drugs.

*iii.* Description of dosage form and quantitative composition.

*b.* Scientific rationale and purpose the drug is to serve.

*c.* Reference number of the investigational drug notice(s) under which this drug was investigated and of any notice, new-drug application, or master file of which any contents are being incorporated by reference to support this application.

*d.* Preclinical studies. (Present all findings including all adverse experiences which may be interpreted as incidental or not drug-related. Refer to date and page number of the investigational drug notice(s) or the volume and page number of this application where complete data and reports appear.)

*i.* Pharmacology (pharmacodynamics, endocrinology, metabolism, etc.).

*ii.* Toxicology and pathology: Acute toxicity studies; subacute and chronic toxicity studies; reproduction and teratology studies; miscellaneous studies.

*e.* Clinical studies. (All material should refer specifically to each clinical investigator and to the volume and page number in the application and any documents incorporated by reference where the complete data and reports may be found.)

*i.* Special studies not described elsewhere.

*ii.* Dose-range studies.

*iii.* Controlled clinical studies.

*iv.* Other clinical studies (for example, uncontrolled or incompletely controlled studies).

*v.* Clinical laboratory studies related to effectiveness.

*vi.* Clinical laboratory studies related to safety.

*vii.* Summary of literature and unpublished reports available to the applicant.

**3. Evaluation of safety and effectiveness.** a. Summarize separately the favorable and unfavorable evidence for each claim in the package labeling. Include references to the volume and page number in the application and in any documents incorporated by reference where the complete data and reports may be found.

*b.* Include tabulation of all side effects or adverse experience, by age, sex, and dosage formulation, whether or not considered to be significant, showing whether administration of the drug was stopped and showing the investigator's name with a reference to the volume and page number in the application and any documents incorporated by reference where the complete data and reports may be found. Indicate those side effects or adverse experiences considered to be drug-related.

**4. Copies of the label and all other labeling to be used for the drug** (a total of 12 copies if in final printed form, 4 copies if in draft form):

*a.* Each label, or other labeling, should be clearly identified to show its position on, or the manner in which it accompanies, the market package.

*b.* If the drug is to be offered over the counter, labeling on or within the retail package should include adequate directions for use by the layman under all the conditions for which the drug is intended for lay use or is to be prescribed, recommended, or suggested in any labeling or advertising sponsored by or on behalf of the applicant and directed to the layman. If the drug is intended or offered for uses under the professional supervision of a practitioner licensed by law to administer it, the application should also contain labeling that includes adequate information for all such uses, including all the purposes for which the over-the-counter drug is to be advertised to, or represented for use by, physicians.

*c.* If the drug is limited in its labeling to use under the professional supervision of a practitioner licensed by law to administer it, its labeling should bear information for use under which such practitioners can use the drug for the purposes for which it is intended, including all the purposes for which it it is to be advertised or represented, in accord with §201.100 (21 CFR 201.100). The application should include any labeling for the drug intended to be made available to the layman.

*d.* If no established name exists for a new-drug substance, the application shall propose a nonproprietary name for use as the established name for the substance.

*e.* Typewritten or other draft labeling copy may be submitted for preliminary consideration of an application. An application will not ordinarily be approved prior to the submission of the final printed label and labeling of the drug.

*f.* No application may be approved if the labeling is false or misleading in any particular.

When mailing pieces, any other labeling, or advertising copy are devised for promotion of the new drug, samples shall be submitted at the time of initial dissemination of such labeling and at the time of initial placement of nay such advertising for a prescription drug (see §310.300 of the new-drug regulations). Approval of a supplemental new-drug application is required prior to use of any promotional claims not covered by the approved application.)

**5. A statement as to whether the drug is (or is not) limited in its labeling and by this application to use under the professional supervision of a practitioner licensed by law to administer it.**

**6. A full list of the articles used as components of the drug.** This list should include all substances used in the synthesis, extraction, or other method of preparation of any new-drug substance, and in the preparation of the finished dosage form, regardless of whether they undergo chemical change or are removed in the process. Each substance should be identified by its established name, if any, or complete chemical name, using structural formulas when necessary for specific identification. If any proprietary preparation is used as a component, the proprietary name should be followed by a complete quantitative statement of composition. Reasonable alternatives for any listed substance may be specified.

**7. A full statement of the composition of the drug.** The statement shall set forth the name and amount of each ingredient, whether active or not, contained in a stated quantity of the drug in the form in which it is to be distributed (for example, amount per tablet or per milliliter) and a batch formula representative of that to be employed for the manufacture of the finished dosage form. All components should be included in the batch formula regardless of whether they appear in the finished product. Any calculated excess of an ingredient over the label declaration should be designated as such and percent excess shown. Reasonable variations may be specified.

**8. A full description of the methods used in, and the facilities and controls used for, the manufacture, processing, and packing of drug.** Included in this description should be full information with respect to any new-drug substance and to the new-drug dosage form, as follows, in sufficient detail to permit evaluation of the adequacy of the described methods of manufacture, processing, and packing and the described facilities and controls to determine and preserve the identity, strength, quality, and purity of the drug:

*a.* A description of the physical facilities including building and equipment used in manufacturing, processing, packaging, labeling, storage, and control operations.

*b.* A description of the qualifications, including educational background and experience, of the technical and professional personnel who are responsible for assuring that the drug has the safety, identity, strength, quality, and purity it purports or is represented to possess, and a statement of their responsibilities.

*c.* The methods used in the synthesis, extraction, isolation, or purification of any new-drug substance. When the specifications and control applied to such substance are inadequate in themselves to determine its identity, strength, quality, and purity, the methods should be described in sufficient detail, including quantities used, times, temperatures, pH, solvents, etc., to determine these characteristics. Alternative methods or variations in methods within reasonable limits that do not affect such characteristics of the substance may be specified.

*d.* Precautions to assure proper, identity, strength, quality, and purity of the raw materials, whether active or not, including the specifications for acceptance and methods of testing for each lot of raw material.

*e.* Whether or not each lot of raw materials is given a serial number to identify it, and the use made of such numbers in subsequent plant operations.

*f.* If the applicant does not himself perform all the manufacturing, processing, packaging, labeling, and control operations for any new-drug substance or the new-drug dosage form, his statement identifying each person who will perform any part of such operations and designating the part; and a signed statement from each such person fully describing, directly or by reference, the methods, facilities, and controls in his part of the operation.

*g.* Method of preparation of the master formula records and individual batch records and manner in which these records are used.

*h.* The instructions used in the manufacturing, processing, packaging, and labeling of each dosage form of the new drug, including any special precautions observed in the operations.

*i.* Adequate information with respect to the characteristics of and the test methods employed for the container, closure, or other component parts of the drug package to assure their suitability for the intended use.

*j.* Number of individuals checking weight or volume of each individual ingredient entering into each batch of the drug.

*k.* Whether or not the total weight or volume of each batch is determined at any stage of the manufacturing process subsequent to making up a batch according to the formula card and, if so, at what stage and by whom it is done.

*l.* Precautions to check the actual package yield produced from a batch of the drug with the theoretical yield. This should include a description of the accounting for such items as discards, breakage, etc., and the criteria used in accepting or rejecting batches of drugs in the event of an unexplained discrepancy.

*m.* Precautions to assure that each lot of the drug is packaged with the proper label and labeling, including provisions for labeling storage and inventory control.

*n.* The analytical controls used during the various stages of the manufacturing, processing, packaging, and labeling of the drug, including a detailed description of the collection of samples and the analytical procedures to which they are subjected. The analytical procedures should be capable of determining the active components within a reasonable degree of accuracy and of assuring the identity of such components. If the article is one that is represented to be sterile, the same information with regard to the manufacturing, processing, packaging, and the collection of samples of the drug should be given for sterility controls. Include the standards used for acceptance of each lot of the finished drug.

*o.* An explanation of the exact significance of the batch control numbers used in the manufacturing, processing, packaging, and labeling of the drug, including the control numbers that appear on the label of the finished article. State whether these numbers enable determination of the complete manufacturing

history of the product. Describe any methods used to permit determination of the distribution of any batch if its recall is required.

*p.* A complete description of, and data derived from, studies of the stability of the drug, including information showing the sutitability of the analytical method used. Describe any additional stability studies underway or contemplated. Stability data should be submitted for any new-drug substance, for the finished dosage form of the drug in the container in which it is to be marketed, including any proposed multiple-dose container, and if it is to be put into solution at the time of dispensing, for the solution prepared as directed. State the expiration date(s) that will be used on the label to preserve the identity, strength, quality, and purity of the drug until it is used. (If no expiration date is proposed, the applicant must justify its absence.)

*q.* Additional procedures employed which are designed to prevent contamination and otherwise assure proper control of the product.

(An application may be refused unless it includes adequate information showing that the methods used in, and the facilities and controls used for, the manufacturing, processing, and packaging of the drug are adequate to preserve its identity, strength, quality, and purity in conformity with good manufacturing practice and identifies each establishment, showing the location of the plant conducting these operations.)

**9. Samples of the drug and articles used as components, as follows:** a. The following samples shall be submitted with the application or as soon thereafter as they become available. Each sample shall consist of four identical, separately packaged subdivisions, each containing at least three times the amount required to perform the laboratory test procedures described in the application to determine compliance with its control specifications for identity and assays:

*i.* A representative sample or samples of the finished dosage form(s) proposed in the application and employed in the clinical investigations and a representative sample or samples of each new-drug substance, as defined in §310.3(g), from the batches(es) employed in the production of such dosage form(s).

*ii.* A representative sample or samples of finished market packages of each dosage form of the drug prepared for inital marketing and, if any such sample is not from a commercial-scale production batch, such a sample from a representative commercial-scale production batch; and a representative sample or samples of each new-drug substance as defined in §310.3(g) of the new-drug regulations, from the batch(es) employed in the production of such dosage form(s).

*iii.* A sample or samples of any reference standard and blank used in the procedures described in the application for assaying each new-drug substance and other assayed components of the finished drug; *Provided, however,* That samples of reference standards recognized in the official U.S. Pharmacopeia or The National Formulary need not be submitted unless requested.

*b.* Additional samples shall be submitted on request.

*c.* Each of the samples submitted shall be appropriately packaged and labeled to preserve its characteristics, to identify the material and the quantity in each subdivision of the sample, and to identify each subdivision with name of the applicant and the new-drug application to which it relates.

*d.* There shall be included a full list of the samples submitted pursuant to Item 9a; a statement of the additional samples that will be submitted as soon as available; and, with respect to each sample submitted, full information with respect to its identity, the origin of any new-drug substance contained therein (including in the case of new-drug substances, a statement whether it was produced on a laboratory, pilot-plant, or full-production scale) and detailed results of all laboratory tests made to determine the identity, strength, quality, and purity of the batch represented by the sample, including assays. Include for any reference standard a complete description of its preparation and the results of all laboratory tests on it. If the test methods used differed from those described in the application, full details of the methods employed in obtaining the reported results shall be submitted.

*e.* The requirements of Item 9a may be waived in whole or in part on request of the applicant or otherwise when any such samples are not necessary.

*f.* If samples of the drug are sent under separate cover, they should be addressed to the attention of the Bureau of Drugs and identified on the outside of the shipping carton with the name of the applicant and the name of the drug as shown on the application.

**10. Full reports of preclinical investigations that have been made to show whether or not the drug is safe for use and effective use.** a. An application may be refused unless it contains full reports of adequate preclinical tests by all methods reasonably applicable to a determination of the safety and effectiveness of the drug under the conditions of use suggested in the proposed labeling.

*b.* Detailed reports of the preclinical investigations, including all studies made on laboratory animals, the methods used, and the results obtained, should be clearly set forth. Such information should include identification of the person who conducted each investigation, a statement of where the investigations were conducted, and where the underlying data are available for inspection. The animal studies may not be considered adequate unless they give proper attention to the conditions of use recommended in the proposed labeling for the drug such as, for example, whether the drug is for short- or long-term administration or whether it is to be used in infants, children, pregnant women, or women of child-bearing potential.

*c.* Detailed reports of any pertinent microbiological and in vitro studies.

*d.* Summarize and provide a list of literature references (if available) to all other preclinical information known to the applicant, whether published or unpublished, that is pertinent to an evaluation of the safety or effectiveness of the drug.

**11. List of investigators.** a. A complete list of all investigators supplied with the drug including the name and post office address of each investigator and, following each name, the volume and page references to the investigator's report(s) in this application and in any documents incorporated by reference, or the explanation of the omission of any reports.

*b.* The unexplained omission of any reports of investigations made with the new drug by the applicant, or submitted to him by an investigator, or the unexplained omission of any pertinent reports of investigations or clinical experience received or otherwise obtained by the applicant from published literature or other sources, whether or not it would bias an evaluation of the safety of the drug or its effectiveness in use, may constitute grounds for the refusal or withdrawal of the approval of an application.

**12. Full reports of clinical investigations that have been made to show whether or not the drug is safe for use and effective in use.** a. An application may be refused unless it contains full reports of adequate tests by all methods reasonably applicable to show whether or not the drug is safe and effective for use as suggested in the labeling.

*b.* An application may be refused unless it includes substantial evidence consisting of adequate and well-controlled investigations, including clinical investigations, by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved, on the basis of which it could fairly and responsibly be concluded by such experts that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, recommended, or suggested in the proposed labeling.

*c.* Reports of all clinical tests sponsored by the applicant or received or other wise obtained by the applicant should be attached. These reports should include adequate information concerning each subject treated with the drug or employed as a control, including age, sex, conditions treated, dosage, frequency of administration of the drug, results of all relevant clincial observations and laboratory examinations made, full information

concerning any other treatment given previously or concurrently, and a full statement of adverse effects and useful results observed, together with an opinion as to whether such effects or results are attributable to the drug under investigation and a statement of where the underlying data are available for inspection. Ordinarily, the reports of clinical studies will not be regarded as adequate unless they include reports from more than one independent, competent investigator who maintains adequate case histories of an adequate number of subjects, designed to record observations and permit evaluation of any and all discernible effects attributable to the drug in each individual treated and comparable records on any individuals employed as controls. An application for a combination drug may be refused unless there is substantial evidence that each ingredient designated as active makes a contribution to the total effect claimed for the drug combination. Except when the disease for which the drug is being tested occurs with such infrequency in the United States as to make testing impractical, some of the investigations should be performed by competent investigators within the United States.

*d.* Attach as a separate section a completed Form FD-1639, Drug Experience Report (obtainable, with instructions, on request from the Food and Drug Administration, Department of HEW. 5600 Fishers Lane, Rockville, Maryland 20852), for each adverse experience or, if feasible, for each subject or patient experiencing one or more adverse effects, described in Item 12c, whether or not full information is available. Form FD-1639 should be prepared by the applicant if the adverse experience was not reported in such form by the investigator. The Drug Experience Report should be cross-referenced to any narrative description included in Item 12c. In lieu of a FD Form 1639, a computer-generated report may be submitted if equivalent in all elements of information with the identical enumerated sequence of events and methods of completion; all formats proposed for such use will require initial review and approval by the Food and Drug Administration.

*e.* All information pertinent to an evaluation of the safety and effectiveness of the drug received or otherwise obtained by the applicant from any source, including information derived from other investigations or commercial marketing (for example, outside the United States), or reports in the scientific literature, involving the drug that is the subject of the application and related drugs. An adequate summary may be acceptable in lieu of a reprint of a published report which only supports other data submitted. Reprints are not required of reports in designated journals, listed in §310.9 of the new-drug regulations, about related drugs; a bibliography will suffice. Include the evaluation of the safety or effectiveness of the drug that has been made by the applicant's medical department, expert committee, or consultants.

*f.* If the drug is a combination of previously investigated or marketed drugs, an adequate summary of preexisting information from preclinical and clinical investigation and experience with its components, including all reports received or otherwise obtained by the applicant suggesting side effects, contraindications, and ineffectiveness in use of such components. Such summary should include an adequate bibliography of publications about the components and may incorporate by reference information concerning such components previously submitted by the applicant to the Food and Drug Administration.

*g.* The complete composition and/or method of manufacture of the new drug used in each submitted report of investigation should be shown to the extent necessary to establish its identity, strength, quality, and purity if it differs from the description in Item 6, 7, or 8 of the application.

*h.* In vivo bioavailability data or information to permit waiver of this requirement in accordance with Subpart B of Part 320 (21 CFR Part 320, Subpart B).

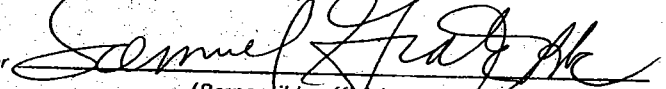
**13. If this is a supplemental application, full information on each proposed change concerning any statement made in the approved application.**

Observe the provisions of §314.8 of the new-drug regulations concerning supplemental applications.

**14. [Reserved]**

**15.** The applicant is required to submit an environmental impact analysis report analyzing the environmental impact of the manufacturing process and the ultimate use or consumption of the drug pursuant to §6.1 of this chapter.

The Lannett Company, Inc.
*(Applicant)*

Per 
*(Responsible official or agent)*

Samuel Gratz, B. Sc.
President

*(Indicate authority)*

(Warning: A willfully false statement is a criminal offense. U.S.C. Tittle 18, sec. 1001.)

Note: This application must be signed by the applicant or by an authorized attorney, agent, or official. If the applicant or such authorized representative does not reside or have a place of business within the United States, the application must also furnish the name and post office address of and must be countersigned by an authorized attorney, agent, or official residing or maintaining a place of business within the United States.

| MEMO RECORD | AVOID ERRORS PUT IT IN WRITING | DATE |
|---|---|---|
| FROM: C. Chang (thru J.L. Meyer) | | OFFICE 8/10/79 HFD-530 |
| TO: Mr. David H. Bryant, Office of Compliance | | DIVISION HFD-322 |

SUBJECT: Inspection Request

SUMMARY

In conncetion with ANDA

for: Methyltestosterone Tab- 87-092

Applicant: Lannett Co. Philadelphia, Pa. 19136

AF -

REQUESTED:

[✓] 1. Evaluation of compliance with CGMP for:

[✓] a. The applicant

[✓] b. Others

[ ] 2. Recommendation for approval/disapproval of the application/ communication/supplement, based on your evaluation of compliance with CGMP

REMARKS: Microbial Limits

[redacted]

JLMeyer

87-092

SIGNATURE

DOCUMENT NUMBER

This permit extension, as issued to the Campbell Soup Co. and such others who participate in accordance with the provisions set out above, expires either on the effective date of an affirmative order ruling on the Campbell Soup Co. petition, or 30 days after a negative order ruling on the petition, whichever the case may be.

Dated: November 16, 1977.

HOWARD R. ROBERTS,
*Acting Director,*
*Bureau of Foods.*

[FR Doc. 77-33675 Filed 11-21-1977; 8:45 am]

[4110-01]

[Docket No. 76N-0185; DESI 3158]

CERTAIN ANDROGEN PREPARATIONS

**Drugs for Human Use; Drug Efficacy Study Implementation; Followup Notice and Opportunity for Hearing**

*Correction*

In FR Doc. 77-28771 appearing at page 52487 in the issue for Friday, September 30, 1977, the date "March 28, 1977" which appears in the "DATES" paragraph and also in the first line of the 9th full paragraph in column one of page 52489, should have read "March 29, 1978."

[4110-03]

[Docket No. 77F-0256]

ICI AMERICAS, INC.

**Filing of Food Additive Petition**

AGENCY: Food and Drug Administration.

ACTION: Notice.

SUMMARY: ICI Americas, Inc., has filed a petition proposing that the food additive regulations be amended concerning 1,2-benzisothiazolin-3-one, to be used for food-contact applications.

FOR FURTHER IMFORMATION CONTACT:

John J. McAuliffe, Bureau of Foods (HFF-334), Food and Drug Administration, Department of Health, Education, and Welfare, 200 C Street SW., Washington, D.C. 20204, 202-472-5690.

SUPPLEMENTARY INFORMATION: Pursuant to provisions of the Federal Food, Drug, and Cosmetic Act (sec. 409(b)(5), 72 Stat. 1786 (21 U.S.C. 348(b)(5)), notice is given that a petition (FAP 3B2882) has been filed by ICI Americas, Inc., proposing that § 175.105(c)(5) (21 CFR 175.105(c)(5)) be amended to include in the list of components of adhesives: 1,2-benzisothiazolin-3-one for use as a preservative; and that § 176.170(a)(5) (21 CFR 176.170(a)(5)) be amended to include 1,2-benzisothiazolin-3-one for use as a preservative in paper and paperboard coating compositions.

The environmental impact analysis report and other relevant material have been reviewed, and it has been determined that the proposed use of the additive will not have a significant environmental impact. Copies of the environmental impact analysis report may be seen in the office of the Hearing Clerk (HFC-20), Food and Drug Administration, Room 4-65, 5600 Fishers Lane, Rockville, Md. 20857, between the hours of 9 a.m. and 4 p.m., Monday through Friday.

Dated: November 16, 1977.

HOWARD R. ROBERTS,
*Acting Director,*
*Bureau of Foods.*

[FR Doc. 77-33676 Filed 11-21-77; 8:45 am]

[4110-08]

National Institutes of Health

ADVISORY COMMITTEE TO THE DIRECTOR, NIH

**Meeting**

Pursuant to Pub. L. 92-463, notice is hereby given of the meeting of the Advisory Committee to the Director, NIH, December 15-16, 1977, National Institutes of Health, Building 31, Conference Room 6C. The meeting will take place from 9 a.m. to 9 p.m. on December 15, and from 9 a.m. to 5 p.m. on December 16. The entire meeting will be open to the public.

The purpose of the meeting will be to consider proposed revised Guidelines for recombinant DNA molecule research conducted and supported by the NIH. The proposed Guidelines were published in the FEDERAL REGISTER September 27, 1977, on pages 49596 to 49609. Attendance by the public will be limited to space available.

In addition to current members of the Committee, a number of other scientific and public representatives have been invited to serve on the Committee for this public hearing. In order to ensure careful review, selected witnesses from the following areas will be invited to comment on the Guidelines at the hearing: environmental, commercial, organized labor, and scientific.

Other witnesses who wish to make oral statements concerning the proposed revisions to the Guidelines will be provided reasonable opportunity to do so at appropriate times indicated on the agenda. All witnesses are requested to confine their comments to the proposed revisions. Persons who wish to make oral statements should notify the Executive Secretary of their intention to speak and the Section of the proposed revisions to which they will direct their comments. Travel expenses will be provided for invited witnesses only.

Written comments on the proposed revised Guidelines should be addressed to: Director, National Institutes of Health, 9000 Rockville Pike, Bethesda, Maryland 20014. The Executive Secretary, Charles R. McCarthy, Ph.D., National Institutes of Health, Building 1, Room 201, Bethesda, Maryland 20014 (301) 496-1485, will furnish rosters of Committee members and guests, and substantive program information.

The tentative agenda for the meeting is as follows:

PROPOSED AGENDA FOR MEETING OF THE ADVISORY COMMITTEE TO THE DIRECTOR, NIH, DECEMBER 15-16, 1977

THURSDAY, DECEMBER 15

9 a.m.—Opening remarks—Dr. Fredrickson.

DISCUSSION OF SECTIONS OF REVISED DNA GUIDELINES

9:30 a.m.—Introduction to revised guidelines—Dr. Littlefield.

*Section I. Physical Containment*

Dr. Barkley

10 a.m.—Comments by invited witnesses.
10:30 a.m.—Coffee break.
10:45 a.m.—Comments by other witnesses.

11:30 a.m.—*Section II. Biological Containment*

Dr. Gottesman

11:45 a.m.—Comments by invited witnesses.
12:30 p.m.—Comments by other witnesses.
1 p.m.—Lunch.

2:15 p.m.—*Section III. Experimental guidelines*

Drs. Helinski, Rowe, and Day

2:45 p.m.—Comments by invited witnesses.
3:30 p.m.—Coffee break.
3:45 p.m.—Comments by invited witnesses.
5 p.m.—Dinner.
7:30 p.m.—Comments by other witnesses.
9 p.m.—Adjournment.

FRIDAY, DECEMBER 16, 1977

9 a.m.—Summary and comments—Dr. Fredrickson.

9:15 a.m.—*Section IV. Roles and Responsibilities*

Dr. Walters

9:45 a.m.—Comments by invited witnesses.
10:45 a.m.—Coffee break.
11 a.m.—Comments by other witnesses.
12 a.m.—Lunch.
1:15 p.m.—Committee discussion.
5 p.m.—Adjourn sine die.

Dated: November 15, 1977.

SUZANNE L. FREMEAU,
*Committee Management Officer.*

[FR Doc. 77-33745 Filed 11-21-77; 8:45 am]

ld be in the public interest and that application should be approved.

On the basis of the record, the application is approved for the reasons summarized above. The transaction shall not be made before the thirtieth calendar day following the effective date of this Order, or later than three months after the effective date of this Order, unless such period is extended by the Board, or by the Federal Reserve Bank of Chicago pursuant to delegated authority.

By order of the Board of Governors,[1] effective September 23, 1977.

GRIFFITH L. GARWOOD,
*Deputy Secretary of the Board.*

[FR Doc.77-28770 Filed 9-29-77;8:45 am]

[6210-01]

## SCHRODERS LIMITED

### Proposed Acquisition of Robert C. Gilkison, Inc.

Schroders Limited, Schroder International Limited, and Schroder International Holdings Limited, all of London, England, and Schroders Inc., New York, N.Y., have applied, pursuant to § 4(c)(8) of the Bank Holding Company Act (12 U.S.C. § 1843(c)(8)) and § 225.4(b)(2) of the Board's Regulation Y (12 CFR § 225.4(b)(2)), for permission to acquire the business and assets of Robert C. Gilkison, Inc., Washington, D.C. Notice of the application was published on August 1, 1977, in The Washington Post, a newspaper circulated in Washington, D.C., and on July 30, 1977, in The New York Times, a newspaper circulated in New York, N.Y.

Applicant states that the proposed acquisition would engage in the activities of acting as investment counselors and registered investment advisor under the Investment Advisors Act of 1940. Such activities have been specified by the Board in § 225.4(a) of Regulation Y as permissible for bank holding companies, subject to Board approval of individual proposals in accordance with the procedures of § 225.4(b).

Interested persons may express their views on the question whether consummation of the proposal can "reasonably be expected to produce benefits to the public, such as greater convenience, increased competition, or gains in efficiency, that outweigh possible adverse effects, such as undue concentration of resources, decreased or unfair competition, conflicts of interests, or unsound banking practices." Any request for a hearing on this question should be accompanied by a statement summarizing the evidence the person requesting the hearing proposes to submit or to elicit at the hearing and a statement of the reasons why this matter should not be resolved without a hearing.

[1] Voting for this action: Governors Wallich, Coldwell, Jackson, Partee, and Lilly. Absent and not voting: Chairman Burns and Governor Gardner.

The application may be inspected at the offices of the Board of Governors or at the Federal Reserve Bank of New York.

Any views or requests for hearing should be submitted in writing and received by the Secretary, Board of Governors of the Federal Reserve System, Washington, D.C. 20551, not later than October 21, 1977.

Board of Governors of the Federal Reserve System, September 23, 1977.

GRIFFITH L. GARWOOD,
*Deputy Secretary of the Board.*

[FR Doc.77-28777 Filed 9-29-77;8:45 am]

[6210-01]

## SCHRODERS LIMITED

### Proposed Retention of Schroder Naess & Thomas

Schroders Limited, Schroder International Limited, and Schroder International Holding Limited, all of London, England, and Schroders Inc., New York, N.Y., have applied, pursuant to § 4(c)(8) of the Bank Holding Company Act (12 U.S.C. § 1843(c)(8)) and § 225.4(b)(2) of the Board's Regulation Y (12 CFR § 225.4(b)(2)), for permission to retain the business and assets of the Schroder Naess & Thomas Division of Schroders Incorporated, New York, N.Y. Notice of the application was published in The Wall Street Journal, as well as newspapers of general circulation in Baltimore, Md., Washington, D.C., New York, N.Y., and Atlanta, Ga.

Applicant states that the division would continue to engage in the activities of acting as investment counselor and registered investment advisor under the Investment Advisors Act of 1940. Such activities have been specified by the Board in § 225.4(a) of Regulation Y as permissible for bank holding companies, subject to Board approval of individual proposals in accordance with the procedures of § 225.4(b).

Interested persons may express their views on the question whether consummation of the proposal can "reasonably be expected to produce benefits to the public, such as greater convenience, increased competition, or gains in efficiency, that outweight possible adverse effects, such as undue concentration of resources, decreased or unfair competition, conflicts of interests, or unsound banking practices." Any request for a hearing on this question should be accompanied by a statement summarizing the evidence the person requesting the hearing proposes to submit or to elicit at the hearing and a statement of the reasons why this matter should not be resolved without a hearing.

The application may be inspected at the offices of the Board of Governors or at the Federal Reserve Bank of New York.

Any views or requests for hearing should be submitted in writing and received by the Secretary, Board of Governors of the Federal Reserve System, Washington, D.C. 20551, not later than October 21, 1977.

Board of Governors of the Federal Reserve System, September 23, 1977.

GRIFFITH L. GARWOOD,
*Deputy Secretary of the Board.*

[FR Doc.77-28778 Filed 9-29-77;8:45 am]

[4110-03]

# DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

## Food and Drug Administration

[Docket No. 76N-0185; DESI 3158]

## CERTAIN ANDROGEN PREPARATIONS

### Drugs for Human Use; Drug Efficacy Study Implementation; Followup Notice and Opportunity for Hearing

AGENCY: Food and Drug Administration.

ACTION: Notice.

SUMMARY: This notice sets forth the conditions for marketing the androgen preparations described below for the indications for which they continue to be regarded as effective and offers an opportunity for a hearing concerning those indications reclassified as lacking substantial evidence of effectiveness.

DATES: Hearing requests due on or before October 31, 1977. Bioavailability supplements to approved new drug applications due on or before March 28, 1977. Other supplements due on or before November 29, 1977.

ADDRESSES: Communications forwarded in response to this notice should be identified with the reference number DESI 3158, directed to the attention of the appropriate office named below, and addressed to the Food and Drug Administration, 5600 Fishers Lane, Rockville, Md. 20857.

Supplements (identify with NDA number): Division of Metabolic and Endocrine Drug Products (HFD-130), Rm. 14B-03, Bureau of Drugs.

Original abbreviated new drug applications and supplements thereto (identify as such): Division of Generic Drug Monographs (HFD-530), Bureau of Drugs.

Requests for Hearing (identify with Docket Number appearing in the heading of this notice): Hearing Clerk, Food and Drug Administration (HFC-20), Rm. 4-65.

Requests for the report of the National Academy of Sciences-National Research Council: Public Records and Document Center (HFC-18), Rm. 4-62.

Requests for opinion of the applicability of this notice to a specific product: Division of Drug Labeling Compliance (HFD-310), Bureau of Drugs.

Other communications regarding this notice: Drug Efficacy Study Implementation Project Manager (HFD-501), Bureau of Drugs.

FOR FURTHER INFORMATION CONTACT:

John H. Hazard, Jr., Bureau of Drugs (HFD-32), Food and Drug Administration, Department of Health, Education, and Welfare, 5600 Fishers Lane, Rockville, Md. 20857 (301-443-3650).

SUPPLEMENTARY INFORMATION: In a notice (DESI 3158; Docket No. FDC-D-183 (now Docket No. 76N-0185)) published in the FEDERAL REGISTER of August 1, 1970 (35 FR 12356), the Food and Drug Administration announced its conclusions that the androgen preparations described below are effective, probably effective, possibly effective, and lacking substantial evidence of effectiveness for their various labeled indications. The drugs are used to treat certain hormone deficiencies. No data were submitted in support of any of the less-than-effective indications and those indications now are reclassified to lacking substantial evidence of effectiveness.

The notice that follows does not pertain to the indications stated in the August 1, 1970, notice to lack substantial evidence of effectiveness. No person requested a hearing concerning them, and they are no longer allowable in the labeling. Any such product labeled for those indications is subject to regulatory action.

1. NDA 3-158; Oreton Methyl Tablets containing 10 milligrams or 25 milligrams of methyltestosterone per tablet; Schering Corp., Galloping Hill Rd., Kenilworth, N.J. 07033.

2. NDA 3-234; Neo-Hombreol (M) Tablets containing 10 milligrams or 25 milligrams methyltestosterone per tablet; Organon, Inc., 375 Mount Pleasant Ave., West Orange, N.J. 07052.

3. NDA 3-240; Metandren Linguets and Tablets containing 5 milligrams or 10 milligrams methyltestosterone per linguet and 10 milligrams or 25 milligrams methyltestosterone per tablet; Ciba Pharmaceutical Co., Division Ciba-Geigy Corp., 556 Morris Ave., Summit, N.J. 07901.

4. NDA 7-029; Perandren Propionate Injection, containing 25 milligrams, 50 milligrams, or 100 milligrams testosterone propionate per milliliter in sesame oil; Ciba Pharmaceutical Co.

5. NDA 9-165; Delatestryl Injection containing 200 milligrams testosterone enanthate per milliliter in sesame oil, and in disposable syringes containing 200 milligrams testosterone enanthate per syringe in sesame oil, E. R. Squibb & Sons, Post Office Box 4000, Princeton, N.J. 08540.

6. NDA 9-349; Parendren Phenylacetate Intramuscular Repository, Aqueous Suspension containing 50 milligrams testosterone phenylacetate per milliliter and 1 percent procaine hydrochloride; Ciba Pharmaceutical Co.

7. NDA 10-611; Halotestin Tablets containing 2 milligrams, 5 milligrams, or 10 milligrams fluoxymesterone per tablet; The Upjohn Co., 7171 Portage Rd., Kalamazoo, Mich. 49002.

8. NDA 11-359; Ora-Testryl Tablets containing 2 milligrams or 5 milligrams fluoxymesterone per tablet; E. R. Squibb and Sons.

9. NDA 11-424; Ultandren Tablets containing 2 milligrams or 5 milligrams fluoxymesterone per tablet; Ciba Pharmaceutical Co.

Such drugs are regarded as new drugs (21 U.S.C. 321(p)). Supplemental new drug applications are required to revise the labeling in and to update previously approved applications providing for such drugs. An approved new drug application is a requirement for marketing such drug products.

In addition to the holder(s) of the new drug application(s) specifically named above, this notice applies to all persons who manufacture or distribute a drug product, not the subject of an approved new drug application, that is identical, related, or similar to a drug product named above, as defined in 21 CFR 310.6. It is the responsibility of every drug manufacturer or distributor to review this notice to determine whether it covers any drug product he manufactures or distributes. Any person may request an opinion of the applicability of this notice to a specific drug product he manufactures or distributes that may be identical, related, or similar to a drug product named in this notice by writing to the Division of Drug Labeling Compliance (address given above).

A. *Effectiveness classification.* The Food and Drug Administration has reviewed all available evidence and concludes that the drugs are effective for the indications in the labeling conditions below. The drugs now lack substantial evidence of effectiveness for the indications evaluated as probably and possibly effective in the August 1, 1970 notice.

B. *Conditions for approval and marketing.* The Food and Drug Administration (FDA) is prepared to approve new drug applications under conditions described herein. The type of new drug applications required for the various products is set forth under *Marketing Status* below.

1. *Form of drug.* a. Testosterone enanthate is in solution form suitable for intramuscular administration.

b. Methyltestosterone is in tablet form suitable for oral or buccal administration.

c. Testosterone propionate is in solution form suitable for intramuscular administration.

d. Testosterone phenylacetate is in suspension form suitable for intramuscular repository administration.

e. Fluoxymesterone is in tablet form suitable for oral administration.

2. *Labeling conditions.* a. The label bears the statement, "Caution: Federal law prohibits dispensing without prescription."

b. The drug is labeled to comply with all requirements of the act and regulations, and the labeling bears adequate information for safe and effective use of the drug. The Indications are as follows:

*Testosterone enanthate solution for intramuscular administration: In the male:*

1. Eunuchism and eunochoidism.
2. Climacteric symptoms when these are secondary to androgen deficiency.
3. Oligospermia.
4. Deficiency after castration.

*Methyltestosterone for oral or buccal administration: In the male:*

1. Eunuchoidism and eunuchism.
2. Climacteric symptoms when these are secondary to androgen deficiency.
3. Impotence due to androgen deficiency.
4. Postpuberal cryptorchidism with evidence of hypogonadism.

*In the female:*

1. Prevention of postpartum breast pain and engorgement. There is no satisfactory evidence that this drug prevents or suppresses lactation.
2. Palliation of androgen-responsive, advancing, inoperable mammary cancer, in women who are more than 1 year, but less than 5 years postmenopausal or who have been proven to have a hormone-dependent tumor as shown by previous beneficial response to castration.

*Testosterone propionate solution for intramuscular administration: In the male:*

1. Postpuberal cryptorchidism with evidence of hypogonadism.
2. Eunuchism and eunochoidism.
3. Impotence due to androgen deficiency.
4. Climacteric symptoms when these are secondary to androgen deficiency.

*In the female:*

1. Prevention of postpartum breast pain and engorgement. There is no satisfactory evidence that this drug prevents or suppresses lactation.
2. Palliation of androgen-responsive, advancing, inoperable mammary cancer in women who are more than 1 year, but less than 5 years postmenopausal or who have been proven to have a hormone-dependent tumor as shown by previous beneficial response to castration.

*Testosterone phenylacetate suspension for intramuscular repository administration: In the male:*

1. Eunuchoidism and eunuchism.
2. Climacteric symptoms when these are secondary to androgen deficiency.

*In the female:*

Palliation of androgen-responsive, advancing, inoperable mammary cancer in women who are more than 1 year, but less than 5 years postmenopausal or who have been proven to have a hormone-dependent cancer. With the use of this long-acting preparation, it would be impossible to properly nullify the untoward effects of tumor progression, hypercalcemia, or salt and water retention.

*Fluoxymesterone for oral administration: In the male:*

The primary indication in the male is replacement therapy in conditions associated with a deficiency or absence of endogenous testicular hormone. Androgen therapy prevents the development of atrophic changes in the accessory male sex organs following castration; as long as replacement therapy is continued, these organs can be maintained in a relatively normal state.

1. Eunuchoidism and eunuchism.
2. Climacteric symptoms when these are secondary to androgen deficiency.
3. Those symptoms of panhypopituitarism related to hypogonadism. Appropriate adrenal cortical and thyroid hormone replacement therapy are still necessary, however, and are actually of primary importance.
4. Impotence due to androgen deficiency.
5. Delayed puberty, provided it has been definitely established as such, and it is not just a familial trait.

*In the female*:

1. Prevention of postpartum breast pain and engorgement. There is no satisfactory evidence that this drug prevents or suppresses lactation.
2. Palliation of androgen-responsive, advancing, inoperable mammary cancer, in women who are more than 1 year, but less than 5 years postmenopausal or who have been proven to have a hormone-dependent tumor as shown by previous beneficial response to castration.

3. *Marketing status.* a. Marketing of such drug products that are now the subject of an approved or effective new drug application may be continued provided that, on or before November 29, 1977, the holder of the application submits, if he has not previously done so, (i) a supplement for revised labeling as needed to be in accord with the labeling conditions described in this notice, and complete container labeling if current container labeling has not been submitted, and (ii) for all products except delayed or prolonged release dosage forms, a supplement to provide updating information with respect to items 6 (components), 7 (composition), and 8 (methods, facilities, and controls) of new drug application form FD-356H (21 CFR 314.1(c)) to the extent required in abbreviated applications (21 CFR 314.1 (f)), and for delayed or prolonged release dosage forms, a supplement to provide full updating information with respect to items 6, 7, and 8 of the new drug application form FD-356H.

In addition, on or before March 28, 1977, the holders of such applications for the following drugs are required to supplement their application to provide (1) for methyltestosterone tablets, evidence from in vivo studies that demonstrates the bioavailability of the tablet relative to the bioavailability of a solution containing the same amount of drug as in the tablet, and also in vitro dissolution rate data, and (2) for methyltestosterone buccal (or sublingual) tablets and fluoxymesterone tablets, only in vitro dissolution rate data. The dissolution profile shall be determined for 12 individual tablets using FDA Paddle Method at 50 revolutions per minute, 37°C and 500 milliliters of medium. Both water and 0.1N HCl are to be used as media. Twelve tablets are to be tested in each medium.

b. Approval of an abbreviated new drug application (ANDA) (21 CFR 314.1 (f)) must be obtained prior to marketing such product. For preparations in delayed or prolonged release dosage forms, the application shall contain full information with respect to items 6 (components), 7 (composition), and 8 (methods, facilities, and controls) of new drug application form FD-356H.

In addition, for the following drugs the abbreviated new drug applications are to provide (1) for methyltestosterone tablets, evidence from in vivo studies that demonstrates the bioavailability of the tablet relative to the bioavailability of a solution containing the same amount of drug as in the tablet, and also in vitro dissolution rate data; and (2) for methyltestosterone buccal (or sublingual) tablets and fluoxymesterone tablets, in vitro dissolution rate data. The dissolution profile shall be determined for 12 individual tablets using FDA Paddle Method at 50 revolutions per minute, 37°C and 500 milliliters of medium. Both water and 0.1N HCl are to be used as media. Twelve tablets are to be tested in each medium.

Marketing prior to approval of a new drug application will subject such products, and those persons who caused the product to be marketed, to regulatory action.

C. *Notice of opportunity for hearing.* On the basis of all the data and information available to him, the Director of the Bureau of Drugs is unaware of any adequate and well-controlled clinical investigation, conducted by experts qualified by scientific training and experience, meeting the requirements of section 505 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355) and 21 CFR Parts 314.111(a)(5) and 300.50, demonstrating the effectiveness of the drug(s) for the indication(s) lacking substantial evidence of effectiveness referred to in paragraph A. of this notice.

Notice is given to the holder(s) of the new drug application(s), and to all other interested persons, that the Director of the Bureau of Drugs proposes to issue an order under section 505(e) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355(e)), withdrawing approval of the new drug application(s) and all amendments and supplements thereto providing for the indication(s) lacking substantial evidence of effectiveness referred to in paragraph A. of this notice, on the ground that new information before him with respect to the drug product(s), evaluated together with the evidence available to him at the time of approval of the application(s), shows there is a lack of substantial evidence that the drug product(s) will have all the effects it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the labeling. An order withdrawing approval will not issue with respect to any application(s) supplemented, in accord with this notice, to delete the claim(s) lacking substantial evidence of effectiveness.

In addition to the ground for the proposed withdrawal of approval stated above, this notice of opportunity for hearing encompasses all issues relating to the legal status of the drug products subject to it (including identical, related, or similar drug products as defined in 21 CFR 310.6), e.g., any contention that any such product is not a new drug because it is generally recognized as safe and effective within the meaning of section 201(p) of the act or because it is exempt from part or all of the new drug provisions of the act pursuant to the exemption for products marketed prior to June 25, 1938, contained in section 201(p) of the act, or pursuant to section 107(c) of the Drug Amendments of 1962; or for any other reason.

In accordance with the provisions of section 505 of the act (21 U.S.C. 355) and the regulations promulgated thereunder (21 CFR Parts 310, 314), the applicant(s) and all other persons who manufacture or distribute a drug product which is identical, related, or similar to a drug product named above (21 CFR 310.6), are hereby given an opportunity for a hearing to show why approval of the new drug application(s) providing for the claim(s) involved should not be withdrawn and an opportunity to raise, for administrative determination, all issues relating to the legal status of a drug product named above and all identical, related, or similar drug products.

If an applicant or any person subject to this notice pursuant to 21 CFR 310.6 elects to avail himself of the opportunity for a hearing, he shall file (1) on or before October 31, 1977, a written notice of appearance and request for hearing and (2) on or before November 29, 1977, the data, information, and analyses on which he relies to justify a hearing, as specified in 21 CFR 314.200. Any other interested person may also submit comments on this proposal to withdraw approval. The procedures and requirements governing this notice of opportunity for hearing, a notice of appearance and request for hearing, a submission of data, information, and analyses to justify a hearing, other comments, and a grant or denial of hearing, are contained in 21 CFR 314.200.

The failure of an applicant or any other person subject to this notice pursuant to 21 CFR 310.6 to file timely written appearance and request for hearing as required by 21 CFR 314.200 constitutes an election by such person not to avail himself of the opportunity for a hearing concerning the action proposed with respect to such drug product and a waiver of any contentions concerning the legal status of such drug product. Any such drug product labeled for the indication(s) lacking substantial evidence of effectiveness referred to in paragraph A. of this notice may not thereafter lawfully be marketed, and the Food and Drug Administration will initiate appropriate regulatory action to remove such drug products from the market. Any new drug product marketed without an approved NDA is subject to regulatory action at any time.

A request for a hearing may not rest upon mere allegations or denials, but must set forth specific facts showing that there is a genuine and substantial issue of fact that requires a hearing. If it conclusively appears from the face of the data, information, and factual analyses

in the request for the hearing that there is no genuine and substantial issue of fact which precludes the withdrawal of approval of the application, or when a request for hearing is not made in the required format or with the required analyses, the Commissioner will enter summary judgment against the person(s) who requests the hearing, making findings and conclusions, denying a hearing.

All submissions pursuant to this notice of opportunity for hearing shall be filed in quintuplicate. Such submissions, except for data and information prohibited from public disclosure pursuant to 21 U.S.C. 331(j) or 18 U.S.C. 1905, may be seen in the office of the Hearing Clerk (address given above) between the hours of 9 a.m. and 4 p.m., Monday through Friday.

This notice is issued under the Federal Food, Drug, and Cosmetic Act (secs. 502, 505, 52 Stat. 1050–1053, as amended (21 U.S.C. 352, 355)) and under the authority delegated to the Director of the Bureau of Drugs (21 CFR 5.82).

Dated: September 22, 1977.

J. RICHARD CROUT,
*Director, Bureau of Drugs.*

[FR Doc.77-28771 Filed 9-29-77;8:45 am]

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[Docket No. 77N-0230]

## DIAMOND SHAMROCK CHEMICAL CO., ET AL.

### Penicillin-Containing Premixes; Opportunity for Hearing

*Corrections*

In FR Doc. 77-24971 appearing at page 43772 in the issue for Tuesday, August 30, 1977, the following corrections should be made.

1. On page 43772, second column, line 7, the citation, "21 CFR 558.78", should read, "21 CFR 558.76".

2. On page 43773, second column, line 37, the citation, "U.S.C. 349", should read, "U.S.C. 348".

3. On page 43774, first column, line 9 of paragraph 2., the designation, "(e)", should read, "(c)".

4. In the third column, line 2, the word, "advisory", should read, "discovery".

5. On page 43780, second column, line 35, the word, "translate", should read, "translocate".

6. In the third column, line 5 of reference 11., now reading, "Biology, 97: 561–515,1975", should read, "Biology, 97:561–575,1975".

7. In line 3 of reference 13, influenzae type "D", should read, "B".

8. In the tables on pages 43781 and 43783, under the heading "Group", "$B^1$" should read, "$B_1$"; "$B^2$", should read, $B_2$"; "$D^1$", should read, "$D_1$", and "$D^2$", should read, "$D_2$".

9. On page 43792, first column, line 8 of paragraph (e), the word, "letter", should read, "latter".

[4110–03]

## HEALTH CARE SERVICES

### Open Meeting

AGENCY: Food and Drug Administration.

ACTION: Notice.

SUMMARY: This document announces the forthcoming Boston regional Ad Hoc Professional and Consumer Meetings to be chaired by the Commisisoner of Food and Drugs.

DATES: The professional meeting will begin at 7:30 p.m., Tuesday, October 18, 1977. The consumer meeting will begin at 9 a.m. on Wednesday, October 19, 1977. Registration will begin one half hour prior to each meeting.

ADDRESS: Both meetings will be held at the Museum of Science (Morris Auditorium), Science Park, Boston, Mass. 02114.

FOR FURTHER INFORMATION CONTACT:

Yolan Harsanyi, Consumer Affairs Officer (HFR–1145), Food and Drug Administration, Department of Health, Education, and Welfare, 585 Commercial St., Boston, Mass. 02109, (167–223–5857).

SUPPLEMENTARY INFORMATION: The purpose of each meeting is to exchange views and information of mutual interest. The professional meeting will focus on medical and other scientific issues relating to the Food and Drug Administration (FDA). In addition, there will be an opportunity for practitioners to identify with the Commissioner ways in which FDA can better serve the practitioners and their patients. The consumer meeting will focus on consumer issues (i.e., food additives, over-the-counter drugs, and other FDA-related topics). It will also provide an opportunity for consumers to discuss with the Commissioner ways in which FDA can better meet their needs. Both meetings are open to all interested persons.

Dated: September 23, 1977.

JOSEPH P. HILE,
*Associate Commissioner for Compliance.*

[FR Doc.77-28578 Filed 9-29-77;8:45 am]

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[4110–03]

## MATRIX APPROACH SUBCOMMITTEE OF THE SCIENCE ADVISORY BOARD

### Meeting Change

AGENCY: Food and Drug Administration.

ACTION: Notice.

SUMMARY: The Matrix Approach Subcommittee of the Science Advisory Board meeting scheduled for September 30, 1977 has been rescheduled for October 18, 1977.

FOR FURTHER INFORMATION CONTACT:

Ruth S. Magee, National Center for Toxicological Research, Jefferson, Ark. 72079, (501–541–4528).

SUPPLEMENTARY INFORMATION: Under the Federal Advisory Committee Act of October 6, 1972 (Pub. L. 92–463, 86 Stat. 770–776 (5 U.S.C. App. I)), the Food and Drug Administration announced in a notice published in the FEDERAL REGISTER of August 12, 1977 (42 FR 40958), meetings of FDA public advisory committees and other required information in accordance with provisions set forth in section 10(a) (1) and (2) of the act.

Notice is hereby given that the meeting of the Matrix Approach Subcommittee of the Science Advisory Board scheduled for September 30, 1977, has been changed to October 18, 1977. The open public hearing will begin at 9 a.m. at the National Center for Toxicological Research, Jefferson, Arkansas.

Dated: September 22, 1977.

WILLIAM F. RANDOLPH,
*Acting Associate Commissioner for Compliance.*

[FR Doc.77-28577 Filed 9-29-77;8:45 am]

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[4110–03]

[Docket No. 77F-0262]

## USS AGRI-CHEMICALS DIVISION

### Filing of Petition for Food Additive Permitted in Animal Feed

AGENCY: Food and Drug Administration.

ACTION: Notice.

SUMMARY: USS Agri-Chemicals Division has filed a petition proposing that the regulations for food additives permitted in animal feed be amended to provide for direct mixing of anhydrous ammonia with corn plant material.

FOR FURTHER INFORMATION CONTACT:

William D. Price, Bureau of Veterinary Medicine (HFV–123), Food and Drug Administration, Department of Health, Education, and Welfare, 5600 Fishers Lane, Rockville, Md. 20857 (301–443–3442).

SUPPLEMENTARY INFORMATION: Pursuant to provisions of the Federal Food, Drug, and Cosmetic Act (sec. 405 (b)(5), 72 Stat. 1786 (21 U.S.C. 348(b)(5))), notice is given that a petition (MF–3673) has been filed by USS Agri-Chemicals Division, United States Steel Corp., P.O. Box 1685, Atlanta, Ga. 30301; proposing that § 573.180 *Anhydrous ammonia* (21 CFR 573.180) be amended to provide for direct mixing of cold liquid ammonia with freshly chopped corn plant material before ensiling, as a source of nonprotein nitrogen in cattle feed.

The Commissioner of Food and Drugs has reviewed the potential environmental impact of the proposed regulation. He has concluded that the proposed action would not significantly affect the quality

others; shall arrange for the payment of interest on and the repayment of such borrowings; shall arrange for the payment of interest on the capital stock of the Corporation; shall coordinate and give general supervision to the claims activities of the Corporation and shall have authority to collect all monies due the Corporation, to receipt therefor and to deposit same for the account of the Corporation; and shall perform such other duties relating to the fiscal and accounting affairs of the Corporation as may be prescribed from time to time by the Controller.

THE CHIEF ACCOUNTANT

21. The Chief Accountant, under the general supervision and direction of the Controller, shall have charge of the general books and accounts of the Corporation and the preparation of financial statements and reports. He shall be responsible for the initiation, preparation and issuance of policies and practices related to accounting matters and procedures, including official inventories, records, accounting and related office procedures where standardized, and adequate subsidiary records of revenues, expenses, assets and liabilities; and shall perform such other duties relating to the fiscal and accounting affairs of the Corporation as may be prescribed from time to time by the Controller.

OTHER OFFICIALS

22. Except as otherwise authorized by the Secretary of Agriculture or the Board, the operations of the Corporation shall be carried out through the facilities and personnel of the Agricultural Stabilization and Conservation Service, the Foreign Agricultural Service, the Export Marketing Service, the Food and Nutrition Service and the Consumer and Marketing Service, in accordance with any assignment of functions and responsibilities made by the Secretary of Agriculture and, within his respective agency, by the Administrators of the Agricultural Stabilization and Conservation Service, Foreign Agricultural Service, Food and Nutrition Service, Consumer and Marketing Service, or the General Sales Manager of the Export Marketing Service.

23. The Directors of the divisions and commodity offices of the Agricultural Stabilization and Conservation Service shall be contracting officers and executives of the Corporation in general charge of the activities of the Corporation carried out through their respective divisions or offices. The responsibilities of such Directors in carrying out activities of the Corporation, which shall include the authority to settle and adjust claims by and against the Corporation arising out of activities under their jurisdiction, shall be discharged in conformity with these bylaws and applicable programs, policies, and procedures.

BONDS

24. Such officers and employees of the Corporation, including officers and employees of the Department of Agriculture who perform duties for the Corporation, as may be specified by the Secretary of Agriculture, shall be bonded in such manner, upon such conditions, and in such amounts as the Secretary of Agriculture may determine. The Corporation shall pay the premium of any bond or bonds.

CONTRACTS OF THE CORPORATION

25. Contracts of the Corporation relating to any of its activities may be executed in its name by the Secretary of Agriculture or the President. The Vice Presidents, the Deputy Vice Presidents, the Comptroller, the Treasurer, and the Directors of the divisions and commodity offices of the Agricultural Stabilization and Conservation Service may execute contracts relating to the activities of the Corporation for which they are respectively responsible.

26. The Executive Vice President who is the Administrator of ASCS and, subject to the written approval by such Executive Vice President of each appointment, the Vice Presidents, the Deputy Vice Presidents, the Comptroller, and the Directors of the divisions and commodity offices of the Agricultural Stabilization and Conservation Service may appoint, by written instrument or instruments such Contracting Officers as they deem necessary, who may, to the extent authorized by such instrument or instruments, execute contracts in the name of the Corporation. A copy of each such instrument shall be filed with the Secretary.

27. Appointments of Contracting Officers may be revoked by written instrument or instruments by the Executive Vice President or by the official who made the appointment. A copy of each such instrument shall be filed with the Secretary.

28. In executing a contract in the name of the Corporation, an official shall indicate his title.

ANNUAL REPORT

29. The Executive Vice President shall be responsible for the preparation of an annual report of the activities of the Corporation, which shall be filed with the Secretary of Agriculture and with the Board.

AMENDMENTS

30. These bylaws may be altered or amended or repealed by the Secretary of Agriculture, or subject to his approval by action of the Board at any regular meeting of the Board or at any special meeting of the Board, if notice of the proposed alteration, amendment, or repeal be contained in the notice of such special meeting.

APPROVAL OF BOARD ACTION

31. The actions of the Board shall be subject to the approval of the Secretary of Agriculture and the Assistant Secretary for International Affairs and Commodity Programs.

I, Seeley G. Lodwick, Acting Secretary, Commodity Credit Corporation, do hereby certify that the above is a full, true, and correct copy of the bylaws of Commodity Credit Corporation, adopted by the Board of Directors, Commodity Credit Corporation, at a meeting held June 30, 1970, and approved by the Secretary of Agriculture, effective close of business July 2, 1970.

In witness whereof I have officially subscribed my name and have caused the corporate seal of the said Corporation to be affixed this second day of July 1970.

[SEAL] SEELEY G. LODWICK,
*Acting Secretary,*
*Commodity Credit Corporation.*

[F.R. Doc. 70-9552; Filed, July 31, 1970; 8:45 a.m.]

# DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

## Food and Drug Administration

[DESI 3158]

[Docket No. FDC-D-183; NDA No. 3-158 et al.]

## CERTAIN ANDROGEN PREPARATIONS

### Drugs for Human Use; Drug Efficacy Study Implementation

The Food and Drug Administration has evaluated reports received from the National Academy of Sciences-National Research Council, Drug Efficacy Study Group, on the following drugs:

1. Perandren Propionate, for Intramuscular Injection. Vials, containing 25 milligrams, 50 milligrams, or 100 milligrams testosterone propionate per milliliter; Ciba Pharmaceutical Co., 556 Morris Avenue, Summit, N.J. 07901 (NDA 7029).

2. Perandren Phenylacetate Intramuscular Repository. Vials, containing 50 milligrams testosterone phenylacetate per milliliter and 1 percent procaine hydrochloride; Ciba Pharmaceutical Company (NDA 9349).

3. Oreton Pellets for Subcutaneous Implantation, containing 75 milligrams testosterone per pellet; Schering Corp., 60 Orange Street, Bloomfield, N.J. 07003 (NDA 4652).

4. Halotestin Tablets, contain 10 milligrams, 5 milligrams; or 2 milligrams fluoxymesterone per tablet; The Upjohn Co., 7171 Portage Road, Kalamazoo, Mich. 49002 (NDA 10-611).

5. Ultandren Tablets containing 2 milligrams or 5 milligrams fluoxymesterone per tablet, Ciba Pharmaceutical Co. (NDA 11-424).

6. Ora-Testryl Tablets, containing 2 milligrams or 5 milligrams fluoxymesterone per tablet; E. R. Squibb and Sons Inc., Georges Road, New Brunswick, N.J. 08903 (NDA 11-359).

7. Delatestryl Sterile Solution, for Intramuscular Injection, containing 200 milligrams testosterone enanthate per milliliter, and in disposable syringes containing 200 mg. testosterone enanthate per syringe; E. R. Squibb and Sons Inc. (NDA 9165).

8. Neo-Hombreol (M). Tablets, containing 10 milligrams or 25 milligrams methyltestosterone per tablet; Organon Inc., 375 Mount Pleasant Avenue, West Orange, N.J. 07052 (NDA 3241).

9. Metandren Linguets and Tablets, containing 5 milligrams or 10 milligrams methyltestosterone per linguet, and 10 milligrams or 25 milligrams methyltestosterone per tablet; Ciba Pharmaceutical Co. (NDA 3240).

10. Oreton Methyl Tablets, containing 10 milligrams or 25 milligrams methyltestosterone per tablet; Schering Corp. (NDA 3153).

The drugs are regarded as new drugs (21 U.S.C. 321(p)). Supplemental new-drug applications are required to revise the labeling in and to update previously approved applications providing for such drugs. A new-drug application is required from any person marketing such drugs without approval.

The Food and Drug Administration is prepared to approve new-drug applications and supplements to previously approved new-drug applications under conditions described in this announcement.

I. *Testosterone for subcutaneous implantation*—A. *Effectiveness classification.* The Food and Drug Administration has considered the Academy report, as well as other available evidence, and concludes that:

1. This drug is effective for eunuchism, eunuchoidism, and male climacteric.

2. It lacks substantial evidence of effectiveness for advanced breast carcinoma.

B. *Form of drug.* This preparation is in pellet form suitable for subcutaneous implantation.

C. *Labeling conditions.* 1. The label bears the statement "Caution: Federal law prohibits dispensing without prescription."

2. The drug is labeled to comply with all requirements of the Act and regulations. Its labeling bears adequate information for safe and effective use of the drug and is in accord with the guideline for uniform labeling published in the FEDERAL REGISTER of February 6, 1970. The "Indications" section of the labeling is as follows:

INDICATIONS

1. Eunuchoidism and eunuchism.
2. Male climacteric symptoms when these are secondary to testosterone deficiency.

D. *Marketing status.* Marketing of the drug may continue under the conditions described in items VIII and IX of this announcement.

II. *Testosterone enanthate solution for intramuscular injection*—A. *Effectiveness classification.* The Food and Drug Administration has considered the Academy report, as well as other available evidence, and concludes that:

1. This drug is effective in the therapy of eunuchism, eunuchoidism, deficiency after castration, male climacteric symptoms, and oligospermia.

2. The drug is probably effective for postmenopausal or senile osteoporosis.

3. This drug is possibly effective for use in senile pruritis, tissue atrophy in geriatric patients; cryptorchidism with evidence of hypogonadism; and for an anabolic effect in protein depletion and chronic debility, depletion of protein osseous tissue during corticoid therapy, spinal paraplegia, and delayed fracture union.

4. Testosterone enanthate lacks substantial evidence of effectiveness for involutional melancholia, dysfunctional uterine bleeding, prevention of postpartum breast engorgement and inhibition of lactation, menopausal syndrome, frigidity, and mammary cancer in premenopausal women.

B. *Form of drug.* Testosterone enanthate preparations are solutions suitable for intramuscular administration.

C. *Labeling conditions.* 1. The label bears the statement "Caution: Federal law prohibits dispensing without prescription."

2. The drug is labeled to comply with all requirements of the Act and regulations. Its labeling bears adequate information for safe and effective use of the drug and is in accord with the guidelines for uniform labeling published in the FEDERAL REGISTER of February 6, 1970. The "indications" section of the labeling is as follows:

INDICATIONS

In the male:
1. Eunuchism, eunuchoidism, deficiency after castration.
2. Male climacteric symptoms when these are secondary to androgen deficiency.
3. Oligospermia.

In the female or male:
1. Postmenopausal or senile osteoporosis. Androgens are without value as a primary therapy, but may be of value as adjunctive therapy. Equal or greater consideration should be given to diet, calcium balance, physiotherapy, and good general health-promoting measures.

D. *Marketing status.* Marketing of the drug may continue under the conditions described in items VIII and IX of this announcement except those claims referenced in item VII below may continue to be included in the labeling for the periods stated.

III. *Methyltestosterone for oral or buccal administration*—A. *Effectiveness classification.* The Food and Drug Administration has considered the Academy reports, as well as other available evidence, and concludes that:

1. This drug is effective for eunuchism and eunuchoidism, male climacteric symptoms when these are secondary to androgen deficiency, impotence due to androgenic deficiency, androgen-responsive breast cancer, prevention of postpartum breast manifestations of pain and engorgement, and postpuberal cryptorchidism with evidence of hypogonadism.

2. This drug is probably effective for postmenopausal osteoporosis.

3. This drug is possibly effective for suppression of lactation, prepuberal cryptorchidism with evidence of hypogonadism, convalescent and cachectic states for anabolic effect.

4. Methyltestosterone lacks substantial evidence of effectiveness for the menopausal syndrome, dysmenorrhea and premenstrual tension, and functional uterine bleeding.

B. *Form of drug.* Methyltestosterone preparations are in tablet form suitable for oral or buccal administration.

C. *Labeling conditions.* 1. The label bears the statement "Caution: Federal law prohibits dispensing without prescription."

2. The drug is labeled to comply with all requirements of the Act and regulations. Its labeling bears adequate information for safe and effective use of the drug and is in accord with the guidelines for uniform labeling published in the FEDERAL REGISTER of February 6, 1970. The "Indications" section of the labeling is as follows:

INDICATIONS

In the male:
1. Eunuchoidism and eunuchism.
2. Male climacteric symptoms when these are secondary to androgen deficiency.
3. Impotence due to androgenic deficiency.
4. Postpuberal cryptorchidism with evidence of hypogonadism.

In the female:
1. Prevention of postpartum breast manifestations of pain and engorgement. There is no satisfactory evidence that this drug prevents or suppresses lactation per se.
2. Postmenopausal osteoporosis. Androgens are without value as a primary therapy, but may be of value as adjunctive therapy. Equal or greater consideration should be given to diet, calcium balance, physiotherapy, and good general health-promoting measures.
3. Palliation of androgen-responsive, advancing, inoperable breast cancer, in women who are more than 1, but less than 5 years postmenopausal or who have been proven to have a hormone-dependent tumor, as shown by previous beneficial response to castration.

D. *Marketing status.* Marketing of the drug may continue under the conditions described in items VIII and IX of the announcement except those claims referenced in item VII below may continue to be included in the labeling for the periods stated.

IV. *Testosterone propionate solution for intramuscular injection*—A. *Effectiveness classification.* The Food and Drug Administration has considered the Academy report, as well as other available evidence, and concludes that:

1. This drug is effective for postpuberal cryptorchidism with evidence of hypogonadism, eunuchism, and eunuchoidism, male climacteric symptoms due to testosterone deficiency; palliation of mammary cancer, impotence due to inadequate androgen production, and for prevention of post-partum pain and engorgement.

2. The drug is probably effective for postmenopausal osteoporosis.

3. The drug is possibly effective for prepuberal cryptorchidism with evidence of hypogonadism, suppression of lactation, convalescence and cachectic states for anabolic effect.

4. Testosterone propionate lacks substantial evidence of effectiveness for

menopause, dysmenorrhea, and premenstrual tension, functional uterine bleeding, menorrhagia, metrorrhagia, endometriosis, and chronic cystic mastitis.

B. *Form of drug.* Testosterone propionate preparations are solutions suitable for intramuscular administration.

C. *Labeling conditions.* 1. The label bears the statement "Caution: Federal law prohibits dispensing without prescription."

2. The drug is labeled to comply with all requirements of the Act and regulations. Its labeling bears adequate information for safe and effective use of the drug and is in accord with the guidelines for uniform labeling published in the FEDERAL REGISTER of February 6, 1970. The "indications" section of the labeling is as follows:

INDICATIONS

In the male:

1. Postpuberal cryptorchidism with evidence of hypogonadism.
2. Eunuchism and eunuchoidism. Treatment is not usually begun until puberty.
3. Impotence (due to inadequate androgen production).
4. Male climacteric symptoms, if these are due to testosterone deficiency.

In the female:

1. Prevention of postpartum breast manifestations of pain and engorgement. There is no satisfactory evidence that this preparation prevents or suppresses lactation itself.
2. Postmenopausal osteoporosis. Androgens are without value as a primary therapy, but may be of value as adjunctive therapy. Equal or greater consideration should be given to diet, calcium balance, physiotherapy, and good general health-promoting measures.
3. Palliation of androgen-responsive, advancing, inoperable mammary cancer in women who are more than 1, but less than 5 years postmenopausal or who have been proven to have hormone-dependent tumor, as shown by previous beneficial response to castration.

D. *Marketing status.* Marketing of the drug may continue under the conditions described in items VIII and IX of this announcement except those claims referenced in item VII below may continue to be included in the labeling for the periods stated.

V. *Testosterone phenylacetate suspension for intramuscular repository*—A. *Effectiveness classification.* The Food and Drug Administration has considered the Academy report, as well as other available evidence, and concludes that:

1. This drug is effective for eunuchoidism, male climacteric symptoms when these are secondary to testosterone deficiency, and palliation of mammary cancer.

2. This drug is probably effective for osteoporosis (postmenopausal).

3. This drug is possibly effective for anabolic effect in fracture after surgery and injury in convalescence to oppose catabolic action of cortisone.

4. Testosterone phenylacetate lacks substantial evidence of effectiveness for prepuberal hypogonadism, memorrhagia and metrorrhagia.

B. *Form of drug.* Testosterone phenylacetate preparations are suspensions suitable for intramuscular repository administration.

C. *Labeling conditions.* 1. The label bears the statement "Caution: Federal law prohibits dispensing without prescription."

2. The drug is labeled to comply with all requirements of the Act and regulations. Its labeling bears adequate information for safe and effective use of the drug and is in accord with the guidelines for uniform labeling published in the FEDERAL REGISTER of February 6, 1970. The "Indications" section of the labeling is as follows:

INDICATIONS

In the male:

1. Eunuchoidism and eunuchism.
2. Climacteric symptoms when these are secondary to testosterone deficiency.

In the female:

1. Postmenopausal osteoporosis. Androgens are without value as a primary therapy, but may be of value as adjunctive therapy. Equal or greater consideration should be given to diet, calcium balance, physiotherapy, and other good general health-promoting measures.
2. Palliation of androgen-responsive, advancing, inoperable mammary cancer in women who are more than 1 year, or less than 5 years postmenopausal who have been proven to have a hormone-dependent cancer. With the use of this long-acting preparation, it would be impossible to properly nullify the untoward effects of tumor progression, hypercalcemia, or salt and water retention.

D. *Marketing status.* Marketing of the drug may continue under the conditions described in items VIII and IX of this announcement except those claims referenced in item VII below may continue to be included in the labeling for the periods stated.

VI. *Fluoxymesterone for oral administration*—A. *Effectiveness classification.* The Food and Drug Administration has considered the Academy reports, as well as other available evidence, and concludes that:

1. This drug is effective for panhypopituitarism, eunuchism and eunuchoidism, delayed puberty, male climacteric symptoms when these are secondary to androgen deficiency, palliation of advanced inoperable mammary cancer, prevention of postpartum breast manifestations and impotence due to androgen deficiency.

2. This drug is probably effective for osteoporosis (postmenopausal).

3. This drug is possibly effective for control of lactation; in the treatment of protein depletion states which occur in geriatric patients, in debilitation disorders, in chronic corticoid therapy; resistant fractures; cryptorchidism; creating a positive nitrogen balance, tissue repair and other anabolic effects.

4. Fluoxymesterone lacks substantial evidence of effectiveness for menorrhagia and metrorrhagia, and treatment of fridity.

B. *Form of drug.* Fluoxymesterone preparations are in tablet form suitable for oral administration.

C. *Labeling conditions.* 1. The label bears the statement "Caution: Federal law prohibits dispensing without prescription."

2. The drug is labeled to comply with all requirements of the Act and regulations. Its labeling bears adequate information for safe and effective use of the drug and is in accord with the guidelines for uniform labeling published in the FEDERAL REGISTER of February 6, 1970. The "Indications" section of the labeling is as follows:

INDICATIONS

In the male:

The primary indication in the male is replacement therapy in conditions associated with a deficiency or absence of endogenous testicular hormone. Androgen therapy prevents the development of atrophic changes in the accessory male sex organs following castration; as long as replacement therapy is continued, these organs can be maintained in a relatively normal state.

1. Primary eunuchoidism and eunuchism.
2. Male climacteric symptoms when these are secondary to androgen deficiency.
3. Those symptoms of panhypopituitarism related to hypogonadism. Appropriate adrenal cortical and thyroid hormone replacement therapy are still necessary, however, and are actually of primary importance.
4. Impotence due to androgen deficiency.
5. Delayed puberty, provided it has been definitely established as such, and it is not just a familial trait.

In the female:

1. Prevention of postpartum breast manifestations of pain and engorgement. There is no satisfactory evidence that this drug prevents or suppresses lactation per se.
2. Postmenopausal osteoporosis. Androgens are without value as a primary therapy, but may be of value as adjunctive therapy. Equal or greater consideration should be given to diet, calcium balance, physiotherapy, and good general health-promoting measures.
3. Palliation of androgen-responsive, advanced, inoperable female breast cancer, in women who are more than 1, but less than 5 years postmenopausal or who have been proven to have a hormone-dependent tumor, as shown by previous beneficial response to castration.

D. *Marketing status.* Marketing of the drug may continue under the conditions described in items VII and IX of this announcement except those claims referenced in item VII below may continue to be included in the labeling for the periods stated.

VII. *Indications permitted during the extended period for obtaining substantial evidence.* A. Those indications for which the drugs are described in paragraphs II.A, III.A, IV.A, V.A, and VI.A above as probably effective are included in the labeling conditions and may continue to be used for 12 months following the date of this publication to allow additional time within which holders of previously approved applications or persons marketing the drugs without approval may obtain and submit to the Food and Drug Administration data to provide substantial evidence of effectiveness.

B. Those indications for which the drugs are described in paragraphs II.A, III.A, IV.A, V.A, and VI.A above as possibly effective (not included in the labeling conditions) may continue to be used for 6 months following the date of this publication to allow additional time within which such persons may obtain

and submit to the Food and Drug Administration data to provide substantial evidence of effectiveness. To be acceptable for consideration in support of the effectiveness of a drug, any such data must be previously unsubmitted, well-organized, and include data from adequate and well-controlled clinical investigations (identified for ready review) as described in § 130.12(a)(5) of the regulations published as a final order in the FEDERAL REGISTER of May 8, 1970 (35 F.R. 7250). Carefully conducted and documented clinical studies obtained under controlled or partially controlled situations are not acceptable as a sole basis for the approval of claims of effectiveness, but such studies may be considered on their merits for corroborative support of efficacy and evidence of safety.

VIII. *Previously approved applications.* 1. Each holder of a "deemed approved" new-drug application (i.e., an application which became effective on the basis of safety prior to Oct. 10. 1962) for such drug is requested to seek approval of the claims of effectiveness and bring the application into conformance by submitting supplements containing:

a. Revised labeling as needed to conform to the labeling conditions described here for the drug, and complete current container labeling, unless recently submitted.

b. Adequate data to assure the biologic availability of the drug in the formulation which is marketed. For preparations claiming sustained action, timed release, or other delayed or prolonged effect, these data should show that the drug is available at a rate of release which is safe and effective. If such data are already included in the application, specific reference thereto may be made.

c. Updating information as needed to make the application current in regard to items 6 (components), 7 (composition), and 8 (methods, facilities, and controls), of the new-drug application form 356H to the extent described for abbreviated new-drug applications, § 130.4(f), published in the FEDERAL REGISTER of April 24, 1970 (35 F.R. 6574). (One supplement may contain all the information described in this paragraph.)

2. Such supplements should be submitted within the following periods after the date of publication of this notice in the FEDERAL REGISTER:

a. 60 days for revised labeling—the supplement should be submitted under the provisions of § 130.9 (d) and (e) of the new drug regulations (21 CFR 130.9) which permit certain changes to be put into effect at the earliest possible time.

b. 180 days for biologic availability data.

c. 60 days for updating information.

3. Marketing of the drug may continue until the supplemental applications submitted in accord with the preceding subparagraphs 1 and 2 are acted upon, provided that within 60 days after the date of this publication, the labeling of the preparation shipped within the jurisdiction of the Act is in accord with the labeling conditions described in this announcement. (It may continue to include the indications referenced in section VII for the periods stated.)

IX. *New applications.* 1. Any other person who distributes or intends to distribute such drug which is intended for the conditions of use for which it has been shown to be effective, as described under A above, should submit an abbreviated new drug application meeting the conditions specified in § 130.4(f) (1), (2), and (3), published in the FEDERAL REGISTER of April 24, 1970 (35 F.R. 6574). Such applications should include proposed labeling which is in accord with the labeling conditions described herein and adequate data to assure the biologic availability of the drug in the formulation which is marketed or proposed for marketing. For preparations claiming sustained action, timed release, or other delayed or prolonged effect, these data should show that the drug is available at a rate of release which will be safe and effective.

2. Distribution of any such preparation currently on the market without an approved new drug application may be continued provided that:

a. Within 60 days from the date of publication of this announcement in the FEDERAL REGISTER, the labeling of such preparation shipped within the jurisdiction of the Act is in accord with the labeling conditions described herein. (It may continue to include the indications referenced in item VII for the periods stated.)

b. The manufacturer, packer, or distributor of such drug submits, within 180 days from the date of this publication, a new drug application to the Food and Drug Administration.

c. The applicant submits within a reasonable time, additional information that may be required for the approval of the application as specified in a written communication from the Food and Drug Administration.

d. The application has not been ruled incomplete or unapprovable.

X. *Exemption from periodic reporting.* The periodic reporting requirements of §§ 130.35(e) and 130.13(b)(4) are waived in regard to applications approved for these drugs solely for the conditions of use for which the drugs are regarded as effective as described herein. The reporting requirements of §§ 130.35(d) and 130.13(b) (1), (2), and (3) are not waived by this exemption and are a continuing obligation of the applicant.

XI. *Opportunity for a hearing.* A. The Commissioner of Food and Drugs proposes to issue an order under the provisions of section 505(e) of the Federal Food, Drug, and Cosmetic Act withdrawing approval of all new-drug applications and all amendments and supplements thereto providing for the indications for which substantial evidence of effectiveness is lacking as described in paragraphs I.A, II.A, III.A, IV.A, V.A and VI.A of this announcement. An order withdrawing approval of the applications will not issue if such applications are supplemented, in accord with this notice, to delete such indications. Promulgation of the proposed order would cause any drug for human use containing the same components and offered for the indicatio for which substantial evidence of effectiveness is lacking, to be a new drug which an approved new-drug applic tion is not in effect. Any such drug th on the market would be subject to reg latory proceedings.

B. In accordance with the provisio of section 505 of the Act (21 U.S.C. 35 and the regulations promulgated thei under (21 CFR Part 130), the Comm sioner will give the holders of any su applications, and any interested pers who would be adversely affected by su an order, an opportunity for a heari to show why such indications should n be deleted from labeling. A request f a hearing must be filed within 30 da after the date of publication of this n tice in the FEDERAL REGISTER. A requ for a hearing may not rest upon mc allegations or denials, but must set for specific facts showing that there is genuine and substantial issue of fact th requires a hearing, together with a we organized and full-factual analysis the clinical and other investigation data the objector is prepared to prove a hearing. Any data submitted in r sponse to this notice must be previous unsubmitted and include data from ad quate and well-controlled clinical i vestigations (identified for ready reviev as described in section 130.12(a)(5) the regulations published in the FEDER REGISTER of May 8, 1970 (35 F.R. 7250 Carefully conducted and document clinical studies obtained under uncc trolled or partially controlled situatio are not acceptabe as a sole basis for a proval of claims of effectiveness, but su studies may be considered on their meri for corroborative support of efficacy a evidence of safety. If a hearing is r quested and is justified by the respon to this notice, the issues will be defin a hearing examiner will be named, a he shall issue a written notice of the tir and place at which the hearing w commence.

XII. *Unapproved use or form of dru* 1. If the article is labeled or advertis for use in any condition other than the provided for in this announcement, may be regarded as an unapproved ne drug subject to regulatory proceedin until such recommended use is approv in a new drug application, or is otherwi in accord with this announcement.

2. If the article is proposed for ma keting in another form or for use oth than the use provided for in this a nouncement, appropriate additional i formation as described in § 130.4 § 130.9 of the regulations (21 CFR 130. 130.9) may be required, including resul of animal and clinical tests intended show whether the drug is safe a effective.

A copy of the NAS–NRC report h been furnished to each firm referred above. Any other interested person m obtain a copy by request to the appr priate office named below.

Communications forwarded in r sponse to this announcement should identified with the reference numb

DESI 3156 and be directed to the attention of the following appropriate office and unless otherwise specified be addressed to the Food and Drug Administration, 5600 Fishers Lane, Rockville, Md. 20852:

Requests for Hearing (identify with docket number): Hearing Clerk, Office of General Counsel (GC-1) Room 6-62, Parklawn.

Supplements (identify with NDA number): Office of Marketed Drugs (BD-200), Bureau of Drugs.

Original abbreviated new-drug applications (identify as such): Office of Marketed Drugs (BD-200) Bureau of Drugs.

All other communications regarding this announcement:

Special Assistant for Drug Efficacy Study Implementation (BD-201), Bureau of Drugs.

Requests for NAS–NRC reports: Press Relations Office (CE-200), Food and Drug Administration, 200 C Street SW., Washington, D.C. 20204.

This notice is issued pursuant to provisions of the Federal Food, Drug, and Cosmetic Act (secs. 502, 505, 52 Stat. 1050–53, as amended; 21 U.S.C. 352, 355) and under authority delegated to the Commissioner of Food and Drugs (21 CFR 2.120).

Dated: July 6, 1970.

SAM D. FINE,
*Associate Commissioner for Compliance.*

[F.R. Doc. 70-9969; Filed, July 31, 1970; 8:47 a.m.]

## GEIGY CHEMICAL CORP.

### Notice of Filing of Petition for Food Additives

Pursuant to provisions of the Federal Food, Drug, and Cosmetic Act (sec. 409 (b)(5), 72 Stat. 1786; 21 U.S.C. 348(b)(5)), notice is given that a petition (FAP 0B2566) has been filed by Geigy Industrial Chemicals, Division of Geigy Chemical Corp., Ardsley, N.Y. 10502, proposing that § 121.2566 *Antioxidants and/or stabilizers for polymers* (21 CFR 121.2566) be amended to provide for the safe use of octadecyl 3,5-di-*tert*-butyl-4-hydroxyhydrocinnamate as an antioxidant and/or stabilizer at levels not to exceed 0.25 by weight of polystyrene and rubber-modified polystyrene, complying with § 121.2510, intended for food-contact use.

Dated: July 23, 1970.

R. E. DUGGAN,
*Acting Associate Commissioner for Compliance.*

[F.R. Doc. 70-9966; Filed, July 31, 1970; 8:46 a.m.]

## o-ISOPROPOXYPHENYL METHYLCARBAMATE

### Notice of Extension of Temporary Tolerance

Chemagro Corp., Post Office Box 4913, Kansas City, Mo. 64120, was granted a temporary tolerance for residues of the insecticide o-isopropoxyphenyl methylcarbamate in or on the raw agricultural commodities: straws of barley, oats, and wheat at 1 part per million and grains of barley, oats, and wheat at 0.5 part per million on April 23, 1969 (notice was published in the FEDERAL REGISTER of May 1, 1969; 34 F.R. 7180) which expired April 23, 1970.

The firm has amended its petition by reducing the tolerance levels to 0.2 part per million for the straws and 0.1 part per million for the grains of barley, oats, and wheat and has requested a 1-year extension to permit additional tests in accordance with temporary permits issued by the U.S. Department of Agriculture.

The Commissioner of Food and Drugs has determined that such extension would protect the public health. Therefore, an extension has been granted and will expire July 24, 1971.

This section is taken pursuant to provisions of the Federal Food, Drug, and Cosmetic Act (sec. 408(j), 68 Stat. 512; 21 U.S.C. 346a(j)) and under authority delegated to the Commissioner (21 CFR 2.120).

Dated: July 24, 1970.

SAM D. FINE,
*Acting Associate Commissioner for Compliance.*

[F.R. Doc. 70-9955; Filed, July 31, 1970; 8:46 a.m.]

# DEPARTMENT OF COMMERCE

## Office of the Secretary

[Department Organization Order 10-1; Amdt. 1]

## ASSISTANT SECRETARY FOR SCIENCE AND TECHNOLOGY

### Delegation of Authority

The following amendment to the order was issued by the Secretary of Commerce on July 1, 1970. This material supersedes the material appearing at 30 F.R. 15042 of December 4, 1965; and amends the material appearing at 34 F.R. 12840 of August 7, 1969.

The Office of State Technical Services (OSTS) is hereby abolished, and Department Organization Order 10-1 of July 25, 1969, is hereby amended as follows:

1. SEC. 3. *Scope of authority.* Paragraph .01 is amended to delete the reference to the Office of State Technical Services, and a new paragraph .02i. is added to read:

"i. To exercise the functions, powers, duties, and authorities of the Secretary of Commerce pursuant to the provisions of the State Technical Services Act of 1965 (Public Law 89-182, 15 U.S.C. 1351-1368), as may be required, including reduction of the Department's activities under the Act in the absence of authorized funds."

2. SEC. 6. *Saving provision.* References in any document or order to OSTS or the Director, OSTS, shall be deemed to relate to or refer to the Assistant Secretary for Science and Technology.

Effective date: July 1, 1970.

LARRY A. JOBE,
*Assistant Secretary for Administration.*

[F.R. Doc. 70-9964; Filed, July 31, 1970; 8:46 a.m.]

# DEPARTMENT OF HOUSING AND URBAN DEVELOPMENT

## ACTING FEDERAL INSURANCE ADMINISTRATOR

### Designation

The following persons are hereby designated to serve as Acting Federal Insurance Administrator during the absence of the Federal Insurance Administrator, with all the powers, functions, and duties delegated or assigned to the Administrator: *Provided*, That no official is authorized to act in the Administrator's capacity, unless all of the officials whose position titles precede his in this designation are unable to act by reason of absence or a vacancy:

1. Charles W. Wiecking, Assistant Administrator for Program Development.

2. Richard W. Krimm, Assistant Administrator for Flood Insurance.

This designation amends the designation effective March 26, 1970 (35 F.R. 5570, Apr. 3, 1970).

(Secretary's delegations of authority effective Feb. 27, 1969 (34 F.R. 2680, Feb. 27, 1969)).

*Effective date.* This designation shall be effective as of Monday, July 22, 1970.

GEORGE K. BERNSTEIN,
*Federal Insurance Administrator.*

[F.R. Doc. 70-9970; Filed, July 31, 1970; 8:47 a.m.]

# DEPARTMENT OF TRANSPORTATION

## Coast Guard

[CGFR 70-104]

## BOSTON HARBOR

### Security Zone

By virtue of the authority vested in the Commandant, U.S. Coast Guard, by Executive Order 10173, as amended (33 CFR Part 6), sec. 6(b)(1), 80 Stat. 937, 49 U.S.C. 1655(b)(1), 49 CFR 1.46(b) and the redelegation of authority to Chief, Office of Operations, U.S. Coast Guard, as contained in the FEDERAL REGISTER of May 27, 1970 (35 F.R. 8279), I hereby affirm for publication in the FEDERAL REGISTER the order of W. B. Ellis, Rear Admiral, U.S. Coast Guard, Commander, First Coast Guard District, who has exercised authority as District Commander, such order reading as follows:

| MEMO RECORD | AVOID ERRORS PUT IT IN WRITIN | DATE 8/9/79 |
|---|---|---|
| FROM: Marvin Seife, M.D. | | OFFICE HFD-500 |
| TO: Division of Biopharmaceutics HFD-520 | | DIVISION HFD-530 |
| SUBJECT: | | |

SUMMARY

ATTENTION: Dr. Jerome P. Skelly

ANDA #: 87-092

PRODUCT: Methyltestosterone Tabs 10mg
The Lannett Co.

Please review the bioavailability study on the above drug.

/S/

Marvin Seife, M.D.

APPEARS THIS WAY
ON ORIGINAL

| SIGNATURE | DOCUMENT NUMBER |
|---|---|

FD FORM 2034 (2/72)

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

DATE: November 2, 1982

TO: Division of Drug Manufacturing (HFD-320)

FROM: Division of Generic Drug Monographs HFD- 534

Requester's Name: Lynn A Davidson Phone: 443-1390

SUBJECT: GMP EVALUATION REQUEST

(A)NDA and Supplement Number: 87-092

Drug TRADE NAME: Methyltestosterone

Drug NON-PROPRIETARY NAME:

PRODUCT CODE: TCM (description of dosage form, e.g., compressed tablet, liquid, etc.)

180 DAY DATE: 2/5/83 DRUG CLASSIFICATION:

APPLICANT'S NAME: The Lannett Company

ADDRESS: 9000 State Road, Philadelphia, PA 19136

FACILITIES TO BE EVALUATED: (Name, Address, and Responsibility)

① Applicant (Manufacturer)

②

/ FOR HFD-320 USE ONLY /

ACTION: DATE: CSO:

cc: HFD- ____ (Original returned to NDE Div.)

/ ADDITIONAL COMMENTS CONCERNING THIS REQUEST SHOULD BE DESCRIBED ON AN ATTACHED SHEET /

Attachment

As a further condition of approval, we request that the package insert be revised within 180 days or at the time of next printing, whichever is sooner, in accord with:

a) 21 CFR 201.100 (e) to include the name and place of business of one of the following at the end of the insert: manufacturer, packager, distributor, or dispenser.

b) the enclosed class labeling guidelines for androgens. Draft labeling should be submitted for review and comment before FPL is prepared.

# NOTICE OF APPROVAL
## NEW DRUG APPLICATION OR SUPPLEMENT

NDA NUMBER: 87-092

DATE APPROVAL LETTER ISSUED:

TO: Press Relations Staff (HFI-40)

FROM:
- [X] Bureau of Drugs
- [ ] Bureau of Veterinary Medicine

ATTENTION

Forward original of this form for publication only after approval letter has been issued and the date of approval has been entered above.

TYPE OF APPLICATION
- [ ] ORIGINAL NDA
- [ ] SUPPLEMENT TO NDA
- [X] ABBREVIATED ORIGINAL NDA
- [ ] SUPPLEMENT TO ANDA

CATEGORY
- [X] HUMAN
- [ ] VETERINA

TRADE NAME (or other designated name) AND ESTABLISHED OR NONPROPRIETARY NAME (if any) OF DRUG

~~Methyltestosterone, 10 mg.~~

DOSAGE FORM: Tablet

ORIGINAL

HOW DISPENSED
- [X] Rx
- [ ] OTC

ACTIVE INGREDIENT(S) (as declared on label. List by established or nonproprietary name(s) and include amount(s), if amount is declared on label.)

Methyltestosterone, 10 mg.

NAME OF APPLICANT (Include City and State)

The Lannett Company
9000 State Road
Philadelphia, PA 19136

PRINCIPAL INDICATION OR PHARMACOLOGICAL CATEGORY

Androgen

COMPLETE FOR VETERINARY ONLY

ANIMAL SPECIES FOR WHICH APPROVED

COMPLETE FOR SUPPLEMENT ONLY

CHANGE APPROVED TO PROVIDE FOR

FORM PREPARED BY

NAME: ~~Lynn Davidson~~ /S/ DATE: 11/4/82

FORM APPROVED BY

NAME: ~~Howard C. Zoll, Ph.D.~~ /S/ DATE: 11/4/82

FORM FD 1642 (2/75) PREVIOUS EDITION MAY BE USED UNTIL SUPPLY IS EXHAUSTED.

# CENTER FOR DRUG EVALUATION AND RESEARCH

# APPLICATION NUMBER:

# 87-092

# CORRESPONDENCE

ANDA 87-092

DEC 1 1988

The Lannett Company
Attention: Amrish R. Patel
9000 State Road
Philadelphia, PA 19136

Dear Sir:

This letter concerns reporting requirements under Section 505(k) of the Federal Food, Drug, and Cosmetic Act for drug products that have been approved in accordance with the provisions of Section 505(j) of the Act.

The New Drug Regulations (Section 314.81(b)(2) set forth requirements for periodic reports which are to be submitted for each product covered by an approved abbreviated new drug application (ANDA), whether or not the drug is marketed. Our records indicate that no reports have been received for Methyltestosterone Tablets, 10 mg.

Failure to submit required reports is a ground for withdrawal of approval of the new drug application under Section 505(e) of the Act. A copy of the required transmittal Form HD-2252 (Transmittal of Periodic Reports for Drugs for Human Use) is enclosed for your convenience.

If you have ceased to market this drug product and you anticipate no further marketing of it in the future, you may, if you wish, request that the Food and Drug Administration withdraw approval of the abbreviated new drug application. If you elect to request withdrawal of approval, you must also indicate that you voluntarily waive your opportunity for a hearing. We would then proceed to publish in the Federal Register a notice withdrawing approval of the application, stating that marketing of the drug has been discontinued and the applicant has requested withdrawal of approval of the application and waived opportunity for a hearing. The grounds for withdrawal of the approval will be that the applicant has requested withdrawal of approval because the product is no longer marketed.

If you choose neither to submit the required reports nor to make such a request with waiver within 30 days of receipt of this letter, we will proceed to publish a notice of opportunity for hearing on a proposal to withdraw approval of the abbreviated new drug application on the grounds of failure to report.

APPEARS THIS WAY
ON ORIGINAL

Please submit all communications regarding this ANDA with the following specific address information:

Center for Drugs and Biologics
Division of Generic Drugs (HFN-230)
Room #17B-25
5600 Fishers Lane
Rockville, Maryland 20857

Sincerely yours,

/S/

12/1/86

Marvin Seife, M.D.
Director
Division of Generic Drugs
Office of Drug Standards
Center for Drugs and Biologics

Enclosure: Form FD 2252

cc: HFN-230
MSeife/DRosen/jt/11-21-86
0405b
Failure to Submit PR

APPEARS THIS WAY
ON ORIGINAL

THE LANNETT COMPANY, INC.
*Manufacturing Pharmaceutical Chemists*

9000 STATE ROAD
PHILADELPHIA, PA. 19136

DEPARTMENT
OF RESEARCH AND
DEVELOPMENT

Drug

October 8, 1982

DRUG NEW CODES

Food and Drug Administration
Division of Generic Drug Monographs
Office of the Associate Director
for Drug Monographs
Office of Drugs
National Center for Drugs and Biologics
5600 Fishers Lane
Rockville, MD 20857

RE: Methyltestosterone Tablets, 10mg.
N.D.A. #87-092

Gentlemen:

Reference is made to your communication dated October 5, 1982 and our telephone conversation with your Mr. David Rosen of this afternoon relative to the above mentioned N.D.A. for Methyltestosterone Tablets, 10mg.

Please be advised that in accordance with your recommendation contained in the above mentioned letter we did submit on August 5, 1982 our updated dissolution specifications which our fully incorporated into our manufacturing controls and stability program.

We trust the above will now enable this application to be approved in accordance with the contents of your letter dated October 5, 1982.

Many thanks.

RECEIVED
OCT 13 1982
GENERIC DRUGS

Cordially yours,

THE LANNETT COMPANY, INC.

Amrish R. Patel, M.S.,
Director
Dept. of Research & Development

ARP/dh

OCT 5 1982

NDA 87-092

The Lannett Company, Inc.
Attention: Amrish R. Patel
9000 State Road
Philadelphia, PA 19136

Gentlemen:

Reference is made to the dissolution data you submitted for Methyltestosterone Tablets, 10 mg.

The data have been reviewed by our Division of Biopharmaceutics and they have the following comments:

> "The firm has not conducted an acceptable in vivo bioavailability study, but the application is approvable from a Biopharmaceutics point of view because other firms have been granted approval on the basis of dissolution only. These approvals, however, have been coded BP in the Approved Products List. Since methyltestosterone has been recognized as a bio-problem drug, the firm must conduct an acceptable in vivo bioavailability study to gain a therapeutic equivalence (AB) rating.

RECOMMENDATION:

1. Dissolution testing conducted by the Lannett Company, Inc., on its methyltestosterone tablets, 10 mg is acceptable. From a biopharmaceutics point of view the application is approvable. The firm, however, has not conducted an in vivo bioavailability study to demonstrate that the test product is bioequivalent to the reference product.

2. The dissolution testing should be incorporated into the firm's manufacturing controls and stability program. The dissolution testing should be conducted in 900 ml of water at 37°C using USP XX apparatus II at 50 rpm. The test product should meet the following specification:

   Not less than — of the labeled amount of drug in the dosage form is dissolved in 60 minutes."

Sincerely yours,

Marvin Seife, M.D.
Director
Division of Generic Drug Monographs
Office of the Associate Director
for Drug Monographs
Office of Drugs
National Center for Drugs and Biologics

cc:
PHI-DO
HFD-530
HFD-520

HFD-616
MSeife/djw:10-4-82 bio

Methyltestosterone Tablets, 10 mg
ANDA 87-092
Reviewer:F. Pelsor
Wang # 9548M

Lannett Company, Inc.
Philadelphia, PA
Submission Date:
August 5, 1982

OCT 4 1982

## REVIEW OF DISSOLUTION DATA

The purpose of this study was to compare dissolution profiles of methyltestosterone tablets, 10 mg manufactured by Lannett and Schering (Oreton$^{R}$). The dissolution tests were conducted on 12 tablets each in 900 ml of water using U.S.P. Method II at 50 rpm. The table below shows the results.

Percent Labeled Amount
Methyltestosterone Dissolved
in 60 Minutes

| Methyltestosterone Tablets, 10 mg Lot #20676 | | | Oreton Tablets, 10 mg Lot #0JD1 P14807 | | |
|---|---|---|---|---|---|
| | | | | | |

*Range.
**Coefficient of Variation.

COMMENTS:

1. Lannett methyltestosterone tablets, 10 mg, lot #20676 were manufactured in 6/79. The expiration date was set as 7/81. For samples of this lot stored at room temperature for 37 1/2 months, i.e., tested on 7/29/82, dissolution (60 min.) averaged [redacted] for 6 tablets. A new lot (21746) manufactured 2/81 was also tested. The average dissolution of 12 tablets was [redacted].

2. The firm has not conducted an acceptable in vivo bioavalability study, but the application is approvable from a Biopharmaceutics point of view because other firms have been granted approval on the basis of dissolution only. These approvals, however, have been coded BP in the Approved Products List. Since methylestosterone has been recognized as a bio-problem drug, the firm must conduct an acceptable in vivo bioavailability study to gain a therapeutic equivalence (AB) rating.

Recommendation:

1. Dissolution testing conducted by the Lannett Company, Inc. on its methyltestosterone tablets, 10 mg is acceptable. From a biopharmaceutics point of view the application is approvable. The firm, however, has not conducted an in vivo bioavailability study to demonstrate that the test product is bioequivalent to the reference product (see Comment #2).

2. The dissolution testing should be incorporated into the firm's manufacturing controls and stability program. The dissolution testing should be conducted in 900 ml of water at 37°C using USP XX apparatus II at 50 rpm. The test product should meet the following specification:

   Not less than — of the labeled amount of drug in the dosage form is dissolved in 60 minutes.

The firm should be informed of the recommendations above as well as Comment #2.

/S/ 9/22/82

Francis R. Pelsor, Pharm. D.
Biopharmaceutics Review Branch

cc: ANDA 87-092 orig., HFD-530(4), HFD-522 (Pelsor), HFD-503 (Hare), Chron File, Drug File, Review File.

FPelsor/dea/9/1/82:9548M

/S/

APPEARS THIS WAY
ON ORIGINAL

Dup in Bio

THE LANNETT COMPANY, INC.

*Manufacturing Pharmaceutical Chemists*

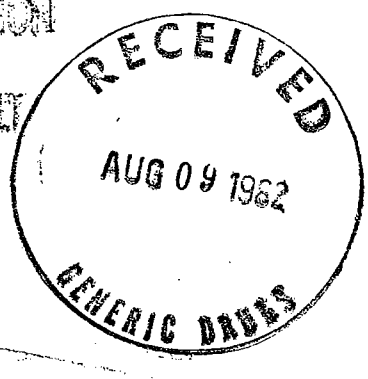
9000 STATE ROAD
PHILADELPHIA, PA. 19136

DEPARTMENT
OF RESEARCH AND
DEVELOPMENT

August 5, 1982

RESUBMISSION

NDA ORIG AMENDMENT




Food and Drug Administration
Bureau of Drugs
Division of Generic Drug Monographs
(HFD-530)
5600 Fishers Lane
Rockville, MD 20857

RE: Methyltestosterone Tablets, 10mg.
N.D.A. #87-092

Gentlemen:

This is in response to your letter of comment of November 17,1980 concerning the above captioned unapproved N.D.A.

We are submitting updated dissolution specifications as requested by Bio-Pharmaceuticals division (per Charles M. Ise, PhD) and dissolution data generated by new specifications.

Also we are submitting comparative dissolution data of Methyltestosterone Tablets, 10mg. versus Oreton Tablets, 10mg. of Shering Corporation. We have analyzed according to our old specifications in which we have used 500ml water as medium instead of 900ml of $H_2O$ water suggested by Bio-Pharmaceuticals. By reviewing our data in 900ml of $H_2O$ of same lot number of Methyltestosterone Tablets you will see that the tablet dissolves more in 900ml water than in 500ml water.

We are committing ourselves to perform all of the proper procedures listed as requested per your letter of October 24, 1979.

We are submitting accelerated stability data along with stability protocol and ongoing stability data. Copies of certificate of analysis are enclosed for all ingredients used in product and finished product certificate of analysis along with product formula copy for your information.

We believe that we have submitted all the above information you requested for approval of our product.

Sincerely,

THE LANNETT COMPANY, INC.

Amrish R. Patel,M.S.,
Director
Dept. of Research & Development

ARP/dh

Enclosures

APPEARS THIS WAY
ON ORIGINAL

APR 7 1982

NDA 87-092

Certified Mail
Return Receipt Requested

The Lannett Company
Attention: Mr. A.R. Patel
9000 State Road
Philadelphia, PA 19136

Gentlemen:

Reference is made to your abbreviated new drug application submitted pursuant to Section 505(b) of the Federal Food, Drug and Cosmetic Act for Methyltestosterone Tablets, 10 mg.

A review of our files indicates that there has been no activity on this application since our letters of November 17, 1980 and November 25, 1980 (Bio) which detailed inadequacies in the application.

If you have no further interest in pursuing this application, we suggest that you request that it be withdrawn in accord with section 314.7 of the regulations (21 CFR 314.7). Such withdrawal may be made without prejudice to future filing.

If we have not received a reply within 60 days of the date of this letter, the application will be considered withdrawn; no further review or evaluation will be undertaken and the application will be sent to the Federal Records Center for storage.

Please let us have your response promptly.

Sincerely yours,

/S/

David L. Rosen
Consumer Safety Officer
Division of Generic Drug Monographs
Office of Drug Monographs
Bureau of Drugs

PHI/DO/HFD 530/Rosen
DRosen/mlb/ft/4-6-82

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA (See attachment)

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

87-092



The Lannett Company, Inc.
Attention: Amrish R. Patel
9000 State Road
Philadelphia, PA 19136

Gentlemen:

Reference is made to your abbreviated new drug applications (outlined in the attachment) submitted pursuant to Section 505(b) of the Federal Food, Drug, and Cosmetic Act.

We have reviewed these abbreviated new drug applications, and other material submitted to them, and request that you appropriately update these applications in accord with currently official compendia with respect to:

1. Specifications and tests for components and the final dosage form.

2. Labeling.

Please let us have your response promptly.

Sincerely yours,

Marvin Seife, M.D.
Director
Division of Generic Drug Monographs
Office of Drug Monographs
Bureau of Drugs

Attachment

V 25

NDA 87-092

The Lannett Company, Inc.
Attention: Mr. A.R. Patel
9000 State Road
Philadelphia, PA 19136

Gentlemen:

Reference is made to the bioavailability studies you submitted for Methyltestosterone Tablets, 10 mg.

The studies have been reviewed by our Division of Biopharmaceutics and they have the following comments:

"1. The firm should perform the bioequivalency study which employs a specific assay for the methyltestosterone.

2. The firm should determine whether enough serum samples are available to repeat the assay for specifically methyltestosterone.

3. If the above is not possible, the firm should repeat the study employing an assay method specific for methyltestosterone.

RECOMMENDATION:

This study is not acceptable as an indication of the bioequivalence of their methyltestosterone tablet product. A study should be performed which employs a specific assay."

Sincerely yours,

[signature] 11/25/80

Marvin Seife, M.D.
Director
Division of Generic Drug Monographs
Office of Drug Monographs
Bureau of Drugs

PHI-DO DUP HFD-614
PHI-DO
HFD-530/HFD-520
MS/cjl/11-24-80 bio

NDA 87-092

The Lannett Company, Inc.
Attention: Mr. Amrish R. Patel
9000 State Road
Philadelphia, PA 19136

Gentlemen:

Reference is made to your abbreviated new drug application submitted pursuant to Section 505(b) of the Federal Food, Drug, and Cosmetic Act for Methyltestosterone Tablets, 10 mg.

Reference is also made to your communications dated June 10 and June 20, 1980.

We have completed the review of this abbreviated new drug application. However, before we are able to reach a final conclusion, the following additional information is necessary:

1. Submit comparative dissolution profiles for the dosage form VS the appropriate reference standards as requested per our letter of October 24, 1979.

2. For the components and dosage form: Submit a commitment to perform all of the procedures listed as requested per our letter of October 24, 1979.

3. Two year expiration dating: It is recommended that data be obtained for production lots at challenge conditions for at least three months to justify the proposed expiration dating prior to approval.

4. The submitted final bioavailability report is under review by our Division of Biopharmaceutics. We will correspond with you further when the results of this review become available.

Please let us have your response promptly.

Sincerely yours,

/s/ 11/17/80

Marvin Seife, M.D.
Director
Division of Generic Drug Monographs
Office of Drug Monographs
Bureau of Drugs

cc:
PHI_DO

HFD-614
HFD-616
JLMeyer/CChang
R/D init JLMeyer/MSeife/11/10/80
pb/11/14/80 rev w/f

/s/ 11-14-80
/s/ 11-14-80

THE LANNETT COMPANY, INC.

*Manufacturing Pharmaceutical Chemists*

9000 STATE ROAD
PHILADELPHIA, PA. 19136

DEPARTMENT
OF RESEARCH AND
DEVELOPMENT

June 20, 1980

Food and Drug Administration
Bureau of Drugs
Division of Generic Drug Monographs (HGD-530)
5600 Fishers Lane
Rockville, MD 20857

Re: NDA# 87-092
Methyltestosterone Tablets, 10mg.

Gentlemen:

This is in response to your letter of comment of October 14, 1979 and December 3, 1979, concerning the above captioned unapproved NDA.

Enclosed please find the following:

1. Final bioavailability report in triplicate.
2. Dissolution methodology and specification.
3. Certificate of analysis of active ingredient by manufacturer and Lannett.
4. Stability protocol.
5. On going stability results including accelerated stability study data.

We will commit ourselves to moniter stability and submit the results to you as they become available, and promptly withdraw from the market any lot which may fall out of specification.

We believe that we have submitted all the information requested.

We will await you comment. Many thanks.

Sincerely yours,

THE LANNETT COMPANY, INC.

Amrish R. Patel, M.S.
Director
Dept. of Research and
Development

ARP/nma

AUG 9 1979

NDA 87-092

The Lannett Company, Inc.
Attention: Samuel Gratz, B. Sc.
9000 State Road
Philadelphia, PA 19136

Gentlemen:

We acknowledge the receipt of your abbreviated new drug application submitted pursuant to Section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

NAME OF DRUG: Methyltestosterone Tablets, 10 mg.

DATE OF APPLICATION: July 26, 1979

DATE OF RECEIPT: Autust 1, 1979

We will correspond with you further after we have had the opportunity to review the application.

Please identify any communications concerning this application with the NDA number shown above.

Sincerely yours,

/S/

Marvin Seife, M.D.
Director
Division of Generic Drug Monographs
Office of Drug Monographs
Bureau of Drugs

pe 8/9/79

PHI-DO Dup HFD-614
JLMeyer/mlb/8-8-79
ack

/S/ 8/9/79

DEC 3 1979

NDA 87-092

The Lannett Company
Attention: Mr. Samuel Gratz
9000 State Road
Philadelphia, PA 19136

Gentlemen:

Reference is made to the protocol you submitted for bioavailability studies for Methyltestosterone Tablets, 10 mg.

The protocol has been reviewed by our Division of Biopharmaceutics and they have the following comments:

"The bioequivalency protocol submitted by the firm for methyltestosterone is acceptable. The dissolution testing data submitted by the firm has been recorded and will be reviewed following receipt of the final bioequivalency reported. This lot should be used in the bioequivalency study.

In addition a sample ( ——— tablets) of this lot should be sent to:

Ms. Colleen Gresham
FDA, Bureau of Drugs
Division of Biopharmaceutics (HFD-522)
5600 Fishers Lane
Rockville, MD 20857"

/S/ 12/3/79

Marvin Seife, M.D.
Director
Division of Generic Drug Monographs
Office of Drug Monographs
Bureau of Drugs

cc:
PHI-DO DUP HFD-614
HFD-520 HFD-530
MSeife/wh/11-30-79
bio

NDA 87-092

The Lannett Company, Inc.
Attention: Samuel Gratz, B.Sc.
9000 State Road
Philadelphia, PA 19136

Gentlemen:

Reference is made to your abbreviated new drug application dated July 26, 1979, submitted pursuant to Section 505(b) of the Federal Food, Drug, and Cosmetic Act for Methyltestosterone Tablets, 10 mg.

We have completed the review of this abbreviated new drug application. However, before we are able to reach a final conclusion the following additional information is necessary:

1. Submit the proposed dissolution release specifications and comparative dissolution profiles for the proposed dosage form vs. the appropriate reference standard.

2. Submit manufacturer's certificate of analysis for the active ingredient.

3. For the components and dosage form: A commitment to perform all of the procedures listed.

4. Stability studies:
   a) Add dissolution testing to the stability protocol.

   b) Two year expiration dating: We are unable to reach any conclusion based on the limited data submitted. It is recommended that data be obtained for production lots at challenge conditions to justify the proposed expiration dating prior to approval.

   c) A signed statement that you will perform stability studies on production lots, to submit the results as they become available, and to promptly withdraw from the market any lots which may fall out of specifications.

   d) Sampling procedures.

e) The report format: The report format should include information on the drug product under test that specifies:

name and potency
formulation
lot/batch #
manufacturing procedure: e.g, research, pilot, production batch
container/closure system(s)
dates: manufactured; released by quality control; placed on stability (zero point stability data).
continuous tabulation of data at test stations and storage conditions of the protocol.

5. The submitted biologic availability protocol is under review by our Division of Biopharmaceutics. We will correspond with you further when the results of this review become available.

Please let us have your response promptly.

Sincerely yours,

/S/ 10/24/79

Marvin Seife, M.D.
Director
Division of Generic Drug Monographs
Office of Drug Monographs
Bureau of Drugs

/S/ 10/24/79

xx:
PHI=DO DUP HFd-614
VVKarusaitis/JMeyer/CChang
r/d/ init. JMeyer/MSeife 10-17-79
Ft/wlh/10-22-79
rev w/f

/S/ 10/23/79

THE LANNETT COMPANY, INC.
MANUFACTURING PHARMACEUTICAL CHEMISTS
9000 STATE ROAD ✱ PHILADELPHIA, PENNA. 19136

87-092

July 26, 1979

OFFICE OF THE
PRESIDENT

ABBREVIATED
NEW DRUG APPLICATION

Bureau of Drugs
Division of Generic Drug Monographs (HFD-530)
5600 Fishers Lane
Rockville, MD 20857

Original Abbreviated NDA-Methyltestosterone Tablets 10mg.

Gentlemen:

In accordance with your announcement in the Federal Register Vol. 42, No. 190-Friday September 30, 1977, we hereby submit an abbreviated NDA for the drug Methyltestosterone Tablets 10mg.

We have submitted, with this application, a protocol for a biological availability study for this drug. This study will not be started untill we receive your comments on this protocol.

Should additional information be required such information will be submitted in a reasonable period of time.

Sincerely yours,

THE LANNETT COMPANY, INC.

Samuel Gratz, B. Sc.
President

SG/maf

RECEIVED
AUG 01 1979
GENERIC DRUGS