CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

83-003

Trade Name:	Stilbestrol
Generic Name:	Diethylstilbestrol Tablets, 0.5mg, Enteric Coated
Sponsor:	Tablicaps, Inc.
Approval Date:	May 30, 1973

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

83-003

CONTENTS

Reviews / Information Included in this ANDA Review.

Approval Letter(s)	X
Tentative Approval Letter(s)	
Final Printed Labeling	X
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:

83-003

APPROVAL LETTER

NDA 83-003

AF _____

Tablicaps, Inc.
Attention: Mr. Richard T. Jackson
P.O. Box 5555
Franklinville, New Jersey 08322

MAY 30 1973

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 Diethylstilbestrol Tablets, 0.5 mg., Enteric Coated.

Reference is also made to your communication dated March 19, 1973, enclosing revised labeling and manufacturing information.

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 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,

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

5/30/73

cc:
NWK-DO
Dup
BD-69 BD-66 BD-100
BD-106 BD-242 BD-340
VVKarusaitis/JLMeyer/RJWolters
Enclosures
Records and Reports Requirement
Conditions of Approval of a New Drug Application
R/D init. JLMeyer, MSeife 5/17/73
Final typing bho 5/17/73 Approval

5/17/73

5/30/73

5/29/73

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

83-003

FINAL PRINTED LABELING

DIETHYLSTILBESTROL

DESCRIPTION

Diethylstilbestrol is a white crystalline or almost white crystalline powder, without odor and essentually tasteless. Diethylstilbestrol is always Trans-Diethylstilbestrol with a melting point form 169 to 172°C, and is only very slightly soluble in water. Diethylstilbestrol is subject to Photo Decomposition on exposure to light and should be protected from excessive light exposure. Diethylstilbestrol is supplied as Compressed tablets or Enteric-release tablets intended for oral administration.

MODE OF ACTION

Diethylstilbestrol is a synthetic orally [illegible] used for the same [illegible] to which natural Estrogen are indicated. Estrogen Hormones stimulate or regulate the growth and developement of the uterus, the vaginal mucous membrane and other structures as mammary glands, subcutaneous fat, axillary and pubic hair and elements of the skin.

An increased risk of thromboembolic disease associated with the use of oral contraceptives containing estrogens and progestins has now been conclusively established. Retrospective studies have shown a statistically significant association between thrombophebitis, pulmonary embolism, and cerebral thrombosis and embolism and the use of these drugs. There have been three principal studies in Great Britain (1-3) and one in the United States (4) leading to this conclusion. As a result of these studies, it has been estimated that users of oral contraceptives containing estrogens are 4 to 7 times more likely than non-users to develop thromboembolic disease without evident cause. The American study also indicated that the increased risk did not persist after discontinuation, nor was it enhanced by long continued administration. Although the American study was not designed to evaluate a difference between products, it did suggest that there might be an increased risk of thromboembolic disease in users of sequential products. Confirmation of this finding requires further study.

In a more recent analysis of data derived from several national adverse reaction reporting systems (5), British investigators concluded that the risk of thromboembolism, including coronary thrombosis, is directly related to the dose of estrogen used in oral contraceptive products. Their analysis did suggest, however, that the quality of estrogen may not be the sole factor involved. Nevertheless, in view of this study, as well as others that have demonstrated a positive relationship between estrogens and thromboembolism, it would seem prudent and in keeping with basic therapeutic principles, to utilize, whenever feasible, the smallest effective dose of estrogen in treating patients.

Risks associated with certain other known adverse reactions, such as elevated blood pressure, liver dysfunction, and reduced tolerance to carbohydrate, have not as yet been quantitated.

Long term administration of both natural and synthetic estrogens in subprimate animal species in multiples of the human dose increases the frequency for some animal carcinomas. These data cannot be transposed directly to man. The possible carcinogenicity due to the estrogens can neither be confirmed nor refuted at this time. Close clinical surveillance of all woman taking estrogens must be continued.

It has been reported in a recent study done in the United States (6) that the maternal ingestion of diethylstilbestrol during pregnancy appears to increase the risk of vaginal adenocarcinoma developing years later in the offspring exposed.

(1) Royal College of General Practitioners: Oral Contraception and Thrombo-Embolic Disease. J. Coll. Gen. Pract. 13:267-279, 1967.
(2) Inman, W.H.W. and Vessey, M.P., Investigation of Deaths from Pulmonary, Coronary and Cerebral Thrombosis and Embolism in Women in Child-Bearing Age, Brit. Med. J., 2:193-199, 1968.
(3) Vessey, M.P. and Doll, R., Investigation of Relation Between Use of Oral Contraceptives and Thromboembolic Disease. A Further Report. Brit. Med. J., 2:651-657, 1969.
(4) Sartwell, P.E., Masi, A.T., Arthes, F.G., Greene, G.r., and Smith, H.E., Thromboembolism and Oral Contraceptives: An Epidemiological Case-Control Study. Am. J. Epidem. 90:365-380, (November) 1969.
(5) Inman, W.H.W., Vessey, M.P., Westerholm, B., Engelund, A., Thromboembolic Disease and the Steroidal Content of Oral Contraceptives. Brit. Med. J., 25th April, 1970.
(6) Herbst et al - Adenocarcinoma of the Vagina - New England Journal fo Medicine, Vol. 284, Number 16 (April 22, 1971).

INDICATIONS

Compressed tablets and enteric-release tablets, Diethylstilbestrol are indicated for replacement therapy of estrogen deficiency associated with: Menopausal syndrome, female hypogonadism (hypogenitalism), amenorrhea, female castration, or primary ovarian failure. They are also indicated for use in abnormal uterine bleeding due to hormonal imbalance in the absence of organic pathology.

CONTRAINDICATIONS

1. Patients with markedly impaired liver function.
2. Patients with known or suspected carcinoma of the breast, except those cases of progressing disease not amenable to surgery or irradiation occurring in women who are at least 5 years postmenopausal, or in men in whom castration is not feasible.
3. Patients with known or suspected estrogen dependent neoplasia, such as carcinoma of the endometrium.
4. Undiagnosed abnormal genital bleeding.
5. Patients with thrombophlebitis, thromboembolic disorders, cerebral apoplexy or with a past history of these conditions.
6. Pregnancy. A statistically significant association has been reported between maternal ingestion during pregnancy of diethylstilbestrol and the occurrence of vaginal carcinoma in the offspring. The use of diethylstilbestrol or any of its closely related congeners is contraindicated in pregnancy.

WARNINGS

1. The physician should be alert to the earliest manifestations of thrombotic disorders (thrombophlebitis, cerebrovascular disorders, pulmonary embolism and retinal thrombosis). If these occur or are suspected the drugs should be discontinued immediately.
2. Discontinue medication pending examination if there is a sudden onset of proptosis, diplopia, or migrane. If examination reveals papilledema or retinal vascular lesions, medication should be withdrawn.
3. Estrogens may be excreted in the mother's milk and an estrogenic effect upon the infant has been described. The long range effect on the nursing infant cannot be determined at this time.
4. Hypercalcemia may occur in as many as 15% of breast cancer patients with metastases and this usually indicates progression of bone metastasses. This occurance depends neither on dose nor on

immobilization. In the presence of untoward effects such as progression of the cancer or hypercalcemia, the effect of estrogen medication should be stopped.
5. Enteric coating retards absorption from the gastrointestional tract and this form of therapy should not be used when rapid action is desired.
6. A statistically significant association has been reported between maternal ingestion during pregnancy of diethylstilbestrol and the occurance of vaginal carcinoma developing years later in the offspring. Whether such an association is applicable to all estrogens is not known at this time. In any event, estrogens are not indicated for use during pregnancy.

PRECAUTIONS

1. Because normal endogenous hormone production varies individually, certain patients may be unusually responsive to estrogenic therapy and may respond with undesirable manifestations of excessive estrogenic stimulation, such as abnormal or excessive uterine bleeding, mastodynia, edema, etc.
2. Because of estrogen induced salt and water retention, these drugs should be used with caution in patients with epilepsy, migraine, asthma, cardiac or renal disease.
3. Patients with a history of psychic depression should be carefully observed and the drug discontinued if the depression recurs to a serious degree.
4. In the event that any unexplained or excessive vaginal bleeding would occur while on estrogen therapy, nonfunctional causes should be borne in mind. The drug should be discontineud and a thorough investigation made as to the cause, being certain to rule out the possibility of malignancy.
5. Pre-existing uterine fibromyomata may increase in size while using this product, therefore, patients should be examined at regular intervals while receiving estrogenic therapy.
6. Women with a strong family history of cancer, recurrent chronic cystic mastitis, or abnormal mammograms should be administered estrogens with caution.
7. Because of a possible decrease in glucose tolerance, diabetic patients should be followed by closely.
8. Because estrogens influence the metabolism of calcium in patients with certain metabolic bone diseases that are associated with hypercalcemia or in patients with renal insufficiency.
9. The pathologist should be advised of estrogen therapy when relevent specimens are submitted.
10. Because of the effects of estrogens on epiphyseal closure, they should be used judiciously in young patients in whom bone growth is not complete.
11. A pre-treatment physical examination should include special reference to breast and pelvic organs as well as a Papanicolaou smear since estrogens have been known to produce tumors, some of them malignant, in five species of animals.
12. When large doses of estrogens are used, urinary stress incontenence may occur in non-pregnant females.
13. Prolonged high doses of estrogens will inhibit anterior pituitary functions. This should be borne in mind when treating patients in whom fertility is desired.
14. Continuous use of estrogens will result in prolonged stimulation of the endometrium and breast. In order to avoid this, oral estrogens should be administered cyclically in the menopausal or hypogonadal patient.
15. The age of the patient constitutes no absolute limiting factor, although treatment with estrogens may mask the onset of the climacteric.
16. Certain endocrine and liver function tests may be affected by treatment with estrogens. If such tests are abnormal in a patient taking these drugs it is recommended that they be repeated after the drug has been withdrawn for two months.
17. Any possible influence of prolonged estrogen therapy on pituitary, ovarian, adrenal, hepatic, or uterine function awaits further study.

ADVERSE REACTIONS

A statistically significant association has been demonstrated between use of estrogen-progestin oral contraceptives and the following serious reactions: Thrombophlebitis, Pulmonary Embolism, and Cerebral Thrombosis.

Although available evidence is suggestive of an association, such a relationship has been neither confirmed nor refuted for the following serious reactions: Coronary Thrombosis and Neuro-ocular lesions (e.g. retinal thrombosis and optic neuritis).

The following adverse reactions are known to occur in patients receiving estrogens: Nausea, Vomiting, Anorexia, Gastrointestinal Symptoms (such as abdominal cramps or bloating), Edema, Breakthrough Bleeding, Spotting or Withdrawal Bleeding, Breast Tenderness and Enlargement, Change in Body Weight (increase or decrease) Headache, Increased Cervical Mucus, Allergic Rash, Loss of Libido and Gynecomastia in the Male, Sterile Abscess, Pain at the Site of Injection or Post-Injection Flare (Injectable forms only), Reactivation of Endometriosis, Aggravation of Migraine Headaches, Hepatic Cutaneous Porphyria Becoming Manifest, Cholestatic Jaundice, Rise in Blood Pressure in Susceptible Individuals, Mental Depression, Cystitis-like Syndrome, Loss of Scalp Hair, Erythema Nodosum, Hemorrhagic Eruption, Premenstrual-like Syndrome, Changes in Libido, Changes in Appetite, Nervousness, Dizziness, Fatigue, Backache, Erythema Multiforme, Itching. Possible diminution in lactation when given immediately post-partum, Irritability and Malaise.

DOSAGE AND ADMINISTRATION

Oral - 0.2 to 0.5 mg. daily, increased as indicated. In the menopause, cyclic therapy is recommended (three weeks' regimen with a one-week rest period). Withdrawal bleeding may occur during the rest period. In functional uterine bleeding, usually 5 mg. three to five times daily until bleeding ceases. In carcinoma of the prostate, 1 to 3 mg. daily increased in advanced cases; later, the dose may be reduced to an average of 1 mg. daily.

In breast cancer, diethylstilbestrol should be used only for palliation in women with progressing inoperable or roentgen resistant disease who are more than five (5) years postmenopausal at a daily dosage of 15 mg.

HOW SUPPLIED

Enteric Coated - Diethylstilbestrol Tablets, U.S.P., are supplied as follows: 0.5 mg., 1.0 mg., and 5.0 mg., in bottles of 100 and 1000.

Compressed Tablets - Diethylstilbestrol Tablets, U.S.P., are available as follows: 0.5 mg., 1.0 mg., and 5.0 mg., in bottles of 100 and 1000.

T.C. G.F.D.

12/1/72

STILBESTROL
(Diethylstilbestrol, U.S.P.)
0.5
ENTERIC COATED RED
100 TABLETS
Mfg. by Tablicaps, Inc.
Franklinville, N.J. 08322
APPROVED
MAY 30 1973
DOSAGE: As directed by physician.
See enclosed literature for full information.
This is a potent drug which should be used under strict medical supervision.
CONTROL No.

STILBESTROL
(Diethylstilbestrol, U.S.P.)
0.5 mg.
ENTERIC COATED RED
APPROVED
MAY 30 1973
1000 TABLETS
Mfg. by Tablicaps, Inc.
Franklinville, N.J. 08322
CAUTION: Federal law prohibits dispensing without prescription.
DOSAGE: As directed by physician.
See enclosed literature for full information.
This is a potent drug which should be used under strict medical supervision.
CONTROL No.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

83-003

CSO LABELING REVIEW(S)

REVIEW OF RESUBMISSION, FPL

DATE COMPLETED: 10-12-72

ANDA #: 83-003

F.R. DATE: 11-10-71

CO. NAME: Tablicaps, Inc.
P.O. Box 5555
Blackwoodtown Road
Franklinville, N.J. 08322

447

NAME OF DRUG: Trade & Generic: Diethylstilbestrol 0.5 mg. enteric coated

DATE OF SUBMISSION: August 4, 1972

TYPE OF SUBMISSION: Resubmission (Reply to F.D.A. letter July 7, 1972)

CLINICAL EVALUATION:

I. Pertinent data is to be reviewed by chemist
II. Bioavailability requirement: Deferred
III. Evaluation of Labeling:

Container labels: Satisfactory (M.O.R. 6-20-72)

Insert labeling: UNsatisfactory
Add: "Actions" section
[Important Notes: etc] Follows "Actions"
"Description"section

INDICATIONS section:
Delete "
Reason: Probably effective claim
Delete
Reason: Possibly effective claim

DESCRIPTION section: Incomplete

DOSAGE AND ADMINISTRATION: Delete reference to:
a)
b) In cancer of breast: Qualify by addition of "Breast cancer:

CONCLUSIONS: Insert labeling requires the aforementioned changes. (Send current guidelines and FR statement.

RECOMMENDATIONS: The firm is to be notified to make the above revisions.

cc:
Dup
BD-69
VVKarusaitis/wlb/10-19-72

V.V. Karusaitis, M.D.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

83-003

CHEMISTRY REVIEW(S)

REVIEW OF ANDA

DATE COMPLETED: 6-12-72

ANDA #: 83-003

F.R. DATE: Nov. 10, 1971

CO. NAME: Tablicaps, Inc.
att: Mr. Richard T. Jackson
P.O. Box 5555
Blackwoodtown Road
Franklinville, N.J. 08322

NAME OF DRUG: Trade: "ASTX" Diethylstilbestrol Tablets, 0.5 mg. Enteric-Coated
&
Generic:

DATE OF SUBMISSION: April 7, 1972

TYPE OF SUBMISSION: ANDA

CLINICAL EVALUATION:

1. Review of Studies:

Adequate data to assure disintegration and dissolution of the drug should be submitted. Comparative dissolution studies with an approved NDA product.

2. Review of Labeling: Container Labels: Satisfactory
0.5 mg. enteric coated red
100 tablet size:
1,000 tablet size:

WARNING is acceptable ("This is a potent drug which should be used under strict medical supervision.")

Package Insert: Unsatisfactory
Requires numerous major labeling revisions.
(send current labeling guidelines)

CONCLUSION: ANDA has satisfactory container label; but unsatisfactory package insert. (send current labeling guidelines)

Dissolution and disintegration studies should be done.

RECOMMENDATIONS:

Firm is to be notified of recommended labeling revisions in package insert.

Firm is to submit studies.

V. V. KARUSAITIS, M.D.

cc:
Dup BD-69
VVKarusaitis/rt/6-20-72

REVIEW OF RESUBMISSION

DATE COMPLETED: 1-11-73

ANDA #: 83-003

F.R. DATE: 11-10-71

CO. NAME: Tablicaps, Inc.
P.O. Box 5555
Blackwoodtown Road
Franklinville, New Jersey 08322

NAME OF DRUG: Trade & Generic: Diethylstilbestrol Tablets 0.5 mg enteric coated.

DATE OF SUBMISSION: Jan. 3, 1973

TYPE OF SUBMISSION: Resubmission (reply to F.D.A. 11-7-72 letter)

CLINICAL EVALUATION:

1. Review of Studies: Pertinent data is to be reviewed by the chemist.
   Bioavailability sequirement: Deferred

2. Review of Labeling:

   a) Container labels: Satisfactory (M.O.R. 6-20-72)

   b) Package insert: Satisfactory

CONCLUSION: Labeling is satisfactory.

RECOMMENDATIONS: The firm is to be so notified. Send F.P.L.

V.V. Karusaitis, M.D.

cc:
Dup
BD-69
VVKarusaitis/wlb/1-15-73

REVIEW OF RESUBMISSION: F.P.L.

DATE COMPLETED: 4-20-73

ANDA #: 83-003

F.R. DATE: 11-10-71

CO. NAME: Tablicaps, Inc.
P.O. Box 5555
Blackwoodtown Rd.
Franklinville, N.J. 08322

NAME OF DRUG: Trade: "Astx"

Generic: Diethylstilbestrol 0.5 mg. Tablets, Enteric Coated

DATE OF SUBMISSION: April 13, 1973

TYPE OF SUBMISSION: Resubmission: F.P.L. (reply to F.D.A. letter 2-27-73)

CLINICAL EVALUATION:

1. Review of Studies: Pertinent data is to be reviewed by the chemist.
None Submitted.
Bioavailability requirement: Deferred

2. Review of Labeling: a) Container Labels: Satisfactory
Enteric Coated: 0.5 mg., bottles of 100: 1,000

b) Insert Labeling: Satisfactory

CONCLUSIONS: Labeling is satisfactory for the safe and effective use of this product.

RECOMMENDATIONS: The firm is to be so notified.
Medically Approvable.

V. V. Karusaitis, M.D.

cc:
Dup
BD-69
VVKarusaitis/rt/4-23-73

CHEMIST'S REVIEW FOR ABBREVIATED NEW DRUG APPLICATION OR SUPPLEMENT

Federal Register Statement Date: 11-10-71

NDA No. 83-003

Original 4-7-72

Amendment

Supplement

Other

Date(s) of Submission(s)

Name & Address of Applicant (City & State)
Tablicaps, Inc.
P.O. Box 5555
Franklinville, New Jersey 08322

Name of Drug: Diethylstilbestrol

Proprietary Name

Purpose of Supplement

Pharmacological Category: Estrogen

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

AF Number: None Records 6-27.

Related NDA & MF: 83-003 0.5 mg. Enteric

Dosage Form(s): Enteric Tablet

Potency (ies): 0.5 mg.

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

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

Satisfactory [ ] Biologic Availability
Date Due: Deferred. See memo 4-21-72
Is data on current formulation? YES [ ] NO [ ]

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

Establishment Inspection
Unsatisfactory 4-7 to 12-72
Requested inspection 6-28-72

Recalls

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

Remarks

Request:
1. Revise labeling per MO's report.
2. Signature on Form FD 356 H.
3. Full list of articles used as components. ____ not listed.
4. For enteric tabs. Composition amount of ____ material not listed.
5. Identify lab. other than ____
6. Include procedures for ____ (Enteric tablets only) and clarify inclusion of Raw Material specs. for ____
7. Outline the actual methods for ____ the tablets (Enteric only)
8. Bio defefred.
9. Satisfactory inspection.

Conclusions

rev w/f

RJWolters RJWolters 7-3-72

PENALTY: SIGNATURE: DATE:

CHEMIST'S REVIEW FOR ABBREVIATED NEW DRUG APPLICATION OR SUPPLEMENT

Federal Register Statement Date: 11-10-71

NDA Number 83-003

Original

Amendment 7-31-72

Supplement

Other

Name & Address of Applicant (City & State)
Tablicaps, Inc.
P.O. Box 5555
Franklinville, New Jersey 08322

Name of Drug

Nonproprietary Name
Diethylstilbestrol

Purpose of Supplement
Revised insert and manufacturing information

Date(s) of Submission(s)

Pharmacological Category
Estrogen

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

AF Number

Related NDA & NF
83-003 0.5 mg. Enteric

Dosage Form(s)
Enteric Coated

Potency (ies)
0.5 mg.

Satisfactory [ ] Labeling
Date Due To be revised (VVKarusaitis)

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

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

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

Establishment Inspection(s) TWX 7-72
Tablicaps Unsatisfactory 2-7 to 12-72

Recalls

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

Remarks
Request: 1. Revised labeling as per MO's review.
2. 83-005 Signature of offical.
3. Enteric coated applications procedures for all components use in ——— the tablet and the outline of the methods use in the ——— of the tablets.
4. A satisfactory inspection.

Conclusions Rev w/f

RJWolters 11-3-72

CHEMIST'S REVIEW FOR
ABBREVIATED NEW DRUG APPLICATION
OR SUPPLEMENT

Request Letter
Statement Date 11-10-71

83-003
Original
Amendment 1-3-73
Supplement
Other
Date(s) of Submission(s)

Name & Address of Applicant (City & State)
Tablicaps, Inc.
P.O. Box 5555
Franklinville, New Jersey 08322

Name of Drug

Nonproprietary Name
Diethylstilbestrol

Purpose of Supplement
Revised labeling and manufacturing information

Pharmacological Category
Estrogen

How Dispensed
Rx [x] O.T.C. [ ]

AF Number

Related NDA & NF
83-003 0.5 mg. Enteric

Dosage Form(s)
Enteric coated Tablet

Potency (Res)
0.5 mg.

Satisfactory [ ] Labeling
Date Due
Satisfactory (Warusaitis)

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

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

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

Establishment Inspection
Unsatisfactory 2-7-73
Satisfactory 7-72

Recalls
NX

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

Remarks
Request: 1. FPL
2. Microbial limit test should be included in
NF ID tests should be included for
and include test for
3. 6-005 Sign form FD 356 H.
4. A satisfactory inspection.

Conclusions
rev w/f

R J Welters 2-27-73
R J Welters

CHEMIST'S REVIEW FOR ABBREVIATED NEW DRUG APPLICATION OR SUPPLEMENT

Federal Register Statement Date: 11-10-71

ORIGINAL [X]

SUPPLEMENT [ ]

Name & Address of Applicant (City & State)

Tablicaps, Inc.
P.O. Box 5555
Franklinville, New Jersey 08322

NDA Number: 83-003

Supplement Date and Number: N/A

Name of Drug

Nonproprietary Name: Diethstilbestrol

Amendment Date(s): 3-19-73

Purpose of Supplement: Printed labeling Enteric coated Manufacturing information.

Other Date(s)

AF Number

Pharmacological Category: Estrogen

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

Related IND/NDA/AF(s): 83-003 0.5 mg. Enteric

Dosage Form(s): Tablet

Potency (ies): 0.5 mg. enteric

Satisfactory [ ] Labeling
Date Due: Satisfactory (VVKarusaitis)

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

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

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

Establishment Inspection

Satisfactory ED 340 memo
4-12-73

Recalls

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

Remarks

APPEARS THIS WAY
ON ORIGINAL

Conclusions: Approval

RJWolters 5-24-73

REVIEWER: SIGNATURE: DATE:

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

83-003

ADMINISTRATIVE DOCUMENTS

NOTICE OF APPROVAL
NEW DRUG APPLICATION OR SUPPLEMENT

NDA NUMBER: 83-003

DATE APPROVAL LETTER ISSUED: MAY 30 1973

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

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

APPROVAL OF ORIGINAL ABBREVIATED NDA

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 [ ] SUPPLEMENT ~~A ORIGINAL NDA~~ TO NDA

CATEGORY: [X] HUMAN [ ] VETERINARY

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

Diethylstilbestrol

DOSAGE FORM: Tablet Enteric coated

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.)*

Diethylstilbestrol 0.5 mg.

APPEARS THIS WAY ON ORIGINAL

NAME OF APPLICANT *(Include City and State)*

Tablicaps. Inc.
Franklinville, N.J. 08322

PRINCIPAL INDICATION OR PHARMACOLOGICAL CATEGORY

Estrogen

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.

MEMO RECORD	AVOID ERRORS PUT IT IN WRITING	DATE April 12, 1973
FROM: Jonas L. Bassen - BD-340		OFFICE
TO: Stanley Stringer - BD-105		DIVISION
SUBJECT: Tablicaps, Inc. Franklinville, New Jersey		

SUMMARY

File 83-003

We have evaluated the current operations of above referenced firm as it relates to compliance with CGMP regulations (21CFR Pt 133). Based on this evaluation we have no objection to your approving the ANDA's listed below in so far as it relates to firm"s certification of c compliance with CGMP's in these pending applications.
ANDA's involved: [redacted]

Jonas L. Bassen

cc:
BD-105
BD-301
BD-310
BD-316
BD-340, 2 cys
CA-226
BD-69
NMK-10

CGBROKER:das

APPEARS THIS WAY
ON ORIGINAL

SIGNATURE	DOCUMENT NUMBER

INSPECTION ENDORSEMENT

1. ESTABLISHMENT

a. ESTABLISHMENT NAME: Tablicaps; Inc.

b. DISTRICT: Newark

c. CENTRAL FILE NO.: 20594

d. ESTABLISHMENT ADDRESS: P.O. Box 5555, Franklinville, N.J. 08322

e. DATE INSPECTED: 1/31/73,2/1,5,7/73

2. ROUTING

a. HEADQUARTERS UNIT TO WHICH REFERRED (Use organizational symbol): BD 310,

HEADQUARTERS USE ONLY

c. DATE REFERRED:

b. REASON FOR REFERRAL: BD 105 TWX dtd 12/20/72

d. AF NUMBER:

3. DISTRICT REMARKS

a. DISTRICT ENDORSEMENT

This inspection was made as a F/U to Newark workschedule and BD 105 TWX dtd 12/20/72 requesting an inspection pending their approval of ANDA's.

Previous inspections were made on 4/7/72 which was indexed as Voluntary Action Indicated. The initial inspection of the firm was made in 2/2/71 and was classified as NAI.

[redacted]

Follow-up

We have requested official samples of the firm's products to document deviations. We recommend BD100 not approving the firm's ANDA's until a re-inspection demonstrates that the firm has made corrections promised. Reinspect July 1973 on a Compliance basis.

NWK-DO/BD 105 TWIX of 2/14/73 summarized results of EI and included NWK-DO recommendation to not approve ANDA until corrections were verified.

APPEARS THIS WAY
ON ORIGINAL

b. REVIEWING OFFICER (Name and title): Charles D. Thorne, Supv. CSO

c. SIGNATURE: [signature]

d. DATE: 5/14/73 5/14/73

e. DISTRIBUTION: CHEx. - NWK-DO; cc-Ex. -BD.300; cc - RF;421,481(a) DEV;NJDH(Foley;V;INF

FD FORM 481a (7/69) PREVIOUS EDITION MAY BE USED UNTIL SUPPLY IS EXHAUSTED.

treated tissues. Application Received by Commissioner of Customs: July 9, 1971.

SETH M. BODNER,
Director, Office of Import Programs.

[FR Doc.71-16363 Filed 11-9-71;8:46 am]

Office of the Secretary

[Dept. Organization Order 30-2B]

NATIONAL BUREAU OF STANDARDS

Organization and Functions

This material further amends the material appearing at 35 F.R. 18550 of December 5, 1970, 36 F.R. 5809 of March 27, 1971, and 36 F.R. 18428 of September 14, 1971.

Department Organization Order 30-2B, dated November 16, 1970, is hereby further amended as follows:

1. In section 9 *Institute for Basic Standards,* subparagraph .02d. is revised as follows:

d. The administrative divisions reporting to the Deputy Director, Institute for Basic Standards/Boulder include:

Supply Services Division.
Plant Division.
Instrument Shops Division.

2. In section 11 *Institute for Applied Technology:* a. Paragraph .05, the Office of Flammable Fabrics is deleted.

b. A new paragraph .05 is added to read:

.05 The Office of Fire Programs shall (a) conduct data gathering, research, education and demonstration programs on fire, its causes, prevention, and control, and on the flammability of products, fabrics, and materials; (b) develop test methods and standards in flammability; and (c) coordinate all other fire research and safety activities of the National Bureau of Standards.

3. The organization chart of August 22, 1971, attached to Amendment 2, is superseded by the organization chart attached to this amendment. (A copy of the organization chart is on file with the original of this document with the Office of the Federal Register.)

Effective date: October 27, 1971.

LARRY A. JOBE,
Assistant Secretary for Administration.

[FR Doc.71-16358 Filed 11-9-71;8:45 am]

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

Food and Drug Administration

[DESI 740; Docket No. FDC-D-327; NDA 740 etc.]

CERTAIN ESTROGENS FOR ORAL OR PARENTERAL USE

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. *Preparations containing dienestrol.*

a. Restrol tablets; The Central Pharmacal Co., 116-128 East Third Street, Seymour, IN 47274 (NDA 6-428). (Two reports.)

b. Synestrol tablets; White Laboratories, Inc., Kenilworth, N.J. 07033 (NDA 5-991).

2. *Preparations containing diethylstilbestrol.*

a. Diethylstilbestrol Enseals; Eli Lilly and Co., Post Office Box 618, Indianapolis, IN 46204 (NDA 4-039 and 4-040). (Two reports.)

b. Diethylstilbestrol tablets; Eli Lilly and Co., (NDA 4-041).

c. Diethylstilbestrol tablets; Vale Chemical Co., Inc., 1201 Liberty Street, Allentown, PA 18102 (NDA 4-638).

d. Diethylstilbestrol (Stilbestrol) tablets; Rexall Drug Co., 3901 North Kingshighway Boulevard, St. Louis, MO 63115 (NDA 6-603).

e. Diethylstilbestrol tablets; S. F. Durst and Co., Inc., 5317 North Third Street, Philadelphia, PA 19120 (NDA 4-297).

f. Stilbestrol tablets; High Chemical Co., 1760 North Howard Street, Philadelphia, PA 19122 (NDA 5-233).

g. Stilbetin tablets and Enteric coated tablets; E. R. Squibb and Sons, Inc., Georges Road, New Brunswick, N.J. 08903 (NDA 4-056).

h. Diethylstilbestrol Perles; The Upjohn Co., 7171 Portage Road, Kalamazoo, MI 49002 (NDA 4-073).

i. Diethylstilbestrol in oil injection; Eli Lilly and Co. (NDA 1-221).

j. Diethylstilbestrol in ethyl oleate injection; Eli Lilly and Co. (NDA 7-844).

3. *Preparations containing other diethylstilbestrol derivatives.*

a. D.S.D. tablets and Enteric coated tablets, containing diethylstilbestrol dipropionate; The Blue Line Chemical Co., 302 South Broadway, St. Louis, MO 63102 (NDA 5-159).

b. Stilphostrol ampules and tablets; containing diethylstilbestrol diphosphate; Dome Laboratories, Division of Miles Laboratories, Inc., 400 Morgan Lane, West Haven, CT 06516 (NDA 10-010).

4. *Preparations containing promethestrol dipropionate.*

a. Meprane Dipropionate tablets; Reed and Carnrick Pharmaceuticals, 30 Boright Avenue, Kenilworth, NJ 07033 (NDA 6-042).

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. A new drug application is required from any person marketing such drug without approval.

The Food and Drug Administration is prepared to approve new drug aplications and supplements to previously approved new drug applications for these drugs under the conditions described in this announcement.

A. *Effectiveness classification.* The Food and Drug Administration has considered the Academy's reports, as well as other available evidence, and concludes that these drugs are:

1. Effective or probably effective for the indications described in the labeling conditions which follow. The probably effective indication is "in selected cases of osteoporosis."

2. Possibly effective for disturbances of the menstrual cycle (hypomenorrhea, oligomenorrhea, irregular cycles); suppression of lactation; to minimize blood loss at surgery; to lessen the incidence of postoperative hemorrhage; and to avoid the risk of multiple transfusions; and to reduce capillary hemorrhage; to reduce the oozing following multiple transfusions; and to prevent or arrest delayed hemorrhage.

3. Diethylstilbestrol preparations were classified as possibly effective for the indication "Prevention of accidents of pregnancy" (threatened abortion and habitual abortion, in diabetic women this includes eclampsia, premature delivery, and death of the fetus). However, in view of the fact that a statistically significant association has been demonstrated between the use of diethylstilbestrol in early pregnancy and the occurrence of adenocarcinoma of the vagina in the offspring, this drug, along with all closely related congeners (including hexestrol, dienestrol, benzestrol, and promethestrol), is contraindicated for use in pregnancy.

4. Lacks substantial evidence of effectiveness when labeled for "relief of pregnancy bleeding;" advanced cases of prostatic carcinoma resistant to other estrogens; hemorrhagic emergencies due to spontaneous bleeding; reducing bleeding due to capillary hemorrhage during and after oral surgery and after dental extraction; pulmonary bleeding and use in hyphema during and after ocular surgery.

B. *Conditions for approval and marketing*—1. *Form of drug.* These preparations are in tablet, enteric coated tablet, or capsule form suitable for oral administration; or are sterile preparations in a form suitable for parenteral administration.

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

b. The drugs are labeled to comply with all requirements of the Act and regulations. The 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" sections are as follows (the possibly effective indications may also be included for 6 months):

INDICATIONS

These drugs are indicated for replacement therapy of estrogen deficiency associated with: Menopausal syndrome, female hypogonadism (hypogenitalism), amenorrhea, female castration, or primary ovarian failure. They are also indicated for the prevention of postpartum breast engorgement; abnormal uterine bleeding due to hormonal imbalance in the absence of organic pathology; and in osteoporosis-depending upon the etiology and then only when used in conjunction with other important therapeutic measures such as diet, calcium, physiotherapy, and good general health promoting measures.

The following indications may be included provided the recommended dosage schedules of these preparations are reevaluated to establish the optimal dosage:

Senile vaginitis; kraurosis vulvae with or without pruritus; inoperable progressing prostatic cancer (for palliation only when castration is not feasible or when castration failures or delayed escape following a response to castration have not occurred); breast cancer (for palliation only in women with progressing inoperable or roentgen resistant disease who are more than 5 years postmenopausal; and in men, in those inoperable cases in which bilateral orchidectomy cannot be performed because of an independent surgical contraindication).

c. The labeling for all diethylstilbestrol preparations, as well as all closely related congeners (including dienestrol, hexestrol, benzestrol, and promethestrol), must contain the following as a Contraindication:

CONTRAINDICATION

A statistically significant association has been reported between maternal ingestion during pregnancy of diethylstilbestrol and the occurrence of vaginal carcinoma in the offspring. The use of diethylstilbestrol or any of its closely related congeners is contraindicated in pregnancy.

3. *Marketing status.* Marketing of such drugs may be continued under the conditions described in the notice entitled "Conditions for Marketing New Drugs Evaluated in Drug Efficacy Study," published in the FEDERAL REGISTER July 14, 1970 (35 F.R. 11273), as follows:

a. For holders of "deemed approved" new drug applications (i.e., an application which became effective on the basis of safety prior to October 10, 1962), the submission of a supplement for revised labeling, an abbreviated supplement for updating information, and adequate data to show the biologic availability of the drug in the formulation which is marketed as described in paragraphs (a) (1) (i), (ii), and (iii) of the notice of July 14, 1970.

b. For any person who does not hold an approved or effective new drug application, the submission of an abbreviated new drug application, to include adequate data to assure the biologic availability of the drug in the formulation which is or is intended to be marketed as described in paragraph (a) (3) (ii) of that notice.

c. For any distributor of the drug, the use of labeling in accord with this announcement for any such drug shipped within the jurisdiction of the Act as described in paragraph (b) of that notice.

d. For indications for which the drug has been classified as probably effective (included in the "Indications" sections above) and possibly effective (not included in the "Indications" sections above), continued use as described in paragraphs (c), (d), (e), and (f) of that notice.

C. *Opportunity for a hearing.* 1. 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 under A. *Effectiveness classification* 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. Any related drug for human use, not the subject of an approved new drug application, offered for the indications for which substantial evidence of effectiveness is lacking may be affected by this action.

2. 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 the labeling. A request for a hearing must be filed within 30 days after the date of publication of this notice in the FEDERAL REGISTER.

3. 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 that 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 § 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 acceptable 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.

4. 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.

A copy of the Academy's report has been furnished to each firm referred to above. Communications forwarded in response to this announcement should be identified with the reference number DESI 740, directed to the attention of the appropriate office listed below, and addressed to the Food and Drug Administration, 5600 Fishers Lane, Rockville, Md. 20852:

Supplements (identify with NDA number): Office of Scientific Evaluation (BD–100), Bureau of Drugs.

Original abbreviated new drug applications (identify as such): Drug Efficacy Study Implementation Project Office (BD–60), Bureau of Drugs.

Request for Hearing (identify with Docket number): Hearing Clerk, Office of General Counsel (GC–1), Room 6–88, Parklawn Building.

Requests for the Academy's report: Drug Efficacy Study Information Control (BD–67), Bureau of Drugs.

All other communications regarding this announcement: Drug Efficacy Study Implementation Project Office (BD–60), Bureau of Drugs.

Received requests for a hearing may be seen in the office of the Hearing Clerk (address given above) during regular business hours, Monday through Friday.

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 the authority delegated to the Commissioner of Food and Drugs (21 CFR 2.120).

Dated: November 5, 1971.

CHARLES C. EDWARDS,
Commissioner of Food and Drugs.

[FR Doc.71–16446 Filed 11–9–71;8:52 am]

DEPARTMENT OF HOUSING AND URBAN DEVELOPMENT

[Docket No. D–71–131]

REGIONAL ADMINISTRATORS ET AL.

Redelegation of Authority Regarding Housing Management

The redelegation of authority by the Assistant Secretary for Housing Management to Regional Administrators et al., published at 35 F.R. 16105, October 14, 1970, amended at 35 F.R. 17964, November 21, 1970, is amended in the following respects:

1. A new section H is added to read as follows:

SEC. H. *Authority redelegated to Directors, Housing Management Division, Area Offices.* Each Director, Housing Management Division, is authorized to exercise the powers and authorities redelegated to the Directors, Housing Services and Property Management Division, in section E.

2. A new section I is added to read as follows:

SEC. I. *Authority redelegated to Chiefs, Housing Programs Management Branch, Area Offices.* Each Chief, Housing Programs Management Branch, is authorized to exercise the powers and authorities redelegated to the Chiefs, Housing Management and Tenant Services Branch, in section F.

3. The present section H is redesignated as section J.

4. The present section I is redesignated as section K and is revised to read as follows:

SEC. K. *Exercise of redelegated authority.* Redelegations of authority made under sections A through I shall not be construed to modify or otherwise affect the administrative and supervisory powers of the Regional Admniistrator, Area Director, HUD–FHA Insuring Office Director, or any of them, to whom a delegate is responsible.

(Secretary's delegation of authority to redelegate published at 36 F.R. 5005, March 16, 1971)

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

83-003

CORRESPONDENCE

83 003

TEL. (609) 445-0500

P.O. BOX 5555
BLACKWOOD ROAD,
FRANKLINVILLE, N.J. 08322

ABBREVIATED NEW DRUG APPLICATION

April 7, 1972

Letter Ref: 4-72-T2-5-15

Food and Drug Administration
Bureau of Drugs
5600 Fishers Lane
Rockville, Maryland 20852

Gentlemen:

We are hereby submitting, in triplicate, our Abbreviated New Drug Application for Diethylstilbestrol 0.5 Mg. Enteric Coated Red tablets, for your review and consideration.

We thank you for giving this matter your attention, and look forward to hearing from you in the very near future since we are preparing a marketing program for this product.

Sincerely,

TABLICAPS, INC.

Robert L. Pillarella
President

Richard T. Jackson
Quality Control Director

RLP/RTJ: js

Enclosures

RECEIVED 1 COPY
PHOTOSTATS OF
COVER LETTER MADE
FOR DUP ___ TRIP ___

RECEIVED
APR 12 1972
BUREAU OF DRUGS

NDA 83-003
AF _____

APR 24 1972

Tablicaps, Inc.
Attention: Mr. Richard T. Jackson
P. O. Box 5555
Blackwoodtown Road
Franklinville, New Jersey 08322

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: Diethylstilbestrol Tablets, 0.5 mg., Enteric Coated

DATE of COVER LETTER: April 7, 1972

DATE of RECEIPT: April 12, 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 4/21/72

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

cc:
NWK-DO
Dup JMeyer 4/21/72
BD-67 BD-69 BD-22 BD-310
JLMeyer/rt 4-21-72
R/D init. JMeyer 4-20-72
Ack.

NDA 83-003
AP

Tablicaps, Inc.
Attention: Mr. Richard T. Jackson
P.O. Box 5555
Blackwoodtown Road
Franklinville, New Jersey 08322

JUL 7 1972

Gentlemen:

Reference is made to your abbreviated new drug application, cover letter dated April 7, 1972, submitted pursuant to Section 505(b) of the Federal Food, Drug, and Cosmetic Act for Diethylstilbestrol Tablets, 0.5 mg., Enteric Coated.

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

1. Package insert: Revise the insert to conform to the accompanying labeling guidelines.

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

1. The signature of the applicant or responsible official or agent on a completed form FD 356H. Four copies are enclosed for your convenience.

2. A full list of articles used as components of the drug.

3. 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.

4. If you elect to employ a laboratory other than _____, regulation 130.4(f) requires the name of the laboratory and a certification statement from the laboratory be submitted as part of your abbreviated new drug application.

5. Procedures that assure that the 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

APPEARS THIS WAY
ON ORIGINAL

article differs from the compendium drug, that the specifications and tests applied to the components are adequate to assure their identity, strength, quality, and purity. The following deficiencies are noted:

a) Include the procedures applied to ——, and the ——— materials.

b) Clarify the inclusion of the "Raw Material Specifications" for ———————, since it is noted that this component is not listed on page 18, "Materials and Quantities of Each Ingredient Found in the Finished Product."

6. Outline the actual methods used in the ———of the drug.

At the present time, the requirement for adequate data to assure the biologic availability of this drug has been deferred by our Division of Clinical Research.

Information in a report of inspection of your facilities, by inspectors of this Administration (covering the methods, facilities, and controls used), indicates that there is disagreement between actual current good manufacturing practice and the commitment made in your application.

Therefore, before we can take final action on this abbreviated new drug application, we should have a satisfactory inspection report.

A copy of this letter has been sent to our Newark District Office. We recommend that you contact the District and arrange for an inspection after the deficiencies have been corrected.

Please let us have your response promptly.

Sincerely yours,

7/6/72

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

Dup
BD-69 BD-67
BD-242 BD-106
VVKarusaitis/JLMeyer/RJWolters
R/D init. by MClark/JMeyer 6-30-72
Finaltyping/wlb/6-30-72
Rev w/f

Enclosures:
Form FD 356H
Labeling guidelines

cc:
NWK-DO

TE (609) 445-0500

P.O. BOX 5555
BLACKWOOD ROAD.
FRANKLINVILLE, N.J. 08322

Rev. w/f

RESUBMISSION
NDA ORIG AMENDMENT

For Quality Generic Pharmaceuticals

FPLI

August 4, 1972

Letter Ref: 8-72-T2-5-7

ORIG

448

Dpartment of Health, Education and Welfare
Public Health Service
Food and Drug Administration
Rockville, Maryland 20852

Gentlemen:

We are submitting in triplicate the following additional information for our Abbreviated New Drug Application No. 83-003 as you requested in your letter of July 7, 1972.

The following comments are submitted as a paragraph by paragraph reply to the above mentioned letter:

1- Please find enclosed a revised insert which conforms to supplied labeling guidelines.

2- Enclosed are forms FD 356H signed by a responsible official of Tablicaps, Inc.

3- a) Please find enclosed a revised list of all components and quantities contained in the drug. This replaces page 18 previously submitted.

b) Also attached are product specifications for all ——— components.

4- At this time only ——————— will be doing the analytical work for this drug. A certification statement was filed in our ANDA No. 83-003. (See page 22)

5- Under item number five of your letter the following submissions are made:

a) Enclosed are specifications for ———

b) The inclusion of ——— specifications were submitted in error, please disregard.

RECEIVED 1 COPY
PHOTOSTATS MADE
FOR DUP_____TRIP_____

BUREAU OF DRUGS
SEP 20 1972
RECEIVED

We have contacted the Newark District Office and have requested another inspection of our facilities with special attention to those deficiencies noted in the earlier report.

Very truly yours,

TABLICAPS, INC.

Robert L. Pillarella
President

Richard T. Jackson
Director of Quality Control

RLP/RTJ:kc

Enclosures

NDA 83-003
AP

Tablicaps, Inc.
Attention: Mr. Richard T. Jackson
P.O. Box 5555
Blackwood Road
Franklinville, New Jersey 08322

NOV 7 1972

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 Diethylstilbestrol Tablets, 0.5 mg., Enteric Coated.

Reference is also made to your amendment dated July 31, 1972, received September 20, 1972, enclosing revised labeling and manufacturing information.

We have completed the review of this abbreviated new drug application and have the following comments regarding the proposed package insert.

1. The DESCRIPTION section is incomplete.

2. An ACTIONS section should follow the DESCRIPTION section, which is to include the Important Notes.

3. In the INDICATIONS section, delete the probably and possibly effective claims:

   a) "_____"

   b) "_____"

4. Revise the DOSAGE and ADMINISTRATION section as follows:

   a) Delete the statement, "_____"

APPEARS THIS WAY
ON ORIGINAL

b) Revise the last sentence to read, [redacted]

Copies of the material relating to these revisions are enclosed for your convenience.

Other information requested in our letter of July 7, 1972:

1. Include the procedures applied to all of the [redacted] materials. In addition clarify the inclusion of "Raw Material Specifications" for [redacted]

2. Outline the procedures used in the [redacted] of the drug.

3. A satisfactory establishment inspection report.

Please let us have your response promptly.

Sincerely yours,

Marvin Seife 11/6/72

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

cc:
NWK-DO
Dup
BD-69
BD-66
BD-166
BD-242
VVKarusaitis/JLMeyer/RJWolters/11-1-72
R/D init. by MClark/JMeyer/11-2-72
Final typing/kim/11-3-72
Enclosures:
Labeling guidelines
F.R. 11-10-71

JLMeyer 11/6/72

Rev w/f

RJWolters 11-3-72

Rev. W/F ORIG E

TEL. (609) 445-0500

P.O. BOX 5555
BLACKWOOD ROAD.
FRANKLINVILLE, N.J. 08322

RESUBMISSION
NDA ORIG AMENDMENT

For Quality Generic Pharmaceuticals

January 3, 1973

Letter Ref: 1-73-T5-3

Department of Health, Education, and Welfare
Public Health Service
Food and Drug Administration
Rockville, Maryland 20852

Gentlemen:

We are hereby submitting, in triplicate, the following additional information for our Abbreviated New Drug Application No. 83-003 as you requested in your letter of November 7, 1972.

The following comments are submitted as a paragraph by paragraph reply to the above mentioned letter.

A. A proposed insert being submitted contains the following changes:

1. Description section of insert has been elaborated.
2. An Actions section which includes Important Notes has been placed after the description section.
3. ——— and ——— effective claim have been removed.
4. Dosage and Administration section has been revised as stipulated in your last letter.

Other information requested and hereby submitted is as follows:

1. Attached please find "Raw Material" specification for all raw materials used in the ——— of the product.
2. Please disregard ——— and ——— specifications since they were submitted in error.
3. Attached please find procedures for tablet ———.

We have contacted the Newark District Office and have requested an inspection of our facilities with special attention to those deficiencies noted in the earlier inspection report.

Very truly yours,

TABLICAPS, INC.

Richard T. Jackson
Director of Quality Control

RTJ/cd

RECEIVED
JAN 8 1973
BUREAU OF DRUGS

NDA 83-003
AF

Tablicaps, Inc.
Attention: Mr. Richard T. Jackson
P.O. Box 5555
Franklinville, New Jersey 08322

FEB 27 1973

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 Diethylstilbestrol Tablets, 0.5 mg., Enteric Coated.

Reference is also made to your communication dated January 3, 1973, 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 labels and package insert.

Regarding the manufacturing information, the following is necessary:

Assurance that the 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 components are adequate to assure their identity, strength, quality, and purity.

1. The microbial limit test should be performed on _____

2. Clarify the omission of the N.F. XIII identification tests for _____

3. Include the specifications and tests applied to the components _____ and

Information in a report of inspection (February 7, 1973) of your facilities, by inspectors of this Administration (covering the methods, facilities, and controls used), indicates that there is disagreement between actual current good manufacturing practice and the commitment made in your application. Therefore, before we can take final action on this abbreviated new drug application, we should have a satisfactory inspection report.

A copy of this letter has been sent to our Newark District Office. We recommend that you contact the District and arrange for an inspection after the deficiencies have been corrected.

Please let us have your response promptly.

Sincerely yours,

Marvin Seife 2/27/73

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

cc:
NWK-DO
Dup
BD-69
BD-66
BD-106
BD-242

VVKarusaitis/JLMeyer/RJWolters/2-21-73
R/D init. by /MSeife/JMeyer
2-26-73
Final typing/kim/2-27-73
Rev w/f

JMeyer 2/27/73

RJWolters 2-27-73

TEL. (609) 445-0500

P.O. BOX 5555
BLACKWOOD ROAD.
FRANKLINVILLE, N.J. 08322

For Quality Generic Pharmaceuticals

Letter Ref: 3-73-T2-18

March 19, 1973

Department of Health, Education, and Welfare
Public Health Service
Food and Drug Administration
Division of Actions Implementation, Drug Efficacy Study
Implementation Project Office
Bureau of Drugs

ATTENTION: MARVIN SEIFE, M.D.

Gentlemen:

Reference is made to abbreviated new drug application

Titled: Diethylstilbestrol Tablets 0.5 mg.

NDA#: 83-003

Dated: February 27, 1973

Enclosed find clarifications requested concerning manufacturing information.

1. ——— Raw Material specifications and reference to test procedures. ——— Microbial Limits test will be performed as routine test procedures by ———.

Enclosed find Raw Material specifications sheet for ANDA application to supersede all previously submitted specifications for ———.

2. Enclosed find ——— Raw Material specification and reference to test methods sheet. Identification test will be performed as routine qualifying test requirement.

March 19, 1973

Department of Health, Education, and Welfare
Public Health Service

3. The following Specifications and test procedures reference sheets for the following Raw Material are enclosed.

[redacted]

Sincerely yours,

TABLICAPS, INC.

Richard T. Jackson
Director of Quality Control

RTJ/cd

Enclosures

P.S. Enclosed please find printed labels and package insert identical in content to the draft copy previously submitted.

APPEARS THIS WAY
ON ORIGINAL

TEL (609) 445-0500

RESUBMISSION
NDA ORIG AMENDMENT

P.O. BOX 5555
BLACKWOOD ROAD.
FRANKLINVILLE, N.J. 08322

FPLI

For Quality Generic Pharmaceuticals

Letter Ref: 4-13-73-T6-14

April 13, 1973

Department of Health, Education, and Welfare
Public Health Service
Food and Drug Administration
Rockville, Maryland 20852

Attention: Dr. Marvin Seife, M.D.

Gentlemen:

Subject NDA 83-003

ENTERIC COATED RED

Enclosed find twelve copies of printed Labels Diethylstilbestrol Tablets 0.5 mg. and twelve copies of inserts for this product.

This information is submitted in reply to your letter of February 27, 1973 requesting the submission of final printed labeling.

Sincerely yours,

TABLICAPS, INC.

Richard T. Jackson
Director of Quality Control

RTJ/cd

Enclosures