CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

80-911

Generic Name: Testosterone Pellets, 75mg

Sponsor: Bartor Pharmacal Company, Inc.

Approval Date: July 13, 1972

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

80-911

CONTENTS

Reviews / Information Included in this ANDA Review.

Approval Letter(s)	X
Tentative Approval Letter(s)	
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CSO Labeling Review(s)	X
Medical Officer Review(s)	
Chemistry Review(s)	X
Microbiology Review(s)	
Bioequivalence Review(s)	
Administrative Document(s)	X
Correspondence	X

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

80-911

APPROVAL LETTER

NDA 80-911
AF 13-758

JUL 13 1972

Bartor Pharmacal Company, Inc.
Attention: Mr. Frank M. Bardani
70 High Street
Rye, New York 10580

Gentlemen:

Reference is made to your abbreviated new drug application dated December 23, 1971, submitted pursuant to Section 505(b) of the Federal Food, Drug, and Cosmetic Act for Testosterone Pellets, 75 mg.

Reference is also made to your communication dated June 12, 1972, enclosing printed labeling.

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.

The periodic reporting requirements of Section 130.13(b)(4) of the new drug regulations are waived in regard to this application as published in the Federal Register of August 1, 1970.

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 130.9 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.

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

Sincerely yours,

Paul A. Bryan, M.D. 7/13/72

Paul A. Bryan, M.D.
Director
Drug Efficacy Study Implementation
Project Office
Bureau of Drugs

Enclosures:
Conditions of Approval of a New Drug Application
Records and Reports Requirement

cc:
NYK-DO
Dup
BD-69
BD-67
BD-106
BD-242
BD-100
BD-300
JBacsanyi/JLMeyer/RJWolters
R/D init. by MAClark/JLMeyer/7-7-72
Final typing/rt 7-7-72
Approved

RJ Wolters 7-11-72
J. Bacsanyi 7-10-972
JLMeyer 7/11/72
M Seife 7/13/72

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

80-911

FINAL PRINTED LABELING

APPROVED JUL 13 1972 PRODUCT INFORMATION

TESTOSTERONE PELLETS

DESCRIPTION: Testosterone pellets for subcutaneous implantation: the pellets are cylindrical, 3.2 mm. (1/8 inch) in diameter, and approximately 8 to 9 mm. in length. Each pellet weighs approximately 75 mg., with 75 mg. label claim of testosterone; each pellet is packaged in an individual vial, and is sterile and ready for implantation. Three vials are packaged in one box.

ACTIONS: Testosterone pellets consist of crystalline testosterone. Implanted subcutaneously, the pellets slowly release the hormone for a long-acting androgenic effect.

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

CONTRAINDICATIONS: Contraindicated in persons with known or suspected carcinoma of the prostate and in carcinoma of the male breast.

PRECAUTIONS: Pellet implantation is much less flexible in regard to adjustment of dosage than oral administration of androgens or intramuscular injection of oil solution or aqueous suspensions. Great care is therefore required in estimating the amount to be used.

Prolonged or excessive dosage of androgens may cause retention of sodium and water. Therefore, use cautiously in persons with compromised cardiac reserve or renal disease.

In treating elderly males, avoid stimulation to the point of increasing the nervous, mental, and physical activities beyond the patient's cardiovascular capacity.

If priapism or other signs of excessive sexual stimulation develop, withdraw therapy temporarily.

In the male, prolonged administration or excessive dosage may cause inhibition of testicular function, with resultant oligospermia and decreased ejaculatory volume.

Hypersensitivity and gynecomastia may rarely occur.

PBI may be decreased in patients taking androgens.

In the face of any of the above complications, obviously the effect of such medication should be stopped. The pellets would thus have to be removed in any of these instances. In addition, at times the pellets may slough out. This accident is usually traceable to superficial implantation or to neglect in regard to aseptic precautions.

ADVERSE REACTIONS:
Sodium and water retention
Oligospermia and decreased ejaculatory volume
Priapism
Hypersensitivity and gynecomastia

DOSAGE AND ADMINISTRATION: The number of testosterone pellets to be implanted depends upon the minimal daily requirement of testosterone propionate determined by a gradual reduction of the amount administered parenterally. The usual ratio is as follows: implant two 75 mg. pellets for each 25 mg. testosterone propionate required weekly. Thus when a patient requires injections of 75 mg. per week, it is usually necessary to implant 450 mg. (6 pellets). With injections of 50 mg. per week, implantation of 300 mg. (4 pellets) may suffice for approximately three months. With lower requirements by injection, correspondingly lower amounts may be implanted. It has been found that approximately one-third of the material is absorbed in the first month, one-fourth in the second month, and one-sixth in the third month. Adequate effect of the pellets ordinarily continues for three to four months, sometimes as long as six months.

HOW SUPPLIED: Pellets of 75 mg. each, one pellet per vial, in box of 3 sterile vials.

BARTOR PHARMACAL CO., INC.
70 High Street, Rye, N.Y. 10580


APPROVED
JUL 13 1972
3 Pellets
Sterile
TESTOSTERONE PELLETS N.F.
For subcutaneous implantation
75 mg
Each pellet contains: 75 mg. testosterone
Read accompanying directions carefully.
Caution: Federal law prohibits dispensing without prescription.
Bartor Pharmacal Co., Inc.
70 High St., Rye, N.Y. 10580
75 mg
brand of testosterone pellets

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

80-911

CSO LABELING REVIEW(S)

REVIEW OF ANDA FPL

DATE COMPLETED: 7-3-72

ANDA #: 80-911

F.R. DATE: 8-1-70

CO. NAME: Bartor Pharmacal Co., Inc.
70 High Street
Rye, New York 10580

NAME OF DRUG: Testosterone Pellets, N.F. 75 mg.
(3 vials/box)

DATE OF SUBMISSION: 6-12-72

TYPE OF SUBMISSION: FPL

CLINICAL EVALUATION:

1. Review of Studies: Bioavailability studies are now deferred for this drug.

2. Review of Labeling:

CONTAINER LABELS: Satisfactory

PACKAGE INSERT: Satisfactory

CONCLUSION: The FPL for both container and package insert is satisfactory from a medical standpoint.

RECOMMENDATIONS: The firm is to be so notified.

J. Bacsanyi, M.D.
J. Bacsanyi, M.D.

cc:
Dup
BD-69
J. Bacsanyi, M.D./kim/7-5-72

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

80-911

CHEMISTRY REVIEW(S)

REVIEW OF ANDA

DATE COMPLETED: March 9, 1972 ANDA #: 80-911

F.R. DATE: August 1, 1970

CO. NAME: Bartor Pharmacal Co., Inc.
70 High Street
Rye, New York 10580

NAME OF DRUG: Trade & Generic: Testosterone Pellets N.F., 75 mg. (3 vials/box)

DATE OF SUBMISSION: February 18, 1972

TYPE OF SUBMISSION: ANDA

CLINICAL EVALUATION:

1. -Review of Studies:

   a) Bioavailability studies are now deferred for this drug.
   b) Manufacturing data, ingredients of the preparation etc. are to be reviewed by the chemist.

2. Review of Labeling:

   Container label: (final) Satisfactory, except that the zipcode number has not been included. This deficiency can be corrected at the time of the next printing.

   Package insert: (draft) Satisfactory, however, it requires the addition of a "HOW SUPPLIED" Section.

CONCLUSION: 1. Package insert (draft) requires addition of a "HOW SUPPLIED" section.
2. The zip code number is to be added to the firm's address on the immediate package container at the time of the next printing.
3. Manufacturing data etc. are to be reviewed by the chemist.

RECOMMENDATIONS: Request FPL with the recommended corrections as listed above.

J. Bacsanyi, M.D.
J. Bacsanyi, M.D.

cc:
Dup
BD-69
JBacsanyi/wlb/3-14-72

REVIEW OF RESUBMISSION

DATE COMPLETED: May 17, 1972

ANDA #: 80-911

F.R. DATE: August 1, 1970

CO. NAME: Bartor Pharmacal Co., Inc.
70 High Street
Rye, New York 10580

NAME OF DRUG: Trade & Generic: Testosterone Pellets, N.F., 75 mg.
(3 vials/box)

DATE OF SUBMISSION: April 29, 1972

TYPE OF SUBMISSION: Resubmission

CLINICAL EVALUATION:

1. Review of Studies:

   a) Bioavailability studies are now deferred for this drug.

   b) Manufacturing data will be reviewed by the chemist.

2. Review of Labeling:

   Container label: Not submitted. The applicant firm promises inclusion of the zip code number on the label.

   Package insert: Not submitted. The proposed "HOW SUPPLIED" section is satisfactory.

CONCLUSION: 1. Manufacturing data - are to be reviewed by the chemist.
2. Labeling will be satisfactory if the proposed corrections are carried out.

RECOMMENDATIONS: Request FPL.

J. Bacsanyi, M.D.
J. Bacsanyi, M.D.

cc:
Dup
BD-69
JBacsanyi/wlb/5-18-72

CHEMIST'S REVIEW FOR ABBREVIATED NEW DRUG APPLICATION OR SUPPLEMENT

Federal Register Statement Date: 8-1-70

NDA Number: 80-911

Original: 12-23-71

Amendment:

Supplement:

Other:

Name Address of Applicant (City & State)

Bartor Pharmacal Company, Inc.
70 High Street
Rye, New York 10580

Name of Drug

Nonproprietary Name: Testosterone Pellets

Purpose of Supplement

Date(s) of Submission(s)

Pharmacological Category: Androgen preparations

How Dispensed: R_x [X] O.T.C. [ ]

AF Number: 13-758

Related NDA & MF

Dosage Form(s): Pellets

Potency (ies): 75 mg.

Satisfactory [ ] Labeling
Date Due: To be revised. (JBacsanyi)

Satisfactory [ ] Components, Composition, Manufacturing and Controls
Date Due: See below

Satisfactory [ ] Biologic Availability
Date Due: Deferred see memo
Is data on current formulation? YES [ ] NO [ ]

APPEARS THIS WAY ON ORIGINAL

Satisfactory [ ] Probably or Possibly Effective Indications (if in labeling)
Date Data Due:

Establishment Inspection

Inspection requested 3-21-72
Satisfactory 4-16-71
satisfactory 10-28-71

Recalls

If relabeling of drug in commercial channels required? YES [ ] NO [ ]
If so, what level:

Remarks

request: 1. Revised labeling per MO's report.
2. Certification statement from _____
3. Submit procedures for components, _____ and clarify analysis of pellets.
4. Clarify use of NF XII and USP XVIII.

Conclusions: rev w/f

R J Wolters 3-31-72
RJWolters

REVIEWER: SIGNATURE: DATE:

CHEMIST'S REVIEW FOR BREVIATED NEW DRUG APPLICATION OR SUPPLEMENT

Federal Register Statement Date 8-1-70

NDA Number 80-911

Original ____

Amendment 4-29-72

Supplement ____

Other 12-23-71

Date(s) of Submission(s)

me & Address of Applicant (City & State)
Bartor Pharmacal Company, Inc.
70 High Street
Rye, New York 10580

me of Drug

Nonproprietary Name
Testosterone Pellets

rpose of Supplement
Revised labeling and manufacturing information.

armacological Category
Androgen Preparations

How Dispensed
R_x [X] O.T.C. [ ]

AF Number 13-758

Related NDA & MF
DMF —

sage Form(s)
Pellets

Potency (ies)
75 mg.

tisfactory [ ] Labeling
Date Due ____ Satisfactory J.Bacsanyi

tisfactory [ ] Components, Composition, Manufacturing and Controls
Date Due Satisfactory See below

tisfactory [ ] Biologic Availability
Date Due Deferred see memo
Is data on current formulation? YES [ ] NO [ ]

tisfactory [ ] Probably or Possibly Effective Indications (if in labeling)
Date Data Due ____

tablishment Inspection
Bartor Satisfactory 4-24-72
Satisfactory 4-16-71
Satisfactory 10-28-71

Recalls

relabeling of drug in commercial channels required? YES [ ] NO [ ]
so, what level:

APPEARS THIS WAY ON ORIGINAL

marks
Request FPL
while not official is listed in Remington and Merck Index and has several uses in pharmaceutical preparation taken internally.
labels the ampule in addition to , and testing.
DMF satisfactory details testing and procedures in the

nclusions
approvable

RJ Wolters 5-31-72
RJWolters

REVIEWER: SIGNATURE: DATE:

CHEMIST'S REVIEW FOR ABBREVIATED NEW DRUG APPLICATION OR SUPPLEMENT

Federal Register Statement Date: 8-1-70

NDA Number: 80-911

Original: ____

Amendment: ____

Supplement: ____

Other: ____

Name & Address of Applicant (City & State)
Bartor Pharmacal Company, Inc.
70 High Street
Pye, New York 10580

Name of Drug:

Nonproprietary Name: Testosterone

Purpose of Supplement: FPL

Date(s) of Submission(s):

Pharmacological Category: Androgen

How Dispensed: R_x [x] O.T.C. [ ]

AF Number: 13-758

Related NDA & MF:

Dosage Form(s): Pellets

Potency (ies): 75 mg.

Satisfactory [ ] Labeling
Date Due: Satisfactory (JBacsanyi)

Satisfactory [x] Components, Composition, Manufacturing and Controls
Date Due: Active ingredient and drug dosage form comly with USP specs.

Satisfactory [ ] Biologic Availability
Date Due: Deferred see memo
Is data on current formulation? YES [ ] NO [ ]

Satisfactory [ ] Probably or Possibly Effective Indications (if in labeling)
Date Data Due: ____

Establishment Inspection: All satisfactory see previous Chem. Rev.

Recalls:

If relabeling of drug in commercial channels required? YES [ ] NO [ ]
If so, what level:

Remarks

APPEARS THIS WAY
ON ORIGINAL

Conclusions: approval

RJ Wolters 7-10-72
RJWolters

REVIEWER: SIGNATURE: DATE:

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

80-911

ADMINISTRATIVE DOCUMENTS

NOTICE OF APPROVAL
NEW DRUG APPLICATION OR SUPPLEMENT

NDA NUMBER: 80-911

DATE APPROVAL LETTER ISSUED: JUL 13 1972

TO: Press Relations Staff *(CE-300)*

FROM:
- [X] Bureau of ~~Medicine~~ 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
- [X] ABBREVIATED ORIGINAL NDA
- [ ] SUPPLEMENT TO NDA

CATEGORY
- [X] HUMAN
- [ ] VETERINARY

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

Testosterone

DOSAGE FORM: Pellets

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.)*

Testosterone 75 mg.

APPEARS THIS WAY ON ORIGINAL

NAME OF APPLICANT *(include City and State)*

Bartor Pharmacal Company, Inc.
Rye, New York 10580

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: R.J. Wolters — DATE:

FORM APPROVED BY

NAME: J.L. Meyer — DATE:

FD FORM 1642 (7/69) PREVIOUS EDITION MAY BE USED UNTIL SUPPLY IS EXHAUSTED.

HA/BUREAU OF DRUGS/OSE/BD-105 ROUTINE UNCLAS

MARCH 21, 1972

X

BRUCE E. BYER 443-4320

FOOD AND DRUG ADMINISTRATION
NEW YORK DISTRICT - NYK-D50

APPLICANT & MFR:
BARTOR PHARMACEUTICAL
COMPANY INC.
RYE, NEW YORK
AF# 13-758

RE: ABBREVIATED NEW DRUG APPLICATION
80-911 TESTOSTERONE PELLETS

THE DESI PROJECT OFFICE IS PRESENTLY CONSIDERING APPROVAL OF THE SUBJECT ABBREVIATED NEW DRUG APPLICATION. THIS PRODUCT IS MANUFACTURED AND PACKAGED BY BARTOR PHARMACEUTICAL CO., 70 HIGH ST., RYE, NEW YORK.

AS YOU ARE AWARE IN THE ANDA THE FIRM CERTIFIES THAT MANUFACTURING, PACKAGING AND TESTING IS DONE IN CONFORMITY WITH GMP (SEE 130.4 (F) OF THE NEW DRUG REGULATIONS REFERENCE ANDAS, PUBLISHED IN THE FEDERAL REGISTER ON APRIL 24, 1970).

SINCE OUR LAST RECORD OF A COMPLETE CONTROL DRUG INSPECTION OF BARTOR PHARMACEUTICAL WAS IN JULY, 1969, WE ARE REQUESTING AN EVALUATION OF THE FIRM'S PRESENT COMPLIANCE STATUS UNDER GMP AND ITS ABILITY TO COMPLY WITH ANDA AND COMPENDIUM COMMITMENTS. IF AN INSPECTION IS INDICATED, PLEASE INSPECT AND REPORT RESULTS.

APPEARS THIS WAY
ON ORIGINAL

IN YOUR REPLY PLEASE INDICATE WHETHER OR NOT THE ANDA CAN BE APPROVED BASED UPON THE FIRM'S COMPLIANCE WITH GMP. A RECOMMENDATION TO WITHHOLD APPROVAL SHOULD BE BASED UPON CRITICAL OR SIGNIFICANT DEVIATIONS FROM GMP WHICH SHOULD BE LISTED.

E WOULD APPRECIATE A REPLY BY TWX FOLLOWED BY EIR OR MEMO.

PROBLEM CATEGORY: 9

ESTIMATED TIME: 24 HOURS OR AS NEEDED

REPLY REQUESTED BY: APRIL 24, 1972

CHARGE TO: BD-100

CONTACT OFFICER: JACK MEYER, PHONE 301-443-3630

ENDORSE REPORT TO: BD-105

CLEARANCE OFFICER: Bruce E. Byer
BRUCE E. BYER
OFFICE OF SCIENTIFIC EVALUATION
PHONE 301-443-4520

CC:
NYK-D50
NYK-F1
BD-100
BD-105
BD-22
BD-69
CA-224
PO-10
D-69 C/O JACK MEYER
BD-105 C/O BEBYER/MW/3/21/72

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

Food and Drug Administration

[DESI 3156]

[Docket No. FDC-D-183; NDA No. 3-156 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 10-511).

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 11-559).

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 3234).

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 3158).

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, eunochoidism, 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 this 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, menorrhagia 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 frigidity.

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 item 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(f) 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 [illegible] for which substantial evidence of effectiveness is lacking, to be a new drug for which an approved new-drug application is not in effect. Any such drug then on the market would be subject to regulatory proceedings.

B. In accordance with the provisions of section 505 of the Act (21 U.S.C. 355) and the regulations promulgated thereunder (21 CFR Part 130), the Commissioner will give the holders of any such applications, and any interested person who would be adversely affected by such an order, an opportunity for a hearing to show why such indications should not be deleted from labeling. A request for a hearing must be filed within 30 days after the date of publication of this notice in the FEDERAL REGISTER. 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, together with a well-organized and full-factual analysis of the clinical and other investigational data the objector is prepared to prove in a hearing. Any data submitted in response to this notice must be previously unsubmitted and include data from adequate and well-controlled clinical investigations (identified for ready review) as described in section 130.12(a)(5) of the regulations published in the FEDERAL REGISTER of May 8, 1970 (35 F.R. 7250). Carefully conducted and documented clinical studies obtained under uncontrolled or partially controlled situations are not acceptabe as a sole basis for approval of claims of effectiveness, but such studies may be considered on their merits for corroborative support of efficacy and evidence of safety. If a hearing is requested and is justified by the response to this notice, the issues will be defined, a hearing examiner will be named, and he shall issue a written notice of the time and place at which the hearing will commence.

XII. *Unapproved use or form of drug.* 1. If the article is labeled or advertised for use in any condition other than those provided for in this announcement, it may be regarded as an unapproved new drug subject to regulatory proceedings until such recommended use is approved in a new drug application, or is otherwise in accord with this announcement.

2. If the article is proposed for marketing in another form or for use other than the use provided for in this announcement, appropriate additional information as described in § 130.4 or § 130.9 of the regulations (21 CFR 130.4, 130.9) may be required, including results of animal and clinical tests intended to show whether the drug is safe and effective.

A copy of the NAS–NRC report has been furnished to each firm referred to above. Any other interested person may obtain a copy by request to the appropriate office named below.

Communications forwarded in response to this announcement should be identified with the reference number

DESI 3158 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.]

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

Form Approved
OMB No. 57-R0003

ABBREVIATED
NEW DRUG APPLICATION *(DRUGS FOR HUMAN USE)*
(Title 21, Code of Federal Regulations, § 130.4)

Name of applicant BARTOR PHARMACAL CO.INC.

Address ~~x~~ 70 High St , Rye,New York 10580

Date Dec.23,1971

Name of new drug TESTOSTERONE PELLETS

- ☐ Original application (regulation § 130.4).
- ☐ Amendment to original, unapproved application (regulation § 130.7).
- ☒ Abbreviated application (regulation § 130.4(f)).
- ☐ Amendment to abbreviated, unapproved application (regulation § 130.7).
- ☐ Supplement to an approved application (regulation § 130.9).
- ☐ 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 §1.106(b) (21 CFR 1.106(b)). 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 §130.9 of the new-drug regulations.

Attached hereto, submitted in the form described in §130.4(e) of the new-drug regulations, and constituting 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, an expanded summary and evaluation as outlined in §130.4(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 is to be advertised or represented, in accord with §1.106(b) (21 CFR 1.106(b)). 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 any such advertising for a prescription drug (see §130.13 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 the 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 controls 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 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 suitability of the analytical methods 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 §130.1(g), from the batch(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 initial 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 §130.1(g), 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 the 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 Medicine 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 in 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, or suggested in the proposed labeling.

c. Reports of all clinical tests sponsored by the applicant or received or otherwise 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 clinical 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 Department of HEW. Food and Drug Administration, Bureau of Drugs *(BD-200)* 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 commerical 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 §130.38 of the new-drug regulations, about related drugs; a bibliography will suffice. Include any 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.

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 §130.9 of the new-drug regulations concerning supplemental applications.

BARTOR PHARMACAL CO. INC.
(Applicant)

Per Harold M Bardan
(Responsible official or agent)

Pres.
(Indicate authority)

(Warning: A willfully false statement is a criminal offense. U.S.C. Title 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.

Amendment published in Federal Register: April 24, 1970; 35 F.R. 6574

Insert this new page in your reprint.

130.4 (f)

★ (f) *Abbreviated new-drug applications.* Such applications shall contain:

(1) Satisfactory information of the kinds described in items 1 (table of contents), 4 (label and all other labeling), 5 (R, or OTC statement), and 6 (components) of the new-drug application form FD-356H, and in lieu of full information described under items 7 and 8 (composition and methods, facilities, and controls), brief statements that:

(i) Include the composition of the drug, stating 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.

(ii) Identify the place where the drug will be manufactured, processed, packaged, and labeled and the name of the supplier of the active ingredient(s).

(iii) Identify any person other than the applicant who performs a part of those operations and designate the part.

(iv) Include certifications from the applicant and from any person identified in subdivision (iii) of this subparagraph that the methods used in, and the facilities and controls used for, the manufacture, processing, packing, and holding of the drug are in conformity with current good manufacturing practice in accord with Part 133 of this chapter.

(v) Assure that the drug dosage form and components will comply with the specifications and tests described in an official compendium, if such article is recognized therein, or, if not listed or if the article differs from the compendium drug, that the specifications and tests applied to the drug and its components are adequate to assure their identity, strength, quality, and purity.

(vi) Outline the methods used in, and the facilities, and controls used for, the manufacture, processing, and packing of the drug.

(2) Labeling that is in accord with the labeling conditions described in the finding that an abbreviated new-drug application is sufficient.

(3) If the drug finding so specifies for the formulation intended for marketing, data adequate to assure the biological availability of the drug. For preparations claiming sustained action, timed-release, or other delayed or prolonged effect, such data should show that the drug is available at a rate of release that will be safe and effective.

(4) Any information available to the applicant, including preclinical or clinical data developed by the applicant or by other persons on behalf of the applicant, on adverse effects of the drug that is not reflected in the labeling.

(5) Additional information that may be required for the approval of the application as specified in a written communication from the Food and Drug Administration.

(6) The signature of the applicant or responsible official or agent on a completed form FD-356H. ★

APPEARS THIS WAY
ON ORIGINAL

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

80-911

CORRESPONDENCE

BARTOR PHARMACAL CO., INC.

ABBREVIATED NEW DRUG APPLICATION 80-911

70 HIGH STREET • RYE, NEW YORK
914 WO 7-4219

February 18,1972

Drug Efficacy Study Implementation
Project Office (DESI)
Attention: Dr Paul A. Bryan,Director
Bureau of Drugs BD69
Food & Drug Administration
5600 Fisher's Lane
Rockville,Md 20852

RE: Abbreviated NDA approval for Testosterone pellet implants

Dear Sir:

Since Aug.25,1971,we have finally been steered correctly to you and form356H for an abbreviated NDA on Testosterone pellet implants for human use.

As you know,this preparation is over 30 years old and has been marketed by Schering Corp. as Oretone Pellets(Implants). I had been active with them in this development.

Bartor Pharmacal wishes to market this preparation under the generic name with considerable cost saving.

Most important,is the dire need for these pellets, for Dr Robert Greenblatt's use. He is at the University of Georgia Medical School,Dep't of Endocrinology,Augusta, Georgia. He has been waiting for the past 12 months. Dr Greenblatt is involved in an NIH grant project.

We would therefore appreciate an A.N.D.A. number, as soon as possible,that we may process our pellets.

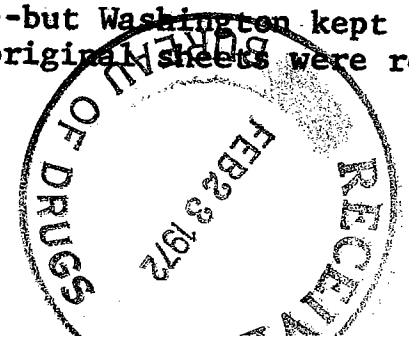
I'm submitting an original and two copies of the ANDA covering form 356H. I would appreciate your expediting the processing of this application.

Yours truly,

Frank Bardani
President

c.c. Dr R.Greenblatt

P.S. When originally submitted incorrectly under an IND in triplicate,two copies were returned---but Washington kept the original. Consequently,a few of the original sheets were replaced with copies.



NDA 80-911
AF 13-758

MAR 2 1972

Barter Pharmacal Co., Inc.
Attention: Mr. Frank Bardani
70 High Street
Rye, New York 10580

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: Testosterone Pellets

DATE of APPLICATION: December 23, 1971

DATE of COVER LETTER: February 18, 1972

DATE of RECEIPT: February 23, 1972

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,

Marvin Seife 3/1/72

Marvin Seife, M.D.
Director
Division of Actions Implementation
Drug Efficacy Study Implementation
Project Office
Bureau of Drugs

cc:
NDK-DO
Dup
BD-69
BD=67
BD-22
BD-310
JLMeyer/wlb/2-29-72
Ack.

JLMeyer 2/29/72

NDA 80-911
AF 13-758

APR 4 1972

Bartor Pharmacal Company, Inc.
Attention: Mr. Frank Bardani
70 High Street
Rye, New York 10580

Gentlemen:

Reference is made to your abbreviated new drug application dated December 23, 1971, submitted pursuant to Section 505(b) of the Federal Food, Drug, and Cosmetic Act for Testosterone Pellets, 75 mg.

We have completed the review of this abbreviated new drug application and have the following comments regarding the proposed labeling:

1. Container label: The zip code should be included in the address. This may be done at the time of the next printing.

2. Package insert: A HOW SUPPLIED section should be added.

Other information required by section 130.4(f) of the regulations:

1. Certification statements from _____, and _____ that the methods used in, and the facilities and controls used for the _____ of the drug are in conformity with current good manufacturing practice in accord with Part 133 (21 CFR) of the regulations.

2. Procedures that assure that the drug dosage form and components will comply with the specifications and tests described in an official compendium if such article is recognized therein, or, if not listed or if the article differs from the compendium drug, that the specifications and tests applied to the drug and its components are adequate to assure their identity, strength, quality and purity.

   In addition, submit the procedures used by _____ and clarify _____' statement that the analysis will be performed on _____

3. It is noted that you refer to N.F. XII and U.S.P. XVII in several places in this abbreviated new drug application. Please clarify.

Please let us have your response promptly.

Sincerely yours,

Margaret F Clark MD for 4/4/72

Marvin Seife, M.D.
Director
Division of Actions Implementation
Drug Efficacy Study Implementation
Project Office
Bureau of Drugs

cc:
NYK-DO
Dup.
BD-67
BD-69
BD-22
BD-242
J Bacsanyi/JIMeyer/RJWolters 3-23-72
R/D init. MClark/JIMeyers 3-27-72
Final Typing/rt 3-29-72
Rev w/f

RJ Wolters 3-31-72 J. Bacsanyi 4-3-972

SJMeyer 4/3/72

Rev. 10/P

RESUBMISSION

NDA ORIG AMENDMENT

E

BARTOR PHARMACAL CO., INC.

70 HIGH STREET • RYE, NEW YORK

WO 7-4219

ORIG

Dr Marvin Seife, Director
Division of Actions Implementation
Drug Efficacy Study Implementation Project Office
Bureau of Drugs

April 29, 1972

RE: Additional information supplemental to Abbreviated NDA 80-911-- your letter 4/4/72

Dear Sir:

We submit the following in response to your inquiry above:

Labeling- 1. Since labels are preprinted for control number inclusion, we will include the Zip Code with the address- 10580.

2. The package insert will have the following added-- "HOW SUPPLIED- Pellets of 75 mg. each, one pellet per vial, in a box of 3 sterile vials."

Other information required by section 130.4(f) of regulations:

1. Certification statements from ——— attesting conformity to GMP in accord with Part 133 (21 CFR) of the regulations are attached.

2. and 3. (are answered in the final part of this letter).

A supplementary letter from ——— explains the ———

The original ——— letter refers to "Estradiol and other similar type products," e.g. Testosterone. This was submitted when both items were requested for clearance-prior to the advice of HEW to submit Testosterone separately. We have enclosed a modified and more pertinent letter from ——— for clarification.

2. To erase any ambiguity of committments in the Abbreviated NDA, Bartor Pharmacal assures that the drug dosage form and components do and will comply with the specifications and tests described in an official compendium, if such article is recognized therein, as to identity, strength, quality and purity.

Bartor, aside from submitted protocols, from reliable U.S. suppliers, will run and will have run the following procedures for all components, as-

Testosterone- NF XIII Pg 687 ALL TESTS
Stearic Acid-USP XVIII Pg 683 ALL TESTS, except Chromatograp
Testosterone Pellet Implants- NF XIII Pg 688 ALL TESTS

Stability data furnished and run by Bartor, by ——— indicates adequacy of quality and purity as well as identity with reference.

——— purchased only from ———, will have the following tests run by Bartor (attached). Bartor Pharmacal assures that ———, not in official compendium as such, meets the requirements of identity, strength, quality & puri

RECEIVED
MAY 3 1972
BUREAU OF DRUGS

BARTOR PHARMACAL CO., INC.

70 HIGH STREET • RYE, NEW YORK

WO 7-4219

CONTINUED Abbrev.NDA 80-911

3. We wish to update our monogram references to the NF XIII and USP XVIII(for the NFXII and USPXVII) wherever mentioned--for whatever specifics have been mentioned in the original submission.
Paragraph number 2 last mentioned in this letter,makes more specific references with pertinent page numbers.

We appreciate your willingness to process this submission as promptly as possible. Thank you for your co-operation and courtesies on behalf of your staff on the ~~x~~telephone.

Yours truly,

Frank M Bardani

Frank Bardani,President

c.c. John Accardi
consulting Chemist

NDA 80-911
AF 13-758

MAY 31 1972

Bartor Pharmacal Company, Inc.
Attention: Mr. Frank Bardani
70 High Street
Rye, New York 10580

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 Testosterone Pellets, 75 mg.

Reference is also made to your communication dated April 29, 1972, enclosing revised labeling and manufacturing information.

We have completed the review of this abbreviated new drug application as submitted with draft labeling. However, before the application may be approved, it will be necessary for you to submit final printed labeling. The labeling should be identical in content to the draft copy.

Please submit twelve copies of the printed labeling.

Sincerely yours,

Paul A. Bryan M.D. 5/31/72

Paul A. Bryan, M.D.
Director
Drug Efficacy Study Implementation
Project Office
Bureau of Drugs

cc:
NYK-DO JLMeyer 5/30/72
Dup
BD-69 BD-67 BD-106 BD-242
JBacsanyi/JLMeyer/RJWolters 5-22-72 RJ Wolters 5-30-72 J. Bacsanyi 5-30-972
R/D init. JLMeyer 5-25-72
Final typing/rt 5-26-72
Approvable

M. Clark MD 5/31/72

E

BARTOR PHARMACAL CO., INC.

ORIGINAL FPL

70 HIGH STREET • RYE, NEW YORK
WO 7-4219

ORIG

June 12, 1972

Drug Efficacy Implementation
Project Office (DESI)
Att: Dr.Paul A. Bryan Director
Food & Drug Administration
5600 Fisher Lane
Rockville, Md. 20852

Ref: Nda-911 Letter of May 31, 1972
80-911

Dear Sir:

Enclosed printed labeling as you requested in your letter of may 31, 1972

Yours Truly
Frank M Bardani
Frank M . Bardani Pres.

RECEIVED__1___COPY
PHOTOSTATS MADE
FOR DUP_____TRIP_____