

CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

ANDA 76-761

Name: Oxandrolone Tablets USP, 2.5 mg

Sponsor: Upsher-Smith Laboratories, Inc.

Approval Date: December 1, 2006

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APPLICATION NUMBER:

ANDA 76-761

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APPLICATION NUMBER:

ANDA 76-761

APPROVAL LETTER



DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville, MD 20857

ANDA 76-761

Upsher-Smith Laboratories, Inc.
Attention: Kimberly C. Oakins
Regulatory Affairs Specialist
6701 Evenstad Drive
Maple Grove, MN 55369

Dear Madam:

This is in reference to your abbreviated new drug application (ANDA) dated June 12, 2003, submitted pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act (the Act), for Oxandrolone Tablets USP, 2.5 mg.

Reference is also made to your amendments dated August 3, 2004; March 29, May 21, and June 6, 2005; and September 14, October 10, and November 8, 16, and 29, 2006. We also refer to your correspondences dated January 14, and December 20, 2005, addressing patent issues listed below.

We have completed the review of this ANDA and have concluded that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly the ANDA is approved. The Division of Bioequivalence has determined your Oxandrolone Tablets, 2.5 mg, to be bioequivalent and, therefore, therapeutically equivalent to the reference listed drug, Oxandrin Tablets, 2.5 mg, of Savient Pharmaceuticals Inc. Your dissolution testing should be incorporated into the stability and quality control program using the same method proposed in your ANDA.

The reference listed drug (RLD) upon which you have based your ANDA, Oxandrin Tablets, 2.5 mg, of Savient Pharmaceuticals Inc., is subject to periods of patent protection. The following patents and expiration dates are currently listed in the Agency's publication titled Approved Drug Products with Therapeutic Equivalence Evaluations (the "Orange Book"):

<u>U.S. Patent No.</u>	<u>Expiration Date</u>
5,872,147 (the '147 patent)	December 5, 2017
6,090,799 (the '799 patent)	July 18, 2017
6,576,659 (the '659 patent)	December 5, 2017
6,670,351 (the '351 patent)	October 20, 2012
6,828,313 (the '313 patent)	December 5, 2017

FDA has determined that information on the '147, '799, '659, and '351 patents was submitted to FDA by the NDA holder after the date of the submission of your ANDA. FDA has also determined that information on the '147, '799, '659, and '351 patents was submitted by the NDA holder more than 30 days after the patent was issued by the U.S. Patent and Trademark Office (PTO). Therefore, under 21 CFR 314.94(a)(12)(vi), no person with an appropriate patent certification at the time of the submission of the patents was required to submit an amended patent certification to address the '147, '799, '659, and '351 patents. You elected not to submit an amended patent certification with respect to these patents.

With respect to the '313 patent, which was submitted to the agency within 30 days of issuance by the PTO, your ANDA contains a statement under section 505(j)(2)(A)(viii) of the Act indicating that the '313 patent is a method of use patent that does not claim any of the indications for which you are seeking approval.

Under section 506A of the Act, certain changes in the conditions described in this ANDA require an approved supplemental application before the change may be made.

Postmarketing reporting requirements for this ANDA are set forth in 21 CFR 314.80-81 and 314.98. The Office of Generic Drugs should be advised of any change in the marketing status of this drug.

Promotional materials may be submitted to FDA for comment prior to publication or dissemination. Please note that these submissions are voluntary. If you desire comments on proposed launch promotional materials with respect to compliance with applicable regulatory requirements, we recommend you submit, in draft or mock-up form, two copies of both the promotional materials and package insert(s) directly to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications
5901-B Ammendale Road
Beltsville, MD 20705

We call your attention to 21 CFR 314.81(b)(3) which requires that all promotional materials be submitted to the Division of Drug Marketing, Advertising, and Communications with a completed Form FDA 2253 at the time of their initial use.

Sincerely yours,

{See appended electronic signature page}

Gary Buehler
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Robert L. West
12/1/2006 01:43:15 PM
for Gary Buehler

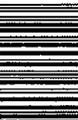
CENTER FOR DRUG EVALUATION AND RESEARCH

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APPROVED LABELING

Oxandrolone Tablets,
USP 2.5 mg



Oxandrolone Tablets,
USP 2.5 mg

Oxandrolone Tablets,
USP 2.5 mg



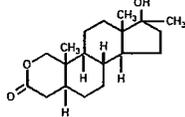
Oxandrolone Tablets,
USP 2.5 mg

Oxandrolone Tablets, USP

Rx only

DESCRIPTION

Oxandrolone Tablets, USP contain 2.5 mg of the anabolic steroid oxandrolone. Oxandrolone is 17 β -hydroxy-17 α -methyl-2-oxa-5 α -androst-3-one with the following structural formula:



Molecular Formula: C₁₈H₃₀O₂

Molecular Weight: 306.44

Inactive ingredients include anhydrous lactose, hypromellose, magnesium stearate, and pregelatinized starch.

USP Dissolution Test Pending.

CLINICAL PHARMACOLOGY

Anabolic steroids are synthetic derivatives of testosterone. Certain clinical effects and adverse reactions demonstrate the androgenic properties of this class of drugs. Complete dissociation of anabolic and androgenic effects has not been achieved. The actions of anabolic steroids are therefore similar to those of male sex hormones with the possibility of causing serious disturbances of growth and sexual development if given to young children. Anabolic steroids suppress the gonadotropic functions of the pituitary and may exert a direct effect upon the testes.

During exogenous administration of anabolic androgens, endogenous testosterone release is inhibited through inhibition of pituitary luteinizing hormone (LH). At large doses, spermatogenesis may be suppressed through feedback inhibition of pituitary follicle-stimulating hormone (FSH).

Anabolic steroids have been reported to increase low-density lipoproteins and decrease high-density lipoproteins. These levels revert to normal on discontinuation of treatment.

INDICATIONS AND USAGE

Oxandrolone Tablets, USP are indicated as adjunctive therapy to offset the protein catabolism associated with prolonged administration of corticosteroids, and for the relief of the bone pain frequently accompanying osteoporosis (see **DOSE AND ADMINISTRATION**).

DRUG ABUSE AND DEPENDENCE

Oxandrolone is classified as a controlled substance under the Anabolic Steroids Control Act of 1990 and has been assigned to Schedule III (non-narcotic).

CONTRAINDICATIONS

1. Known or suspected carcinoma of the prostate or the male breast.
2. Carcinoma of the breast in females with hypercalcemia (androgenic anabolic steroids may stimulate osteolytic bone resorption).
3. Pregnancy, because of possible masculinization of the fetus. Oxandrolone has been shown to cause embryotoxicity, fetotoxicity, infertility, and masculinization of female animal offspring when given in doses 9 times the human dose.
4. Nephrosis, the nephrotic phase of nephritis.
5. Hypercalcemia.

WARNINGS

PELIOSIS HEPATIS, A CONDITION IN WHICH LIVER AND SOMETIMES SPLENIC TISSUE IS REPLACED WITH BLOOD-FILLED CYSTS, HAS BEEN REPORTED IN PATIENTS RECEIVING ANDROGENIC ANABOLIC STEROID THERAPY. THESE CYSTS ARE SOMETIMES PRESENT WITH MINIMAL HEPATIC DYSFUNCTION, BUT AT OTHER TIMES THEY HAVE BEEN ASSOCIATED WITH LIVER FAILURE. THEY ARE OFTEN NOT RECOGNIZED UNTIL LIFE-THREATENING LIVER FAILURE OR INTRA-ABDOMINAL HEMORRHAGE DEVELOPS. WITHDRAWAL OF DRUG USUALLY RESULTS IN COMPLETE DISAPPEARANCE OF LESIONS.

LIVER CELL TUMORS ARE ALSO REPORTED. MOST OFTEN THESE TUMORS ARE BENIGN AND ANDROGEN-DEPENDENT, BUT FATAL MALIGNANT TUMORS HAVE BEEN REPORTED. WITHDRAWAL OF DRUG OFTEN RESULTS IN REGRESSION OR CESSATION OF PROGRESSION OF THE TUMOR. HOWEVER, HEPATIC TUMORS ASSOCIATED WITH ANDROGENS OR ANABOLIC STEROIDS ARE MUCH MORE VASCULAR THAN OTHER HEPATIC TUMORS AND MAY BE SILENT UNTIL LIFE-THREATENING INTRA-ABDOMINAL HEMORRHAGE DEVELOPS. BLOOD LIPID CHANGES THAT ARE KNOWN TO BE ASSOCIATED WITH INCREASED RISK OF ATHEROSCLEROSIS ARE SEEN IN PATIENTS TREATED WITH ANDROGENS OR ANABOLIC STEROIDS. THESE CHANGES INCLUDE DECREASED HIGH-DENSITY LIPOPROTEINS AND SOMETIMES INCREASED LOW-DENSITY LIPOPROTEINS. THE CHANGES MAY BE VERY MARKED AND COULD HAVE A SERIOUS IMPACT ON THE RISK OF ATHEROSCLEROSIS AND CORONARY ARTERY DISEASE.

Cholestatic hepatitis and jaundice may occur with 17-alpha-alkylated androgens at a relatively low dose. If cholestatic hepatitis with jaundice appears or if liver function tests become abnormal, oxandrolone should be discontinued and the etiology should be determined. Drug-induced jaundice is reversible when the medication is discontinued.

In patients with breast cancer, anabolic steroid therapy may cause hypercalcemia by stimulating osteolysis. Oxandrolone therapy should be discontinued if hypercalcemia occurs.

Edema with or without congestive heart failure may be a serious complication in patients with pre-existing cardiac, renal, or hepatic disease. Concomitant administration of adrenal cortical steroid or ACTH may increase the edema.

In children, androgen therapy may accelerate bone maturation without producing compensatory gain in linear growth. This adverse effect results in compromised adult height. The younger the child, the greater the risk of compromising final mature height. The effect on bone maturation should be monitored by assessing bone age of the left wrist and hand every 6 months (see **PRECAUTIONS, Laboratory Tests**).

Geriatric patients treated with androgenic anabolic steroids may be at an increased risk for the development of prostatic hypertrophy and prostatic carcinoma.

ANABOLIC STEROIDS HAVE NOT BEEN SHOWN TO ENHANCE ATHLETIC ABILITY.

PRECAUTIONS

Concurrent dosing of oxandrolone and warfarin may result in unexpectedly large increases in the International Normalized Ratio (INR) or prothrombin time (PT). When oxandrolone is prescribed to patients being treated with warfarin, doses of warfarin may need to be decreased significantly to maintain the desirable INR level and diminish the risk of potentially serious bleeding. (See **PRECAUTIONS, Drug Interactions).**

General

Women should be observed for signs of virilization (deepening of the voice, hirsutism, acne, clitoromegaly). Discontinuation of drug therapy at the time of evidence of mild virilism is necessary to prevent irreversible virilization. Some virilizing changes in women are irreversible even after prompt discontinuance of therapy and are not prevented by concomitant use of estrogens. Menstrual irregularities may also occur.

Anabolic steroids may cause suppression of clotting factors II, V, VII, and X, and an increase in prothrombin time.

Information for Patients

The physician should instruct patients to report immediately any use of warfarin and any bleeding.

The physician should instruct patients to report any of the following side effects of androgens:

- Males:** Too frequent or persistent erections of the penis, appearance or aggravation of acne.
Females: Hoarseness, acne, changes in menstrual periods, or more facial hair.
All patients: Nausea, vomiting, changes in skin color, or ankle swelling.

Geriatric Use:

Certain geriatric use information is protected by marketing exclusivity.

Laboratory Tests

Women with disseminated breast carcinoma should have frequent determination of urine and serum calcium levels during the course of therapy (see **WARNINGS**).

Because of the hepatotoxicity associated with the use of 17-alpha-alkylated androgens, liver function tests should be obtained periodically.

Periodic (every 6 months) x-ray examinations of bone age should be made during treatment of children to determine the rate of bone maturation and the effects of androgen therapy on the epiphyseal centers.

Androgenic anabolic steroids have been reported to increase low-density lipoproteins and decrease high-density lipoproteins. Therefore, caution is required when administering these agents to patients with a history of cardiovascular disease or who are at risk for cardiovascular disease. Serum determination of lipid levels should be performed periodically and therapy adjusted accordingly.

Hemoglobin and hematocrit should be checked periodically for polycythemia in patients who are receiving high doses of anabolic steroids.

Drug Interactions

Anticoagulants:

Anabolic steroids may increase sensitivity to oral anticoagulants. Dosage of the anticoagulant may have to be decreased in order to maintain desired prothrombin time. Patients receiving oral anticoagulant therapy require close monitoring, especially when anabolic steroids are started or stopped.

Warfarin: A multidose study of oxandrolone, given as 5 or 10 mg BID in 15 healthy subjects concurrently treated with warfarin, resulted in a mean increase in S-warfarin half-life from 26 to 48 hours and AUC from 4.55 to 12.08 ng•hr/mL; similar increases in R-warfarin half-life and AUC were also detected. Microscopic hematuria (9/15) and gingival bleeding (1/15) were also observed. A 5.5-fold decrease in the mean warfarin dose from 6.13 mg/day to 1.13 mg/day (approximately 80-85% reduction of warfarin dose), was necessary to maintain a target INR of 1.5. When oxandrolone therapy is initiated in a patient already receiving treatment with warfarin, the INR or prothrombin time (PT) should be monitored closely and the dose of warfarin adjusted as necessary until a stable target INR or PT has been achieved.

Furthermore, in patients receiving both drugs, careful monitoring of the INR or PT, and adjustment of the warfarin dosage if indicated are recommended when the oxandrolone dose is changed or discontinued. Patients should be closely monitored for signs and symptoms of occult bleeding.

Oral Hypoglycemic Agents:

Oxandrolone may inhibit the metabolism of oral hypoglycemic agents.

Adrenal Steroids or ACTH:

In patients with edema, concomitant administration with adrenal cortical steroids or ACTH may increase the edema.

Drug/Laboratory Test Interactions

Anabolic steroids may decrease levels of thyroxine-binding globulin, resulting in decreased total T₄ serum levels and increased resin uptake of T₃ and T₄. Free thyroid hormone levels remain unchanged. In addition, a decrease in PBI and radioactive iodine uptake may occur.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Animal Data:

Oxandrolone has not been tested in laboratory animals for carcinogenic or mutagenic effects. In 2-year chronic oral rat studies, a dose-related reduction of spermatogenesis and decreased organ weights (testes, prostate, seminal vesicles, ovaries, uterus, adrenals, and pituitary) were shown.

Human Data:

Liver cell tumors have been reported in patients receiving long-term therapy with androgenic anabolic steroids in high doses (see **WARNINGS**). Withdrawal of the drugs did not lead to regression of the tumors in all cases.

Geriatric patients treated with androgenic anabolic steroids may be at an increased risk for the development of prostatic hypertrophy and prostatic carcinoma.

Pregnancy

Teratogenic effects – Pregnancy Category X (see **CONTRAINDICATIONS**).

Nursing Mothers

It is not known whether anabolic steroids are excreted in human milk. Because of the potential of serious adverse reactions in nursing infants from oxandrolone, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use

Anabolic agents may accelerate epiphyseal maturation more rapidly than linear growth in children and the effect may continue for 6 months after the drug has been stopped. Therefore, therapy should be monitored by x-ray studies at 6-month intervals in order to avoid the risk of compromising adult height. Androgenic anabolic steroid therapy should be used very cautiously in children and only by specialists who are aware of the effects on bone maturation (see **WARNINGS**).

ADVERSE REACTIONS

Patients with moderate to severe COPD or COPD patients who are unresponsive to bronchodilators should be monitored closely for COPD exacerbation and fluid retention.

The following adverse reactions have been associated with use of anabolic steroids:

Hepatic

Cholestatic jaundice with, rarely, hepatic necrosis and death. Hepatocellular neoplasms and peliosis hepatitis with long-term therapy (see **WARNINGS**). Reversible changes in liver function tests also occur including increased bromsulphthalein (BSP) retention, changes in alkaline phosphatase and increases in serum bilirubin, aspartate aminotransferase (AST, SGOT) and alanine aminotransferase (ALT, SGPT).

In Males

Prepubertal: Phallic enlargement and increased frequency or persistence of erections.

Postpubertal: Inhibition of testicular function, testicular atrophy and oligospermia, impotence, chronic priapism, epididymitis, and bladder irritability.

In Females

Clitoral enlargement, menstrual irregularities.

CNS: Habituation, excitation, insomnia, depression, and changes in libido.

Hematologic: Bleeding in patients on concomitant oral anticoagulant therapy.

Breast: Gynecomastia.

Larynx: Deepening of the voice in females.

Hair: Hirsutism and male pattern baldness in females.

Skin: Acne (especially in females and prepubertal males).

Skeleton: Premature closure of epiphyses in children (see **PRECAUTIONS, Pediatric Use**).

Fluid and Electrolytes: Edema, retention of serum electrolytes (sodium chloride, potassium, phosphate, calcium).

Metabolic/Endocrine: Decreased glucose tolerance (see **PRECAUTIONS, Laboratory Tests**), increased creatinine excretion, increased serum levels of creatinine phosphokinase (CPK). Masculinization of the fetus. Inhibition of gonadotropin secretion.

OVERDOSAGE

No symptoms or signs associated with overdosage have been reported. It is possible that sodium and water retention may occur.

The oral LD₅₀ of oxandrolone in mice and dogs is greater than 5,000 mg/kg. No specific antidote is known, but gastric lavage may be used.

DOSE AND ADMINISTRATION

Therapy with anabolic steroids is adjunctive to and not a replacement for conventional therapy. The duration of therapy with Oxandrolone Tablets, USP will depend on the response of the patient and the possible appearance of adverse reactions. Therapy should be intermittent.

Adults

The response of individuals to anabolic steroids varies. The daily adult dosage is 2.5 mg to 20 mg given in 2 to 4 divided doses. The desired response may be achieved with as little as 2.5 mg or as much as 20 mg daily. A course of therapy of 2 to 4 weeks is usually adequate. This may be repeated intermittently as indicated.

Children

For children the total daily dosage of Oxandrolone Tablets, USP is ≤ 0.1 mg per kilogram body weight or ≤ 0.045 mg per pound of body weight. This may be repeated intermittently as indicated.

HOW SUPPLIED

Oxandrolone Tablets, USP 2.5 mg are oval, white, scored, uncoated tablets, debossed with "2.5" on one side and "U" to the left and "S" to the right of the score on the other side. Oxandrolone Tablets, USP are available in bottles of 100 tablets (NDC 0245-0271-1), bottles of 1000 tablets (NDC 0245-0271-10) and in unit dose cartons of 100 tablets (10 cards containing 10 tablets each) (NDC 0245-0271-01).

Store at 20-25°C (68-77°F). Excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature]. Dispense in a light, light-resistant container with a child-resistant closure as defined in the USP.

Keep out of reach of children.

Manufactured for
UPSHER-SMITH LABORATORIES, INC.
Minneapolis, MN 55447

by: Pharmaceutics International, Inc.
Hunt Valley, MD 21031
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40-27100-05

Revised 1106A

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 76-761

LABELING REVIEW(S)

**REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH**

ANDA Number:	76-761
Date of Submission:	June 12, 2003 (Original Submission)
Applicant's Name:	Upsher-Smith Laboratories, Inc.
Established Name:	Oxandrolone Tablets USP, 2.5 mg
Proposed Proprietary Name:	_____

Labeling Deficiencies:

1. GENERAL

Your proposed proprietary name _____ is under review. We will inform you of our comments when they become available. Please note that in the event that your application is approved after 90 days of the current submission then the name with its associated labels and labeling must be re-evaluated approximately 90 days prior to the expected approval of the ANDA. A re-review of the name prior to ANDA approval will rule out any objections based upon approvals of other proprietary and established names from this date forward.

2. CONTAINER (Bottles of 5s, 100s, 1000s)

- a. 21 CFR 201.109(g)(2) requires that the established name be printed in letters at least half as large as the proprietary name with commensurate prominence.
- b. Please revise the storage statement to read: "Store at 20°-25°C (68°-77°F) [see USP Controlled Room Temperature]"
- c. The Poison Prevention Packaging Act notes that special packaging (child-resistant closures) should be the responsibility of the manufacturer when the container is clearly intended to be utilized in dispensing (unit-of-use packaging). We believe the container of 5s to be unit-of-use packaging. Please comment.

3. UNIT DOSE BLISTER (2 X 5 Tablets)

Revise each blister to read "(Oxandrolone Tablet, USP)" [singular rather than plural]

4. CARTON (10 x Unit Dose Blister of 10 Tablets)

Refer to comments 2.a and 2.b.

5. PHYSICIAN INSERT

a. Add "Rx only" to a location just under the TITLE of the package insert.

b. PRECAUTIONS

- i. Add the following paragraph in bold print before the "General" subsection: "**Concurrent dosing of oxandrolone and warfarin may result in unexpectedly large increases in the INR or prothrombin time (PT). When oxandrolone is prescribed to patients being treated with warfarin, doses of warfarin may need to be decreased significantly to maintain the desirable INR level and diminish the risk of potentially serious bleeding. (See PRECAUTIONS: Drug Interactions).**"
- ii. Information for the patient-add as the first sentence in this subsection: "The physician should instruct patients to report immediately any use of warfarin and any bleeding."
- iii. Drug interactions-add the following paragraph immediately after the Anticoagulants section. The paragraph should appear as a "sub-section" of the Anticoagulants section: "*Warfarin*: A multidose study of oxandrolone, given as 5 or 10 mg BID in 15 healthy subjects concurrently treated with warfarin, resulted in a mean increase in S-warfarin half-life from 26 to 48 hours and AUC from 4.55 to 12.08 ng*hr/mL: similar increases in R-warfarin half-life and AUC were

REVIEW OF PROFESSIONAL LABELING CHECK LIST

Established Name	Yes	No	N.A.
Different name than on acceptance to file letter?		X	
Is this product a USP item? If so, USP supplement in which verification was assured. USP 27	X		
Is this name different than that used in the Orange Book?		X	
If not USP, has the product name been proposed in the PF?			X
Error Prevention Analysis			
Has the firm proposed a proprietary name? If yes, complete this subsection. D. Catterson sent the name _____ to DMETS for consult September 2003.	X		
Do you find the name objectionable? List reasons in FTR, if so. Consider: Misleading? Sounds or looks like another name? USAN stem present? Prefix or Suffix present?			X
Has the name been forwarded to the Labeling and Nomenclature Committee? If so, what were the recommendations? If the name was unacceptable, has the firm been notified?			X
Packaging			
Is this a new packaging configuration, never been approved by an ANDA or NDA? If yes, describe in FTR.	X		
Is this package size mismatched with the recommended dosage? If yes, the Poison Prevention Act may require a CRC.		X	
Does the package proposed have any safety and/or regulatory concerns?		X	
If IV product packaged in syringe, could there be adverse patient outcome if given by direct IV injection?			X
Conflict between the DOSAGE AND ADMINISTRATION and INDICATIONS sections and the packaging configuration?		X	
Is the strength and/or concentration of the product unsupported by the insert labeling?		X	
Is the color of the container (i.e. the color of the cap of a mydriatic ophthalmic) or cap incorrect?		X	
Individual cartons required? Issues for FTR: Innovator individually cartoned? Light sensitive product which might require cartoning? Must the package insert accompany the product?		X	
Are there any other safety concerns?		X	
Labeling			
Is the name of the drug unclear in print or lacking in prominence? (Name should be the most prominent information on the label).	X		
Has applicant failed to clearly differentiate multiple product strengths?		X	
Is the corporate logo larger than 1/3 container label? (No regulation - see ASHP guidelines)		X	
Labeling(continued)			
Does RLD make special differentiation for this label? (i.e., Pediatric strength vs Adult; Oral Solution vs Concentrate, Warning Statements that might be in red for the NDA)		X	
Is the Manufactured by/Distributor statement incorrect or falsely inconsistent between labels and labeling? Is "Jointly Manufactured by..." statement needed?		X	
Failure to describe solid oral dosage form identifying markings in HOW SUPPLIED?		X	
Has the firm failed to adequately support compatibility or stability claims which appear in the insert labeling? Note: Chemist should confirm the data has been adequately supported.		X	
Scoring: Describe scoring configuration of RLD and applicant (page #) in the FTR			
Is the scoring configuration different than the RLD?		X	
Has the firm failed to describe the scoring in the HOW SUPPLIED section?		X	
Inactive Ingredients: (FTR: List page # in application where inactives are listed)			
Does the product contain alcohol? If so, has the accuracy of the statement been confirmed? Need more info from firm	X		
Do any of the inactives differ in concentration for this route of administration?		X	
Any adverse effects anticipated from inactives (i.e., benzyl alcohol in neonates)?		X	
Is there a discrepancy in inactives between DESCRIPTION and the composition statement?		X	
Has the term "other ingredients" been used to protect a trade secret? If so, is claim supported?		X	
Failure to list the coloring agents if the composition statement lists e.g., Opacode, Opaspray?			X
Failure to list gelatin, coloring agents, antimicrobials for capsules in DESCRIPTION?			X
Failure to list dyes in imprinting inks? (Coloring agents e.g., iron oxides need not be listed)			X
USP Issues: (FTR: List USP/NDA/ANDA dispensing/storage recommendations)			
Do container recommendations fail to meet or exceed USP/NDA recommendations? If so, are the recommendations supported and is the difference acceptable?		X	
Because of proposed packaging configuration or for any other reason, does this applicant meet fail to meet all of the unprotected conditions of use of referenced by the RLD?		X	
Does USP have labeling recommendations? If any, does ANDA meet them?		X	
Is the product light sensitive? If so, is NDA and/or ANDA in a light resistant container?	X		
Failure of DESCRIPTION to meet USP Description and Solubility information? If so, USP information should be used.		X	

However, only include solvents appearing in innovator labeling.			
Bioequivalence Issues: (Compare bioequivalency values: insert to study. List Cmax, Tmax, T 1/2 and date study acceptable)			
Insert labeling references a food effect or a no-effect? If so, was a food study done?		X	
Has CLINICAL PHARMACOLOGY been modified? If so, briefly detail where/why.		X	
Patent/Exclusivity Issues?: FTR: Check the Orange Book edition or cumulative supplement for verification of the latest Patent or Exclusivity. List expiration date for all patents, exclusivities, etc. or if none, please state.		X	

NOTES/QUESTIONS TO THE CHEMIST:

Please note the following Labeling Deficiency: "The Poison Prevention Packaging Act notes that special packaging (child-resistant closures) should be the responsibility of the manufacturer when the container is clearly intended to be utilized in dispensing (unit-of-use packaging). We believe the container of 5s to be unit-of-use packaging. Please comment." The applicant will need to submit appropriate closure information to the CMC portion of the ANDA.

The USP recommends that this product be stored in tight light resistant containers. Do the proposed containers, blisters, and closures satisfy this recommendation?

****First Generic****

FOR THE RECORD:

- MODEL LABELING - This review is based on the labeling of Oxandrin® by Bio-Technology General Pharmaceuticals NDA 13-718/S-022 approved April 21, 2003
Packaging and storage— Preserve in tight, light-resistant containers

2. PATENTS AND EXCLUSIVITIES

Patent Data

Patent No.	Patent Expiration	Use Code	Description	How Filed	Labeling Impact
None	None	None	There are no unexpired patents for this product in the Orange Book Database.	N/A	None

Exclusivity Data

Code	Reference	Expiration	Labeling Impact
None	There is no unexpired exclusivity for this product in the Orange Book Database.	N/A	None

The firm's statements are accurate. [Vol. A1.1, pg. 9]

3. MANUFACTURING FACILITY (Vol A1.4, pg. 1234)

Pharmaceutics International, Inc.
10819 Gilroy Road
Hunt Valley, MD 21031

4. STORAGE CONDITIONS:

NDA: Store at Controlled Room Temperature (59°-77°F)

ANDA: Same as RLD. Will ask firm to revise to read-Store at 20°-25°C (68°-77°F) [see USP Controlled Room Temperature].

Test conditions: Long-Term Controlled Room Temperature Testing: 25±2°C/60±5%RH

5. DISPENSING RECOMMENDATIONS:

NDA: Dispense in a tight, light-resistant, child-resistant container.

ANDA: Container-Dispense in a tight, light-resistant container with a child-resistant closure.

Blister Carton-Dispense in a tight, light-resistant container with a child-resistant closure.

6. PRODUCT LINE:

The innovator: 2.5 mg-Bottles of 100s and 10 mg-Bottles of 60s

The applicant: 2.5 mg- Bottles of 5s, 100s, 1000s and Unit dose blister cartons of 100s

7. CONTAINER/CLOSURE SYSTEM: [Vol. A1.4, pg. 1461 & 1499 & 1549]

5s: 30cc White, Wide-mouth, Round, HDPE Bottle; Screw Cap

100s: 60cc White, Wide-mouth, Round, Squat, HDPE Bottle; Screw Cap

1000s: 250cc White, Wide-mouth, Round, HDPE Bottle; Screw Cap

Blister: 10 mil, clear, polyvinyl chloride blister with paper-backed, laminated foil as the backing

8. PRODUCT DESCRIPTION:

RLD- Scored tablets

ANDA- White oval-shaped, scored, uncoated tablets, debossed with "2.5" on the unscored side and with "U" to the left of the score and "S" to the right of the score on the reverse side. (Vol. A1.5, pg. 1705)

9. INACTIVE INGREDIENTS:

The listing of inactive ingredients in the DESCRIPTION section of the package insert appears to be consistent with the listing of inactive ingredients found in the statement of components and composition appearing on page 995 [Vol. A1.4].

Component	mg/Tablet
Oxandrolone	2.5
Anhydrous Lactose	—
Pregelatinized Starch (—
Hypromellose	—
Magnesium Stearate	—

10. BIOEQUIVALENCE: pending as of January 21, 2004.

Date of Review: January 22, 2004

Date of Submission: June 12, 2003

Primary Reviewer: Ruby Wu (for Debbie Catterson) Date: 1/22/04

Team Leader: John Grace

Date: 2/2/04

cc: ANDA 76-761
DUP/DIVISION FILE
HFD-613/RWu for DCatterson/JGrace (no cc)
V:\FIRMSNZIUPSHER\LTRS&REV\76761.na1.L.doc
Review

****First Generic****

**Approval Summary
REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH**

ANDA Number: 76-761
Date of Submission: April 16, 2004 (Amendment-FPL)
Applicant's Name: Upsher-Smith Laboratories, Inc.
Established Name: Oxandrolone Tablets USP, 2.5 mg
Proposed Proprietary Name: _____

APPROVAL SUMMARY:

Do you have 12 Final Printed Labels and Labeling? Final printed labeling submitted in electronic format.

CONTAINER (Bottles of 5s, 100s, 1000s)

Satisfactory in final print as of the April 16, 2004 submission.
Electronic Document location: \\Cdsesubogd1\n76761\N 000\2004-04-16\Labeling.

UNIT DOSE BLISTER (2 X 5 Tablets)

Satisfactory in final print as of the April 16, 2004 submission.
Electronic Document location: \\Cdsesubogd1\n76761\N 000\2004-04-16\Labeling.

CARTON (10 x Unit Dose Blister of 10 Tablets)

Satisfactory in final print as of the April 16, 2004 submission.
Electronic Document location: \\Cdsesubogd1\n76761\N 000\2004-04-16\Labeling.

Professional Package INSERT:

Satisfactory in final print as of the April 16, 2004 submission. [Revised 0204]
Electronic Document location: \\Cdsesubogd1\n76761\N 000\2004-04-16\Labeling.
*Proprietary name must be re-evaluated approximately 90 days prior to the expected approval of the ANDA!
There is one note to the chemist that still needs to be addressed.*

Revisions needed post-approval: Yes

The following is a requested labeling revision from my review of your amendment dated April 16, 2004 for ANDA 76-761 for Oxandrolone Tablets USP, 2.5 mg. The revision is a "POST-APPROVAL" revision and may be submitted in an annual report, provided the change is described in full.

CONTAINER, CARTON, and INSERT: Revise the storage recommendation to read " Store at 20°-25°C (68°-77°F) excursions permitted to 15°-30°C (59°-86°F)[see USP Controlled Room Temperature]" [delete

BASIS OF APPROVAL:

Was this approval based upon a petition? No
What is the RLD on the 356(h) form: Oxandrin®
NDA Number: 13-718
NDA Drug Name: Oxandrolone Tablets
NDA Firm: Bio-Technology General Pharmaceuticals
Date of Approval of NDA Insert and supplement: NDA 13-718/S-022 approved April 21, 2003
Has this been verified by the MIS system for the NDA? Yes
Was this approval based upon an OGD labeling guidance? No
Basis of Approval for the Container Labels: Side-by-side comparison with innovator labels in jacket.

PATENTS/EXCLUSIVITIES

Patent Data

Patent No.	Patent Expiration	Use Code	Description	How Filed	Labeling Impact
None	None	None	There are no unexpired patents for this product in the Orange Book Database.	N/A	None

Exclusivity Data

Code	Reference	Expiration	Labeling Impact
None	There is no unexpired exclusivity for this product in the Orange Book Database.	N/A	None

REVIEW OF PROFESSIONAL LABELING CHECK LIST

Established Name	Yes	No	N.A.
Different name than on acceptance to file letter?		X	
Is this product a USP item? If so, USP supplement in which verification was assured. USP 27	X		
Is this name different than that used in the Orange Book?		X	
If not USP, has the product name been proposed in the PF?			X
Error Prevention Analysis			
Has the firm proposed a proprietary name? If yes, complete this subsection. D. Catterson sent the name _____ to DMETS for consult September 2003; name found acceptable 2/18/04 Consult #03-0257.	X		
Do you find the name objectionable? List reasons in FTR, if so. Consider: Misleading? Sounds or looks like another name? USAN stem present? Prefix or Suffix present?			X
Has the name been forwarded to the Labeling and Nomenclature Committee? If so, what were the recommendations? If the name was unacceptable, has the firm been notified?			X
Packaging			
Is this a new packaging configuration, never been approved by an ANDA or NDA? If yes, describe in FTR.	X		
Is this package size mismatched with the recommended dosage? If yes, the Poison Prevention Act may require a CRC.		X	
Does the package proposed have any safety and/or regulatory concerns?		X	
If IV product packaged in syringe, could there be adverse patient outcome if given by direct IV injection?			X
Conflict between the DOSAGE AND ADMINISTRATION and INDICATIONS sections and the packaging configuration?		X	
Is the strength and/or concentration of the product unsupported by the insert labeling?		X	
Is the color of the container (i.e. the color of the cap of a mydriatic ophthalmic) or cap incorrect?		X	
Individual cartons required? Issues for FTR: Innovator individually cartoned? Light sensitive product which might require cartoning? Must the package insert accompany the product?		X	
Are there any other safety concerns?		X	
Labeling			
Is the name of the drug unclear in print or lacking in prominence? (Name should be the most prominent information on the label).	X		
Has applicant failed to clearly differentiate multiple product strengths?		X	
Is the corporate logo larger than 1/3 container label? (No regulation - see ASHP guidelines)		X	
Labeling(continued)			
Does RLD make special differentiation for this label? (i.e., Pediatric strength vs Adult; Oral Solution vs Concentrate, Warning Statements that might be in red for the NDA)		X	
Is the Manufactured by/Distributor statement incorrect or falsely inconsistent between labels and labeling? Is "Jointly Manufactured by..." statement needed?		X	
Failure to describe solid oral dosage form identifying markings in HOW SUPPLIED?		X	
Has the firm failed to adequately support compatibility or stability claims which appear in the insert labeling? Note: Chemist should confirm the data has been adequately supported.		X	
Scoring: Describe scoring configuration of RLD and applicant (page #) in the FTR			
Is the scoring configuration different than the RLD?		X	
Has the firm failed to describe the scoring in the HOW SUPPLIED section?		X	
Inactive Ingredients: (FTR: List page # in application where inactives are listed)			
Does the product contain alcohol? If so, has the accuracy of the statement been confirmed? Need more info from firm		X	
Do any of the inactives differ in concentration for this route of administration?		X	
Any adverse effects anticipated from inactives (i.e., benzyl alcohol in neonates)?		X	
Is there a discrepancy in inactives between DESCRIPTION and the composition statement?		X	
Has the term "other ingredients" been used to protect a trade secret? If so, is claim supported?		X	
Failure to list the coloring agents if the composition statement lists e.g., Opacode, Opaspray?			X
Failure to list gelatin, coloring agents, antimicrobials for capsules in DESCRIPTION?			X
Failure to list dyes in imprinting inks? (Coloring agents e.g., iron oxides need not be listed)			X
USP Issues: (FTR: List USP/NDA/ANDA dispensing/storage recommendations)			
Do container recommendations fall to meet or exceed USP/NDA recommendations? If so, are the recommendations supported and is the difference acceptable?		X	
Because of proposed packaging configuration or for any other reason, does this applicant meet fail to meet all of the unprotected conditions of use of referenced by the RLD?		X	
Does USP have labeling recommendations? If any, does ANDA meet them?		X	
Is the product light sensitive? If so, is NDA and/or ANDA in a light resistant container?	X		
Failure of DESCRIPTION to meet USP Description and Solubility information? If so, USP information should be used. However, only include solvents appearing in innovator labeling.		X	
Bioequivalence Issues: (Compare bioequivalency values: insert to study. List Cmax, Tmax, T 1/2 and date study acceptable)			
Insert labeling references a food effect or a no-effect? If so, was a food study done?		X	
Has CLINICAL PHARMACOLOGY been modified? If so, briefly detail where/why.		X	
Patent/Exclusivity Issues?: FTR: Check the Orange Book edition or cumulative supplement for verification of the latest Patent or Exclusivity. List expiration date for all patents, exclusivities, etc. or if none, please state.		X	

NOTES/QUESTIONS TO THE CHEMIST:

Please note the following Labeling Deficiency: "The Poison Prevention Packaging Act notes that special packaging (child-resistant closures) should be the responsibility of the manufacturer when the container is clearly intended to be utilized in dispensing (unit-of-use packaging). We believe the container of 5s to be unit-of-use packaging. Please comment." The applicant will need to submit appropriate closure information to the CMC portion of the ANDA. *In the April 16, 2004 amendment, the firm provided info on CRC caps for the bottles of 5's.*

The USP recommends that this product be stored in tight light resistant containers. Do the proposed containers, blisters, and closures satisfy this recommendation?

****First Generic******FOR THE RECORD:**

1. MODEL LABELING - This review is based on the labeling of Oxandrin® by Bio-Technology General Pharmaceuticals NDA 13-718/S-022 approved April 21, 2003
Packaging and storage— Preserve in tight, light-resistant containers

2. PATENTS AND EXCLUSIVITIES

Patent Data

Patent No.	Patent Expiration	Use Code	Description	How Filed	Labeling Impact
None	None	None	There are no unexpired patents for this product in the Orange Book Database.	N/A	None

Exclusivity Data

Code	Reference	Expiration	Labeling Impact
None	There is no unexpired exclusivity for this product in the Orange Book Database.	N/A	None

The firm's statements are accurate. [Vol. A1.1, pg. 9]

3. MANUFACTURING FACILITY (Vol. A1.4, pg. 1234)

Pharmaceutics International, Inc.
10819 Gilroy Road
Hunt Valley, MD 21031

4. STORAGE CONDITIONS:

NDA: Store at Controlled Room Temperature (59°-77°F)

ANDA: Same as RLD. Will ask firm to revise to read-Store at 20°-25°C (68°-77°F) [see USP Controlled Room Temperature].

Test conditions: Long-Term Controlled Room Temperature Testing: 25±2°C/60±5%RH

5. DISPENSING RECOMMENDATIONS:

NDA: Dispense in a tight, light-resistant, child-resistant container.

ANDA: Container-Dispense in a tight, light-resistant container with a child-resistant closure.

Blister Carton-Dispense in a tight, light-resistant container with a child-resistant closure.

6. PRODUCT LINE:

The innovator: 2.5 mg-Bottles of 100s and 10 mg-Bottles of 60s

The applicant: 2.5 mg- Bottles of 5s, 100s, 1000s and Unit dose blister cartons of 100s

7. CONTAINER/CLOSURE SYSTEM: [Vol. A1.4, pg. 1461 & 1499 & 1549]

5s: 30cc White, Wide-mouth, Round, HDPE Bottle; CRC cap [see 4/16/04 amendment; pg. 11]

100s: 60cc White, Wide-mouth, Round, Squat, HDPE Bottle; Screw Cap

1000s: 250cc White, Wide-mouth, Round, HDPE Bottle; Screw Cap

Blister: 10 mil, clear, polyvinyl chloride blister with paper-backed, laminated foil as the backing

8. PRODUCT DESCRIPTION:

RLD: Scored tablets

ANDA- White oval-shaped, scored, uncoated tablets, debossed with "2.5" on the unscored side and with "U" to the left of the score and "S" to the right of the score on the reverse side. (Vol. A1.5, pg. 1705)

9. INACTIVE INGREDIENTS:

The listing of inactive ingredients in the DESCRIPTION section of the package insert appears to be consistent with the listing of inactive ingredients found in the statement of components and composition appearing on page

Component	mg/Tablet
Oxandrolone	25
Anhydrous Lactose	
Pregelatinized Starch	
Hypromellose	
Magnesium Stearate	

10. BIOEQUIVALENCE: pending as of May 13, 2004.

11. PROPRIETARY NAME: D. Catterson sent the name to DMETS for consult September 2003; name found acceptable 2/18/04 Consult #03-0257.

Date of Review: May 17, 2004

Date of Submission: April 16, 2004

Primary Reviewer: Ruby Wu (for ^{Ruby}Debbie Catterson) Date: 5/17/04

Team Leader: John Grace

Date:

cc: ANDA 76-761
 DUP/DIVISION FILE
 HFD-613/RWu for DCatterson/JGrace (no cc)
 V:\FIRMSNZUPHER\LTRS&REV\76761.ap.L.doc
 Review

Grace 5/24/04 for John Grace

****First Generic****

This approval summary supersedes the November 8, 2006 approval summary.

**APPROVAL SUMMARY
REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH**

ANDA Number: 76-761
Date of Submission: November 16, 2006
Applicant's Name: Upsher-Smith Laboratories, Inc.
Established Name: Oxandrolone Tablets USP, 2.5 mg

APPROVAL SUMMARY:

CONTAINER (Bottles of 5s, 100s, 1000s)

Satisfactory in final print as of the November 8, 2006 submission.

UNIT DOSE BLISTER (2 X 5 Tablets)

Satisfactory in final print as of the November 8, 2006 submission.

CARTON (10 x Unit Dose Blister of 10 Tablets)

Satisfactory in final print as of the November 8, 2006 submission.

PROFESSIONAL PACKAGE INSERT:

Satisfactory in final print as of the November 16, 2006 submission.

Post-approval revisions:

In the DESCRIPTION section insert the route of administration.

REFERENCE LISTED DRUG:

Was this approval based upon a petition? Yes, citizens petition

What is the RLD on the 356(h) form: Oxandrin® tablets

NDA Number: NDA 13-718

NDA Drug Name: Oxandrin® tablets

NDA Firm: BTG Pharmaceuticals

Date of Approval of NDA Insert and supplement #: June 20, 2005/S-023

Has this been verified by the MIS system for the NDA? Yes

Was this approval based upon an OGD labeling guidance? Yes, **OGD labeling template**

Basis of Approval for the Container Labels: side-by-side

Basis of Approval for the Carton Labeling: side-by-side

Other Comments: Upsher-Smith also has a 10 mg tablet, ANDA 78-033.

PATENT/ EXCLUSIVITIES

Patent Data – NDA 13-718

No	Expiration	Use Code	Use	File	Labeling Impact
5872147	12/05/2017	U-585	To promote weight gain after weight loss in certain types of patients	Firm declined to address due to late file	None See FTR
6090799	07/18/2017	U-585	To promote weight gain after weight loss in certain types of patients	Firm declined to address due to late file	None See FTR
6576659	12/05/2017	U-585	To promote weight gain after weight loss in certain types of patients	Firm declined to address due to late file	None See FTR
6670351	10/20/2012	U-585	To promote weight gain after weight loss in certain types of patients	Firm declined to address due to late file	None See FTR
6828313	12/05/2017	U-585	To promote weight gain after weight loss in certain types of patients	MOU	Carve-out

Exclusivity Data -

Code/sup	Expiration	Use Code	Description	Labeling Impact
M-42	6/20/2008		Addition of a geriatric use subsection to the precautions section of the package insert and geriatric dosing information	Carve-Out

***First Generic
FOR THE RECORD:**

1. Review based on an OGD labeling template created on November 3, 2006.
2. PATENT/ EXCLUSIVITIES
See above.
3. MANUFACTURING FACILITY (Vol. A1.4, pg. 1234)
Pharmaceutics International, Inc.
10819 Gilroy Road
Hunt Valley, MD 21031
4. STORAGE CONDITIONS:
NDA: Store at Controlled Room Temperature (59°-77°F)
ANDA: Store at 20°-25°C (68°-77°F) Excursions permitted to 15°-30°C (59°-77°F) [see USP Controlled Room Temperature].
Test conditions: Long-Term Controlled Room Temperature Testing: 25±2°C/60±5%RH
5. DISPENSING RECOMMENDATIONS:
NDA: Dispense in a tight, light-resistant, child-resistant container.
ANDA: Container-Dispense in a tight, light-resistant container with a child-resistant closure.
Blister Carton-Dispense in a tight, light-resistant container with a child-resistant closure as defined in the USP.
6. PRODUCT LINE:
The innovator: 2.5 mg-Bottles of 100s and 10 mg-Bottles of 60s
The applicant: 2.5 mg- Bottles of 100s, 1000s and Unit dose blister cartons of 100s
7. CONTAINER/CLOSURE SYSTEM: [Vol. A1.4, pg. 1461 & 1499 & 1549]
100s: 60cc White, Wide-mouth, Round, Squat, HDPE Bottle; Screw Cap
1000s: 250cc White, Wide-mouth, Round, HDPE Bottle; Screw Cap

Blister: 10 mil, clear, polyvinyl chloride blister with paper-backed, laminated foil as the backing
8. PRODUCT DESCRIPTION:
RLD- Scored tablets
ANDA- White oval-shaped, scored, uncoated tablets, debossed with "2.5" on the unscored side and with "U" to the left of the score and "S" to the right of the score on the reverse side. (Vol. A1.5, pg. 1705)
9. INACTIVE INGREDIENTS:
The listing of inactive ingredients in the DESCRIPTION section of the package insert appears to be consistent with the listing of inactive ingredients found in the statement of components and composition appearing on page 995 [Vol. A1.4].
10. USP Dissolution Test is Pending. Firm used a dissolution test not recognized by the USP. Once the test is listed in the USP, firm will update the statement in the DESCRIPTION section of package insert.

Date of Review: November 20, 2006 Date of Submission: November 16, 2006

Primary Reviewer: Postelle Birch-Smith

Team Leader: John Grace

cc: ANDA 76-761
DUP/DIVISION FILE

1 PAGE WITHHELD IN FULL

**Oxandrolone
Tablets, USP**

2.5 mg
5 Tablets

UPSHER-SMITH

PROFESSIONAL SAMPLE
Not for Sale



Rx only

Manufactured for
UPSHER-SMITH LABORATORIES, INC.
Minneapolis, MN 55447
by: Pharmacia International, Inc.
Kalamazoo, MI 49001
42-27166-01

PROFESSIONAL SAMPLE: Not for Sale
Each tablet contains: Oxandrolone 2.5 mg
Usual adult dosage: See package insert for full
prescribing information.
Keep out of reach of children.
SEALED FOR YOUR PROTECTION.

Store at 20°-25° C (68°-77° F) and excursions permitted to
15°-30° C (59°-86° F) (see USP Controlled Room Temperature).
Keep tightly closed. Protect from light and moisture. Dispense in
a light-resistant container with a child-resistant closure.



N
3 0245-0271-66 6

LoVExp.

R0906

NDC 0245-0271-11

Oxandrolone Tablets, USP

2.5 mg



100 Tablets

Rx only

UPSHER-SMITH

Each tablet contains: Oxandrolone 2.5 mg
Usual adult dosage: See package insert for full
prescribing information.
Store at 20°-25°C (68°-77°) and
excursions permitted to 15°-30°C (59°-86°F)
(see USP Controlled Room Temperature)
Keep tightly closed. Protect from light and moisture.
Dispense in a light, light-resistant container with a
child-resistant closure.
Keep out of reach of children.
SEALED FOR YOUR PROTECTION.
Manufactured for
UPSHER-SMITH LABORATORIES, INC.
Minneapolis, MN 55447
by: Pharmaceutics International, Inc.
Hunt Valley, MD 21031
42-27111-01



N 0245-0271-11 6

Lot/Exp.

R0906

NDC 0245-0271-10

Oxandrolone Tablets, USP

2.5 mg

1000 Tablets

UPSHER-SMITH



Rx only

Each tablet contains: Oxandrolone 2.5 mg

Usual adult dosage: See package insert for full prescribing information.
Store at 20°-25°C (68°-77°F) and excursions permitted to 15°-30°C(59°-86°F)
[see USP Controlled Room Temperature]. Keep tightly closed. Protect from
light and moisture. Dispense in a tight, light-resistant container with a
child-resistant closure.

Keep out of reach of children.

SEALED FOR YOUR PROTECTION.

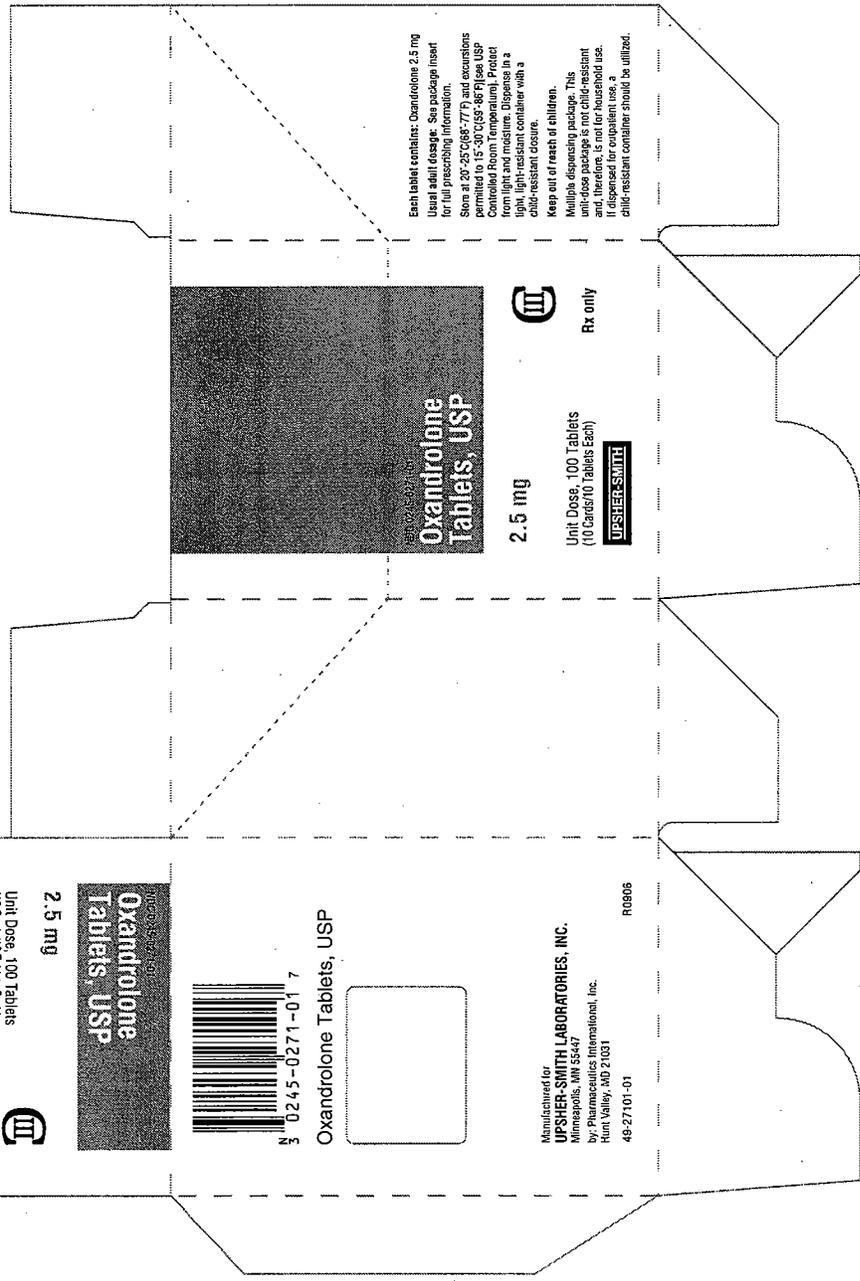
Manufactured for
UPSHER-SMITH LABORATORIES, INC.
Minneapolis, MN 55447
by: Pharmaceutics International, Inc.
Hunt Valley, MD 21031

42-27110-01

R0906



<p>Oxandrolone Tablet, USP </p> <p>2.5 mg Dist. by: UPSHER-SMITH Minneapolis, MN 55447 245-271-02 LOT EXP</p> <p>R0906</p> <p>(0100302459271995)</p> 	<p>Oxandrolone Tablet, USP </p> <p>2.5 mg Dist. by: UPSHER-SMITH Minneapolis, MN 55447 245-271-02 LOT EXP</p> <p>R0906</p> <p>(0100302459271995)</p> 
<p>Oxandrolone Tablet, USP </p> <p>2.5 mg Dist. by: UPSHER-SMITH Minneapolis, MN 55447 245-271-02 LOT EXP</p> <p>R0906</p> <p>(0100302459271995)</p> 	<p>Oxandrolone Tablet, USP </p> <p>2.5 mg Dist. by: UPSHER-SMITH Minneapolis, MN 55447 245-271-02 LOT EXP</p> <p>R0906</p> <p>(0100302459271995)</p> 
<p>Oxandrolone Tablet, USP </p> <p>2.5 mg Dist. by: UPSHER-SMITH Minneapolis, MN 55447 245-271-02 LOT EXP</p> <p>R0906</p> <p>(0100302459271995)</p> 	<p>Oxandrolone Tablet, USP </p> <p>2.5 mg Dist. by: UPSHER-SMITH Minneapolis, MN 55447 245-271-02 LOT EXP</p> <p>R0906</p> <p>(0100302459271995)</p> 
<p>Oxandrolone Tablet, USP </p> <p>2.5 mg Dist. by: UPSHER-SMITH Minneapolis, MN 55447 245-271-02 LOT EXP</p> <p>R0906</p> <p>(0100302459271995)</p> 	<p>Oxandrolone Tablet, USP </p> <p>2.5 mg Dist. by: UPSHER-SMITH Minneapolis, MN 55447 245-271-02 LOT EXP</p> <p>R0906</p> <p>(0100302459271995)</p> 
<p>Oxandrolone Tablet, USP </p> <p>2.5 mg Dist. by: UPSHER-SMITH Minneapolis, MN 55447 245-271-02 LOT EXP</p> <p>R0906</p> <p>(0100302459271995)</p> 	<p>Oxandrolone Tablet, USP </p> <p>2.5 mg Dist. by: UPSHER-SMITH Minneapolis, MN 55447 245-271-02 LOT EXP</p> <p>R0906</p> <p>(0100302459271995)</p> 



UP-SHER-SMITH
Unit Dose, 100 Tablets
(10 Cards/10 Tablets Each)



**Oxandrolone
Tablets, USP**



5 0245-0271-01 7

Oxandrolone Tablets, USP



Manufactured for
UP-SHER-SMITH LABORATORIES, INC.
Minneapolis, MN 55447
by: Pharmacia Inc. International, Inc.
Hunt Valley, MD 21031
48-27101-01

R0806

Each tablet contains: Oxandrolone 2.5 mg
Usual adult dosage: See package insert
for full prescribing information.
Store at 20°-25°C (68°-77°F) and excursions
permitted to 15°-30°C (59°-86°F) (see USP
Controlled Room Temperature). Protect
from light and moisture. Dispense in a
light-resistant container with a
child-resistant closure.
Keep out of reach of children.
Multiple dispensing package. This
unit-dose package is not child-resistant
if there are 15 or more tablets and use
of a child-resistant container
child-resistant container should be utilized.

**Oxandrolone
Tablets, USP**



2.5 mg

Unit Dose, 100 Tablets
(10 Cards/10 Tablets Each)



Rx only

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Postelle Birch
11/21/2006 10:50:07 AM
MEDICAL OFFICER

John Grace
11/21/2006 11:00:52 AM
MEDICAL OFFICER

****First Generic****

This approval summary supersedes the April 16, 2004 approval summary.

**APPROVAL SUMMARY
REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH**

ANDA Number: 76-761
Date of Submission: November 8, 2006
Applicant's Name: Upsher-Smith Laboratories, Inc.
Established Name: Oxandrolone Tablets USP, 2.5 mg

APPROVAL SUMMARY:

CONTAINER (Bottles of 5s, 100s, 1000s)
Satisfactory in final print as of the November 8, 2006 submission.

UNIT DOSE BLISTER (2 X 5 Tablets)
Satisfactory in final print as of the November 8, 2006 submission.

CARTON (10 x Unit Dose Blister of 10 Tablets)
Satisfactory in final print as of the November 8, 2006 submission.

PROFESSIONAL PACKAGE INSERT:
Satisfactory in final print as of the November 8, 2006 submission.

Post-approval revisions:
In the DESCRIPTION section insert the route of administration.

REFERENCE LISTED DRUG:

Was this approval based upon a petition? Yes, citizens petition
What is the RLD on the 356(h) form: Oxandrin® tablets
NDA Number: NDA 13-718
NDA Drug Name: Oxandrin® tablets
NDA Firm: BTG Pharmaceuticals
Date of Approval of NDA Insert and supplement #: June 20, 2005/S-023
Has this been verified by the MIS system for the NDA? Yes
Was this approval based upon an OGD labeling guidance? Yes, **OGD labeling template**
Basis of Approval for the Container Labels: side-by-side
Basis of Approval for the Carton Labeling: side-by-side
Other Comments: Upsher-Smith also has a 10 mg tablet, ANDA 78-033.

PATENT/ EXCLUSIVITIES

Patent Data – NDA 13-718

No	Expiration	Use Code	Use	File	Labeling Impact
5872147	12/05/2017	U-585	To promote weight gain after weight loss in certain types of patients	Firm declined to address due to late file	None See FTR
6090799	07/18/2017	U-585	To promote weight gain after weight loss in certain types of patients	Firm declined to address due to late file	None See FTR
6576659	12/05/2017	U-585	To promote weight gain after weight loss in certain types of patients	Firm declined to address due to late file	None See FTR
6670351	10/20/2012	U-585	To promote weight gain after weight loss in certain types of patients	Firm declined to address due to late file	None See FTR
6828313	12/05/2017	U-585	To promote weight gain after weight loss in certain types of patients	MOU	Carve-out

Exclusivity Data -

Code/sup	Expiration	Use Code	Description	Labeling Impact
M-42	6/20/2008		Addition of a geriatric use subsection to the precautions section of the package insert and geriatric dosing information	Carve-Out

***First Generic**

FOR THE RECORD:

1. Review based on an OGD labeling template created on November 3, 2006.
2. PATENT/ EXCLUSIVITIES
See above.
3. MANUFACTURING FACILITY (Vol. A1.4, pg. 1234)
Pharmaceuticals International, Inc.
10819 Gilroy Road
Hunt Valley, MD 21031
4. STORAGE CONDITIONS:
NDA: Store at Controlled Room Temperature (59°-77°F)
ANDA: Store at 20°-25°C (68°-77°F) Excursions permitted to 15°-30°C (59°-77°F) [see USP Controlled Room Temperature].
Test conditions: Long-Term Controlled Room Temperature Testing: 25±2°C/60±5%RH
5. DISPENSING RECOMMENDATIONS:
NDA: Dispense in a tight, light-resistant, child-resistant container.
ANDA: Container-Dispense in a tight, light-resistant container with a child-resistant closure.
Blister Carton-Dispense in a tight, light-resistant container with a child-resistant closure as defined in the USP.
6. PRODUCT LINE:
The innovator: 2.5 mg-Bottles of 100s and 10 mg-Bottles of 60s
The applicant: 2.5 mg- Bottles of 100s, 1000s and Unit dose blister cartons of 100s
7. CONTAINER/CLOSURE SYSTEM: [Vol. A1.4, pg. 1461 & 1499 & 1549]
100s: 60cc White, Wide-mouth, Round, Squat, HDPE Bottle; Screw Cap
1000s: 250cc White, Wide-mouth, Round, HDPE Bottle; Screw Cap

Blister: 10 mil, clear, polyvinyl chloride blister with paper-backed, laminated foil as the backing
8. PRODUCT DESCRIPTION:
RLD- Scored tablets
ANDA- White oval-shaped, scored, uncoated tablets, debossed with "2.5" on the unscored side and with "U" to the left of the score and "S" to the right of the score on the reverse side. (Vol. A1.5, pg. 1705)
9. INACTIVE INGREDIENTS:
The listing of inactive ingredients in the DESCRIPTION section of the package insert appears to be consistent with the listing of inactive ingredients found in the statement of components and composition appearing on page 995 [Vol. A1.4].
10. 147, 799, 659, 351 were not timely filed. 313 filed an MOU and M-42 carve-out per Jeanne Skanchy on 10/23/2006 per Martin Shimer's comments.

Date of Review: November 14, 2006 Date of Submission: November 9, 2006

Primary Reviewer: Postelle Birch-Smith

Team Leader: John Grace

cc: ANDA 76-761
DUP/DIVISION FILE

1 PAGE WITHHELD IN FULL

**Oxandrolone
Tablets, USP**

2.5 mg

5 Tablets

UPSHER-SMITH

PROFESSIONAL SAMPLE
Not for Sale



Rx only

PROFESSIONAL SAMPLE: Not for Sale
Each tablet contains Oxandrolone 2.5 mg.
Usual adult dosage: See package insert for full
prescribing information.
Keep out of reach of children.
SEALED FOR YOUR PROTECTION.

Manufactured for
UPSHER-SMITH LABORATORIES, INC.
Kenilworth, NJ 07033
by Pharmacia International Inc.
Hart Valley, NJ 07023
42-27156-01

Store at 20°-25° (68°-77°F) and excursions permitted to
15°-30° (59°-86°F) (see USP Controlled Room Temperature).
Keep tightly closed. Protect from light and moisture. Dispense in
a light, light-resistant container with a child-resistant closure.



N
3 0245-0271-66 6

Lot/Exp.

PRO36

**Oxandrolone
Tablets, USP**

2.5 mg

100 Tablets

UPsher-SMITH



Rx only

Each labeled container: Oxandrolone 2.5 mg
Usual adult dosage: See package insert for full
prescribing information.

Store at 20°-25°C (68°-77°F) and
excursions permitted to 15°-30°C (59°-86°F)
(see USP Controlled Room Temperature).
Keep tightly closed. Protect from light and moisture.
Dispense in a light-resistant container with a
child-resistant closure.

Keep out of reach of children.
SEALED FOR YOUR PROTECTION.
Manufactured for
UPsher-SMITH LABORATORIES, INC.
Merrifield, VA 22067

By Pharmacia International, Inc.
Parsippany, NJ 07054
42-2711-01

R906



N 0245-0271-11 6
Lot/Exp.

NDC 0245-0271-10

Oxandrolone Tablets, USP

2.5 mg

1000 Tablets

UPsher-SMITH



Rx only

Each tablet contains: Oxandrolone 2.5 mg

Usual adult dosage: See package insert for full prescribing information.
Store at 20°-25°C (68°-77°F) and excursions permitted to 15°-30°C (59°-86°F)
[see USP Controlled Room Temperature]. Keep tightly closed. Protect from
light and moisture. Dispense in a tight, light-resistant container with a
child-resistant closure.

Keep out of reach of children.

SEALED FOR YOUR PROTECTION.

Manufactured for
UPsher-SMITH LABORATORIES, INC.
Minneapolis, MN 55447

by: Pharmaceuticals International, Inc.
Hunt Valley, MD 21031

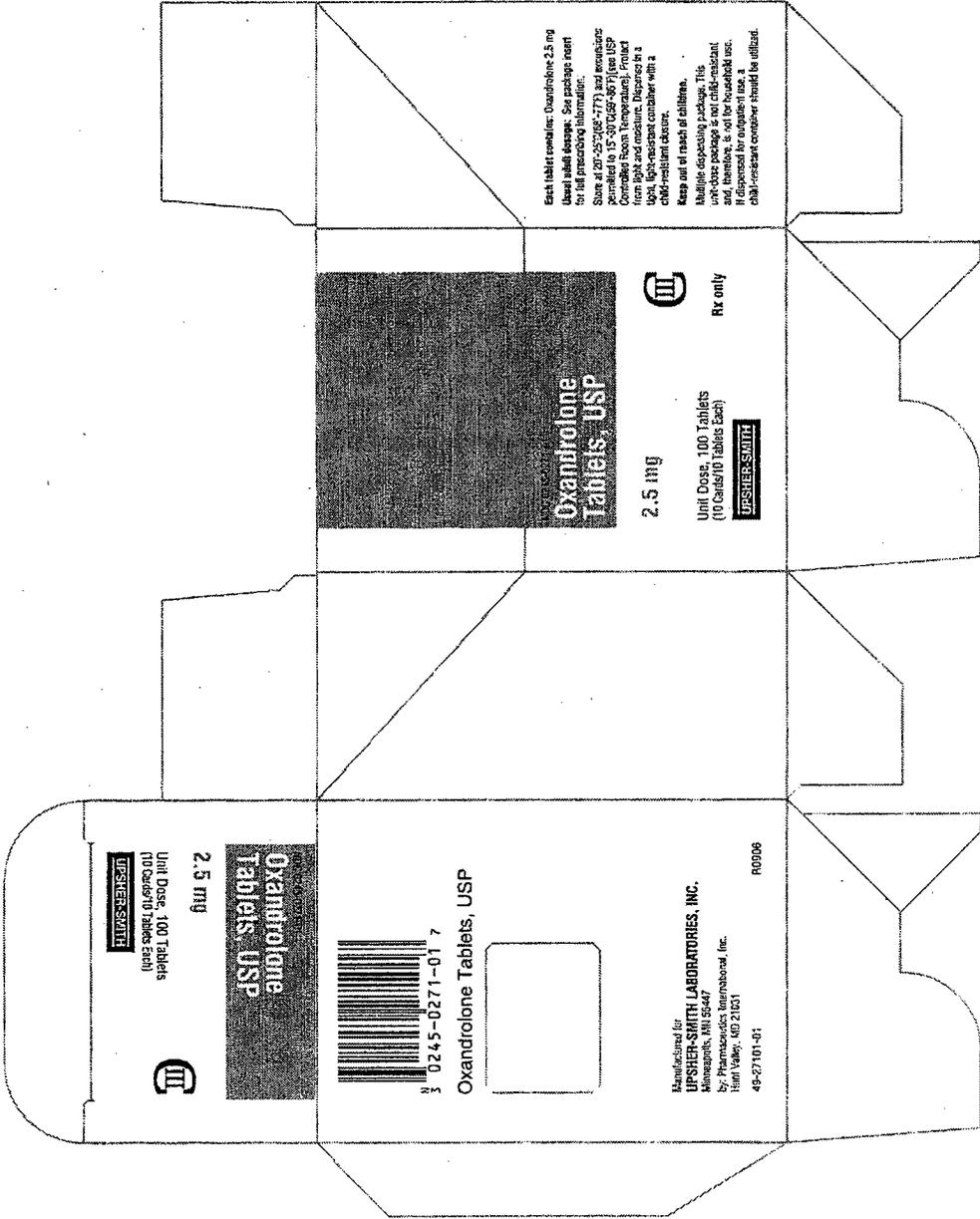
42-27110-01

R0906



N 0245-0271-10 9
Lot/Exp.

<p>Oxandrolone Tablet, USP </p> <p>2.5 mg Dist. by: UPSHER-SMITH Minneapolis, MN 55447 245-271-02 LOT EXP R0906</p> <p>(01)1003024502718B5</p>	<p>Oxandrolone Tablet, USP </p> <p>2.5 mg Dist. by: UPSHER-SMITH Minneapolis, MN 55447 245-271-02 LOT EXP R0906</p> <p>(01)1003024502718B5</p>
<p>Oxandrolone Tablet, USP </p> <p>2.5 mg Dist. by: UPSHER-SMITH Minneapolis, MN 55447 245-271-02 LOT EXP R0906</p> <p>(01)1003024502718B5</p>	<p>Oxandrolone Tablet, USP </p> <p>2.5 mg Dist. by: UPSHER-SMITH Minneapolis, MN 55447 245-271-02 LOT EXP R0906</p> <p>(01)1003024502718B5</p>
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<p>Oxandrolone Tablet, USP </p> <p>2.5 mg Dist. by: UPSHER-SMITH Minneapolis, MN 55447 245-271-02 LOT EXP R0906</p> <p>(01)1003024502718B5</p>	<p>Oxandrolone Tablet, USP </p> <p>2.5 mg Dist. by: UPSHER-SMITH Minneapolis, MN 55447 245-271-02 LOT EXP R0906</p> <p>(01)1003024502718B5</p>



UPsher-SMITH

Unit Dose, 100 Tablets
(100 Tablets per Box)

2.5 mg

**Oxandrolone
Tablets, USP**



3 0245-0271-01 7

Oxandrolone Tablets, USP



Manufactured for
UPsher-SMITH LABORATORIES, INC.
Minneapolis, MN 55447
by: Pharmacia International, Inc.
Kalamazoo, MI 49001
49-27101-01

R0006

Each tablet contains Oxandrolone 2.5 mg
Level tablet design. See package insert
for full prescribing information.

Store at 20°-25°C (68°-77°) and excursions
permitted to 15°-30°C (59°-86°F) (see USP
Controlled Room Temperature). Protect
from moisture. Do not use if the
unit-dose resistant container shows any
other-resistant damage.

Keep out of reach of children.
Multiple-dose package. This
unit-dose package is not child-resistant
and, therefore, is not for household use.
If dispensed for outpatient use, a
child-resistant container should be utilized.



Rx only

2.5 mg

Unit Dose, 100 Tablets
(100 Tablets per Box)

UPsher-SMITH

**Oxandrolone
Tablets, USP**

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Postelle Birch
11/14/2006 12:14:20 PM
MEDICAL OFFICER

Charles Hoppes
11/14/2006 01:25:53 PM
MEDICAL OFFICER
Charlie Hoppes for John Grace

****First Generic****

This approval summary supersedes the November 16, 2006 approval summary.

**APPROVAL SUMMARY
REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH**

ANDA Number: 76-761 Date of Submission: November 29, 2006

Applicant's Name: Upsher-Smith Laboratories, Inc.

Established Name: Oxandrolone Tablets USP, 2.5 mg

APPROVAL SUMMARY:

CONTAINER (Bottles of 5s, 100s, 1000s)

Satisfactory in final print as of the November 8, 2006 submission.

UNIT DOSE BLISTER (2 X 5 Tablets)

Satisfactory in final print as of the November 8, 2006 submission.

CARTON (10 x Unit Dose Blister of 10 Tablets)

Satisfactory in final print as of the November 8, 2006 submission.

PROFESSIONAL PACKAGE INSERT:

Satisfactory in final print as of the November 29, 2006 submission.

Post-approval revisions:

In the DESCRIPTION section insert the route of administration.

REFERENCE LISTED DRUG:

Was this approval based upon a petition? Yes, citizens petition

What is the RLD on the 356(h) form: Oxandrin® tablets

NDA Number: NDA 13-718

NDA Drug Name: Oxandrin® tablets

NDA Firm: BTG Pharmaceuticals

Date of Approval of NDA Insert and supplement #: June 20, 2005/S-023

Has this been verified by the MIS system for the NDA? Yes

Was this approval based upon an OGD labeling guidance? Yes, **OGD labeling template**

Basis of Approval for the Container Labels: side-by-side

Basis of Approval for the Carton Labeling: side-by-side

Other Comments: Upsher-Smith also has a 10 mg tablet, ANDA 78-033.

PATENT/ EXCLUSIVITIES

Patent Data – NDA 13-718

No	Expiration	Use Code	Use	File	Labeling Impact
5872147	12/05/2017	U-585	To promote weight gain after weight loss in certain types of patients	Firm declined to address due to late file	None See FTR
6090799	07/18/2017	U-585	To promote weight gain after weight loss in certain types of patients	Firm declined to address due to late file	None See FTR
6576659	12/05/2017	U-585	To promote weight gain after weight loss in certain types of patients	Firm declined to address due to late file	None See FTR
6670351	10/20/2012	U-585	To promote weight gain after weight loss in certain types of patients	Firm declined to address due to late file	None See FTR
6828313	12/05/2017	U-585	To promote weight gain after weight loss in certain types of patients	MOU	Carve-out

Exclusivity Data -

Code/sup	Expiration	Use Code	Description	Labeling Impact
M-42	6/20/2008		Addition of a geriatric use subsection to the precautions section of the package insert and geriatric dosing information	OGD Labeling template

***First Generic
FOR THE RECORD:**

- This review was based on a revised OGD labeling template created on November 29, 2006. We note that the initial directions to applicants on the appropriate labeling for oxandrolone tablets contained inadvertent errors. We instructed applicants to make revisions to correct these errors and re-submit revised labeling. We have reviewed the revised labeling and have determined that the errors have been corrected.*
- PATENT/ EXCLUSIVITIES**
See above.
- MANUFACTURING FACILITY** (Vol. A1.4, pg. 1234)
Pharmaceuticals International, Inc.
10819 Gilroy Road
Hunt Valley, MD 21031
- STORAGE CONDITIONS:**
NDA: Store at Controlled Room Temperature (59°-77°F)
ANDA: Store at 20°-25°C (68°-77°F) Excursions permitted to 15°-30°C (59°-77°F) [see USP Controlled Room Temperature].
Test conditions: Long-Term Controlled Room Temperature Testing: 25±2°C/60±5%RH
- DISPENSING RECOMMENDATIONS:**
NDA: Dispense in a tight, light-resistant, child-resistant container.
ANDA: Container-Dispense in a tight, light-resistant container with a child-resistant closure.
Blister Carton-Dispense in a tight, light-resistant container with a child-resistant closure as defined in the USP.
- PRODUCT LINE:**
The innovator: 2.5 mg-Bottles of 100s and 10 mg-Bottles of 60s
The applicant: 2.5 mg- Bottles of 100s, 1000s and Unit dose blister cartons of 100s
- CONTAINER/CLOSURE SYSTEM:** [Vol. A1.4, pg. 1461 &1499 & 1549]
100s: 60cc White, Wide-mouth, Round, Squat, HDPE Bottle; Screw Cap
1000s: 250cc White, Wide-mouth, Round, HDPE Bottle; Screw Cap

Blister: 10 mil, clear, polyvinyl chloride blister with paper-backed, laminated foil as the backing
- PRODUCT DESCRIPTION:**
RLD- Scored tablets
ANDA- White oval-shaped, scored, uncoated tablets, debossed with "2.5" on the unscored side and with "U" to the left of the score and "S" to the right of the score on the reverse side. (Vol. A1.5, pg. 1705)
- INACTIVE INGREDIENTS:**
The listing of inactive ingredients in the DESCRIPTION section of the package insert appears to be consistent with the listing of inactive ingredients found in the statement of components and composition appearing on page 995 [Vol. A1.4].
- USP Dissolution Test is Pending. Firm used a dissolution test not recognized by the USP. Once the test is listed in the USP, firm will update the statement in the DESCRIPTION section of package insert.

Date of Review: November 30, 2006 Date of Submission: November 29, 2006

Primary Reviewer: Postelle Birch-Smith

Team Leader: John Grace

cc: ANDA 76-761
DUP/DIVISION FILE

**Oxandrolone
Tablets, USP**

2.5 mg

5 Tablets

UPSHER-SMITH

PROFESSIONAL SAMPLE
Not for Sale



Rx only

PROFESSIONAL SAMPLE: Not for Sale
Each tablet contains Oxandrolone 2.5 mg
Usual adult dosage: See package insert for full
prescribing information.
Keep out of reach of children.
SEALED FOR YOUR PROTECTION.

Manufactured for
UPSHER-SMITH LABORATORIES, INC.,
Minneapolis, MN 55447
by: Pharmaceuticals International, Inc.
Hunt Valley, MD 21031
42-27166-01

Store at 20°-25°C (68°-77°F) and excursions permitted to
15°-30°C (59°-86°F) [see USP Controlled Room Temperature].
Keep tightly closed. Protect from light and moisture. Dispense in
a light-resistant container with a child-resistant closure.



N
3 0245-0271-66 6

Lot/Exp.

RD606

NDC 0245-0271-11

Oxandrolone Tablets, USP

2.5 mg

100 Tablets

UPSHER-SMITH



Rx only

Each tablet contains: Oxandrolone 2.5 mg
Usual adult dosage: See package insert for full
prescribing information.
Store at 20°-25° C (68°-77° F) and
excursions permitted to 15°-30° C (59°-86° F)
(see USP Controlled Room Temperature).
Keep tightly closed. Protect from light and moisture.
Dispense in a light, light-resistant container with a
child-resistant closure.

Keep out of reach of children.
SEALED FOR YOUR PROTECTION.

Manufactured for
UPSHER-SMITH LABORATORIES, INC.
Minneapolis, MN 55447
by: Pharmaceutics International, Inc.
Hunt Valley, MD 21031
42-27111-01

R0906



N 0245-0271-11 6

Lot/Exp.

NDC 0245-0271-10

Oxandrolone Tablets, USP

2.5 mg

1000 Tablets

UPSHER-SMITH



Rx only

Each tablet contains: Oxandrolone 2.5 mg

Usual adult dosage: See package insert for full prescribing information.

Store at 20°-25°C (68°-77°F) and excursions permitted to 15°-30°C (59°-86°F) [see USP Controlled Room Temperature]. Keep tightly closed. Protect from light and moisture. Dispense in a tight, light-resistant container with a child-resistant closure.

Keep out of reach of children.

SEALED FOR YOUR PROTECTION.

Manufactured for
UPSHER-SMITH LABORATORIES, INC.

Minneapolis, MN 55447

by: Pharmaceuticals International, Inc.

Hunt Valley, MD 21031

42-27110-01

R0906



N
3 0245-0271-10 9

Lot/Exp.

<p>Oxandrolone Tablet, USP </p> <p>2.5 mg Dist. by: UPSHER-SMITH Minneapolis, MN 55447 245-271-02 LOT EXP</p> <p>R0906</p> <p>(01003024)9271895</p> 	<p>Oxandrolone Tablet, USP </p> <p>2.5 mg Dist. by: UPSHER-SMITH Minneapolis, MN 55447 245-271-02 LOT EXP</p> <p>R0906</p> <p>(01003024)9271895</p> 
<p>Oxandrolone Tablet, USP </p> <p>2.5 mg Dist. by: UPSHER-SMITH Minneapolis, MN 55447 245-271-02 LOT EXP</p> <p>R0906</p> <p>(01003024)9271895</p> 	<p>Oxandrolone Tablet, USP </p> <p>2.5 mg Dist. by: UPSHER-SMITH Minneapolis, MN 55447 245-271-02 LOT EXP</p> <p>R0906</p> <p>(01003024)9271895</p> 
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<p>Oxandrolone Tablet, USP </p> <p>2.5 mg Dist. by: UPSHER-SMITH Minneapolis, MN 55447 245-271-02 LOT EXP</p> <p>R0906</p> <p>(01003024)9271895</p> 	<p>Oxandrolone Tablet, USP </p> <p>2.5 mg Dist. by: UPSHER-SMITH Minneapolis, MN 55447 245-271-02 LOT EXP</p> <p>R0906</p> <p>(01003024)9271895</p> 

UP-SHER-SMITH

Unit Dose, 100 Tablets
(10 Cards/10 Tablets Each)

2.5 mg

**Oxandrolone
Tablets, USP**



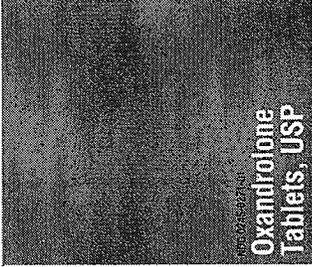
N 3 0245-0271-01 7

Oxandrolone Tablets, USP



Manufactured for
UP-SHER-SMITH LABORATORIES, INC.
Minneapolis, MN 55447
by Pharmacia Inc.
Kalamazoo, MI 49001
49-27101-01

R0806



Each tablet contains Oxandrolone 2.5 mg

Usual adult dosage: See package insert for full prescribing information.

Store at 20°-25°C (68°-77°F) and excursions permitted to 15°-30°C (59°-86°F) (see USP Controlled Room Temperature). Protect from light and moisture. Dispense in a child-resistant container with a child-resistant cap.

Keep out of reach of children.

Multiple dispensing package. This unit dose package is not child-resistant and is not intended for use.

If dispensed for outpatient use, a child-resistant container should be utilized.



Rx only

2.5 mg

Unit Dose, 100 Tablets
(10 Cards/10 Tablets Each)

UP-SHER-SMITH



Oxandrolone Tablets,
USP 2.5 mg



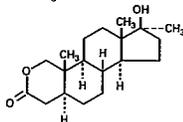
Oxandrolone Tablets,
USP 2.5 mg

Oxandrolone Tablets, USP

Rx only

DESCRIPTION

Oxandrolone Tablets, USP contain 2.5 mg of the anabolic steroid oxandrolone. Oxandrolone is 17 β -hydroxy-17 α -methyl-2-oxa-5 α -androst-3-one with the following structural formula:



Molecular Formula: C₁₉H₃₀O₃

Molecular Weight: 306.44

Inactive ingredients include anhydrous lactose, hypromellose, magnesium stearate, and pregelatinized starch.

USP Dissolution Test Pending.

CLINICAL PHARMACOLOGY

Anabolic steroids are synthetic derivatives of testosterone. Certain clinical effects and adverse reactions demonstrate the androgenic properties of this class of drugs. Complete dissociation of anabolic and androgenic effects has not been achieved. The actions of anabolic steroids are therefore similar to those of male sex hormones with the possibility of causing serious disturbances of growth and sexual development if given to young children. Anabolic steroids suppress the gonadotropic functions of the pituitary and may exert a direct effect upon the testes.

During exogenous administration of anabolic androgens, endogenous testosterone release is inhibited through inhibition of pituitary luteinizing hormone (LH). At large doses, spermatogenesis may be suppressed through feedback inhibition of pituitary follicle-stimulating hormone (FSH).

Anabolic steroids have been reported to increase low-density lipoproteins and decrease high-density lipoproteins. These levels revert to normal on discontinuation of treatment.

INDICATIONS AND USAGE

Oxandrolone Tablets, USP are indicated as adjunctive therapy to offset the protein catabolism associated with prolonged administration of corticosteroids, and for the relief of the bone pain frequently accompanying osteoporosis (see **DOSE AND ADMINISTRATION**).

DRUG ABUSE AND DEPENDENCE

Oxandrolone is classified as a controlled substance under the Anabolic Steroids Control Act of 1990 and has been assigned to Schedule III (non-narcotic).

CONTRAINDICATIONS

- Known or suspected carcinoma of the prostate or the male breast.
- Carcinoma of the breast in females with hypercalcemia (androgenic anabolic steroids may stimulate osteolytic bone resorption).
- Pregnancy, because of possible masculinization of the fetus. Oxandrolone has been shown to cause embryotoxicity, fetotoxicity, infertility, and masculinization of female animal offspring when given in doses 9 times the human dose.
- Nephrosis, the nephrotic phase of nephritis.
- Hypercalcemia.

WARNINGS

PELLOSIS HEPATIS, A CONDITION IN WHICH LIVER AND SOMETIMES SPLENIC TISSUE IS REPLACED WITH BLOOD-FILLED CYSTS, HAS BEEN REPORTED IN PATIENTS RECEIVING ANDROGENIC ANABOLIC STEROID THERAPY. THESE CYSTS ARE SOMETIMES PRESENT WITH MINIMAL HEPATIC DYSFUNCTION, BUT AT OTHER TIMES THEY HAVE BEEN ASSOCIATED WITH LIVER FAILURE. THEY ARE OFTEN NOT RECOGNIZED UNTIL LIFE-THREATENING LIVER FAILURE OR INTRA-ABDOMINAL HEMORRHAGE DEVELOPS. WITHDRAWAL OF DRUG USUALLY RESULTS IN COMPLETE DISAPPEARANCE OF LESIONS.

LIVER CELL TUMORS ARE ALSO REPORTED. MOST OFTEN THESE TUMORS ARE BENIGN AND ANDROGEN-DEPENDENT, BUT FATAL MALIGNANT TUMORS HAVE BEEN REPORTED. WITHDRAWAL OF DRUG OFTEN RESULTS IN REGRESSION OR CESSATION OF PROGRESSION OF THE TUMOR. HOWEVER, HEPATIC TUMORS ASSOCIATED WITH ANDROGENS OR ANABOLIC STEROIDS ARE MUCH MORE VASCULAR THAN OTHER HEPATIC TUMORS AND MAY BE SILENT UNTIL LIFE-THREATENING INTRA-ABDOMINAL HEMORRHAGE DEVELOPS. BLOOD LIPID CHANGES THAT ARE KNOWN TO BE ASSOCIATED WITH INCREASED RISK OF ATHEROSCLEROSIS ARE SEEN IN PATIENTS TREATED WITH ANDROGENS OR ANABOLIC STEROIDS. THESE CHANGES INCLUDE DECREASED HIGH-DENSITY LIPOPROTEINS AND SOMETIMES INCREASED LOW-DENSITY LIPOPROTEINS. THE CHANGES MAY BE VERY MARKED AND COULD HAVE A SERIOUS IMPACT ON THE RISK OF ATHEROSCLEROSIS AND CORONARY ARTERY DISEASE.

Cholestatic hepatitis and jaundice may occur with 17-alpha-alkylated androgens at a relatively low dose. If cholestatic hepatitis with jaundice appears or if liver function tests become abnormal, oxandrolone should be discontinued and the etiology should be determined. Drug-induced jaundice is reversible when the medication is discontinued.

In patients with breast cancer, anabolic steroid therapy may cause hypercalcemia by stimulating osteolysis. Oxandrolone therapy should be discontinued if hypercalcemia occurs.

Edema with or without congestive heart failure may be a serious complication in patients with pre-existing cardiac, renal, or hepatic disease. Concomitant administration of adrenal cortical steroid or ACTH may increase the edema.

In children, androgen therapy may accelerate bone maturation without producing compensatory gain in linear growth. This adverse effect results in compromised adult height. The younger the child, the greater the risk of compromising final mature height. The effect on bone maturation should be monitored by assessing bone age of the left wrist and hand every 6 months (see **PRECAUTIONS, Laboratory Tests**).

Geriatric patients treated with androgenic anabolic steroids may be at an increased risk for the development of prostatic hypertrophy and prostatic carcinoma.

ANABOLIC STEROIDS HAVE NOT BEEN SHOWN TO ENHANCE ATHLETIC ABILITY.

PRECAUTIONS

Concurrent dosing of oxandrolone and warfarin may result in unexpectedly large increases in the International Normalized Ratio (INR) or prothrombin time (PT). When oxandrolone is prescribed to patients being treated with warfarin, doses of warfarin may need to be decreased significantly to maintain the desirable INR level and diminish the risk of potentially serious bleeding. (See **PRECAUTIONS, Drug Interactions).**

General

Women should be observed for signs of virilization (deepening of the voice, hirsutism, acne, clitoromegaly). Discontinuation of drug therapy at the time of evidence of mild virilism is necessary to prevent irreversible virilization. Some virilizing changes in women are irreversible even after prompt discontinuance of therapy and are not prevented by concomitant use of estrogens. Menstrual irregularities may also occur.

Anabolic steroids may cause suppression of clotting factors II, V, VII, and X, and an increase in prothrombin time.

Information for Patients

The physician should instruct patients to report immediately any use of warfarin and any bleeding.

The physician should instruct patients to report any of the following side effects of androgens:

- | | |
|----------------------|---|
| Males: | Too frequent or persistent erections of the penis, appearance or aggravation of acne. |
| Females: | Hoarseness, acne, changes in menstrual periods, or more facial hair. |
| All patients: | Nausea, vomiting, changes in skin color, or ankle swelling. |

Geriatric Use:

Certain geriatric use information is protected by marketing exclusivity.

Laboratory Tests

Women with disseminated breast carcinoma should have frequent determination of urine and serum calcium levels during the course of therapy (see **WARNINGS**).

Because of the hepatotoxicity associated with the use of 17-alpha-alkylated androgens, liver function tests should be obtained periodically.

Periodic (every 6 months) x-ray examinations of bone age should be made during treatment of children to determine the rate of bone maturation and the effects of androgen therapy on the epiphyseal centers.

Androgenic anabolic steroids have been reported to increase low-density lipoproteins and decrease high-density lipoproteins. Therefore, caution is required when administering these agents to patients with a history of cardiovascular disease or who are at risk for cardiovascular disease. Serum determination of lipid levels should be performed periodically and therapy adjusted accordingly.

Hemoglobin and hematocrit should be checked periodically for polycythemia in patients who are receiving high doses of anabolic steroids.

Drug Interactions

Anticoagulants:

Anabolic steroids may increase sensitivity to oral anticoagulants. Dosage of the anticoagulant may have to be decreased in order to maintain desired prothrombin time. Patients receiving oral anticoagulant therapy require close monitoring, especially when anabolic steroids are started or stopped.

Warfarin: A multiple study of oxandrolone, given as 5 or 10 mg BID in 15 healthy subjects concurrently treated with warfarin, resulted in a mean increase in S-warfarin half-life from 26 to 48 hours and AUC from 4.55 to 12.08 ng•hr/mL; similar increases in R-warfarin half-life and AUC were also detected. Microscopic hematuria (9/15) and gingival bleeding (1/15) were also observed. A 5.5-fold decrease in the mean warfarin dose from 6.13 mg/day to 1.13 mg/day (approximately 80-85% reduction of warfarin dose), was necessary to maintain a target INR of 1.5. When oxandrolone therapy is initiated in a patient already receiving treatment with warfarin, the INR or prothrombin time (PT) should be monitored closely and the dose of warfarin adjusted as necessary until a stable target INR or PT has been achieved.

Furthermore, in patients receiving both drugs, careful monitoring of the INR or PT, and adjustment of the warfarin dosage if indicated are recommended when the oxandrolone dose is changed or discontinued. Patients should be closely monitored for signs and symptoms of occult bleeding.

Oral Hypoglycemic Agents:

Oxandrolone may inhibit the metabolism of oral hypoglycemic agents.

Adrenal Steroids or ACTH:

In patients with edema, concomitant administration with adrenal cortical steroids or ACTH may increase the edema.

Drug/Laboratory Test Interactions

Anabolic steroids may decrease levels of thyroxine-binding globulin, resulting in decreased total T₄ serum levels and increased resin uptake of T₃ and T₄. Free thyroid hormone levels remain unchanged. In addition, a decrease in PBI and radioactive iodine uptake may occur.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Animal Data:

Oxandrolone has not been tested in laboratory animals for carcinogenic or mutagenic effects. In 2-year chronic oral rat studies, a dose-related reduction of spermatogenesis and decreased organ weights (testes, prostate, seminal vesicles, ovaries, uterus, adrenals, and pituitary) were shown.

Human Data:

Liver cell tumors have been reported in patients receiving long-term therapy with androgenic anabolic steroids in high doses (see **WARNINGS**). Withdrawal of the drugs did not lead to regression of the tumors in all cases.

Geriatric patients treated with androgenic anabolic steroids may be at an increased risk for the development of prostatic hypertrophy and prostatic carcinoma.

Pregnancy

Teratogenic effects – Pregnancy Category X (see **CONTRAINDICATIONS**).

Nursing Mothers

It is not known whether anabolic steroids are excreted in human milk. Because of the potential of serious adverse reactions in nursing infants from oxandrolone, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use

Anabolic agents may accelerate epiphyseal maturation more rapidly than linear growth in children and the effect may continue for 6 months after the drug has been stopped. Therefore, therapy should be monitored by x-ray studies at 6-month intervals in order to avoid the risk of compromising adult height. Androgenic anabolic steroid therapy should be used very cautiously in children and only by specialists who are aware of the effects on bone maturation (see **WARNINGS**).

ADVERSE REACTIONS

Patients with moderate to severe COPD or COPD patients who are unresponsive to bronchodilators should be monitored closely for COPD exacerbation and fluid retention.

The following adverse reactions have been associated with use of anabolic steroids:

Hepatic

Cholestatic jaundice with, rarely, hepatic necrosis and death. Hepatocellular neoplasms and peliosis hepatitis with long-term therapy (see **WARNINGS**). Reversible changes in liver function tests also occur including increased bromsulphthalein (BSP) retention, changes in alkaline phosphatase and increases in serum bilirubin, aspartate aminotransferase (AST, SGOT) and alanine aminotransferase (ALT, SGPT).

In Males

Prepubertal: Phallic enlargement and increased frequency or persistence of erections.

Postpubertal: Inhibition of testicular function, testicular atrophy and oligospermia, impotence, chronic priapism, epididymitis, and bladder irritability.

In Females

Clitoral enlargement, menstrual irregularities.

CNS: Habituation, excitation, insomnia, depression, and changes in libido.

Hematologic: Bleeding in patients on concomitant oral anticoagulant therapy.

Breast: Gynecomastia.

Larynx: Deepening of the voice in females.

Hair: Hirsutism and male pattern baldness in females.

Skin: Acne (especially in females and prepubertal males).

Skeletal: Premature closure of epiphyses in children (see **PRECAUTIONS, Pediatric Use**).

Fluid and Electrolytes: Edema, retention of serum electrolytes (sodium chloride, potassium, phosphate, calcium).

Metabolic/Endocrine: Decreased glucose tolerance (see **PRECAUTIONS, Laboratory Tests**), increased creatinine excretion, increased serum levels of creatine phosphokinase (CPK). Masculinization of the fetus. Inhibition of gonadotropin secretion.

OVERDOSAGE

No symptoms or signs associated with overdosage have been reported. It is possible that sodium and water retention may occur.

The oral LD50 of oxandrolone in mice and dogs is greater than 5,000 mg/kg. No specific antidote is known, but gastric lavage may be used.

DOSE AND ADMINISTRATION

Therapy with anabolic steroids is adjunctive to and not a replacement for conventional therapy. The duration of therapy with Oxandrolone Tablets, USP will depend on the response of the patient and the possible appearance of adverse reactions. Therapy should be intermittent.

Adults

The response of individuals to anabolic steroids varies. The daily adult dosage is 2.5 mg given in 2 to 4 divided doses. The desired response may be achieved with as little as 2.5 mg or as much as 20 mg daily. A course of therapy of 2 to 4 weeks is usually adequate. This may be repeated intermittently as indicated.

Children

For children the total daily dosage of Oxandrolone Tablets, USP is ≤ 0.1 mg per kilogram body weight or ≤ 0.045 mg per pound of body weight. This may be repeated intermittently as indicated.

HOW SUPPLIED

Oxandrolone Tablets, USP 2.5 mg are oval, white, scored, uncoated tablets, debossed with "2.5" on one side and "U" to the left and "S" to the right of the score on the other side. Oxandrolone Tablets, USP are available in bottles of 100 tablets (NDC 0245-0271-11), bottles of 1000 tablets (NDC 0245-0271-10) and in unit dose cartons of 100 tablets (10 cards containing 10 tablets each) (NDC 0245-0271-01).

Store at 20-25°C (68-77°F). Excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature]. Dispense in a light, light-resistant container with a child-resistant closure as defined in the USP.

Keep out of reach of children.

Manufactured for
UPsher-Smith LABORATORIES, INC.
Minneapolis, MN 55447

by: Pharmaceutics International, Inc.
Hunt Valley, MD 21031

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40-27100-05

Revised 1106A

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this page is the manifestation of the electronic signature.**

/s/

Postelle Birch
11/30/2006 05:32:45 PM
MEDICAL OFFICER

John Grace
12/1/2006 10:13:06 AM
MEDICAL OFFICER

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 76-761

CHEMISTRY REVIEW(S)

ANDA 76-761

Oxandrolone Tablets USP, 2.5 mg

Upsher-Smith Laboratories, Inc.

**Mike Darj
Division of Chemistry I**



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Chemistry Review Data Sheet

1. ANDA 76-761 (First Generic)
2. REVIEW #: 1
3. REVIEW DATE: 29OCT2003
07NOV2003
4. REVIEWER: Mike Darj
5. PREVIOUS DOCUMENTS: N/A

Previous DocumentsDocument Date

Original Submission

12-JUN-2003

New Correspondence regarding Form FDA 3454

16-JUL-2003

6. SUBMISSION(S) BEING REVIEWED:

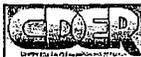
Submission(s) ReviewedDocument Date

Original Application

12-JUN-2003

7. NAME & ADDRESS OF APPLICANT:

Name: Upsher-Smith Laboratories, Inc.
Address: 14905 23rd Avenue North
Minneapolis, MN 55447
Representative: Mark S. Robbins
Telephone: (763) _____



CHEMISTRY REVIEW



Chemistry Assessment Section

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: First Choice: _____ Second Choice: _____
b) Non-Proprietary Name (USAN): Oxandrolone

9. LEGAL BASIS FOR SUBMISSION:

The basis for the Upsher-Smith Laboratories, Inc. proposed ANDA for Oxandrolone Tablets USP, 2.5 mg is the approved reference listed drug Oxandrin[®] 2.5 mg, the subject of NDA No. 13-718 held by Bio-Technology General Pharmaceuticals (Approved prior to January 1, 1982).

Oxandrin[®] (RLD) is available in 2.5 mg and 10 mg strengths, but Upsher-Smith (the firm) is pursuing approval only for the 2.5 mg tablets at this time.

Patent Certification: Patent has expired (vol. 1.1, Page 9)

Exclusivity: No unexpired exclusivity (vol. 1.1, Page 9)

10. PHARMACOL. CATEGORY: Adjunctive Therapy to Promote Weight Gain

11. DOSAGE FORM: Immediate-Release Tablet

12. STRENGTH/POTENCY: 2.5 mg

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: Rx OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

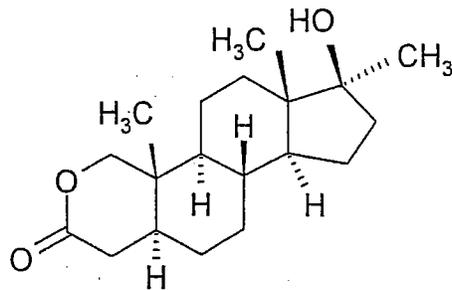
SPOTS product – Form Completed

Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Chemical name: 17 β -Hydroxy-17-methyl-2-oxa-5 α -androstane-3-one
Molecular formula: C₁₉H₃₀O₃
Molecular weight: 306 g/mol
Structural formula:

Chemistry Assessment Section





CHEMISTRY REVIEW



Chemistry Assessment Section

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS
			Oxandrolone, USP	1	Inadequate	22Oct2003	M. Darj (original review)
				4			
				4			
				4			
				4			
				4			
				4			
				4			
				4			
				4			



CHEMISTRY REVIEW



Chemistry Assessment Section

	4		
	4		
	4		

¹ Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 – Type 1 DMF

3 – Reviewed previously and no revision since last review

4 – Sufficient information in application

5 – Authority to reference not granted

6 – DMF not available

7 – Other (explain under "Comments")

² Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents: N/A

DOCUMENT	APPLICATION NUMBER	DESCRIPTION

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	N/A		
EES	Pending		
Methods Validation	N/A		
Labeling	Pending		
Bioequivalence	Pending		
EA	Acceptable	30Oct2003	M. Darj
Radiopharmaceutical	N/A		



CHEMISTRY REVIEW



Chemistry Assessment Section

19. ORDER OF REVIEW

The application submission(s) covered by this review was taken in the date order of receipt. Yes No If no, explain reason(s) below:



The Chemistry Review for ANDA 76-761

The Executive Summary

Oxandrolone Tablets, 2.5 mg is based on Bio-Technology General Pharmaceuticals listed drug product Oxandrin[®] Tablets, 2.5 mg (NDA #13-718).

OXANDRIN[®] (Oxandrolone) is indicated as adjunctive therapy to promote weight gain after weight loss following extensive surgery, chronic infections, or severe trauma, and in some patients who without definite pathophysiologic reasons fail to gain or to maintain normal weight. It is a synthetic derivative of testosterone. The chemical designation is 17 β -hydroxy-17 α -methyl-2-oxa-5 α -androstan-3-one. Its molecular formula is C₁₉H₃₀O₃ and its molecular weight is 306 g/mol. The structural formula is shown in the Chemistry Review Data Sheet section.

Paragraph II Certification: Upsher-Smith Laboratories, Inc. certifies that in its opinion and to the best of its knowledge the patent which was applicable to the reference listed drug product referred to in this application has expired, and there is no unexpired exclusivity.

Based on stability data, Upsher-Smith is seeking 2-year tentative expiration of the drug product.

I. Recommendations

A. Recommendation and Conclusion on Approvability

The ANDA is Not Approvable

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

Not Applicable

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

The drug product is Oxandrolone Tablets USP, 2.5 mg

The drug substance is Oxandrolone USP, manufactured by _____

B. Description of How the Drug Product is Intended to be Used

The drug product is a tablet that is taken orally.



CHEMISTRY REVIEW



Chemistry Assessment Section

C. Basis for Approvability or Not-Approval Recommendation

The recommendation of Not-Approvability is based on the deficiencies that were identified in the following sections: Synthesis, Raw Material Controls, Laboratory Controls, and Stability.

In addition to the above CMC issues, the bioequivalence review, labeling review and EER are pending.

The drug product, Oxandrolone Tablets, cannot be classified as safe and effective in this review based on the deficiencies described above.

III. Administrative

A. Reviewer's Signature

B. Endorsement Block

HFD-623/M. Darj, Ph.D., RC/

HFD-623/D. Gill, Ph.D., TL/

HFD-617/S. Kim, PM/

F/T by:

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Type of Letter: Not Approvable – Minor

C. CC Block

ANDA 76-761

ANDA DUP

DIV FILE

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30 PAGES WITHHELD IN FULL

ANDA 76-761

Oxandrolone Tablets USP, 2.5 mg

Upsher-Smith Laboratories, Inc.

**Mike Darj
Office of Generic Drugs
Division of Chemistry III**



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35. Environmental Impact Considerations/Categorical Exclusion.....	20



Chemistry Review Data Sheet

1. ANDA 76-761 (First Generic)

2. REVIEW #: 2

3. REVIEW DATE: 13SEP2004
REVISION DATE: 27SEP2004

4. REVIEWER: Mike Darj

5. PREVIOUS DOCUMENTS:

<u>Previous Documents</u>	<u>Document Date</u>
Original Submission	12-JUN-2003
New Correspondence regarding Form FDA 3454	16-JUL-2003
Deficiency Letter (first review)	20-NOV-2003

6. SUBMISSION(S) BEING REVIEWED:

<u>Submission(s) Reviewed</u>	<u>Document Date</u>
Minor Amendment	16-APR-2004
Unsolicited Amendment	04-JUN-2004

7. NAME & ADDRESS OF APPLICANT:

Name: Upsher-Smith Laboratories, Inc.
Address: 6701 Evenstad Drive
Maple Grove, MN 55369
Representative: Mark S. Robbins
Telephone: (763) 315-2000



8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: First Choice:
b) Non-Proprietary Name (USAN): Oxandrolone

9. LEGAL BASIS FOR SUBMISSION:

The basis for the Upsher-Smith Laboratories, Inc. proposed ANDA for Oxandrolone Tablets USP, 2.5 mg is the approved reference listed drug Oxandrin[®] 2.5 mg, the subject of NDA No. 13-718 held by Bio-Technology General Pharmaceuticals (Approved prior to January 1, 1982).

Oxandrin[®] (RLD) is available in 2.5 mg and 10 mg strengths, but Upsher-Smith (the firm) is pursuing approval only for the 2.5 mg tablets at this time.

Patent Certification: Patent has expired (vol. 1.1, Page 9)
Exclusivity: No unexpired exclusivity (vol. 1.1, Page 9)

10. PHARMACOL. CATEGORY: Adjunctive Therapy to Promote Weight Gain

11. DOSAGE FORM: Immediate-Release Tablet

12. STRENGTH/POTENCY: 2.5 mg

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: Rx OTC15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

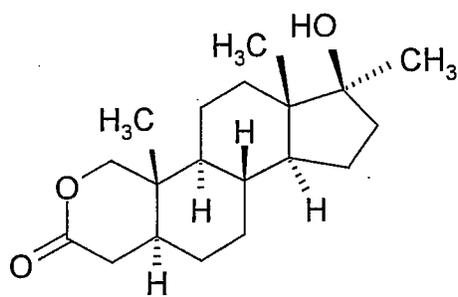
SPOTS product – Form Completed

Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Chemical name: 17 β -Hydroxy-17-methyl-2-oxa-5 α -androstan-3-one
Molecular formula: C₁₉H₃₀O₃
Molecular weight: 306 g/mol
Structural formula:

Chemistry Assessment Section



Chemistry Assessment Section

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS
			Oxandrolone, USP	1	Inadequate	09Sep2004	Reviewed by M. Darj
				4			
				4			
				4			
				4			
				4			
				4			
				4			
				4			

Chemistry Assessment Section

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	4			
	4			
	4			

¹ Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 – Type 1 DMF

3 – Reviewed previously and no revision since last review

4 – Sufficient information in application

5 – Authority to reference not granted

6 – DMF not available

7 – Other (explain under "Comments")

² Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents: N/A

DOCUMENT	APPLICATION NUMBER	DESCRIPTION

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	N/A		
EES	Acceptable	14May2004	
Methods Validation	N/A (per OGD Policy)		
Labeling	Acceptable	24May2004	R. Wu
Bioequivalence	Acceptable	25Aug2004	S. Pradhan
EA	Acceptable	30Oct2003	M. Darj
Radiopharmaceutical	N/A		



19. ORDER OF REVIEW

The application submission(s) covered by this review was taken in the date order of receipt. Yes No If no, explain reason(s) below:



The Chemistry Review for ANDA 76-761

The Executive Summary

Oxandrolone Tablets, 2.5 mg is based on Bio-Technology General Pharmaceuticals listed drug product Oxandrin[®] Tablets, 2.5 mg (NDA #13-718).

OXANDRIN[®] (Oxandrolone) is indicated as adjunctive therapy to promote weight gain after weight loss following extensive surgery, chronic infections, or severe trauma, and in some patients who without definite pathophysiologic reasons fail to gain or to maintain normal weight. It is a synthetic derivative of testosterone. The chemical designation is 17 β -hydroxy-17 α -methyl-2-oxa-5 α -androstane-3-one. Its molecular formula is C₁₉H₃₀O₃ and its molecular weight is 306 g/mol. The structural formula is shown in the Chemistry Review Data Sheet section.

Paragraph II Certification: Upsher-Smith Laboratories, Inc. certifies that in its opinion and to the best of its knowledge the patent which was applicable to the reference listed drug product referred to in this application has expired, and there is no unexpired exclusivity.

Based on stability data, Upsher-Smith is seeking 2-year tentative expiration of the drug product.

I. Recommendations

A. Recommendation and Conclusion on Approvability

The ANDA is Not Approvable

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

Not Applicable

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

The drug product is Oxandrolone Tablets USP, 2.5 mg

The drug substance is Oxandrolone USP, manufactured by Upsher-Smith Laboratories, Inc.

B. Description of How the Drug Product is Intended to be Used

The drug product is a tablet that is taken orally.



CHEMISTRY REVIEW



Chemistry Assessment Section

C. Basis for Approvability or Not-Approval Recommendation

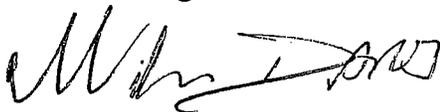
The recommendation of Not-Approvability is based on the deficiencies that were identified in the following sections: Synthesis, Raw Material Controls, Laboratory Controls, and Stability.

The drug product, Oxandrolone Tablets, cannot be classified as safe and effective in this review based on the deficiencies described above.

The labeling and bioequivalence portions of the ANDA are acceptable.

III. Administrative

A. Reviewer's Signature

 06 Oct 2004

B. Endorsement Block

HFD-623/M. Darj, Ph.D., RC/
HFD-623/D. Gill, Ph.D., TL/

F/T by:

V:\FIRMSNZ\UPSHER\LTRS&REV\76761.CR2.DOC

Type of Letter: Not Approvable – Minor

C. CC Block

ANDA 76-761
ANDA DUP
DIV FILE
Field Copy

11 PAGES WITHHELD IN FULL

ANDA 76-761

Oxandrolone Tablets USP, 2.5 mg

Upsher-Smith Laboratories, Inc.

**Mike Darj
Office of Generic Drugs
Division of Chemistry III**



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29. Stability.....19

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31. Samples and Results/Method Validation Status.....20

32. Labeling.....20

33. Establishment Inspection.....20

34. Bioequivalence.....20

35. Environmental Impact Considerations/Categorical Exclusion.....20



Chemistry Review Data Sheet

1. ANDA 76-761 (First Generic)
2. REVIEW #: 3
3. REVIEW DATE: 11MAR2005
4. REVIEWER: Mike Darj, Ph.D.
5. PREVIOUS DOCUMENTS:

<u>Previous Documents</u>	<u>Document Date</u>
Original Submission	12-JUN-2003
New Correspondence regarding Form FDA 3454	16-JUL-2003
Deficiency Letter (first review)	20-NOV-2003
Minor Amendment	16-APR-2004
Unsolicited Amendment	04-JUN-2004

6. SUBMISSION(S) BEING REVIEWED:

<u>Submission(s) Reviewed</u>	<u>Document Date</u>
Minor Amendment	10-NOV-2004

7. NAME & ADDRESS OF APPLICANT:

Name: Upsher-Smith Laboratories, Inc.
Address: 6701 Evenstad Drive
Maple Grove, MN 55369
Representative: Kimberly C. Oakins
Telephone: (763) 315-2000

**8. DRUG PRODUCT NAME/CODE/TYPE:**

- a) Proprietary Name: First Choice: _____
b) Non-Proprietary Name (USAN): Oxandrolone

9. LEGAL BASIS FOR SUBMISSION:

The basis for the Upsher-Smith Laboratories, Inc. proposed ANDA for Oxandrolone Tablets USP, 2.5 mg is the approved reference listed drug Oxandrin® 2.5 mg, the subject of NDA No. 13-718 held by Bio-Technology General Pharmaceuticals (Approved prior to January 1, 1982).

Oxandrin® (RLD) is available in 2.5 mg and 10 mg strengths, but Upsher-Smith (the firm) is pursuing approval only for the 2.5 mg tablets at this time.

Patent Certification: Patent has expired (vol. 1.1, Page 9)
Exclusivity: No unexpired exclusivity (vol. 1.1, Page 9)

10. PHARMACOL. CATEGORY: Adjunctive Therapy to Promote Weight Gain**11. DOSAGE FORM: Immediate-Release Tablet****12. STRENGTH/POTENCY: 2.5 mg (MDD = 20 mg)****13. ROUTE OF ADMINISTRATION: Oral****14. Rx/OTC DISPENSED: Rx OTC****15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):**

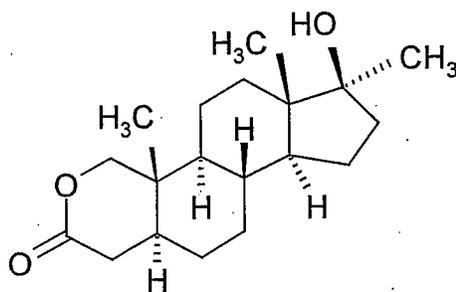
SPOTS product – Form Completed

Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Chemical name: 17 β -Hydroxy-17-methyl-2-oxa-5 α -androstan-3-one
Molecular formula: C₁₉H₃₀O₃
Molecular weight: 306 g/mol
Structural formula:

Chemistry Assessment Section





CHEMISTRY REVIEW



Chemistry Assessment Section

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS
T			Oxandrolone, USP	1	Inadequate	03Mar2005	Reviewed by M. Darj
L				4			
T				4			
				4			
				4			
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				4			
				4			
				4			
				4			



CHEMISTRY REVIEW



Chemistry Assessment Section

r 7 L J				
	4			
	4			
	4			

¹ Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 – Type 1 DMF

3 – Reviewed previously and no revision since last review

4 – Sufficient information in application

5 – Authority to reference not granted

6 – DMF not available

7 – Other (explain under "Comments")

² Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents: N/A

DOCUMENT	APPLICATION NUMBER	DESCRIPTION

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	N/A		
EES	Acceptable	14May2004	
Methods Validation	N/A (per OGD Policy)		
Labeling	Acceptable	24May2004	R. Wu
Bioequivalence	Acceptable	25Aug2004	S. Pradhan
EA	Acceptable	30Oct2003	M. Darj
Radiopharmaceutical	N/A		



CHEMISTRY REVIEW



Chemistry Assessment Section

19. ORDER OF REVIEW

The application submission(s) covered by this review was taken in the date order of receipt. Yes No If no, explain reason(s) below:



The Chemistry Review for ANDA 76-761

The Executive Summary

Oxandrolone Tablets, 2.5 mg is based on Bio-Technology General Pharmaceuticals listed drug product Oxandrin[®] Tablets, 2.5 mg (NDA #13-718).

OXANDRIN[®] (Oxandrolone) is indicated as adjunctive therapy to promote weight gain after weight loss following extensive surgery, chronic infections, or severe trauma, and in some patients who without definite pathophysiologic reasons fail to gain or to maintain normal weight. It is a synthetic derivative of testosterone. The chemical designation is 17 β -hydroxy-17 α -methyl-2-oxa-5 α -androstan-3-one. Its molecular formula is C₁₉H₃₀O₃ and its molecular weight is 306 g/mol. The structural formula is shown in the Chemistry Review Data Sheet section.

Paragraph II Certification: Upsher-Smith Laboratories, Inc. certifies that in its opinion and to the best of its knowledge the patent which was applicable to the reference listed drug product referred to in this application has expired, and there is no unexpired exclusivity.

Based on stability data, Upsher-Smith is seeking 2-year tentative expiration of the drug product.

I. Recommendations

A. Recommendation and Conclusion on Approvability

The ANDA is Not Approvable

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

Not Applicable

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

The drug product is Oxandrolone Tablets USP, 2.5 mg

The drug substance is Oxandrolone USP, manufactured by _____

B. Description of How the Drug Product is Intended to be Used

The drug product is a tablet that is taken orally.

C. Basis for Approvability or Not-Approval Recommendation

The recommendation of Not-Approvability is based on the deficiencies that were identified in the following sections: Synthesis and Raw Material Controls.



CHEMISTRY REVIEW



Chemistry Assessment Section

The drug product, Oxandrolone Tablets, cannot be classified as safe and effective in this review based on the deficiencies described above.

The labeling and bioequivalence portions of the ANDA are acceptable.

III. Administrative

A. Reviewer's Signature

M. Darj 11 APR 2005

B. Endorsement Block

HFD-630/M. Darj, Ph.D., RC/
HFD-630/D. Gill, Ph.D., TL/

F/T by:

V:\FIRMSNZ\UPSHER\LTRS&REV\76761.CR3.DOC

Type of Letter: Not Approvable – Minor

C. CC Block

ANDA 76-761
ANDA DUP
DIV FILE
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11 PAGES WITHHELD IN FULL

ANDA 76-761

Oxandrolone Tablets USP, 2.5 mg

Upsher-Smith Laboratories, Inc.

**Mike Darj
Office of Generic Drugs
Division of Chemistry III**



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Chemistry Review Data Sheet

1. ANDA 76-761 (First Generic)

2. REVIEW #: 4

3. REVIEW DATE: 23SEP2005
15SEP2006 (review of Telephone Amendment dated 14Sep2006)
27Nov2006 (review of Telephone Amendment dated 16Nov2006)

4. REVIEWER: Mike Darj, Ph.D.

5. PREVIOUS DOCUMENTS:

<u>Previous Documents</u>	<u>Document Date</u>
Original Submission	12-JUN-2003
New Correspondence regarding Form FDA 3454	16-JUL-2003
Deficiency Letter (first review)	20-NOV-2003
Minor Amendment	16-APR-2004
Unsolicited Amendment	04-JUN-2004
Minor Amendment	10-NOV-2004
Minor Amendment	06-JUN-2005
Unsolicited Amendment	21-May-2005
Unsolicited Amendment	29-Mar-2005
Telephone Amendment	14-SEP-2006

6. SUBMISSION(S) BEING REVIEWED:

<u>Submission(s) Reviewed</u>	<u>Document Date</u>
Telephone Amendment	16-NOV-2006

7. NAME & ADDRESS OF APPLICANT:

Name: Upsher-Smith Laboratories, Inc.
Address: 6701 Evenstad Drive
Maple Grove, MN 55369



CHEMISTRY REVIEW



Chemistry Assessment Section

Representative: Kimberly C. Oakins
Telephone: (763) 315-2000
Fax: (763) 315-2001

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: First Choice:
b) Non-Proprietary Name (USAN): Oxandrolone

9. LEGAL BASIS FOR SUBMISSION:

The basis for the Upsher-Smith Laboratories, Inc. proposed ANDA for Oxandrolone Tablets USP, 2.5 mg is the approved reference listed drug Oxandrin[®] 2.5 mg, the subject of NDA No. 13-718 held by Bio-Technology General Pharmaceuticals (Approved prior to January 1, 1982).

Oxandrin[®] (RLD) is available in 2.5 mg and 10 mg strengths, but Upsher-Smith (the firm) is pursuing approval only for the 2.5 mg tablets at this time.

Patent Certification: provided in vol. 1.1, page 9
Exclusivity: provided in vol. 1.1, page 9

10. PHARMACOL. CATEGORY: Adjunctive Therapy to Promote Weight Gain

11. DOSAGE FORM: Immediate-Release Tablet

12. STRENGTH/POTENCY: 2.5 mg (MDD = 20 mg)

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: X Rx OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

 SPOTS product – Form Completed

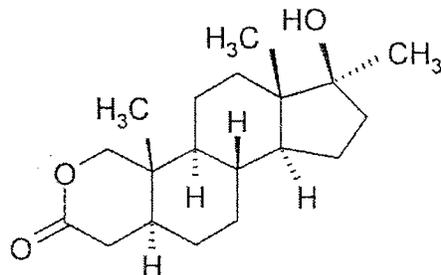
 X Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Chemical name: 17 β -Hydroxy-17-methyl-2-oxa-5 α -androstan-3-one

Chemistry Assessment Section

Molecular formula: $C_{19}H_{30}O_3$
 Molecular weight: 306 g/mol
 Structural formula:





CHEMISTRY REVIEW



Chemistry Assessment Section

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS
			Oxandrolone, USP	1	adequate	15Sep2006	Reviewed by M. Darj
				4			
				4			
				4			
				4			
				4			
				4			
				4			
				4			
				4			
				4			



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	4			
	4			
	4			

¹ Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 – Type 1 DMF

3 – Reviewed previously and no revision since last review

4 – Sufficient information in application

5 – Authority to reference not granted

6 – DMF not available

7 – Other (explain under "Comments")

² Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents: N/A

DOCUMENT	APPLICATION NUMBER	DESCRIPTION

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	N/A		
EES	Acceptable	06Jul2005	
Methods Validation	N/A (per OGD Policy)		
Labeling	Acceptable	21Nov2006	P. Birch
Bioequivalence	Acceptable	25Aug2004	S. Pradhan
EA	Acceptable	30Oct2003	M. Darj
Radiopharmaceutical	N/A		



CHEMISTRY REVIEW



Chemistry Assessment Section

19. ORDER OF REVIEW

The application submission(s) covered by this review was taken in the date order of receipt. Yes No If no, explain reason(s) below:



The Chemistry Review for ANDA 76-761

The Executive Summary

Oxandrolone Tablets, 2.5 mg is based on Bio-Technology General Pharmaceuticals listed drug product Oxandrin[®] Tablets, 2.5 mg (NDA #13-718).

OXANDRIN[®] (Oxandrolone) is indicated as adjunctive therapy to promote weight gain after weight loss following extensive surgery, chronic infections, or severe trauma, and in some patients who without definite pathophysiologic reasons fail to gain or to maintain normal weight. It is a synthetic derivative of testosterone. The chemical designation is 17 β -hydroxy-17 α -methyl-2-oxa-5 α -androstan-3-one. Its molecular formula is C₁₉H₃₀O₃ and its molecular weight is 306 g/mol. The structural formula is shown in the Chemistry Review Data Sheet section.

The drug product manufacturer has adopted the same test and specification for the drug substance release.

Based on stability data, Upsher-Smith is seeking 2-years tentative expiration of the drug product.

I. Recommendations

A. Recommendation and Conclusion on Approvability

The ANDA is Approvable.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

Not Applicable

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

The drug product is Oxandrolone Tablets USP, 2.5 mg

The drug substance is Oxandrolone USP, manufactured by _____

B. Description of How the Drug Product is Intended to be Used

The drug product is a tablet that is taken orally.



Chemistry Assessment Section

C. Basis for Approvability or Not-Approval Recommendation

The recommendation of Approvability is based on satisfactory resolution of all deficiencies.

The bioequivalence and labeling portions, and EER are acceptable.

The drug product, Oxandrolone Tablets USP, 2.5 mg can be classified as safe and effective in this review.

10 PAGE WITHHELD IN FULL



CHEMISTRY REVIEW



Chemistry Assessment Section

36. CHEMISTRY COMMENTS TO BE PROVIDED TO THE APPLICANT

None .



CHEMISTRY REVIEW



Chemistry Assessment Section

cc: ANDA 76-761
ANANDA DUP
DIV FILE
Field Copy

Endorsements (Draft and Final with Dates):

HFD-630/M. Darj, Ph.D., RC/27Nov2006/ *M. Darj 27 Nov 2006*
HFD-630/H. Khorshidi, Ph.D., TL/ *H. Khorshidi 11/28/06*
HFD-617/J. Skanchy, R.Ph., PM/ *J. Skanchy 11/28/06*

F/T by /

V:\FIRMS\NZAUP\SHER\LTRS&REV\76761.CR4.DOC

TYPE OF LETTER: APPROVABLE

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 76-761

BIOEQUIVALENCE REVIEW(S)

DIVISION OF BIOEQUIVALENCE REVIEW

ANDA No. 76-761
Drug Product Name Oxandrolone Tablet, USP
Strength 2.5 mg
Applicant Name Upsher-Smith Laboratories, Inc.
Address 14905 23rd Avenue North, Minneapolis, MN
Submission Date(s) June 12, 2003
Amendment Date(s) None
Reviewer Sikta Pradhan
First Generic Yes
File Location V:\firmsnz\Upsher-Smith\ltrs&rev\76761N0603

I. Executive Summary

The firm has submitted a single-dose, 2-way crossover fasting bioequivalence study comparing the test product, Oxandrolone Tablets, USP 2.5 mg, with the RLD product, Oxandrin® Tablets, 2.5 mg manufactured by G.D. Searle & Co. for BTG Pharmaceuticals. The fasting study was performed in 17 healthy subjects (15 males and 2 females) at a dose of 4x2.5 mg. The in vivo study results (point-estimate, 90% CI) that demonstrate BE in the fasted state (AUC_t 0.91, 87.62-95.53; AUC_{inf} 0.95, 90.93-99.12; C_{max} 0.84, 81.19-87.89) are incomplete due to analytical deficiencies. The firm has also submitted comparative dissolution data for the test and reference products using its own and the FDA-recommended dissolution method. The FDA method uses alcohol-water media and the firm's method uses 0.75% SDS in 0.1 N HCl. Since the use of hydro-alcoholic medium is discouraged, the firm's proposed dissolution method is acceptable. However, the firm is recommended a specification of NLT ~~_____~~ (Q) in 90 minutes. The application is incomplete.

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III. Submission Summary

A. Drug Product Information

Test Product	Upsher-Smith's Oxandrolone Tablets USP, 2.5 mg
Reference Product	Oxandrin ^R 10 mg Tablets of BTG Pharmaceuticals. Upsher-Smith is pursuing approval for only the 2.5 mg tablet. Therefore, 2.5 mg Oxandrin ^R was used as the RLD.
RLD Manufacturer	G.D. Searle & Co.
NDA No.	13-718
RLD Approval Date	The 2.5 mg strength was approved prior to Jan. 1, 1982 (as per Orange Book). The 10 mg strength was approved on Nov. 5, 2001.
Indication	As adjunctive therapy to promote weight gain after weight loss following extensive surgery, chronic infections, or severe trauma.

B. PK/PD Information**Bioavailability**

Oxandrin® (oxandrolone) is the synthetic derivative of testosterone. NDA studies indicated that the bioavailability of oral Oxandrin® tablets (2.5 mg) is greater than that of oral suspension. This difference between tablet and suspension was probably due to the poor delivery of the highly nonpolar oxandrolone suspension.

There is a great difference in pharmacokinetic values of Oxandrin® tablets reported in NDA 13-718 and published literature. This difference could be attributed to differences in assay methodology and/or different formulations.

Absorption of oxandrolone is rapid and complete, peak blood levels occurred approximately 1.1 hours after oral administration. Binding of oxandrolone to plasma protein is extensive (95%). (Ref. Bio-Technology General Corp., NDA 13-718, S-014). Not known; no statement of food effect in the RLD product labeling.

Food Effect**T_{max}**

3.1±1.4 hours

Metabolism

Orally administered oxandrolone does not undergo significant hepatic metabolism and is excreted mainly unchanged and unconjugated in the urine (Ref. Bio-Technology General Corp., NDA 13-718, S-014). (No active oxandrolone metabolites were identified and taken into consideration for measuring bioequivalence in the NDA application).

Excretion

Excreted mainly unchanged in the urine with urinary excretion approximating 60%, 96 hours after an orally administered dose. Fecal excretion is less than 3% over the same period.

Half-life

9.4±1.3 hours

Relevant OGD or DBE

OGD did not receive any ANDA for bioequivalence for this drug product before.

History

Protocol #00-046 (09/29/00) and Control Document 99-111 (03/16/99): The DBE accepted the fasting study protocol by _____, informed the firm that a food effect study is not requested for the drug product.

Agency Guidance

None on this product

Drug Specific Issues (if any)

None

C. Contents of Submission

Study Types	Yes/No?	How many?
Single-dose fasting	Yes	1
Single-dose fed	No	
Steady-state	No	
In vitro dissolution	Yes	1
Waiver requests	No	
BCS Waivers	N/A	
Vasoconstrictor Studies	N/A	
Clinical Endpoints	N/A	
Failed Studies	No	
Amendments	No	

D. Pre-Study Bioanalytical Method Validation

	Parent	Metabolite
Analyte name	Oxandrolone	
Internal Standard	4-lactone-oxandrolone	
Method description	LC-MS-MS	
QC range	1.50 to 40.0 ng/mL	To
Standard curve range	0.5 to 50.0 ng/mL	To
Limit of quantitation	0.50 ng/mL	
Average recovery of Drug (%)	77.1-92.1	
Average Recovery of Int. Std (%)	82.6	
QC Intraday precision range (%)	0.90 to 3.5	To
QC Intraday accuracy range (%)	95.0 to 98.7	To
QC Interday precision range (%)	1.6 to 2.9	To
QC Interday accuracy range (%)	96.5 to 98.9	To
Bench-top stability (hrs)	3.0	
Stock stability (days)	Not reported	
Processed stability (hrs)	24	
Freeze-thaw stability (cycles)	4	
Long-term storage stability (days)	At least 63 days at -20°C	
Dilution integrity	4X (CV% 1.8; n=6)	
Specificity	Yes	
SOPs submitted	No	
Bioanalytical method is acceptable	No, Incomplete	
20% Validation Chromatograms included (Y/N)	Yes	
Random or Serial Selection of Chrom	Serial Selection	

E. In Vivo Studies

1. Single-dose Fasting Bioequivalence Study

Study Summary	
Study No.	Upsher-Smith: P02-006; 2 R01-794; 11-458-T1
Study Design	Two-way crossover
No. of subjects enrolled	18
No. of subjects completing	17
No. of subjects analyzed	17
Subjects (Healthy or Patients?)	Healthy
Sex(es) included (how many?)	Male: 15 Female: 2
Test product	Oxandrolone of Upsher-Smith
Reference product	Oxandrin ^R of BTG Pharmaceuticals
Strength tested	2.5 mg
Dose	4x2.5 mg

Summary of Statistical Analysis		
Parameter	Point Estimate	90% Confidence Interval
AUC _{0-t}	0.91	87.62-95.53
AUC _∞	0.95	90.93-99.12
C _{max}	0.84	81.19-87.89

Reanalysis of Study Samples Additional information in Appendix, Table 6 and Table 7									
Reason why assay was repeated	Number of samples reanalyzed				Number of recalculated values used after reanalysis				
	Actual number		% of total assays		Actual number		% of total assays		
	T	R	T	R	T	R	T	R	
Not Reported	2	3	0.13	0.19	2	3	0.13	0.19	
ALQ>(50.0)	1	7	0.06	0.46	1	7	0.06	0.46	
BLQ<(1.00)	7	10	0.46	0.66	7	10	0.46	0.66	
BLQ<(0.50)	0	2	0	0.13	0	2	0	0.13	
Total	10	22	0.66	1.45	10	22	0.66	1.45	

Total number of samples analyzed: 1512 samples

For five repeats, the reasons for repeating are not clear.

2. Single-dose Fed Bioequivalence Study:

None

F. Formulation

Location in appendix	Section IV.B, Page 16
Are inactive ingredients within IIG limits?	Yes
If no, list ingredients outside of limits	
If a tablet, is the product scored?	Yes
If yes, which strengths are scored?	2.5 mg
Is scoring of RLD the same as test?	Yes
Is the formulation acceptable?	Yes
If not acceptable, why?	

G. In Vitro Dissolution:

(a) FDA Proposed Method:

Source of Method (USP, FDA or Firm)	FDA
Medium	30% Isopropyl alcohol (IPA)
Volume (mL)	500
USP Apparatus type	II (Paddle)
Rotation (rpm)	100
Firm's proposed specifications	None
FDA-recommended specifications	— in 60 min. (Dissolution data base updated on 1/9/2002)
F2 metric calculated?	Yes, 46.9 test vs. ref using 10,20,30 &40 min
If no, reason why F2 not calculated	
Is method acceptable?	No
If not then why?	The DBE discourages use of hydroalcoholic medium.

(b) Firm's proposed Method:

Source of Method (USP, FDA or Firm)	Firm
Medium	0.75% SDS in 0.1 N HCl
Volume (mL)	500
USP Apparatus type	II (Paddle)
Rotation (rpm)	75
Firm's proposed specifications	Q=—, in 90 min.
FDA-recommended specifications	N/A
F2 metric calculated?	Yes, 64.8 test vs. ref using 15,30,45 &60 min
If no, reason why F2 not calculated	
Is method acceptable?	Yes, with a specification of NLT — (Q) in 90 minutes.

If not then why?

The USP monograph for oxandrolone tablets does not contain a dissolution method.

H. Deficiency Comments

1. Manufacturing date of Test Product was not provided.

- 2. Reasons for five samples re-assayed were not provided along with SOPs.
- 3. Stock solution stability (days) not provided.
- 4. Firm's proposed dissolution method is acceptable. The firm should be requested to use a specification of NLT ~~---~~(Q) in 90 minutes.

Conclusion: The application is incomplete.

I. Recommendations

1. The single-dose, fasting bioequivalence conducted by Upsher-Smith Laboratories, Inc. on the test product, Oxandrolone Tablets USP, 2.5 mg, lot # 2801.003/20862, comparing it with the reference product, BTG's Oxandrin® Tablets, 2.5 mg, lot # 0D092, has been found incomplete.

2. The dissolution testing conducted by Upsher-Smith Laboratories, Inc. on the test product, Oxandrolone Tablets USP, 2.5 mg is acceptable. The firm's proposed dissolution method is acceptable.

The dissolution testing should be conducted in 500 mL of 0.75% SDS in 0.1 N HCl at 37°C using USP apparatus II (paddle) at 75 rpm. The test product should meet the following specification:

Not less than ~~---~~ (Q) of the labeled amount of the drug in the dosage form is dissolved in 90 minutes.

Sikta Pradhan 5/24/04
Sikta Pradhan, Review Branch IV Date

Kuldeep R. Dhariwal 5/24/2004
Kuldeep R. Dhariwal Ph. D. Date
Team Leader, Review Branch IV

for Barbara M. Savitt 5/24/04
Dale P. Conner, Pharm. D. Date
Director, Division of Bioequivalence
Office of Generic Drugs

IV. Appendix

A. Individual Study Reviews

1. Single-dose Fasting Bioequivalence Study

a) Study Design

Study Information	
Study Number	Upsher-Smith: P02-006; R01-794; 11-458-T1
Study Title	A Relative Bioavailability Pilot Study of 2.5 mg Oxandrolone Tablets under Fasting conditions
Clinical Site	
Principal Investigator	 , Pharm. D.
Study/Dosing Dates	Period I: September 21-23, 2002 Period II: September 28-30, 2002
Analytical Site	
Analytical Director	
Analysis Dates	November 1, 2002 – November 8, 2002
Storage Period (no. of days from the first day of sample collection to the last day of sample analysis)	49 days

Treatment ID	A	B
Test or Reference	Test	Reference
Product Name	Oxandrolone Tablet USP	Oxandrin ^R
Manufacturer	Upsher-Smith Laboratories, Inc.	G.D. Searle & Co. for BTG Pharmaceuticals
Batch/Lot No.	2801.003/20862	0D092
Manufacture Date	Not Reported	N/A
Expiration Date	Not Reported	04/05
Strength	2.5 mg	2.5 mg
Dosage Form	Tablet	Tablet
Batch Size	 Tablets	N/A
Production Batch Size	 Tablets	
Potency	98.7%	99.8%
Content Uniformity (mean, %CV)	100.3, 1.6	102.4, 1.3
Formulation	See Appendix Section B	
Dose Administered	4x2.5 mg	4x2.5 mg
Route of Administration	Oral	

No. of Sequences	2
No. of Periods	2
No. of Treatments	2
No. of Groups	1
Washout Period	7 days
Randomization Scheme	AB: 1,4,5,7,10,11,14,17,18 BA: 2,3,6,8,9,12,13,15,16,
Blood Sampling Times	0, 0.33, 0.67, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 6, 8, 10, 12, 16, 24, 30, 36, and 48 hours.
Blood Volume Collected/Sample	10 mL/sample
Blood Sample Processing/Storage	The blood samples were collected in EDTA vacutainers, centrifuged, and the plasma separated, frozen and stored at -20 ⁰ C until shipment for analysis.
IRB Approval	Yes
Informed Consent	Yes
Subjects Demographics	See Table 1
Length of Fasting	At least 10 hours prior to until 4 hours after dosing
Length of Confinement	At least 10 hours prior to until 24 hours after dosing
Safety Monitoring	Vital signs were measured prior to dosing and at 3,12 and 24 hours after each dose.

Comments on Study Design: Study design is acceptable.

b) Clinical Results

Table 1 Demographics of Study Subjects

Age		Weight		Age Groups		Gender		Race	
				Range	%	Sex	%	Category	%
				<18	0			Caucasian	100
Mean	24.7	Mean	76.3	18-40	88	Male	88	Afr. Amer.	0
SD	8.7	SD	10.6	41-64	12	Female	12	Hispanic	0
Range	18-52	Range	54.5-94.4	65-75	0			Asian	0
				>75	0			Others	0

Note: Oxandrin[®] is a Pregnancy Category X drug, therefore only postmenopausal or surgically sterile women were eligible to participate in this study.

Table 2 Dropout Information

Subject No.	Reason	Period	Replaced?
16	Personal	Prior to Period 2 dosing	N

Table 3 Study Adverse Events

Adverse Event Description	# in Test Group	# in Ref. Group
Dizziness		1
Pallor	1	
Seasonal allergies		1
Total:	1	2

Table 4 Protocol Deviations: No significant protocol deviation was reported.

Type	Subject #s (Test)	Subject #s (Ref.)

Comments on Dropouts/Adverse Events/Protocol Deviations:

1. There were no serious adverse events or any events which required terminating any subject from study participation.
2. No significant protocol deviation was reported.

c) Bioanalytical Results

Table 5 Assay Quality Control – Within Study

	Parent								Metabolite
QC Conc. (ng/mL)	1.50	20.0	40.0	100 (4xdilution)					N/A
Inter day Precision (%CV)	14.5	6.2	6.6	6.5					
Inter day Accuracy (%)	110.7	102.5	95.0	96.5					
Cal. Standards Conc. (ng/mL)	0.50	1.00	2.00	5.00	10.0	25	45	50	
Inter day Precision (%CV)	2.9	5.8	6.3	4.0	4.4	4.9	4.5	5.4	
Inter day Accuracy (%)	107.2	109	107	108.8	104	94.8	92.4	92.2	
Linearity Range (range of R ² values)	0.9969 (mean)								

Comments on Study Assay Quality Control: Acceptable

Any interfering peaks in chromatograms?	No
Were 20% of chromatograms included?	Yes
Were chromatograms serially or randomly selected?	Serially selected

Comments on Chromatograms: None

Table 6 SOP's dealing with analytical repeats of study samples

The firm did not provide SOPs.

Table 7 Additional Comments on Repeat Assays

Thirty-two (32) samples were repeated. Eight (8) of them were repeated as the ALQ>(50.0). Nineteen (17) samples were repeated as the BLQ<(1.00) of those samples. However, there were five (5) repeats (Subj.#4,P1, T:1.5hr; Subj.#4, P2, T:1.5Hr.; Subj.#9, P1, T:1.5hr.; Subj.#10, P2, T:4.5hr.; Subj.2, P2, T:48hr.), the reasons for repeating those are not clear. The firm should be requested to provide the reasons for these repeats along with the SOP. If these samples were repeated due to anomalous values, then the firm should provide the justification for using the re-assay values and also repeat the statistical analysis using the original values.

Summary/Conclusions, Study Assays: Incomplete

d) Pharmacokinetic Results

Table 8 Arithmetic Mean Pharmacokinetic Parameters (N=17)

(Mean plasma concentrations are presented in Table 11 and Figure 1)

	MEAN1	CV1	MEAN2	CV2	RMEAN12
PARAMETER					
AUCI (ng·hr/mL)	466.67	21.75	489.83	20.07	0.95
AUCT (ng·hr/mL)	439.73	20.33	480.40	20.27	0.92
C_{MAX} (ng/mL)	39.28	15.30	46.54	16.82	0.84
KE (1/hr)	0.07	29.36	0.11	17.58	0.62
LAUCI	456.47	0.05	480.69	0.04	0.95
LAUCT	431.30	0.05	471.30	0.04	0.92
LC_{MAX}	38.84	0.40	45.98	0.34	0.84
T_{HALE} (hr)	10.93	31.74	6.43	17.15	1.70
T_{MAX} (hr)	2.47	59.21	2.97	29.32	0.83

1=Test, 2=Reference

Table 9 Geometric Means and 90% Confidence Intervals

	LSM1	LSM2	RLSM12	LOWCI12	UPPCI12
PARAMETER					
AUCI	468.63	491.95	0.95	91.49	99.02
AUCT	441.61	482.57	0.92	87.66	95.36
C_{MAX}	39.45	46.76	0.84	80.17	88.57
LAUCI	458.23	482.68	0.95	90.93	99.12
LAUCT	433.04	473.33	0.91	87.62	95.53
LC_{MAX}	39.02	46.19	0.84	81.19	87.89

1=Test, 2=Reference

Table 10 Additional Study Information

Root mean square error, AUC_{0-t}	0.071778
Root mean square error, AUC_{∞}	0.071640
Root mean square error, C_{max}	0.065837
Ke and AUC_i determined for how many subjects?	17
Do you agree or disagree with firm's decision?	Agree
Indicate the number of subjects with the following:	
-measurable drug concentrations at 0 hr	None
-first measurable drug concentration as C_{max}	None
Were the subjects dosed as more than one group?	No

Comments on Pharmacokinetic Analysis: Acceptable

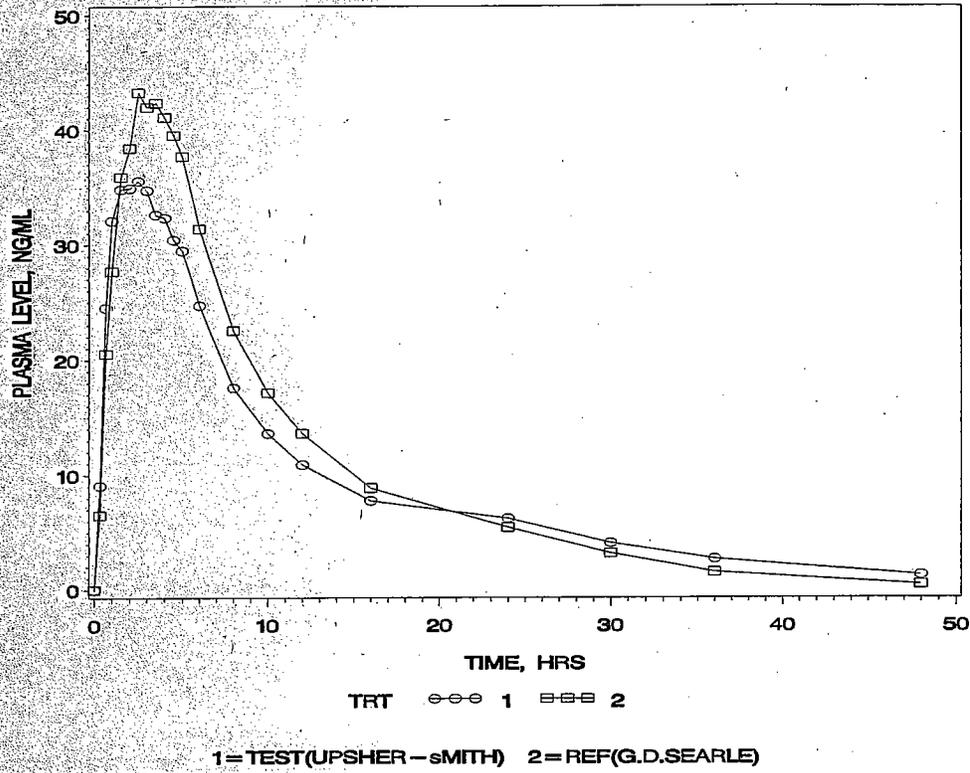
Summary and Conclusions, Single-Dose Fasting Bioequivalence Study:
Single-Dose Fasting Bioequivalence Study is incomplete.

**Table 11 Mean Plasma Concentrations, Single-Dose Fasting Bioequivalence Study
(N=17)**

TIME HR	MEAN1 (ng/mL)	CV1	MEAN2 (ng/mL)	CV2	RMEAN12
0	0.00	.	0.00	.	.
0.33	9.09	88.85	6.52	64.82	1.39
0.67	24.53	48.64	20.53	34.59	1.19
1	32.08	35.13	27.68	25.20	1.16
1.5	34.82	24.53	35.87	22.25	0.97
2	34.90	22.94	38.41	13.79	0.91
2.5	35.54	19.67	43.26	17.41	0.82
3	34.73	15.34	41.98	20.34	0.83
3.5	32.61	16.06	42.34	13.72	0.77
4	32.34	17.72	41.08	22.50	0.79
4.5	30.41	20.41	39.51	16.45	0.77
5	29.47	21.25	37.68	15.41	0.78
6	24.72	16.27	31.37	14.45	0.79
8	17.58	20.67	22.52	19.67	0.78
10	13.60	25.11	17.13	22.80	0.79
12	10.89	21.95	13.60	24.92	0.80
16	7.76	32.13	8.86	29.64	0.88
24	6.20	28.96	5.42	37.81	1.14
30	4.06	35.46	3.17	59.03	1.28
36	2.67	39.04	1.52	71.05	1.75
48	1.25	72.62	0.43	132.64	2.89

Figure 1 Mean Plasma Concentrations, Single-Dose Fasting Bioequivalence Study

PLASMA OXANDROLONE LEVELS
OXANDROLONE TABLET, 2.5 MG, ANDA # 76761
UNDER FASTING CONDITIONS
DOSE=4 X 2.5 mg Tablet



B. Formulation Data

Ingredients	Amount per tablet (mg)	%w/w
Oxandrolone, USP	2.5	
Anhydrous Lactose, NF		
Pregelatinized Starch, NF		
Hypromellose (Hydroxypropyl Methylcellulose), USP*		
Magnesium Stearate, NF**		

*Referred to as Hydroxypropyl Methylcellulose, USP on the Bioequivalence/Test Batch record. The name changed to Hypromellose, USP after the manufacture of the Bioequivalence/Test Batch.

** Referred to as Magnesium Stearate _____, USP/NF on the batch record and PII Master Specifications.

C. Dissolution Data

(a) FDA Proposed Method:

Source of Method (USP, FDA or Firm) FDA
Medium 30% Isopropyl alcohol (IPA)
Volume (mL) 500
USP Apparatus type II (Paddle)
Rotation (rpm) 100
Firm's proposed specifications None
FDA-recommended specifications — in 60 min.
Is method acceptable? No
If not then why? The DBE discourages use of hydro-alcoholic medium.

Table 1

Sampling Time (min)	Test Product, Strength 2.5 mg Tablets Lot No.2801.003			Reference Product, Strength 2.5 mg Tablets Lot No. 0D092		
	Mean	%CV	Range	Mean	%CV	Range
10	29	6.7	✓	29	10.5	✓
20	61	9.9		54	9.5	
30	88	5.6		73	6.2	
40	98	2.5		82	7.3	
50	101	2.1		91	4.4	
60	103	1.9		97	4.4	

(b) Firm's Proposed Method:

Source of Method (USP, FDA or Firm) Firm
Medium 0.75% SDS in 0.1N HCl
Volume (mL) 500
USP Apparatus type II (Paddle)
Rotation (rpm) 75
Firm's proposed specifications Q= — in 90 minutes
Is method acceptable? Yes, with a specification of NLT — (Q) in 90 minutes

If not then why?

Sampling Time (min)	Test Product, Strength 2.5 mg Tablets Lot No.2801.003			Reference Product, Strength 2.5 mg Tablets Lot No. 0D092		
	Mean	%CV	Range	Mean	%CV	Range
15	45.6	11.4	✓	43.3	11.0	✓
30	75.7	8.1		77.1	8.6	
45	85.7	7.9		91.7	7.9	
60	89.5	8.8		96.9	4.5	
90	95.7	6.3		100.6	2.5	

D. Consult Reviews

E. SAS Output

STUDY	DATA	SAS PROGRAM	SAS OUTPUT
Fasting Study	 M:\ESD\76761\ CONCPK.XPT	 M:\ESD\76761\ 76761BE02dp1.SAS	 M:\ESD\76761\ 76761_stat.TXT
Fed Study	None	None	None

BIOEQUIVALENCE COMMENTS

ANDA: 76-761

APPLICANT: Upsher-Smith Laboratories, Inc.

DRUG PRODUCT: Oxandrolone Tablets, USP 2.5 mg

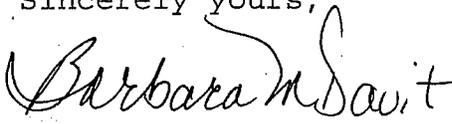
The Division of Bioequivalence has completed its review of your submission(s) acknowledged on the cover sheet. The following deficiencies have been identified:

1. The reasons for reassaying five samples (Subj.#4, P1, T:1.5hr; Subj.#4, P2, T:1.5Hr.; Subj.#9, P1, T:1.5hr.; Subj.#10, P2, T:4.5hr.; Subj.2, P2, T:48hr.) are not clear. If these samples were reassayed due to anomalous values, please provide the justification for using the reassay values along with the SOP for sample reassays. Also, include the statistical analysis using the original assay values.
2. Please provide data demonstrating stability of the stock solutions of oxandrolone and internal standard.
3. Please provide manufacturing date of the test product.
4. Your proposed dissolution specification is not acceptable. We recommend the use of the following method and specifications:

The dissolution testing should be conducted in 500 mL of 0.75% SDS in 0.1N HCl at 37°C using USP apparatus II (paddle) at 75 rpm. The test product should meet the following specification:

Not less than (Q) of the labeled amount of the drug in the dosage form is dissolved in 90 minutes.

Sincerely yours,

for 

Dale P. Conner, Pharm. D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

CC:ANDA 76-761
ANDA DUPLICATE
DIVISION FILE
FIELD COPY

HFD- / Bio Drug File
HFD- / Reviewer: S. Pradhan

Endorsments: (Final with Dates)

HFD-6 / S. Pradhan *SP*

HFD-6 / K. Dhariwal, *MD 5/24/04*

In HFD-650/ D. Conner *B2D 5/25/04*

HFD-6 / Fritsch

V:\FIRMSNZ\Upsher-Smith\ltrs&rev\76761N0603.doc

Printed in final on 5/24/2004

BIOEQUIVALENCE - Incomplete

Submission date: 06-12-03

✓ 1. FASTING STUDY (STF)

Strength: 2.5 mg

Outcome: IC

OUTCOME DECISIONS: Incomplete

-----Original Message-----

From: Tran, Nhan L
Sent: Monday, May 24, 2004 10:04 AM
To: Pradhan, Sikta
Cc: Dhariwal, Kuldeep R
Subject: RE: REVIEW 76761 Upsher-Smith Oxandrolone Tab Sikta 6-12-03

I agree with Barbara suggestion. Although we have few cases where we have accepted hydro-alcoholic medium (see Atovaquone), both USP and FDA discourage the use of hydro-alcoholic medium as a dissolution medium because this medium is not physiologic in nature.

For your product, the Upsher-Smith's method is more acceptable than the FDA method. Based on data submitted, we can recommend the following specification: NLT \leq in 90 minutes. With that spec, the firm can meet the S1 stage with no problems.

Thanks,

-----Original Message-----

From: Pradhan, Sikta
Sent: Monday, May 24, 2004 9:40 AM
To: Tran, Nhan L
Cc: Pradhan, Sikta
Subject: FW: REVIEW 76761 Upsher-Smith Oxandrolone Tab Sikta 6-12-03

Nhan: Please, let me know your recommendation today.

Thanks
 Sikta

-----Original Message-----

From: Dhariwal, Kuldeep R
Sent: Monday, May 24, 2004 9:16 AM
To: Pradhan, Sikta
Subject: FW: REVIEW 76761 Upsher-Smith Oxandrolone Tab Sikta 6-12-03

-----Original Message-----

From: Davit, Barbara M
Sent: Friday, May 21, 2004 2:05 PM
To: Dhariwal, Kuldeep R; Conner, Dale P
Subject: RE: REVIEW 76761 Upsher-Smith Oxandrolone Tab Sikta 6-12-03

Kuldeep:

I have a question about the FDA-recommended dissolution method, which uses alcohol-water media. It is my understanding that the FDA encourages the use of alcohol in the media only if all other dissolution methods fail. I think that a low concentration of surfactant is considered better than alcohol-water dissolution media, even if this the RLD method.

Can you please check with Nhan about whether it is reasonable for us to accept Upsher-Smith's proposed method instead of the FDA method?

Also, maybe we could ask for the FDA method dissolution method just for comparison, but with the thought that we would compare both sets of dissolution data (FDA versus Upsher Smith) and see which method was better.

Thanks,

Barbara

OFFICE OF GENERIC DRUGS
DIVISION OF BIOEQUIVALENCE

ANDA #: 76-761 SPONSOR: Upsher-Smith Laboratories, Inc.

DRUG AND DOSAGE FORM : Oxandrolone Tablet
STRENGTH(S) : 2.5 mg
TYPES OF STUDIES : Fasting
CLINICAL STUDY SITE(S) : _____
ANALYTICAL SITE(S) : _____

STUDY SUMMARY: Fasting study on 2.5 mg tablets is acceptable.

DISSOLUTION : The dissolution testing is acceptable..

DSI INSPECTION STATUS

Inspection needed: No	Inspection status: Pending	Inspection results:
First Generic Yes	Inspection requested: 6/3/2004	
New facility _____	Inspection completed: (date)	
For cause _____		
Other _____		

PRIMARY REVIEWER: Sikta Pradhan, Ph. D.
INITIAL : Sikta Pradhan

BRANCH: IV
DATE: 8/25/04

TEAM LEADER: Kuldeep R. Dhariwal, Ph. D.
INITIAL : MD

BRANCH: IV
DATE: 8/25/04

fn

DIRECTOR, DIVISION OF BIOEQUIVALENCE : DALE P. CONNER, Pharm. D.
INITIAL : B m D DATE: 8/25/04

DIVISION OF BIOEQUIVALENCE REVIEW

ANDA No.	76-761
Drug Product Name	Oxandrolone Tablet USP
Strength	2.5 mg
Applicant Name	Upsher-Smith Laboratories, Inc.
Address	14905 23 rd Avenue North, Minneapolis, MN
Submission Date(s)	N/A
Amendment Date(s)	August 3, 2004
Reviewer	Sikta Pradhan
First Generic	Yes
File Location	V:\firmsnz\Upsher-Smith\ltrs&rev\76761A0804

I. Executive Summary

The firm submitted a single-dose, 2-way crossover fasting bioequivalence study comparing the test product, Oxandrolone Tablets, USP 2.5 mg, with the RLD product, Oxandrin® Tablets, 2.5 mg manufactured by G.D. Searle & Co. for BTG Pharmaceuticals. The fasting study was incomplete due to analytical deficiencies. The firm also submitted comparative dissolution data for the test and reference products using the FDA-recommended dissolution method. The test product met the FDA-recommended specification. The firm was recommended FDA's specification. The application was incomplete.

In this amendment the firm has responded to the Agency comments. The firm's responses are acceptable. The fasting study and dissolution data are acceptable. The application is acceptable with no deficiencies.

II. Agency Comments and Firms Responses:

Agency Comments #1: The reasons for reassaying five samples (Subj.#4,P1, T:1.5hr; Subj.#4, P2, T:1.5Hr.; Subj.#9, P1, T:1.5hr.; Subj.#10, P2, T:4.5hr.; Subj.2, P2, T:48hr.) are not clear. If these samples were reassayed due to anomalous values, please provide the justification for using the reassay values along with the SOP for sample reassays. Also, include the statistical analysis using the original assay values.

Firm's Response #1: The samples specified above were all re-assayed for analytical reasons.

- Subject 4, period 1, 1.5 hour, Subject 4, period 2, 1.5 hr. and subject 9, period 1, 1.5 hr. samples were re-assayed because the original injection had a high internal standard value.
- Subject 10, period 2, 4.5 hr. and Subject 2, period 2, 48 hr. samples were re-assayed because the original injection had a low internal standard value.

The table below provides the original result along with the re-assay value. (), section 6.0 discusses the procedure for re-assaying samples. A copy of has been provided.

Subject	Period	Time	Original Value (ng/mL)	Reassay Value (ng/mL)	Reported Value (ng/mL)
004	1	1.5 hr			
004	2	1.5 hr			
009	1	1.5 hr			
010	2	4.5 hr			
002	2	48 hr			

The statistical analysis provided in the original application was performed using the repeated assay results only. Although the original assay values were disregarded due to aberrant internal standard values, statistical analysis is provided in the current amendment using the original results, per FDA's request. All bioequivalence acceptance criteria were met for both the re-assay and the original assay values. The following table provides a comparison of the pharmacokinetic results using the re-assay results, reported in the ANDA, versus the original assay results.

Parameters (Ln transformed)	Reassay Results (ANDA submission)		Original Results (FDA requested)	
	T/R % Ratio	90% C.I.	T/R % Ratio	90% C.I.
C _{max}	84.48	81.19-87.89	84.48	81.19-87.89
AUC(0-t)	91.49	87.62-95.53	91.43	87.57-95.47
AUC(0-inf)	94.93	90.93-99.12	94.87	90.87-99.05

Agency Comments #2: Please provide data demonstrating stability of the stock solutions of Oxandrolone and Internal Standard.

Firm's Response #2: The firm has provided the stock solution stability data for Oxandrolone and Internal Standard along with its SOP, SOP PS-081. Oxandrolone's stock stability is 2 months, 6 days (on refrigeration). Internal Standard's stock stability is 26 days (on refrigeration). The response is acceptable.

Agency Comments #3: Please provide manufacturing date of the test product.

Firm's Response #3: The test product was manufactured in July 2002. The response is acceptable.

Agency Comments #4: Your proposed dissolution specification is not acceptable. We recommend the use of the following method and specifications:

The dissolution testing should be conducted in 500 mL of 0.75% SDS in 0.1N HCl at 37°C using USP apparatus II (paddle) at 75 rpm. The test product should meet the following specification:

Not less than ~~8~~ (Q) of the labeled amount of the drug in the dosage form is dissolved in 90 minutes.

Firm's Response #4: The dissolution method parameters recommended by the Agency are the same as those proposed in the original ANDA (500 mL of 0.75% SDS in 0.1N HCl at 37°C using USP apparatus II (paddle) at 75 rpm. In response to the Agency's request, Upsher-Smith has revised the dissolution acceptance criterion to not less than ~~8~~ (Q) of the labeled amount of the drug in the dosage form dissolved in 90 minutes.

III. Overall Comments:

The firm has met all requirements for in vivo and in vitro bioequivalence studies on its test product, Oxandrolone Tablets USP, 2.5 mg. The application is acceptable.

IV. Recommendations

1. The single-dose, fasting bioequivalence conducted by Upsher-Smith Laboratories, Inc. on the test product, Oxandrolone Tablets USP, 2.5 mg, lot # 2801.003/20862, comparing it with the reference product, BTG's Oxandrin® Tablets, 2.5 mg, lot # 0D092, is acceptable to the Division of Bioequivalence.

2. The dissolution testing conducted by Upsher-Smith Laboratories, Inc. on the test product, Oxandrolone Tablets USP, 2.5 mg is acceptable.

The dissolution testing should be conducted in 500 mL of 0.75% SDS in 0.1 N HCl at 37°C using USP apparatus II (paddle) at 75 rpm. The test product should meet the following specification:

Not less than (Q) of the labeled amount of the drug in the dosage form is dissolved in 90 minutes.

Sikta Pradhan 8/25/04
Sikta Pradhan, Review Branch IV Date

Moharawal 8/25/04
Kuldeep R. Dhariwal, Ph. D. Date
Team Leader, Review Branch IV

Barbara M. Conner 8/25/04
Dale P. Conner, Pharm. D. Date
Director, Division of Bioequivalence
Office of Generic Drugs

BIOEQUIVALENCE COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 76-761 APPLICANT: Upsher-Smith Laboratories, Inc.

DRUG PRODUCT: Oxandrolone Tablets, USP 2.5 mg

The Division of Bioequivalence has completed its review and has no further questions at this time.

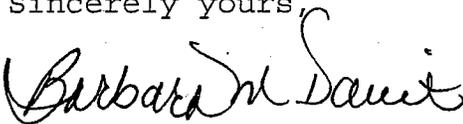
We acknowledge that you have accepted the following dissolution method and specification:

The dissolution testing should be conducted in 500 mL of 0.75% SDS in 0.1N HCl at 37°C using USP apparatus II (paddle) at 75 rpm. The test product should meet the following specification:

Not less than ~~—~~ (Q) of the labeled amount of the drug in dosage form is dissolved in 90 minutes.

Please note that the bioequivalence comments provided in this communication are preliminary. These comments are subject to revision after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling, or other scientific or regulatory issues. Please be advised that these reviews may result in the need for additional bioequivalence information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

Sincerely yours,

pr 

Dale P. Conner, Pharm. D.
Director

Division of Bioequivalence
Office of Generic Drugs

Center for Drug Evaluation and Research

CC: ANDA 76-761
ANDA DUPLICATE
DIVISION FILE
FIELD COPY

HFD-650 / Bio Drug File
HFD-650 / Reviewer: S. Pradhan

Endorsements: (Final with Dates)

HFD-650 / S. Pradhan *SP 8/25/04*

HFD-650 / K. Dhariwal *KD 8/25/04*

HFD-650 / D. Conner

HFD-650 / Fritsch *DF 8/25/04*

lu

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Printed in final on 8/25/04

BIOEQUIVALENCE - Acceptable

Submission date: 08-03-04

✓ 1. STUDY AMENDMENT (STA)

Strength: 2.5 mg
Outcome: AC

OUTCOME DECISIONS: ACCEPTABLE

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 76-761

ADMINISTRATIVE DOCUMENTS

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION			REQUEST FOR CONSULTATION	
HFD-420, PKLN Rm 6-34, Office of Drug Safety/Division of Medication Errors and Technical Support (DMETS) - Sammie Beam, Project Manager			FROM: Debra Catterson, HFD-613, Labeling Review Branch, OGD	
DATE: September 4, 2003	IND NO. N/A	ANDA NO. 76-761	TYPE OF DOCUMENT: Original Application	DATE OF DOCUMENT June 12, 2003
NAME OF DRUG Oxandrolone Tablets USP, 2.5 mg		REFERENCE LISTED DRUG: Oxandrin® Tablets NDA 13-718	CLASSIFICATION OF DRUG: Anabolic Steroid	DESIRED COMPLETION DATE November 4, 2003
NAME OF FIRM Upsher-Smith Laboratories, Inc.				
REASON FOR REQUEST				
I. GENERAL				
<input type="checkbox"/> NEW PROTOCOL <input type="checkbox"/> PRE NDA MEETING <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER <input type="checkbox"/> PROGRESS REPORT <input type="checkbox"/> END OF PHASE II MEETING <input type="checkbox"/> FINAL PRINTED LABELING <input type="checkbox"/> NEW CORRESPONDENCE <input type="checkbox"/> RESUBMISSION <input type="checkbox"/> LABELING REVISION <input type="checkbox"/> DRUG ADVERTISING <input type="checkbox"/> SAFETY/EFFICACY <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE <input type="checkbox"/> ADVERSE REACTION REPORT <input type="checkbox"/> PAPER NDA <input type="checkbox"/> FORMULATIVE REVIEW <input type="checkbox"/> MANUFACTURING CHANGE/ADDITION <input type="checkbox"/> CONTROL SUPPLEMENT <input checked="" type="checkbox"/> OTHER: Proposed Proprietary Name <input type="checkbox"/> MEETING PLANNED BY _____				
II. BIOMETRICS				
STATISTICAL EVALUATION BRANCH			STATISTICAL APPLICATION BRANCH	
<input type="checkbox"/> TYPE A OR B NDA REVIEW <input type="checkbox"/> END OF PHASE II MEETING <input type="checkbox"/> CONTROLLED STUDIES <input type="checkbox"/> PROTOCOL REVIEW <input type="checkbox"/> OTHER			<input type="checkbox"/> CHEMISTRY <input type="checkbox"/> PHARMACOLOGY <input type="checkbox"/> BIOPHARMACEUTICS <input type="checkbox"/> OTHER	
III. BIOPHARMACEUTICS				
<input type="checkbox"/> DISSOLUTION <input type="checkbox"/> PROTOCOL-- BIOPHARMACEUTICS <input type="checkbox"/> IN--VIVO WAIVER REQUEST			<input type="checkbox"/> DEFICIENCY LETTER RESPONSE <input type="checkbox"/> BIOAVAILABILITY STUDIES <input type="checkbox"/> PHASE IV STUDIES	
IV. DRUG EXPERIENCE				
<input type="checkbox"/> PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL <input type="checkbox"/> DRUG USE e.g., POPULATION EXPOSURE ASSOCIATED DIAGNOSES <input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below) <input type="checkbox"/> COMPARATIVE RISK ASSESSEMENT ON GENERIC DRUG GROUP			<input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY <input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE <input type="checkbox"/> POISON RISK ANALYSIS	
V. SCIENTIFIC INVESTIGATIONS				
<input type="checkbox"/> CLINICAL			<input type="checkbox"/> PRECLINICAL	
COMMENTS/SPECIAL INSTRUCTIONS (Attach additional sheets if necessary)				
Upsher-Smith has submitted two proposed proprietary names for your review, in the hopes that you will find one of them acceptable for their drug product. The proposed names, in order of preference, are "_____" and "_____". Attached is the firm's draft labeling for your review.				
SIGNATURE OF REQUESTER <i>Debra M. Catterson</i> 9/4/03			827-5835	
SIGNATURE OF RECEIVER			METHOD OF DELIVERY (Check one) <input type="checkbox"/> MAIL <input type="checkbox"/> HAND	
			SIGNATURE OF DELIVERER	

CONSULTATION RESPONSE

**DIVISION OF MEDICATION ERRORS AND TECHNICAL SUPPORT
OFFICE OF DRUG SAFETY
(DMETS; HFD-420)**

DATE RECEIVED: Sept. 9, 2003
DOCUMENT DATE: June 12, 2003

DESIRED COMPLETION DATE:
November 9, 2003

ODS CONSULT #: 03-0257

TO: Peter Rickman
Director, Division of Labeling and Program Support, Office of Generic Drugs
HFD-610

THROUGH: Harvey Greenberg
Project Manager
HFD-615

PRODUCT NAME:

(Oxandrolone Tablets, USP)
2.5 mg

ANDA #: 76-761

SPONSOR: Upsher-Smith Laboratories, Inc.

SAFETY EVALUATOR: Tia M. Harper-Velazquez, Pharm.D.

RECOMMENDATIONS:

1. DMETS has no objections to the use of the proprietary name, _____ This is considered a tentative decision and the firm should be notified that this name with its associated labels and labeling must be re-evaluated approximately 90 days prior to the expected approval date of the ANDA. A re-review of the name prior to ANDA approval will rule out any objections based upon approvals of other proprietary or established names from the signature date of this document.
2. DMETS recommends implementation of the labeling revisions as outlined in Section III of this review to minimize potential errors with the use of this product.
3. DDMAC finds the name _____ acceptable from a promotional perspective.
4. The Division of Metabolic and Endocrine Drug Products did not have any concerns with the proposed name, _____

Carol Holquist 2/18/04

Carol Holquist, R.Ph.
Deputy Director
Division of Medication Errors and Technical Support
Office of Drug Safety
Phone: (301) 827-3242 Fax: (301) 443-9664

Carol Holquist for 2/18/04

Jerry Phillips, R.Ph.
Associate Director
Office of Drug Safety
Center for Drug Evaluation and Research
Food and Drug Administration

**Division of Medication Errors and Technical Support
Office of Drug Safety
HFD-420; Parklawn, Rm. 6-34
Center for Drug Evaluation and Research**

PROPRIETARY NAME REVIEW

DATE OF REVIEW: November 18, 2003

ANDA NUMBER: 76-761

NAME OF DRUG: _____
(Oxandrolone Tablets, USP)
2.5 mg

ANDA SPONSOR: Upsher-Smith Laboratories, Inc.

I. INTRODUCTION

This consult was written in response to a request from the Labeling Review Branch in the Division of Labeling and Program Support, Office of Generic Drugs (HFD-613), for an assessment of the proposed proprietary name _____ the draft container labels, blister labels, as well as carton and package insert labeling were reviewed for possible interventions in minimizing medication errors.

PRODUCT INFORMATION

_____ is the proposed name for oxandrolone tablets. _____ is a Class III controlled substance, indicatr _____

_____, to off set the protein catabolism associated with prolonged administration of corticosteroids, and for the relief of bone pain accompanying osteoporosis. The recommend daily dose for _____ is 2.5 mg to 20 mg given in two to four divided doses. A course of therapy of 2 weeks to 4 weeks is usually adequate. This may be repeated intermittently as indicated. The reference listed drug (RLD) for _____ is Oxandrin Tablets, USP. Although Oxandrin Tablets, USP is available in strengths of 2.5 mg and 10 mg, Upsher-Smith Laboratories, Inc. is only pursuing the 2.5 mg strength at this time.

II. RISK ASSESSMENT

The medication error staff of DMETS conducted a search of several standard published drug product reference textsⁱ as well as several FDA databasesⁱⁱⁱ for existing drug names which sound-alike or look-alike to _____ to a degree where potential confusion between drug names could occur under the usual clinical practice settings. A search of the electronic online version of the U.S. Patent

ⁱ MICROMEDEX Integrated Index, 2003, MICROMEDEX, Inc., 6200 South Syracuse Way, Suite 300, Englewood, Colorado 80111-4740, which includes all products/databases within ChemKnowledge, DrugKnowledge, and RegsKnowledge Systems.

ⁱⁱ Facts and Comparisons, online version, Facts and Comparisons, St. Louis, MO.

ⁱⁱⁱ AMF Decision Support System [DSS], the Division of Medication Errors and Technical Support proprietary name consultation requests, New Drug Approvals 98-03, and the electronic online version of the FDA Orange Book.

and Trademark Office's Text and Image Database^{iv} and the data provided by Thomson & Thomson's SAEGISTM Online Service^v were also conducted. An expert panel discussion was conducted to review all findings from the searches. In addition, DMETS conducted three prescription analysis studies consisting of two written prescription studies (both inpatient) and one verbal prescription study, involving health care practitioners within FDA. This exercise was conducted to simulate the prescription ordering process in order to evaluate potential errors in handwriting and verbal communication of the name.

A. EXPERT PANEL DISCUSSION

An Expert Panel discussion (EPD) was held by DMETS to gather professional opinions on the safety of the proprietary name, _____. Potential concerns regarding drug marketing and promotion related to the proposed name was also discussed. This group is composed of DMETS Medication Errors Prevention Staff and representation from the Division of Drug Marketing, Advertising, and Communications (DDMAC). The group relies on their clinical and other professional experiences and a number of standard references when making a decision on the acceptability of a proprietary name.

1. DDMAC did not have any concerns with _____ ith regard to promotional claims.
2. The Expert Panel identified three currently marketed names as having potential for confusion with _____. These products are listed in Table 1 (see page 4), along with the usual dosage and available dosage form. Additionally, the Panel noted that the proposed name looks similar to the medical term, _____.

^{iv} WWW location <http://www.uspto.gov>.

^v Data provided by Thomson & Thomson's SAEGIS(tm) Online Service, available at www.thomson-thomson.com.

4 PAGES WITHHELD IN FULL

B. CONTAINER LABEL (5 count professional sample, 100 count, and 1000 count)

1. Ensure that the established name is at least ½ the size of the proprietary name, per 21 CFR 201.10(g)(2).
2. See comments under Blister Pack Carton Labeling.

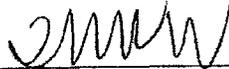
C. PACKAGE INSERT LABELING

No comments.

IV. RECOMMENDATIONS

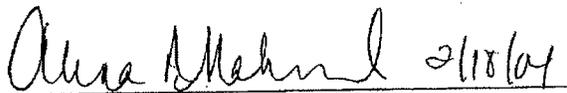
- A. DMETS has no objections to the use of the proprietary name, _____ . This is considered a tentative decision and the firm should be notified that this name with its associated labels and labeling must be re-evaluated approximately 90 days prior to the expected approval date of the ANDA. A re-review of the name prior to ANDA approval will rule out any objections based upon approvals of other proprietary or established names from the signature date of this document.
- B. DMETS recommends implementation of the labeling revisions as outlined in Section III of this review to minimize potential errors with the use of this product.
- C. DDMAC finds the name _____ acceptable from a promotional perspective

DMETS would appreciate feedback of the final outcome of this consult (e.g., copy of revised labels/labeling). We are willing to meet with the Division for further discussion as well. If you have any questions concerning this review, please contact Sammie Beam at 301-827-3242.

 2/17/04

Tia M. Harper-Velazquez, Pharm.D.
Safety Evaluator
Division of Medication Errors and Technical Support
Office of Drug Safety

Concur:

 2/18/04

Alina Mahmud, R.Ph.
Team Leader
Division of Medication Errors and Technical Support
Office of Drug Safety

Appendix A. DMETS prescription study results for _____

Voice mail

Inpatient

Outpatient

RECORD OF TELEPHONE CONVERSATION

<p>Agency initiated the teleconference with Upsher-Smith and requested the following:</p> <ol style="list-style-type: none"> 1. Please revise both titration and HPLC assay specification for drug substance to be compliant with the current USP method. Also, please delete "pending USP petition" from the DS specification test parameter column, and provide a footnote stating the DS monograph is official in the current USP. Lastly, please provide data to demonstrate that the in-house assay method is better or comparable to the current USP method. 2. Please revise the drug insert labeling to reflect the USP dissolution test is pending. 	<p>ANDA NUMBER 76-761</p>
	<p>IND NUMBER</p>
	<p>TELECON</p>
	<p>INITIATED BY</p> <p>SPONSOR</p> <p>FDA X</p>
	<p>PRODUCT NAME</p> <p>Oxandrolone Tablets USP, 2.5 mg</p>
	<p>FIRM NAME</p> <p>Upsher-Smith Laboratories, Inc.</p>
	<p>NAME OF PERSON WITH WHOM CONVERSATION WAS HELD</p> <p>Tanya Carone</p>
	<p>TELEPHONE NUMBER</p> <p>_____</p>
<p>SIGNATURE</p> <p>Neeru Takiar <i>NT 11/16/06</i></p> <p>Jeanne Skanchy <i>JSkanchy 11/16/06</i></p>	

Signed off on 4/18/06

CONSULTATION RESPONSE

**DIVISION OF MEDICATION ERRORS AND TECHNICAL SUPPORT
OFFICE OF DRUG SAFETY
(DMETS; WO22, Mailstop 4447)**

DATE RECEIVED: December 8, 2005	DESIRED COMPLETION DATE: February 8, 2006	ODS CONSULT #: 03-0257-1
---	---	---------------------------------

TO: Peter Rickman
Director, Division of Labeling and Program Support, Office of Generic Drugs
HFD-610

THROUGH: Linda Y. Kim-Jung, PharmD, Team Leader
Denise P. Toyer, PharmD, Deputy Director
Carol A. Holquist, RPh, Director
Division of Medication Errors and Technical Support

FROM: Loretta Holmes, PharmD, Safety Evaluator
Division of Medication Errors and Technical Support

PRODUCT NAME: _____
(Oxandrolone Tablet) 2.5 mg

ANDA#: 76-761

SPONSOR: Upsher-Smith Laboratories, Inc.

RECOMMENDATIONS:

1. DMETS has no objections to the use of the proposed proprietary name, _____ provided that only one name _____ (ANDA 76-761) or _____,*** (NDA _____), is approved. DMETS believes the names may not co-exist in the marketplace since orthographic similarities and product characteristics may increase the potential for confusion. Therefore, the application that receives approval first is entitled to the name. Coordination between the two affected divisions (the Office of Generic Drugs and the Division of Neurology Products) and DMETS will ensure that only one name is allowed.
2. No new container labels, carton and insert labeling were submitted for review and comment. However, DMETS refers to ODS Consult 03-0257, dated November 18, 2003, for previous label and labeling recommendations.
3. DDMAC finds the proprietary name, _____, acceptable from a promotional perspective.
4. The Division of Metabolism and Endocrinology Products (HFD-510) did not have any concerns with the proposed name, _____, as per ODS Consult 03-0257.

DMETS would appreciate feedback of the final outcome of this consult. We would be willing to meet with the Division for further discussion, if needed. If you have further questions or need clarifications, please contact Diane Smith, Project Manager, at 301-796-0538.

*****NOTE:** This review contains proprietary and confidential information that should not be released to the public.***

Division of Medication Errors and Technical Support (DMETS)
Office of Drug Safety
White Oak Bldg #22, Mailstop 4447
Center for Drug Evaluation and Research

PROPRIETARY NAME REVIEW

DATE OF REVIEW: December 27, 2005
ANDA#: 76-761
NAME OF DRUG: _____
(Oxandrolone Tablets, USP) 2.5 mg
ANDA HOLDER: Upsher-Smith Laboratories, Inc.

*****NOTE: This review contains proprietary and confidential information that should not be released to the public.*****

I. INTRODUCTION:

This consult was written in response to a request from the Division of Labeling and Program Support (HFD-610), for reassessment of the proprietary name, _____, regarding potential name confusion with other proprietary or established drug names. This is the second proprietary name review of _____. In the initial consult (ODS Consult 03-0257, dated November 18, 2003), DMETS had no objections to the use of the proprietary name, _____.

DMETS reviewed the _____ labels and labeling during the initial review of the proposed proprietary name (ODS Consult 03-0257). Revised container labels, carton and insert labeling were not submitted and therefore have not been reviewed at this time.

PRODUCT INFORMATION

_____ contains oxandrolone, an anabolic steroid. _____ is a Schedule III controlled substance indicated as _____

_____ to offset the protein catabolism associated with prolonged administration of corticosteroids; and for the relief of bone pain frequently accompanying osteoporosis. The duration of therapy with _____ will depend on the response of the patient and the possible appearance of adverse reactions. Therapy should be intermittent. The recommended daily adult dosage is 2.5 mg to 20 mg given in 2 to 4 divided doses. A course of therapy of 2 to 4 weeks is usually adequate. This may be repeated intermittently as indicated. The reference listed drug (RLD) for _____ is Oxandrin® (Oxandrolone Tablets, USP) NDA 13-718. Although Oxandrin® tablets are available in strengths of 2.5 mg and 10 mg, Upsher-Smith Laboratories, Inc. is only pursuing the 2.5 mg strength at this time.

II. RISK ASSESSMENT:

The medication error staff of DMETS conducted a search of several standard published drug product reference texts^{1,2}, as well as several FDA databases^{3,4} for existing drug names which sound-alike or look-alike to _____ to a degree where potential confusion between drug names could occur under the usual clinical practice settings. A search of the electronic online version of the U.S. Patent and Trademark Office's Text and Image Database was also conducted⁵. The Saegis⁶ Pharma-In-Use database was searched for drug names with potential for confusion. An expert panel discussion was conducted to review all findings from the searches. In addition, DMETS conducted three prescription analysis studies consisting of two written prescription studies (inpatient and outpatient) and one verbal prescription study, involving health care practitioners within FDA. This exercise was conducted to simulate the prescription ordering process in order to evaluate potential errors in handwriting and verbal communication of the name.

A. EXPERT PANEL DISCUSSION (EPD)

An Expert Panel discussion was held by DMETS to gather professional opinions on the safety of the proprietary name, _____. Potential concerns regarding drug marketing and promotion related to the proposed name was also discussed. This group is composed of DMETS Medication Errors Prevention Staff and representation from the Division of Drug Marketing, Advertising, and Communications (DDMAC). The group relies on their clinical and other professional experiences and a number of standard references when making a decision on the acceptability of a proprietary name.

1. DDMAC finds the proprietary name, _____, acceptable from a promotional perspective.
2. The Expert Panel identified two proprietary names that were thought to have the potential for confusion with _____. These products are listed in Table 1 (see page 4), along with the dosage forms available and usual dosage.

¹ MICROMEDEX Integrated Index, 2005, MICROMEDEX, Inc., 6200 South Syracuse Way, Suite 300, Englewood, Colorado 80111-4740, which includes all products/databases within ChemKnowledge, DrugKnowledge, and RegsKnowledge Systems.

² Facts and Comparisons, online version, Facts and Comparisons, St. Louis, MO.

³ AMF Decision Support System [DSS], the Division of Medication Errors and Technical Support [DMETS] database of Proprietary name consultation requests, New Drug Approvals 98-05, and the electronic online version of the FDA Orange Book.

⁴ Phonetic and Orthographic Computer Analysis (POCA)

⁵ WWW location <http://www.uspto.gov/tmdb/index.html>.

⁶ Data provided by Thomson & Thomson's SAEGIS™ Online Service, available at www.thomson-thomson.com

5 PAGES WITHHELD IN FULL

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 76-761

CORRESPONDENCE

Mr. Gary Buehler
Director, Office of Generic Drugs
June 12, 2003
Page 2

This original ANDA is being submitted, in duplicate, as an archival and review copy. The archival copy (blue jackets) consists of 6 volumes. The review copy contains two parts: the chemistry, manufacturing and controls data consisting of 4 volumes (red jackets), and the bioavailability/bioequivalence data consisting of 2 volumes (orange jackets).

The bioequivalence clinical data are provided on disk in SAS transport format. These disks are submitted in the beginning of Section VI (Volume 2) of the archival and review copies of this application.

As required per 21 CFR 314.94(d)(5), we hereby certify that a field copy of the chemistry, manufacturing and controls sections of the ANDA has been submitted to the Minneapolis, MN District Office and the Baltimore, MD District Office for their review. These field copies are "true" copies of the technical sections of this application.

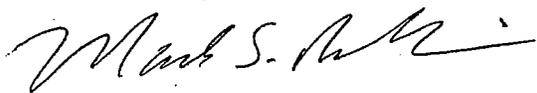
Upsher-Smith Laboratories, Inc. commits to resolving any issues identified in the methods validation process after approval.

We request that information related to this application be treated as confidential within the meaning of 21 CFR 314.430, and that no information, except as provided in 21 CFR 314.430, be released without our written consent to an authorized member of your office.

If you have any questions or comments regarding this submission, please contact Kimberly Oakins, Regulatory Affairs Coordinator, at (763) _____

Sincerely,

UPSHER-SMITH LABORATORIES, INC.



Mark S. Robbins, Ph.D., J.D.
Vice President, Legal and Regulatory Affairs

Enclosures

UPSHER-SMITH

Pharmaceuticals Since 1919

III. PARAGRAPH II PATENT CERTIFICATION AND EXCLUSIVITY STATEMENT

June 12, 2003

Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II, Room 150
7500 Standish Place
Rockville, MD 20855-2773

**RE: Reference Listed Drug Product: Bio-Technology General Pharmaceuticals, Inc.,
OXANDRIN[®] (oxandrolone tablets, USP)**

Dear Sir/Madam:

Pursuant to Section 505(j)(2)(A)(vii) of the Federal Food, Drug, and Cosmetic Act, in the opinion and to the best knowledge of Upsher-Smith Laboratories, Inc., the patent which was applicable to the reference listed drug product referred to in this application has expired.] Patent

Pursuant to 505(j)(2)(D) of the Federal Food, Drug and Cosmetic Act, there is no unexpired exclusivity for the reference listed drug product referred to in this application.] exclus.

The following pages are copies from a patent status query from the current edition of the Electronic Orange Book (current through April 2003) regarding the Reference Listed Drug, OXANDRIN[®] (oxandrolone tablets, USP) (NDA 13-718), which indicate no current patents or exclusivity for OXANDRIN[®] as of April 2003.

0009

UPSHER-SMITH LABORATORIES, INC.

14905 23RD AVENUE NORTH MINNEAPOLIS, MN USA 55447-4709
763-473-4412 FAX 763-476-4026 SALES & DISTRIBUTION 1-800-654-2299
www.upsher-smith.com

Excellence Through Innovation

June 12, 2003

Page 2

This application is being filed in accordance with 505(j) of the Act, for a generic copy of the approved reference listed drug. No changes in dosage form, active ingredient(s) or route of administration are submitted in this application under 505(j)(2)(C) suitability petitions. Therefore, this application is exempt from a pediatric assessment as required under the Pediatric Rule, 21 CFR 314.55(a).

Sincerely,

UPSHER-SMITH LABORATORIES, INC.

A handwritten signature in black ink, appearing to read "Mark S. Robbins", with a stylized flourish at the end.

Mark S. Robbins, Ph.D., J.D.
Vice President, Legal and Regulatory Affairs

0010

Patent and Exclusivity Search Results from query on 013718 001.

Patent Data

There are no unexpired patents for this product in the Orange Book Database.

[Note: Title I of the 1984 Amendments does not apply to drug products submitted or approved under the former Section 507 of the Federal Food, Drug and Cosmetic Act (antibiotic products). Drug products of this category will not have patents listed.]

Exclusivity Data

There is no unexpired exclusivity for this product.

Thank you for searching the Electronic Orange Book

[Patent and Exclusivity Terms](#)

[Return to Electronic Orange Book Home Page](#)

UPSHER-SMITH

Pharmaceuticals Since 1919

July 16, 2003

TELEFAX/CERTIFIED MAIL/RETURN RECEIPT REQUESTED

Gary Buehler
Director, Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Document Control Room
Metro Park North II, Room 150
7500 Standish Place
Rockville, MD 20855-2773

NEW CORRESP

(NC)

Dear Mr. Buehler

**RE: ANDA 76-761, Oxandrolone Tablets, USP
Telephone Amendment to Provide Sponsor Signed Copy of Form FDA 3454**

Reference is made to the Upsher-Smith Laboratories, Inc. pending ANDA 76-761 for the above reference drug product.

Reference is also made to the July 16, 2003 telephone communication requesting a sponsor signed copy of Form FDA 3454. This signed Form FDA 3454 is intended to replace page 0063 submitted in the original ANDA submission.

This amendment has been designated as a telephone amendment and is being submitted via telefacsimile as directed by the Agency. A hard copy of this amendment is also being submitted in duplicate for incorporation into our file.

If there are any questions or additional information is required, please contact Kimberly Oakins, Regulatory Affairs Associate, at (763) _____

UPSHER-SMITH LABORATORIES, INC.
14905 23RD AVENUE NORTH MINNEAPOLIS, MN USA 55447-4709
CORPORATE 763-473-4412 FAX 763-476-4026
SALES & DISTRIBUTION 1-800-654-2299 SALES FAX 763-475-3410
www.upsher-smith.com

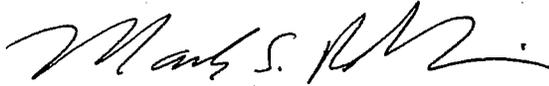
Excellence Through Innovation

RECEIVED
JUL 25 2003
OGD/CDER

Mr. Gary Buehler
Director, Office of Generic Drugs
July 16, 2003
Page 2

Sincerely,

UPSHER-SMITH LABORATORIES, INC.

A handwritten signature in black ink, appearing to read "Mark S. Robbins". The signature is fluid and cursive, with a long horizontal stroke at the end.

Mark S. Robbins, Ph.D., J.D.
Vice President, Legal and Regulatory Affairs

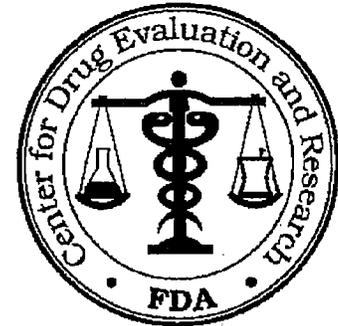
Enclosures

Desk Copy: Beth Fabian-Fritsch
Project Manager
Regulatory Support Branch
Division of Labeling and Program Support
Office of Generic Drugs
CDER, FDA

MINOR AMENDMENT

ANDA 76-761

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773 (301-594-0320)



NOV 20 2003

APPLICANT: Upsher-Smith Laboratories, Inc.

TEL: _____

ATTN: Mark Robbins

FAX: _____ (verified by Kay)

FROM: Sarah Kim

PROJECT MANAGER: 301-827-5725

Dear Sir:

This facsimile is in reference to your abbreviated new drug application dated June 12, 2003, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Oxandrolone Tablets USP, 2.5 mg.

The application is deficient and, therefore, Not Approvable under Section 505 of the Act for the reasons provided in the attachments (2 pages). This facsimile is to be regarded as an official FDA communication and unless requested, a hard copy will not be mailed.

The file on this application is now closed. You are required to take an action described under 21 CFR 314.120 which will either amend or withdraw the application. Your amendment should respond to all of the deficiencies listed. Facsimiles or partial replies will not be considered for review, nor will the review clock be reactivated until all deficiencies have been addressed. The response to this facsimile will be considered to represent a MINOR AMENDMENT and will be reviewed according to current OGD policies and procedures. The designation as a MINOR AMENDMENT should appear prominently in your cover letter. You have been/will be notified in a separate communication from our Division of Bioequivalence of any deficiencies identified during our review of your bioequivalence data. If you have substantial disagreement with our reasons for not approving this application, you may request an opportunity for a hearing.

SPECIAL INSTRUCTIONS:

Chemistry comments provided. Labeling and Bioequivalency comments will be provided under separate covers.

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, OR PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW.

If received by someone other than the addressee or a person authorized to deliver this document to the addressee, you are hereby notified that any disclosure, dissemination, copying, or other action to the content of this communication is not authorized. If you have received this document in error, please immediately notify us by telephone and return it to us by mail at the above address.

SKM
11/20/03

36. CHEMISTRY COMMENTS TO BE PROVIDED TO THE APPLICANT

NOV 20 2010

ANDA: 76-761

APPLICANT: Upsher-Smith Laboratories, Inc.

DRUG PRODUCT: Oxandrolone Tablets USP, 2.5mg

The deficiencies presented below represent MINOR deficiencies.

A. Deficiencies:

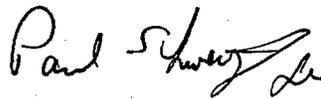
1. The Drug Master File (DMF) for Oxandrolone, USP has been found to be deficient. The deficiencies have been transmitted to the DMF holder. Please do not respond to this deficiency letter until you have received notification from the DMF holder that the deficiencies have been addressed.
2. In addition to your current specifications for the particle size at μ and μ distribution, please establish specification at μ distribution as well.
3. Your limits for the residual solvents do not reflect the observed values. Please obtain revised limits from your drug substance manufacturer.
4. Please include test and specification for the melting range of the drug substance.
5. Please lower your specifications for Each Specified Related Compounds and Total (specified and unspecified) impurities in finished product release and stability to reflect the observed values.
6. Please show that your method is equivalent to the USP method for the assay of the drug substance.
7. We notice in your validation report VR 776, the tailing factor for the Oxandrolone peak is not more than μ and only under forced degradation conditions it is not more than μ . We also notice that the tailing factor for the Oxandrolone peak shown on page 1865 is μ . This value represents fronting, not tailing. We recommend that you revise the tailing factor limit of NMT μ in methods μ and μ to be more in line with the observed values, and represent a range (i.e. tailing factor = μ).
8. The criterion for the tailing factor stated in Method μ / on page 1794 (NMT μ) is different than the criterion stated in Table 10 on page 1828 (NMT μ). Please explain.

9. On page 2373, you have stated that photostability study was performed under ICH guidelines, and after — hours no physical or chemical degradation was observed. The ICH Q1B requires an overall illumination of not less than 1.2 million lux hours and an integrated near ultraviolet energy of not less than 200 watt hours/square meter. Please justify the conditions you have used in your photostability study.

B. In addition to responding to the deficiencies presented above, please note and acknowledge the following comments in your response:

1. Please provide all available room temperature stability data for your product.
2. The Labeling and Bioequivalence portions of your application are under review. Deficiencies, if any, will be conveyed to you under separate covers.
3. Please note that your release and stability specifications and data for dissolution testing are contingent upon approval by the Division of Bioequivalence.
4. USP methods are the regulatory methods, and in case of any dispute, USP methods should be used.
5. A satisfactory cGMP compliance evaluation for the firms referenced in the ANDA is required for approval. We have requested an evaluation from the Division of Manufacturing and Product Quality.

Sincerely yours,



Rashmikant M. Patel, Ph.D.
Director
Division of Chemistry I
Office of Generic Drugs
Center for Drug Evaluation and Research

Fax Cover Sheet



**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Generic Drugs
Rockville, Maryland**

This document is intended only for the use of the party to whom it is addressed and may contain information that is privileged, confidential, and protected from disclosure under applicable law. If you are not the addressee, or a person authorized to deliver the document to the addressee, this communication is not authorized. If you have received this document in error, immediately notify us by telephone and return it to us at the above address by mail. Thank you.

To: Mark Robbins
Upsher-Smith Laboratories, Inc.

Fax: _____ **Phone:** _____

From: Ruby Wu

Fax: 301-443-3847

Phone: 301-827-5846

Number of Pages (including cover sheet): 3 **Date:** February 2, 2004

Comments:

Labeling comments provided for ANDA 76-761 Oxandrolone Tablets USP, 2.5 mg

Please send a courtesy copy of the labeling amendment to my attention. Please clearly identify it as "DESK COPY FOR LABELING REVIEWER".

76761

MODE = MEMORY TRANSMISSION

START=FEB-25 14:55

END=FEB-25 14:56

FILE NO.=001

STN NO.	COMM.	ABBR NO.	STATION NAME/TEL NO.	PAGES	DURATION
001	OK	2		002/002	00:00:20

-FDA CDER OGD LPS -

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To: Mark Robbins
Upsher-Smith Laboratories, Inc.

Fax: _____ Phone: _____

From: Ruby Wu

Fax: 301-443-3847 Phone: 301-827-5846

Number of Pages (including cover sheet): 2 Date: February 25, 2004

Comments:

This is to inform you that the Division of Medication Errors and Technical Support (DMETS) in the Office of Drug Safety (ODS) has completed its review of your proposed name " _____ " for your ANDA 76-761 Oxandrolone Tablets USP, 2.5 mg.

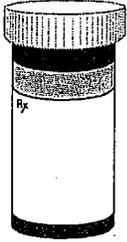
DMETS has no objection to the use of the proposed proprietary name ' _____ '. Please see the attached for additional comments from the DMETS review.

DMETS Comments:

DMETS has no objections to the use of the proprietary name, ' _____ '. This is considered a tentative decision. This name with its associated labels and labeling must be re-evaluated approximately 90 days prior to the expected approval date of the ANDA. A re-review of the name prior to ANDA approval will rule out any objections based upon approvals of other proprietary or established names from the signature date of this document.

W.P. 101

Fax Cover Sheet



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Rockville, Maryland**

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To: Mark Robbins
Upsher-Smith Laboratories, Inc.

Fax: _____ **Phone:** _____

From: Ruby Wu

Fax: 301-443-3847 **Phone:** 301-827-5846

Number of Pages (including cover sheet): 2 **Date:** February 25, 2004

Comments:

This is to inform you that the Division of Medication Errors and Technical Support (DMETS) in the Office of Drug Safety (ODS) has completed its review of your proposed name ' _____ ' for your ANDA 76-761 Oxandrolone Tablets USP, 2.5 mg.

DMETS has no objection to the use of the proposed proprietary name " _____ " . Please see the attached for additional comments from the DMETS review.

DMETS Comments:

DMETS has no objections to the use of the proprietary name, " _____ ". This is considered a tentative decision. This name with its associated labels and labeling must be re-evaluated approximately 90 days prior to the expected approval date of the ANDA. A re-review of the name prior to ANDA approval will rule out any objections based upon approvals of other proprietary or established names from the signature date of this document.

In review of the draft blister label, container label, as well as the blister carton and package insert labeling for — DMETS has focused on safety issues relating to possible medication errors, and has identified areas of possible improvement, which might minimize potential user error.

BLISTER PACK CARTON LABELING

1. The black text against a blue background is difficult to read. Increase the prominence of the established name by revising the background color or text.
2. Relocate the net quantity statement so that it appears away from the product strength.

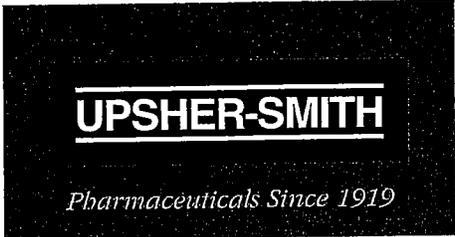
CONTAINER LABEL (5 count professional sample, 100 count, and 1000 count)

1. Ensure that the established name is at least $\frac{1}{2}$ the size of the proprietary name, per *21 CFR 201.10(g)(2)*.
2. See comments under Blister Pack Carton Labeling.

PACKAGE INSERT LABELING

No comments.

3.1



April 16, 2004

ORIGINAL

FEDERAL EXPRESS – NEXT DAY SERVICE

Mr. Gary Buehler
 Director, Office of Generic Drugs
 Center for Drug Evaluation and Research
 Food and Drug Administration
 Document Control Room
 Metro Park North II
 7500 Standish Place, Room 150
 Rockville, MD 20855

ORIG AMENDMENT
N/AM

**RE: ANDA 76-761; Oxandrolone Tablets, USP, 2.5 mg
 MINOR AMENDMENT responding to the Agency's November 20, 2003 Chemistry
 Deficiency Letter and February 2, 2004 Labeling Deficiency Letter**

Dear Mr. Buehler:

Reference is made to the Upsher-Smith Laboratories, Inc.'s (Upsher-Smith) pending ANDA 76-761 for the above referenced product.

Reference is also made to the Agency's November 20, 2003 MINOR Chemistry Deficiency Letter, the Agency's February 2, 2004 Labeling Deficiency Letter and February 25, 2004 letter conveying the acceptability of the proposed proprietary name . Copies of these Agency communications are provided in **Attachment 1**.

This amendment is submitted herewith to the above referenced ANDA to address the Chemistry and Labeling comments noted. This amendment has been designated as a MINOR AMENDMENT. The following deficiency items, shown in bold print, have been addressed in the order presented in the respective deficiency letters.

The chemistry and labeling deficiency responses are provided as paper. Final Printed Labeling discussed in the labeling responses are provided electronically. These labeling components are provided on a virus-free CD, consuming approximately 0.9 MB of storage space. The software used to determine that this disc is virus-free was Symantec AntiVirus Corporate Edition, version 8.1.0.825, Scan Engine 4.2.0.7, virus definition file version 4/14/2004 rev. 19. The CD is provided in **Attachment 2** of the archival copy.

UPsher-SMITH LABORATORIES, INC.
 6701 EVENSTAD DRIVE, MAPLE GROVE, MN USA 55369-6026
 CORPORATE 763-315-2000 FAX 763-315-2001
 SALES & DISTRIBUTION 1-800-654-2299 SALES FAX 763-315-2244
 www.upsher-smith.com

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A. Chemistry Deficiencies:

- 1. The Drug Master File (DMF) _____ for Oxandrolone, USP has been found to be deficient. The deficiencies have been transmitted to the DMF holder. Please do not respond to this deficiency letter until you have received notification from the DMF holder that the deficiencies have been addressed.**

In response to a deficiency letter dated November 21, 2003, _____ submitted an amendment to DMF _____ for Oxandrolone, USP on February 27, 2004. A copy of the cover letter and brief summary for this amendment is provided in **Attachment 3**.

- 2. In addition to your current specifications for the particle size at _____ and _____ distribution, please establish specification at _____ distribution as well.**

Six lots of oxandrolone drug substance were tested by _____ and/or PII (finished dosage form manufacturer) to establish a specification for particle size at _____ distribution. Individual data from these lots are summarized below:

Data			PII Data	
Batch	Lot No.	$D(v)$, μm	Lot No.	$D(v)$, μm
02/030	04-1602-01	_____	02-0176	_____
02/066B	02-1403-02		not available	
03/110	08-1903-03		03-0406	_____
03/014	02-1403-02		not available	
03/073	06-2003-01		not available	
04/009	01-2904-01	_____	04-0036	_____

**Particle size Data,
 continued**

	Combined Data
	$D(v = \mu m)$
Mean	_____
Standard Deviation	_____
Minimum	_____
Maximum	_____
Min - sd	_____
Max + sd	_____

Particle size data from _____ is presented for _____ lots: _____ of these lots were also tested at PII. Based on analysis of multiple lots and evaluation of _____ sd below the minimum and above the maximum of observed particle size, the recommended range for drug substance release is $D(v = \mu m)$ NLT _____ and NMT _____.

A specification of NLT _____ μm and NMT _____ μm is proposed based on _____ SD from the high and low end of observed values. The table below summarizes the specification for particle size distributions at _____ and _____ distribution:

Particle Size	Previous Specification	Revised Specification
$D(v = \mu m)$	NLT _____ μm	NLT _____ μm
$D(v = \mu m)$	N/A	NLT _____ μm and NMT _____ μm
$D(v = \mu m)$	NMT _____ μm	NMT _____ μm

A copy of the revised drug substance specification from _____ (_____) and from PII (_____) is included in **Attachment 4**. Note that the PII material code for Oxandrolone, USP has been revised from _____ which represents an administrative change only.

- Your limits for the residual solvents do not reflect the observed values. Please obtain revised limits from your drug substance manufacturer.**

Residual solvent limits were adjusted by the drug substance manufacturer (_____) based on statistical analysis of available data. Specifications for receipt of drug substance at PII were revised to be consistent with the API manufacturer's specifications, and are summarized in the following table.

Solvent	Previous Specification	Revised Specification
_____	NMT _____ ppm	NMT _____ ppm
_____	NMT _____ ppm	NMT _____ ppm
_____	NMT _____ ppm	NMT _____ ppm
_____	NMT _____ ppm	NMT _____ ppm

A copy of the revised drug substance specification from _____ and from PII (_____) is included (Attachment 4).

4. Please include test and specification for the melting range of the drug substance.

_____ tested _____ lots of Oxandrolone drug substance to establish a specification for melting range. Samples were _____ at _____ for _____ hours and the melting range determined according to USP <741> (Class Ia, Apparatus I). _____ of these lots were also tested at PII to confirm the results. Individual data are summarized in the table below:

Data				PII Data		
Batch	Lot No.	Start, °C	End, °C	Lot No.	Start, °C	End, °C
02/030	04-1602-01	_____	_____	02-0176	_____	_____
02/066B	02-1403-02			not available		
03/110	08-1903-03			03-0406	_____	_____
03/014	02-1403-01			not available		
03/073	06-2003-01			not available		
04/009	01-2904-01			not available		
USP Lot G0B220				not available		

**Melting Point Data,
continued**

	Combined Data	
	<i>Start, °C</i>	<i>End, °C</i>
Mean	7	7
Standard Deviation		
Minimum		
Maximum		

USP lists melting temperature for oxandrolone as "about 225"

Based on the minimum and maximum values observed over — lots tested by at least two analysts, a melting point range of one degree below and above the observed values is recommended for the drug substance specification (i.e., — to — C)

A melting range of — °C is proposed. The proposed specification represents an expanded range of 1°C beyond observed values (+1°C on the high end, and -1°C on the low end of the observed values). Copies of the revised — drug substance specification — and PII drug substance specification (— are provided in **Attachment 4**. A copy of PII test method (— based on USP <741>) is included in **Attachment 5**.

5. Please lower your specifications for Each Specified Related compounds (— and Total (specified and unspecified) impurities in finished product release and stability to reflect the observed values.

Data from the biolot and ongoing stability studies were reviewed to determine appropriate revised specifications for — and total (specified and unspecified) impurities in the finished product. Data has been obtained through the 12-month stability interval in all 4-package configurations (5-count bottle, 100-count bottle, 1000-count bottle and unit dose packaging).

Based on data generated, Upsher-Smith proposes to revise the — specification from NMT — to NMT —, which is consistent with the drug substance manufacturer's specification. Based on 12 months of real-time data collected in all packaging configurations, Upsher-Smith proposes a total (specified and unspecified) impurity specification revision from NMT — to NMT —. The data demonstrate — in total impurities. Due to the limited amount of data (i.e., number of manufacturing lots) upon which the specifications are based, — represents a reasonable specification to establish at this time. The table below summarizes

changes to the related substance specifications for the finished product. The drug substance specifications are also provided in the table for the reviewer's convenience.

Related Compounds	Previous Finished Product Release and Stability Specification	Revised Finished Product Release and Stability Specification	Drug Substance Specification
Specified identified ()	NMT	NMT	NMT
Specified unidentified (RRT =)	NMT	NMT	NMT
Unspecified	NMT	NMT	Single, NMT Total, NMT
Total	NMT	NMT	NMT

A copy of the revised PII drug product release and stability specification () is included in **Attachment 6**. Copies of Upsher-Smith's revised drug product specifications are provided in **Attachment 7**.

6. Please show that your method () is equivalent to the USP method for the assay of the drug substance.

PII test method () is the same method as () test method () test method () was shown to be equivalent to the USP titration assay. Therefore, a separate demonstration of equivalence is not necessary. Data for the method comparison between () and the USP monograph method is reported in the DMF (Section 6, Page 7, Table V) (see **Attachment 8**). A maximum difference of () was obtained between average purity by titration (USP method) and purity by HPLC () Method () was transferred into PII's format and identified as () at PII. Method () was transferred from () to PII under protocols () (assay and ID portion) and MTP 3 (related substances portion). Results of the method transfer are reported in MTPR 1 and MTPR 3. Copies of the method transfer protocols and reports are provided in **Attachment 9**.

7. We notice in your validation report VR 776, the tailing factor for the Oxandrolone peak is not more than ~~_____~~ and only under forced degradation conditions it is not more than ~~_____~~. We also notice that the tailing factor for the Oxandrolone peak shown on page 1865 is ~~_____~~. This value represents fronting, not tailing. We recommend that you revise the tailing factor limit of NMT ~~_____~~ in methods ~~_____~~ and ~~_____~~ to be more in line with the observed values, and represent a range (i.e. tailing factor = ~~_____~~).

At the time method validation was performed for the assay method ~~_____~~ reported in VR776), the specification for tailing factor was NMT ~~_____~~. All data acquired during validation met this requirement. As noted, the maximum tailing factor observed during robustness studies was ~~_____~~ (Table 10 on page 24 of VR776, page 1828 of ANDA 76-761) and the maximum tailing factor observed during forced degradation studies was ~~_____~~ (with either ~~_____~~ the normal mode of detection, or ~~_____~~, which was used only during forced degradation to establish peak purity). Although the example chromatogram shown on page 1865 of ANDA 76-761 does represent fronting, this example is from a severely degraded sample analyzed with ~~_____~~ array) detection. This example does not reflect either the expected sample condition or typical method parameters (methods ~~_____~~ and ~~_____~~, both use ~~_____~~). The dissolution method ~~_____~~, uses a shorter ~~_____~~ and the medium contains a ~~_____~~, therefore the peak shape observed with the dissolution method ~~_____~~ is somewhat wider than that observed with the assay method ~~_____~~. As a result of these differences, a single specification for both methods is not appropriate. Tailing factors obtained during validation of the referenced methods were evaluated and the system suitability criteria revised to reflect ranges appropriate for routine performance of each method. A tailing factor of ~~_____~~ is proposed for the assay method ~~_____~~, and a tailing factor of ~~_____~~ is proposed for the dissolution method ~~_____~~. Copies of the revised test methods, ~~_____~~ and ~~_____~~, are included in Attachment 10.

8. The criterion for the tailing factor stated in Method ~~_____~~ on page 1794 (NMT ~~_____~~ is different than the criterion stated in Table 10 on page 1828 (NMT ~~_____~~). Please explain.

The tailing factor specified in prior versions of test method ~~_____~~, used during validation (from 4/25/02 until 3/27/03), was NMT ~~_____~~ as stated in the method validation report, VR 776 (page 1828 of ANDA 76-761). No significant changes in the tailing factor were noted during the method validation or early stability analyses and it was not considered a critical factor in determining ~~_____~~ suitability. Therefore, the tailing factor of NMT ~~_____~~ was considered acceptable for routine performance of this method, as stated on page 1794 of the ANDA, for the post-validation version of the test method. However, the tailing factor requirement in ~~_____~~

_____ has been modified to _____, as proposed in response to comment 7 above.
See Attachment 10 for a copy of test method _____

9. On page 2373, you have stated that photostability study was performed under ICH guidelines, and after _____ hours no physical or chemical degradation was observed. The ICH Q1B requires an overall illumination of not less than 1.2 million lux hours and an integrated near ultraviolet energy of not less than 200 watt hours/square meter. Please justify the conditions you have used in your photostability study.

The photostability statement of 1000 lux hours on page 2373 was a typographical error.

The contract laboratory _____ conducted photostability studies for Oxandrolone Tablets, 2.5 mg, using a _____ equipped with a _____

_____ The conditions employed meet the requirements of Option 1 specified under part 1(b) light sources in ICH Q1B Guidance "Stability Testing: Photostability Testing of New Drug Substances and Products", which specifies exposure to an overall illumination of 1.2 million lux hours and an integrated near ultraviolet energy of not less than 200 watt hours/square meter.

_____ Samples were exposed to _____ for _____ hours, for a total exposure of 1.2 million lux hours. _____ exposure for the samples was confirmed as not less than _____ through the use of _____

- B. In addition to responding to the deficiencies presented above, please note and acknowledge the following comments in your response:

1. Please provide all available room temperature stability data for your product.

Current room temperature stability data have been generated through the 12-month test interval. Data are provided in Attachment 11.

The data for the 5-count bottle demonstrates acceptable stability at 12 months. Trending indicates that 18 months is an appropriate expiration period for the 5-count bottles.

The proposed expiration dating for the other packaging configurations (100-count bottle, 1000-count bottle, unit-dose carton of 100 tablets) remains at 24 months, consistent with that proposed in the original ANDA.

- 2. The Labeling and Bioequivalence portions of your application are under review. Deficiencies, if any, will be conveyed to you under separate covers.**

Upsher-Smith received a Labeling Deficiency from the Division of Labeling and Program Support on February 2, 2004. The responses to the Labeling Deficiency follow the responses to the Chemistry Deficiencies.

Upsher-Smith acknowledges that the Bioequivalence portion of the application is under review by the Division of Bioequivalence.

- 3. Please note that your release and stability specifications and data for dissolution testing are contingent upon approval by the Division of Bioequivalence.**

Upsher-Smith acknowledges that the release and stability specifications and data for dissolution testing are contingent upon approval by the Division of Bioequivalence.

- 4. USP methods are the regulatory methods, and in case of any dispute, USP methods should be used.**

Upsher-Smith acknowledges that the USP methods are the regulatory methods, and in the case of any dispute, the USP methods should be utilized.

- 5. A satisfactory cGMP compliance evaluation for the firms referenced in the ANDA is required for approval. We have requested an evaluation from the Division of Manufacturing and Product Quality.**

Upsher-Smith acknowledges that the firms referenced in our ANDA application relative to the manufacturing and testing of the drug product must be in compliance with the cGMPs at the time of approval. Upsher-Smith also acknowledges that the Agency has requested an evaluation from the Division of Manufacturing and Product Quality.

Upsher-Smith's manufacturing and testing facilities were inspected by the Minneapolis District Office September 22-24, 30 and October 3, 2003. The Minneapolis District Office recommended approval at the District Level.

Labeling Deficiencies

GENERAL

1. Your proposed name ' ' is under review. We will inform you of our comments when they become available. Please note that in the event that your application is approved after 90 days of the current submission, then the name with its associated labels and labeling must be re-evaluated approximately 90 days prior to the expected approval of the ANDA. A re-review of the name prior to ANDA approval will rule out any objections based upon approvals of other proprietary and established names from this date forward.

Upsher-Smith received a letter from the Agency on February 25, 2004 stating the Division of Medication Errors and Technical Support (DMETS) has no objection to the use of the proposed name ' ' (Attachment 1).

2. CONTAINER (Bottles of 5s, 100s, 1000s)
 - a. 21 CFR 201.109(g)(2) requires that the established name be printed in letters at least half as large as the proprietary name with commensurate prominence.

Upsher-Smith has revised the labeling for the 5-count, 100-count and 1000-count bottle and ensured that the established name is printed in letters at least half as large as the proprietary name with commensurate prominence.

- b. Please revise the storage statement to read: "Store at 20° - 25°C (68° - 77°F)[see USP Controlled Room Temperature]".

Upsher-Smith contacted Dr. Ruby Wu and obtained concurrence that it was acceptable to revise the storage statement to be consistent with USP's definition of Controlled Room Temperature; "Store at 20° - 25°C (68° - 77°F) and excursions permitted to 15° - 30°C (59° - 86°F) [see USP Controlled Room Temperature]." All of the labeling has been updated to incorporate this revised storage statement.

- c. The Poison Prevention Packaging Act notes that special packaging (child-resistant closures) should be the responsibility of the manufacturer when the container is clearly intended to be utilized in dispensing (unit-of-use packaging). We believe the container of 5s to be unit-of-use packaging. Please comment.

Although the 5-count bottle is intended to be distributed as not-for-sale prescription samples, and not as a marketed for sale unit-of-use container to be dispensed in fulfillment of a prescription, Upsher-Smith proposes to change to a child-resistant closure (CRC) for this packaging configuration.

The new CRC cap is manufactured by _____ and has the same product contact surface as previously submitted in the original application for the 28 mm non-CRC cap for the 5-count bottle. Due to the CRC component, an _____ is present in the cap.

The table below compares the previously submitted non-CRC 28 mm cap to the proposed CRC 28 mm cap:

Component	Original 28mm non-CRC Cap DMF # _____	Proposed 28mm Cap DMF # _____
Outer Resin	Manufactured by _____ DMF # _____	Manufactured by _____ DMF # _____ NOTE: The _____ resin is formerly the _____ resin (as specified for the cap in the original ANDA) The DMF # has also been changed to _____ The formulation of the resin remains exactly the same.
Inner Resin (CRC component)	NA	_____ Resin Manufactured by _____ DMF # _____
Liner	_____ Plain Liner Manufactured by _____ DMF # _____	_____ Plain Liner Manufactured by _____ DMF # _____
Colorant	_____ White Polypropylene Colorant Manufactured by _____	_____ White Polypropylene Colorant Manufactured by _____

The following supporting documentation for this CRC cap is provided in Attachment 12:

- [REDACTED] DMF # [REDACTED] Authorization Letter
- [REDACTED] cGMP Letter
- [REDACTED] Indirect Food Additive Compliance Letter
- [REDACTED] Certificate of Compliance
- 28 mm CRC Cap Drawing
- [REDACTED] Resin Specification
- [REDACTED] Letter Regarding change from [REDACTED] to [REDACTED]
- [REDACTED] Indirect Food Additive Compliance Letter
- [REDACTED] DMF # [REDACTED] Authorization Letter
- [REDACTED] Resin Specification
- [REDACTED] DMF # [REDACTED] Authorization Letter
- [REDACTED] Indirect Food Additive Regulation Compliance Letter
- [REDACTED] Specification
- [REDACTED] DMF # [REDACTED] Authorization Letter
- [REDACTED] Technical Data Sheet
- [REDACTED] Indirect Food Additive Regulation Compliance Letter
- [REDACTED] CRC Study Report

3. UNIT DOSE BLISTER (2 X 5 Tablets)

Revise each blister to read “(Oxandrolone Tablet, USP)” [singular rather than plural]

The blister text has been revised to read “(Oxandrolone Tablet, USP)”.

Upsher-Smith also commits to having a bar code printed on the unit dose blister text within 60 days of approval, per FDA’s final rule “Bar Code Label Requirements for Human Drug Products and Biological Products” issued February 26, 2004.

4. CARTON (10 x Unit Dose Blister of 10 Tablets)

Refer to comments 2.a. and 2.b.

The unit dose carton has been revised to ensure the established name is printed in letters at least half as large as the proprietary name with commensurate prominence, and also to incorporate the revised storage statement, consistent with USP’s definition of Controlled Room Temperature (see discussion above under 2.a. and 2.b.).

5. **PHYSICIAN INSERT**

- a. Add "Rx only" to a location just under the **TITLE** of the package insert.

Although not required text on the physician package insert per the July 1998 Guidance for Industry, Implementation of Section 126 of the FDA Modernization Act of 1997 – Elimination of Certain Labeling Requirements, the statement "Rx only" has been added just under the **TITLE** of the package insert.

b. **PRECAUTIONS**

- i. Add the following paragraph in bold print before the "General" subsection. "Concurrent dosing of oxandrolone and warfarin may result in unexpectedly large increases in the INR or prothrombin time (PT). When oxandrolone is prescribed to patients being treated with warfarin, doses of warfarin may need to be decreased significantly to maintain the desirable INR level and diminish the risk of potentially serious bleeding. (See **PRECAUTIONS: Drug Interactions**)."

The paragraph described above has been added to the **PRECAUTIONS** section of the package insert.

- ii. **Information for the patient** – add as the first sentence in this subsection: "The physician should instruct patients to report immediately any use of warfarin and any bleeding."

The sentence "The physician should instruct patients to report immediately any use of warfarin and any bleeding." has been added as the first sentence in the subsection "Information for the patient".

- iii. **Drug Interactions** – add the following paragraph immediately after the **Anticoagulants** section. The paragraph should appear as a "sub-section" of the **Anticoagulants** section: "*Warfarin:* A multidose study of oxandrolone, given as 5 or 10 mg BID in 15 healthy subjects concurrently treated with warfarin, resulted in a mean increase in S-warfarin half-life from 26 to 48 hours and AUC from 4.55 to 12.08 ng*hr/mL; similar increases in R-warfarin half-life and AUC were also detected. Microscopic hematuria (9/15) and gingival bleeding (1/15) were also observed. A 5.5-fold decrease in the mean warfarin dose from 6.13 mg/day to 1.13 mg/day (approximately 80-85% reduction of warfarin dose), was necessary to maintain target INR of 1.5. When oxandrolone therapy is initiated in a patient already receiving treatment with warfarin, the INR or prothrombin time (PT) should be monitored closely and the dose of warfarin adjusted as necessary until a stable target INR or PT has

been achieved. Furthermore, in patients receiving both drugs, careful monitoring of the INR or PT, and adjustment of the warfarin dosage if indicated are recommended when the oxandrolone dose is changed or discontinued. Patients should be closely monitored for signs and symptoms of occult bleeding.”

The above mentioned paragraph has been added to the Drug Interactions section of the package insert.

c. ADVERSE REACTIONS, In Females, Hematologic: “...concomitant oral anticoagulant therapy.” [add “oral”]

The word “oral” has been added as specified above in the Adverse Reactions section of the package insert.

Please revise your labels and labeling, as instructed above and submit in final print.

Upsher-Smith is submitting Final Printed Labeling electronically for the 5-count bottle, 100-count bottle, 1000-count bottle, unit dose carton (10 x unit dose blister of 10 tablets), blister text, and physician insert. A copy of the CD is provided in **Attachment 2 of the archival copy**. The file names are as follows:

5-count bottle label:	<i>2.5mg5bottlelabel.pdf</i>
100-count bottle label:	<i>2.5mg100bottlelabel.pdf</i>
1000-count bottle label:	<i>2.5mg1000bottlelabel.pdf</i>
Unit dose carton	<i>2.5mgunitdosecarton.pdf</i>
Blister text:	<i>2.5mgunitdoseblister.pdf</i>
Physician insert:	<i>pi.pdf</i>

For the reviewer’s convenience, Upsher-Smith is also providing one-set or printer’s proofs for the above-mentioned labeling (**Attachment 13**).

To facilitate review of your next submission, please provide a side-by-side comparison of your proposed labeling with your last submission with all differences annotated and explained.

To facilitate in the review of this amendment, Upsher-Smith is providing an annotated side-by-side comparison of the proposed labeling in **Attachment 14**.

Upsher-Smith is also acknowledging the following from the DMETS February 25, 2004 letter (see **Attachment 1**). The DMETS items are listed below, followed by Upsher-Smith’s comment to each:

BLISTER PACK CARTON LABELING

- 1. The black text against a blue background is difficult to read. Increase the prominence of the established name by revising the background color or text.**

Due to the limitations inherent with printers proofs, the blue background color is not accurately represented in the draft labeling that was provided in the original ANDA. This specially customized blue color is consistent with Upsher-Smith corporate tradedress and is utilized on commercial labeling for all products. For the reviewer's convenience, Upsher-Smith has provided a label for Pacerone® in **Attachment 15** to see what the actual labeling looks like.

FDA has approved labeling for multiple products submitted in other applications from Upsher-Smith utilizing this same tradedress. Upsher-Smith declines to make any changes to the labeling at this time, due to a lack of awareness of substantive concerns regarding the use of black text against the Upsher-Smith customized blue background.

- 2. Relocate the net quantity statement so that it appears away from the product strength.**

The net quantity statement and the product strength are distinguished on the labeling by different colors. The placement of each is consistent with all labeling regulations and is consistent with Upsher-Smith's corporate tradedress. FDA has approved labeling for multiple products submitted in other applications from Upsher-Smith utilizing the same tradedress. Upsher-Smith declines to make any changes to the labeling at this time regarding the placement of the net quantity statement relative to the product strength.

CONTAINER LABEL (5 count professional sample, 100 count, and 1000 count)

- 1. Ensure that the established name is at least ½ the size of the proprietary name, per 21 CFR 201.10(g)(2).**

Upsher-Smith has revised all of the labeling and increased the size of the established name to ensure it is at least ½ the size of the proprietary name.

- 2. See comments under Blister Pack Carton Labeling**

Refer to items 1 and 2 above under Blister Pack Carton Labeling for comments.

PACKAGE INSERT LABELING

No comments.

We request that all information related to this application be treated as confidential within the meaning of 21 CFR 314.430, and that no information, except as provided in 21 CFR 314.430 be released without Upsher-Smith's written consent to an authorized member of the Office of Generic Drugs.

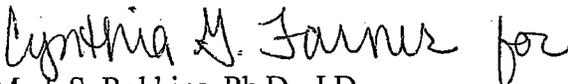
This amendment is being submitted in duplicate as an archival and a review copy, for incorporation into our file. A courtesy copy of the labeling sections is also provided, per the labeling reviewer's request.

As required per 21 CFR 314.96(b), Upsher-Smith hereby certifies that a field copy of this amendment, dated April 16, 2004, has been submitted to the Minneapolis District Office for their review. This third (field) copy is a "true" copy of this amendment.

If there are any questions or comments regarding this amendment, please contact Kimberly Oakins, Regulatory Affairs Associate, at ()

Sincerely,

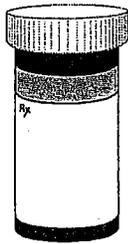
UPSHER-SMITH LABORATORIES, INC.


Mark S. Robbins, Ph.D., J.D.
Vice President, Legal and Regulatory Affairs

Enclosures

Desk Copy: Ruby Wu
Labeling Reviewer
Division of Labeling and Program Support
Office of Generic Drugs
Metro Park North II, HFD-613
7500 Standish Place, Room 200N
Rockville, MD 20855

Fax Cover Sheet



Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Generic Drugs
Rockville, Maryland

This document is intended only for the use of the party to whom it is addressed and may contain information that is privileged, confidential, and protected from disclosure under applicable law. If you are not the addressee, or a person authorized to deliver the document to the addressee, this communication is not authorized. If you have received this document in error, immediately notify us by telephone and return it to us at the above address by mail. Thank you.

To: Mark Robbins
Upsher-Smith Laboratories, Inc.

Fax: _____ Phone: _____

From: Ruby Wu

Fax: 301-443-3847 Phone: 301-827-5846

Number of Pages (including cover sheet): 1 Date: May 24, 2004

Comments:

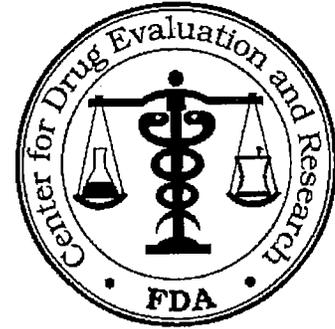
The following is a requested labeling revision from my review of your amendment dated April 16, 2004 for ANDA 76-761 for Oxandrolone Tablets USP, 2.5 mg. The revision is a "POST-APPROVAL" revision and may be submitted in an annual report, provided the change is described in full.

CONTAINER, CARTON, and INSERT: Revise the storage recommendation to read "Store at 20°-25°C (68°-77°F) excursions permitted to 15°-30°C (59°-86°F)[see USP Controlled Room Temperature]." [delete " _____"

BIOEQUIVALENCY AMENDMENT

ANDA 76-761

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773 (301-594-0320)



MAY 28 2004

APPLICANT: Upsher-Smith Laboratories, Inc.

TEL: _____

ATTN: Mark Robbins

FAX: _____

FROM: Beth Fabian-Fritsch *BFF*

PROJECT MANAGER: (301) 827-5847

Dear Sir:

This facsimile is in reference to the bioequivalency data submitted on June 12, 2003, pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Oxandrolone Tablets, 2.5 mg.

The Division of Bioequivalence has completed its review of the submission(s) referenced above and has identified deficiencies which are presented on the attached page. This facsimile is to be regarded as an official FDA communication and unless requested, a hard-copy will not be mailed.

You should submit a response to these deficiencies in accord with 21 CFR 314.96. Your amendment should respond to all the deficiencies listed. **Facsimiles or partial replies will not be considered for review**, nor will the review clock be reactivated until all deficiencies have been addressed. Your cover letter should clearly indicate that the response is a "Bioequivalency Amendment" and clearly identify any new studies (i.e., fasting, fed, multiple dose, dissolution data, waiver or dissolution waiver) that might be included for each strength. We also request that you include a copy of this communication with your response. **Please submit a copy of your amendment in both an archival (blue) and a review (orange) jacket.** Please direct any questions concerning this communication to the project manager identified above.

SPECIAL INSTRUCTIONS:

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, OR PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW.

If received by someone other than the addressee or a person authorized to deliver this document to the addressee, you are hereby notified that any disclosure, dissemination, copying, or other action to the content of this communication is not authorized. If you have received this document in error, please immediately notify us by telephone and return it to us by mail at the above address.

MAY 28 2004

BIOEQUIVALENCE COMMENTS

ANDA: 76-761

APPLICANT: Upsher-Smith Laboratories, Inc.

DRUG PRODUCT: Oxandrolone Tablets, USP 2.5 mg

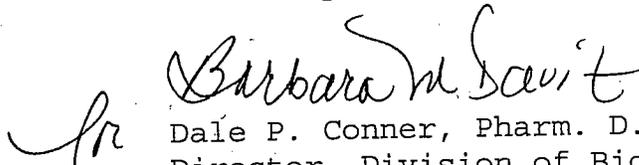
The Division of Bioequivalence has completed its review of your submission(s) acknowledged on the cover sheet. The following deficiencies have been identified:

1. The reasons for reassaying five samples (Subj.#4, P1, T:1.5hr; Subj.#4, P2, T:1.5Hr.; Subj.#9, P1, T:1.5hr.; Subj.#10, P2, T:4.5hr.; Subj.2, P2, T:48hr.) are not clear. If these samples were reassayed due to anomalous values, please provide the justification for using the reassay values along with the SOP for sample reassays. Also, include the statistical analysis using the original assay values.
2. Please provide data demonstrating stability of the stock solutions of oxandrolone and internal standard.
3. Please provide manufacturing date of the test product.
4. Your proposed dissolution specification is not acceptable. We recommend the use of the following method and specifications:

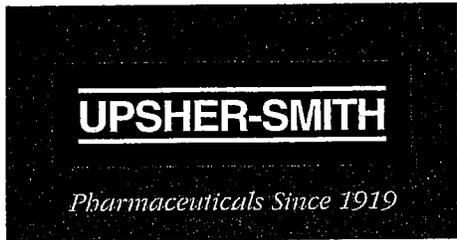
The dissolution testing should be conducted in 500 mL of 0.75% SDS in 0.1N HCl at 37°C using USP apparatus II (paddle) at 75 rpm. The test product should meet the following specification:

Not less than — (Q) of the labeled amount of the drug in the dosage form is dissolved in 90 minutes.

Sincerely yours,



Dale P. Conner, Pharm. D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research



ORIG AMENDMENT

N/AA

June 4, 2004

FEDERAL EXPRESS

Mr. Gary Buehler
Acting Director, Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855

**RE: ANDA 76-761; Oxandrolone Tablets, USP, 2.5 mg
UNSOLICITED AMENDMENT**

Dear Mr. Buehler:

Reference is made to the Upsher-Smith Laboratories, Inc. (Upsher-Smith) pending ANDA 76-761 for the above referenced product.

This unsolicited amendment is being submitted to the above referenced ANDA to provide notification of a DMF amendment submitted to the agency on May 27, 2004, by _____, manufacturer of the API. The changes are considered enhancements to the process, and are not intended to adversely affect the identity, strength, quality, purity or potency of the product. A copy of the DMF amendment cover letter and summary of changes is provided in Attachment 1.

We request that all information related to this application be treated as confidential within the meaning of 21 CFR 314.430, and that no information, except as provided in 21 CFR 314.430 be released without Upsher-Smith's written consent to an authorized member of the Office of Generic Drugs.

This amendment is being submitted in duplicate as an archival and a review copy, for incorporation into our file.

UPSHER-SMITH LABORATORIES, INC.
6701 EVENSTAD DRIVE, MAPLE GROVE, MN USA 55369-6026
CORPORATE 763-315-2000 FAX 763-315-2001
SALES & DISTRIBUTION 1-800-654-2299 SALES FAX 763-315-2244
www.upsher-smith.com

RECEIVED
JUN 07 2004
OGD/CDER

As required per 21 CFR 314.96(b), Upsher-Smith hereby certifies that a field copy of this amendment, dated June 4, 2004, has been submitted to the Minneapolis District Office for their review. This third (field) copy is a "true" copy of this amendment.

If there are any questions or comments regarding this amendment, please contact me at (763)

Sincerely,

UPSHER-SMITH LABORATORIES, INC.

A handwritten signature in cursive script that reads "Kimberly C. Oakins".

Kimberly C. Oakins
Regulatory Affairs Specialist

Enclosures

UPsher-SMITH

Pharmaceuticals Since 1919

August 3, 2004

FEDERAL EXPRESS – NEXT DAY SERVICE

Mr. Gary Buehler
Director, Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855

**Bioequivalency and
Chemistry
Amendment**

ORIG AMENDMENT
N/AB

**RE: ANDA 76-761; Oxandrolone Tablets, USP, 2.5 mg
MINOR AMENDMENT responding to the Agency's May 28, 2004 Bioequivalence
Deficiency Letter**

Dear Mr. Buehler:

Reference is made to Upsher-Smith Laboratories, Inc.'s (Upsher-Smith) pending ANDA 76-761 for the above referenced product.

Reference is also made to the Agency's May 28, 2004 Bioequivalence Deficiency Letter (**Attachment 1**).

This amendment is submitted herewith to the above referenced ANDA and provides a complete response to the bioequivalence deficiencies noted. The following deficiency items, shown in bold print, have been addressed in the order presented in the Agency's May 28, 2004 letter.

- 1. The reasons for reassaying five samples (Subj. #4, P1, T:1.5hr; Subj.#4, P2, T:1.5Hr.; Subj.#9, P1, T:1.5hr.; Subj.#10, P2, T:4,5hr.; Subj. 2,P2, T:48hr.) are not clear. If these samples were reassayed due to anomalous values, please provide the justification for using the reassay values along with the SOP for sample reassays. Also, include the statistical analysis using the original assay values.**

UPsher-SMITH LABORATORIES, INC.
6701 EVENSTAD DRIVE, MAPLE GROVE, MN USA 55369-6026
CORPORATE 763-315-2000 FAX 763-315-2001
SALES & DISTRIBUTION 1-800-654-2299 SALES FAX 763-315-2244
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AUG 04 2004
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The samples specified above were all reassayed for analytical reasons. The bioanalytical laboratory, _____, repeats sample analyses when the internal standard area count is _____ or _____ of the established mean area for the internal standards in the run batch, consistent with current laboratory practices. Samples with internal standards that exceed these limits are automatically selected for reanalysis and the first value with an acceptable internal standard result is reported.

Specifically, the samples were reassayed for the following reasons:

- Subject 4, period 1, 1.5 hour; subject 4, period 2, 1.5 hour; and subject 9, period 1, 1.5 hour samples were reassayed because the original injection had a high internal standard value.
- Subject 10, period 2, 4.5 hour and subject 2, period 2, 48 hour samples were reassayed because the original injection had a low internal standard value.

The table below provides the original result along with the reassay value. _____, SOP-PS-076 _____ section 6.0 discusses the procedure for reassaying samples. A copy of SOP PS-076 is provided in **Attachment 2**.

Subject	Period	Time	Original ng/mL	Reassay ng/mL	Reported ng/mL
004	1	1.5 hr	_____	_____	_____
004	2	1.5 hr	_____	_____	_____
009	1	1.5 hr	_____	_____	_____
010	2	4.5 hr	_____	_____	_____
002	2	48 hr	_____	_____	_____

The statistical analysis provided in the original application was performed using the repeated assay results only. Although the original assay values were disregarded due to aberrant internal standard values, statistical analysis is provided in **Attachment 3** using the original results, per FDA's request. All bioequivalence acceptance criteria were met for both the reassay and the original assay values. The following table provides a comparison of the pharmacokinetic results using the reassay results, reported in the ANDA, versus the original assay results.

Parameter (Ln transformed)	Reassay Results (ANDA submission)		Original Results (FDA requested)	
	T/R % Ratio	90% C.I.	T/R % Ratio	90% C.I.
C _{max}	84.48	81.19-87.89	84.48	81.19-87.89
AUC _{0-t}	91.49	87.62-95.53	91.43	87.57-95.47
AUC _{0-inf}	94.93	90.93-99.12	94.87	90.87-99.05

The bioequivalence clinical data are provided on disk in SAS transport format. This disk is submitted in the archival copy of this application

2. Please provide data demonstrating stability of the stock solutions of oxandrolone and internal standard.

SOP PS-081 is the procedure

Testing is conducted with a minimum of 6 injections (in this case, by _____, of each control and test solution. The acceptance criteria, as defined in SOP PS-081, are loss of _____ for reference standard solution and _____ for internal standard solution. SOP PS-081 is included as **Attachment 4**.

The difference between solutions was _____%, which is within the acceptance criteria.

The difference between solutions was _____%, which is within the acceptance criteria. Stability data for the oxandrolone standard solutions is provided in **Attachment 5**.

Internal standard _____, stability was performed by _____ an

The difference between solutions was _____, which is within the acceptance criteria. Internal standard bench-top stability was performed by

The difference between solutions was _____%, which is within the acceptance criteria. Stability data for the internal standard, is provided in **Attachment 6**.

3. Please provide manufacturing date of the test product.

The test product was manufactured in July 2002.

4. Your proposed dissolution specification is not acceptable. We recommend the use of the following method and specifications:

The dissolution testing should be conducted in 500 mL of 0.75% SDS in 0.1N HCl at 37°C using USP apparatus II (paddle) at 75 rpm. The test product should meet the following specification:

Not less than ~~10%~~ (Q) of the labeled amount of the drug in the dosage form is dissolved in 90 minutes.

The dissolution method parameters recommended by the Agency in the deficiency letter are the same as those proposed in the original ANDA (500 mL of 0.75% SDS in 0.1N HCl at 37°C using USP apparatus II (paddle) at 75 rpm). In response to the Agency's request, Upsher-Smith has revised the dissolution acceptance criterion to not less than ~~10%~~ (Q) of the labeled amount of the drug in the dosage form dissolved in 90 minutes.

The PII dissolution method, PII finished product specification, PII stability specification, and the Upsher-Smith finished product release specifications (one per packaging configuration) have been updated to incorporate the revised dissolution acceptance criterion. Copies of the test method and corresponding specifications are provided in **Attachment 7**.

We request that all information related to this application be treated as confidential within the meaning of 21 CFR 314.430, and that no information, except as provided in 21 CFR 314.430 be released without Upsher-Smith's written consent to an authorized member of the Office of Generic Drugs.

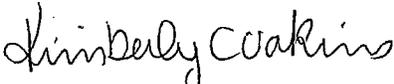
This amendment being submitted in triplicate, as an archival (blue jacket) copy, bioavailability/bioequivalence review (orange jacket) copy and CMC review (red jacket) copy.

As required per 21 CFR 314.96(b), Upsher-Smith hereby certifies that a field copy of this amendment, dated August 3, 2004, has been submitted to the Minneapolis District Office for their review. This forth (field) copy is a "true" copy of this amendment.

If there are any questions or comments regarding this amendment, please contact me at ()

Sincerely,

UPSHER-SMITH LABORATORIES, INC.



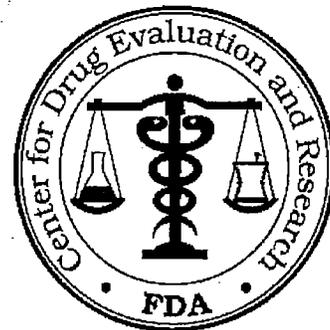
Kimberly C. Oakins
Regulatory Affairs Specialist

Enclosures

MINOR AMENDMENT

ANDA 76-761

OCT - 6 2004



OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773 (301-594-0320)

APPLICANT: Upsher-Smith Laboratories, Inc.

TEL: 763-315-2000

ATTN: Mark Robbins

FAX: 763-315-2260

FROM: Sarah Park

PROJECT MANAGER: 301-827-5725

Dear Sir:

This facsimile is in reference to your abbreviated new drug application dated June 12, 2003, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Oxandrolone Tablets USP, 2.5 mg.

Reference is also made to your amendments dated April 16, and June 4, 2004.

The application is deficient and, therefore, Not Approvable under Section 505 of the Act for the reasons provided in the attachments (2 pages). This facsimile is to be regarded as an official FDA communication and unless requested, a hard copy will not be mailed.

The file on this application is now closed. You are required to take an action described under 21 CFR 314.120 which will either amend or withdraw the application. Your amendment should respond to all of the deficiencies listed. Facsimiles or partial replies will not be considered for review, nor will the review clock be reactivated until all deficiencies have been addressed. The response to this facsimile will be considered to represent a MINOR AMENDMENT and will be reviewed according to current OGD policies and procedures. The designation as a MINOR AMENDMENT should appear prominently in your cover letter. You have been/will be notified in a separate communication from our Division of Bioequivalence of any deficiencies identified during our review of your bioequivalence data. If you have substantial disagreement with our reasons for not approving this application, you may request an opportunity for a hearing.

SPECIAL INSTRUCTIONS:

Chemistry and Bioequivalence comments provided.

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, OR PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW.

If received by someone other than the addressee or a person authorized to deliver this document to the addressee, you are hereby notified that any disclosure, dissemination, copying, or other action to the content of this communication is not authorized. If you have received this document in error, please immediately notify us by telephone and return it to us by mail at the above address.

SEP 10 10/16/04

OCT - 6 2004

36. CHEMISTRY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 76-761

APPLICANT: Upsher-Smith Laboratories, Inc.

DRUG PRODUCT: Oxandrolone Tablets USP, 2.5mg

The deficiencies presented below represent MINOR deficiencies.

A. Deficiencies:

1. The Drug Master File (DMF) # _____ for Oxandrolone, USP has been found to be deficient. The deficiencies have been transmitted to the DMF holder. Please do not respond to this deficiency letter until you have received notification from the DMF holder that the deficiencies have been addressed.
2. The melting point specification of _____ is too wide. Please obtain the most recent specification from the drug substance manufacturer.
3. Please obtain the most recent Related Substances specifications from the drug substance manufacturer and revise your specifications accordingly.
4. Based on the recommendation from the Division of Bioequivalence, you revised the dissolution specification to "NLT _____ of the labeled amount of the drug in the dosage form is dissolved in 90 minutes." Please revise the drug product release and stability specifications to reflect this change.

Sincerely yours,

DSC:el

for Vilayat A. Sayeed, Ph.D.
Director
Division of Chemistry III
Office of Generic Drugs
Center for Drug Evaluation and Research

BIOEQUIVALENCE COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 76-761

APPLICANT: Upsher-Smith Laboratories, Inc.

DRUG PRODUCT: Oxandrolone Tablets, USP 2.5 mg

The Division of Bioequivalence has completed its review and has no further questions at this time.

We acknowledge that you have accepted the following dissolution method and specification:

The dissolution testing should be conducted in 500 mL of 0.75% SDS in 0.1N HCl at 37°C using USP apparatus II (paddle) at 75 rpm. The test product should meet the following specification:

Not less than ~~90%~~ (Q) of the labeled amount of the drug in dosage form is dissolved in 90 minutes.

Please note that the bioequivalence comments provided in this communication are preliminary. These comments are subject to revision after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling, or other scientific or regulatory issues. Please be advised that these reviews may result in the need for additional bioequivalence information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

Sincerely yours,



Dale P. Conner, Pharm. D.
Director

Division of Bioequivalence
Office of Generic Drugs

Center for Drug Evaluation and Research

UPSHER-SMITH

Pharmaceuticals Since 1919

ORIG AMENDMENT
N/AEM

November 10, 2004

FEDERAL EXPRESS

Mr. Gary Buehler
Acting Director, Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855

**MINOR CHEMISTRY
AND
BIOEQUIVALENCE
AMENDMENT**

**RE: ANDA 76-761; _____ (Oxandrolone Tablets, USP), 2.5 mg
MINOR AMENDMENT responding to the Agency's October 6, 2004 Chemistry and
Bioequivalence Deficiency Letter**

Dear Mr. Buehler:

Reference is made to the Upsher-Smith Laboratories, Inc. (Upsher-Smith) pending ANDA 76-761 for the above referenced product.

Reference is also made to the Agency's October 6, 2004 Deficiency Letter. A copy of the Deficiency Letter is provided in **Attachment 1**.

This amendment is submitted herewith to the above referenced ANDA to address the Chemistry and Bioequivalence comments noted. This amendment has been designated as a MINOR AMENDMENT. The following deficiency items, shown in bold print, have been addressed in the order presented in the deficiency letter.

Deficiencies:

- 1. The Drug Master File (DMF) # _____ for Oxandrolone, USP has been found to be deficient. The deficiencies have been transmitted to the DMF holder. Please do not respond to this deficiency letter until you have received notification from the DMF holder that the deficiencies have been addressed.**

UPSHER-SMITH LABORATORIES, INC.
6701 EVENSTAD DRIVE, MAPLE GROVE, MN USA 55369-6026
CORPORATE 763-315-2000 FAX 763-315-2001
SALES & DISTRIBUTION 1-800-654-2299 SALES FAX 763-315-2244
www.upsher-smith.com

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NOV 12 2004
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A copy of the revised drug substance specification (API 02-480.06) from the drug product manufacturer, PII, is provided in **Attachment 3**. For the reviewer's convenience, a copy of the drug substance specification (API-003) from the drug substance manufacturer, is provided in **Attachment 4**.

A copy of the new test method, is provided in **Attachment 6**.

4. **Based on the recommendation from the Division of Bioequivalence, you revised the dissolution specification to "NLT (Q) of the labeled amount of the drug in the dosage form dissolved in 90 minutes." Please revise the drug product release and stability specifications to reflect this change.**

The drug product release and stability specifications were revised to reflect the change in the dissolution specification to NLT (Q) of the labeled amount of the drug in the dosage form dissolved in 90 minutes. These revised specifications were provided as part of the August 3, 2004 Bioequivalence and Chemistry deficiency response. Copies of the revised PII finished product specification, PII stability specification, and Upsher-Smith finished product release specifications (one per packaging configuration) are provided in **Attachment 7** for the reviewer's convenience.

Additional API Specification Changes

For consistency with the drug substance manufacturer's specifications, the assay acceptance criteria has been changed from to 97.0 - 100.5% to comply with the current USP monograph. Upsher-Smith is concerned that highly pure drug substance (near 100%) could potentially be tested out of specification due to inherent method variability. FDA has acknowledged this concern. Please refer to the telephone communication record dated October 22, 2004 (**Attachment 8**). Although we commit to utilizing the current USP acceptance limits of 97.0 - 100.5%, Upsher-Smith proposes to adopt the revised Oxandrolone, USP specifications as soon as they become official. The drug substance specifications from and PII were revised to incorporate this change. A copy of the revised drug substance specification (API 02-480.06) from the drug product manufacturer, PII, is provided in **Attachment 3**. For the reviewer's convenience, a copy of the drug substance specification (API-003) from the drug substance manufacturer, is provided in **Attachment 4**.

We request that all information related to this application be treated as confidential within the meaning of 21 CFR 314.430, and that no information, except as provided in 21 CFR

Mr. Gary Buehler
November 10, 2004
Minor Amendment to ANDA 76-761
Page 4 of 4

314.430 be released without Upsher-Smith's written consent to an authorized member of the Office of Generic Drugs.

This amendment is being submitted in duplicate as an archival and a review copy, for incorporation into our file.

As required per 21 CFR 314.96(b), Upsher-Smith hereby certifies that a field copy of this amendment, dated November 10, 2004, has been submitted to the Minneapolis District Office for their review. This third (field) copy is a "true" copy of this amendment.

If there are any questions or comments regarding this amendment, please contact me at (763) _____

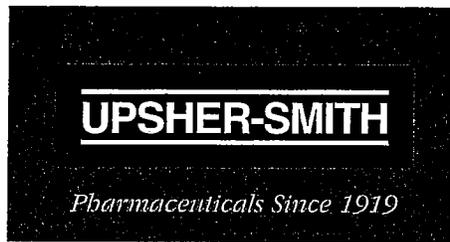
Sincerely,

UPSHER-SMITH LABORATORIES, INC.



Kimberly C. Oakins
Regulatory Affairs Specialist

Enclosures



PA: State Patent
-147, -799, -659 & -351
were untimely filed
MOU to -31
ORIG AMENDMENT
~~N/AA~~
N/XP
2/1/05

January 14, 2005

CERTIFIED MAIL/RETURN RECEIPT REQUESTED

Mr. Gary Buehler
Director, Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855

RECEIVED
JAN 27 2005
OGD / CDER

**RE: ANDA 76-761; Oxandrolone Tablets, USP, 2.5 mg
UNSOLICITED AMENDMENT Providing Updated Patent and Exclusivity
Statements**

Dear Mr. Buehler:

Reference is made to the Upsher-Smith Laboratories, Inc. (Upsher-Smith) pending ANDA 76-761 for the above referenced product.

This amendment is being submitted to the above referenced ANDA providing an updated patent certification and exclusivity statement to the referenced listed drug product, OXANDRIN® (oxandrolone tablets, USP), 2.5 mg. At the time the original ANDA was filed, there were no unexpired patents for OXANDRIN® listed in the Orange Book. Recently, 5 patents for OXANDRIN® have been listed. A copy of Upsher-Smith's revised patent certification and exclusivity statement is provided in **Attachment 1**. Provided in **Attachment 2** is a copy of a patent status query from the current edition of the Orange Book regarding the Reference Listed Drug.

We request that all information related to this application be treated as confidential within the meaning of 21 CFR 314.430, and that no information, except as provided in 21 CFR 314.430 be released without Upsher-Smith's written consent to an authorized member of the Office of Generic Drugs.

UPSHER-SMITH LABORATORIES, INC.
6701 EVENSTAD DRIVE, MAPLE GROVE, MN USA 55369-6026
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SALES & DISTRIBUTION 1-800-654-2299 SALES FAX 763-315-2244
www.upshe-smith.com

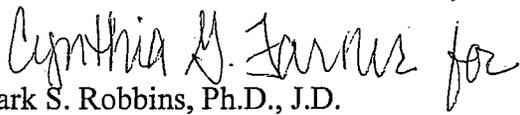
Excellence Through Innovation

This amendment is being submitted in duplicate as an archival and a review copy, for incorporation into our file.

If there are any questions or comments regarding this amendment, please contact Kimberly Oakins, Regulatory Affair Specialist, at (763) _____

Sincerely,

UPSHER-SMITH LABORATORIES, INC.


Mark S. Robbins, Ph.D., J.D.
Vice President, Scientific Affairs

Enclosures

This application contains the following items: (Check all that apply)

<input type="checkbox"/>	1. Index
<input type="checkbox"/>	2. Labeling (check one) <input type="checkbox"/> Draft Labeling <input type="checkbox"/> Final Printed Labeling
<input type="checkbox"/>	3. Summary (21 CFR 314.50 (c))
<input type="checkbox"/>	4. Chemistry section
<input type="checkbox"/>	A. Chemistry, manufacturing, and controls information (e.g., 21 CFR 314.50(d)(1); 21 CFR 601.2)
<input type="checkbox"/>	B. Samples (21 CFR 314.50 (e)(1); 21 CFR 601.2 (a)) (Submit only upon FDA's request)
<input type="checkbox"/>	C. Methods validation package (e.g., 21 CFR 314.50(e)(2)(i); 21 CFR 601.2)
<input type="checkbox"/>	5. Nonclinical pharmacology and toxicology section (e.g., 21 CFR 314.50(d)(2); 21 CFR 601.2)
<input type="checkbox"/>	6. Human pharmacokinetics and bioavailability section (e.g., 21 CFR 314.50(d)(3); 21 CFR 601.2)
<input type="checkbox"/>	7. Clinical Microbiology (e.g., 21 CFR 314.50(d)(4))
<input type="checkbox"/>	8. Clinical data section (e.g., 21 CFR 314.50(d)(5); 21 CFR 601.2)
<input type="checkbox"/>	9. Safety update report (e.g., 21 CFR 314.50(d)(5)(vi)(b); 21 CFR 601.2)
<input type="checkbox"/>	10. Statistical section (e.g., 21 CFR 314.50(d)(6); 21 CFR 601.2)
<input type="checkbox"/>	11. Case report tabulations (e.g., 21 CFR 314.50(f)(1); 21 CFR 601.2)
<input type="checkbox"/>	12. Case report forms (e.g., 21 CFR 314.50 (f)(2); 21 CFR 601.2)
<input type="checkbox"/>	13. Patent information on any patent which claims the drug (21 U.S.C. 355(b) or (c))
<input checked="" type="checkbox"/>	14. A patent certification with respect to any patent which claims the drug (21 U.S.C. 355 (b)(2) or (j)(2)(A))
<input type="checkbox"/>	15. Establishment description (21 CFR Part 600, if applicable)
<input type="checkbox"/>	16. Debarment certification (FD&C Act 306 (k)(1))
<input type="checkbox"/>	17. Field copy certification (21 CFR 314.50 (l)(3))
<input type="checkbox"/>	18. User Fee Cover Sheet (Form FDA 3397)
<input type="checkbox"/>	19. Financial Information (21 CFR Part 54)
<input type="checkbox"/>	20. OTHER (Specify)

CERTIFICATION

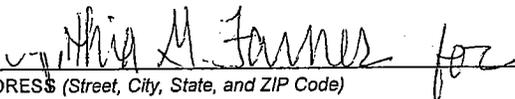
I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA.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

1. Good manufacturing practice regulations in 21 CFR Parts 210, 211 or applicable regulations, Parts 606, and/or 820.
2. Biological establishment standards in 21 CFR Part 600.
3. Labeling regulations in 21 CFR Parts 201, 606, 610, 660, and/or 809.
4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR Part 202.
5. Regulations on making changes in application in FD&C Act section 506A, 21 CFR 314.71, 314.72, 314.97, 314.99, and 601.12.
6. Regulations on Reports in 21 CFR 314.80, 314.81, 600.80, and 600.81.
7. Local, state and Federal environmental impact laws.

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

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

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

SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT 	TYPED NAME AND TITLE Mark S. Robbins, Ph.D., J.D. Vice President, Legal and Regulatory Affairs	DATE: 1/14/05
ADDRESS (Street, City, State, and ZIP Code) 6701 Evenstad Drive, Maple Grove, MN 55369		Telephone Number (763) 315-2000

Public reporting burden for this collection of information is estimated to average 24 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Department of Health and Human Services
Food and Drug Administration
CDER, HFD-99
1401 Rockville Pike
Rockville, MD 20852-1448

Food and Drug Administration
CDER (HFD-94)
12229 Wilkins Avenue
Rockville, MD 20852

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

UPSHER-SMITH

Pharmaceuticals Since 1919

III. PATENT CERTIFICATION AND EXCLUSIVITY STATEMENT

January 14, 2005

Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855

**RE: Updated Patent Certification and Exclusivity Statement for Reference Listed Drug
Product: Savient Pharmaceuticals, Inc. OXANDRIN[®] (oxandrolone tablets, USP)**

Dear Sir/Madam:

Upsher-Smith Laboratories, Inc. ("USL") submitted an Abbreviated New Drug Application ("ANDA") on June 12, 2003 seeking the Food and Drug Administration's ("FDA's") approval to market a generic version of OXANDRIN[®] (oxandrolone tablets, USP) (NDA #13-718) for use as ~~_____~~

~~_____~~ to offset the protein catabolism associated with prolonged administration of corticosteroids, and for the relief of the bone pain frequently accompanying osteoporosis.

Section 505(j)(2)(A)(viii) of the Federal Food, Drug, and Cosmetic Act ("FDC Act") and FDA's implementing regulations at 21 CFR 314.94(a)(12)(iii) require the sponsor of an ANDA to provide the agency with a statement with respect to each method-of-use patent listed in FDA's Orange Book for the reference listed drug that does not claim any of the proposed indications for which ANDA approval is sought.

Upsher-Smith's original ANDA contained a Paragraph II patent certification, as no unexpired patents were listed in the "Approved Drug Products with Therapeutic

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Equivalence Evaluations: (“Orange Book”). Subsequent to USL’s submission of its ANDA, the NDA holder submitted five patents to FDA for listing in the Orange Book. Four of these patents (U.S. patent number 5,872,147, U.S. patent number 6,090,799, U.S. patent number 6,576,659; and U.S. patent number 6,670,351) were untimely filed by the NDA holder. Pursuant to 21 CFR 314.94(a)(12)(vi), Upsher-Smith is not required to amend the original patent certification as it pertains to these four patents because of the untimely filing.

A fifth patent, U.S. patent number 6,828,313 (“the ‘313 patent”), was issued on December 7, 2004 and was timely filed with FDA for Orange Book listing. Pursuant to 21 CFR 314.94(a)(12)(iii), Upsher-Smith is providing herein an amended patent certification and exclusivity statement as it pertains to the ‘313 patent.

With respect to the reference listed drug, OXANDRIN[®], for which information was filed by the NDA holder, Savient Pharmaceuticals, Inc., under 505(b) and (c) of the FDC Act, and pursuant to 21 CFR 314.53, for the ‘313 patent, USL hereby states that the labeling for its generic product does not claim the methods-of-use claimed in the ‘313 patent.

The patent claims a method of use of oxandrolone in the treatment of burns and other wounds.¹ The patent use code listed in the Orange Book for the ‘313 patent, “U-585,” describes the use as “to promote weight gain after weight loss in certain types of patients.” USL is neither seeking approval for burn-induced trauma or other wounds covered by the ‘313 patent, nor is OXANDRIN[®] approved for burn-induced trauma or the specific wounds mentioned in the ‘313 patent.

Pursuant to 505(j)(2)(D) of the Federal Food, Drug and Cosmetic Act, there is no unexpired exclusivity for the reference listed drug product referred to in this application.

This application has been filed in accordance with 505(j) of the Act, for a generic copy of the approved reference listed drug. No changes in dosage form, active ingredient(s) or route of administration are submitted in this application under 505(j)(2)(C) suitability petitions. Therefore this application is exempt from a pediatric assessment a required under the Pediatric Rule, 21 CFR 315.55(a).

¹ Specifically, the abstract for the ‘313 patent states: “The subject invention provides a method of treating burn-induced weight loss in a burn patient . . . [and] also provides a method of treating a wound in a patient suffering from a wound..”

Sincerely,

UPSHER-SMITH LABORATORIES, INC.

Cynthia A. Farmer for

Mark S. Robbins, Ph.D., J.D.

Vice President, Legal and Regulatory Affairs

Patent and Exclusivity Search Results from query on Appl No 013718 Product 001 in the OB_Rx list.**Patent Data**

Appl No	Prod No	Patent No	Patent Expiration	Drug Substance Claim	Drug Product Claim	Patent Use Code
013718	001	5872147	DEC 05,2017			<u>U-585</u>
013718	001	6090799	JUL 18,2017			<u>U-585</u>
013718	001	6576659	DEC 05,2017			<u>U-585</u>
013718	001	6670351	OCT 20,2012			<u>U-585</u>
013718	001	6828313	DEC 05,2017			<u>U-585</u>

Exclusivity Data**There is no unexpired exclusivity for this product.**

Additional information:

1. Patents are published upon receipt by the Orange Book Staff and may not reflect the official receipt date as described in 21 CFR 314.53(d)(5).
2. Patents submitted on FDA Form 3542 and listed after August 18, 2003 will have one to three patent codes indicating specific patent claims as submitted by the sponsor and are detailed in the above table.
3. Patents listed prior to August 18, 2003 are flagged with method of use claims only as applicable and submitted by the sponsor. These patents may not be flagged with respect to other claims which may apply.
4. *PED and PED represent pediatric exclusivity. Patents with pediatric exclusivity granted after August 18, 2003 will be indicated with *PED as was done prior to August 18, 2003. Patents with *PED added after August 18, 2003 will not contain any information relative to the patent itself other than the *PED extension. Information related specifically to the patent will be conveyed on the original patent only.

[View a list of all patent use codes](#)[View a list of all exclusivity codes](#)[Return to Electronic Orange Book Home Page](#)

FDA/Center for Drug Evaluation and Research

Office of Generic Drugs

Division of Labeling and Program Support

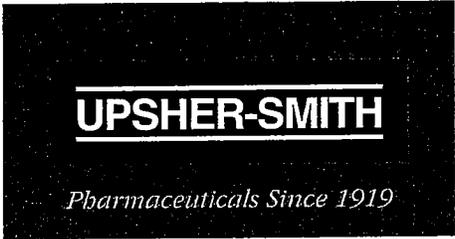
Update Frequency:

Orange Book Data - **Monthly**

Orange Book Data Updated Through November, 2004

Orange Book Patent Data Only - **Daily**

Patent Data Last Updated: January 14, 2005



ORIG AMENDMENT
N/AA

March 29, 2005

FEDERAL EXPRESS

**Bioequivalence and
Chemistry Unsolicited
Amendment**

Mr. Gary Buehler
Director, Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855

**RE: ANDA 76-761; (Oxandrolone Tablets, USP) 2.5 mg
UNSOLICITED AMENDMENT Proposing Revised Dissolution Acceptance
Criteria**

Dear Mr. Buehler:

Reference is made to the Upsher-Smith Laboratories, Inc. (Upsher-Smith) pending ANDA 76-761 for the above referenced product.

Reference is also made to the February 25, 2005 facsimile submitted to the Agency providing additional dissolution data and recent information from USP pertaining to the Oxandrolone Tablets monograph.

On March 10, 2005, Upsher-Smith had a teleconference with the Agency to discuss the data provided in the February 25, 2005 facsimile. Upsher-Smith proposed revising the dissolution specification from Q= to Q= based on additional data generated from stability studies and process validation lots. At the conclusion of the teleconference, Upsher-Smith agreed to submit additional dissolution data and revised drug product specifications incorporating the proposed specification of Q=, for the Agency's consideration.

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Provided in **Attachment 1** is a report "Justification of Dissolution Acceptance Criteria for Oxandrolone Tablets, 2.5 mg" summarizing dissolution data which support the proposed acceptance criteria of Q=

Provided in **Attachment 2** are copies of the revised finished product release and stability specifications from Pharmaceuticals International Inc. (PII) and finished product release specifications from Upsher-Smith Laboratories, Inc. (USL) incorporating the proposed dissolution acceptance criteria (Q=

We request that all information related to this application be treated as confidential within the meaning of 21 CFR 314.430, and that no information, except as provided in 21 CFR 314.430 be released without Upsher-Smith's written consent to an authorized member of the Office of Generic Drugs.

This amendment is being submitted in duplicate as an archival and a review copy, for incorporation into our file.

As required per 21 CFR 314.96(b), Upsher-Smith hereby certifies that a field copy of this amendment, dated March 29, 2005, has been submitted to the Minneapolis District Office for their review. This third (field) copy is a "true" copy of this amendment.

If there are any questions or comments regarding this amendment, please contact me at (763) -

Sincerely,

UPSHER-SMITH LABORATORIES, INC.



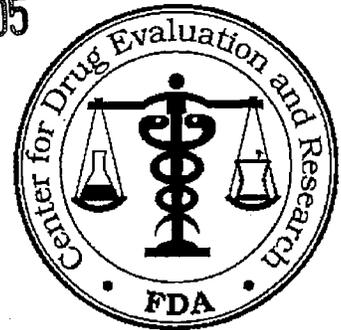
Kimberly C. Oakins
Regulatory Affairs Specialist

Enclosures

MINOR AMENDMENT

ANDA 76-761

APR 14 2005



OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773 (301-594-0320)

APPLICANT: Upsher-Smith Laboratories, Inc.

TEL: 763-315-2000

ATTN: Kimberly Oakins

FAX: 763-258-5578

FROM: Sarah Park

PROJECT MANAGER: (301) 827-5724

Dear Madam:

This facsimile is in reference to your abbreviated new drug application dated June 12, 2003, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Oxandrolone Tablets, USP, 2.5 mg.

Reference is also made to your amendment dated November 10, 2004.

The application is deficient and, therefore, Not Approvable under Section 505 of the Act for the reasons provided in the attachments (pages). This facsimile is to be regarded as an official FDA communication and unless requested, a hard copy will not be mailed.

The file on this application is now closed. You are required to take an action described under 21 CFR 314.120 which will either amend or withdraw the application. Your amendment should respond to all of the deficiencies listed. Facsimiles or partial replies will not be considered for review, nor will the review clock be reactivated until all deficiencies have been addressed. The response to this facsimile will be considered to represent a MINOR AMENDMENT and will be reviewed according to current OGD policies and procedures. The designation as a MINOR AMENDMENT should appear prominently in your cover letter. You have been/will be notified in a separate communication from our Division of Bioequivalence of any deficiencies identified during our review of your bioequivalence data. If you have substantial disagreement with our reasons for not approving this application, you may request an opportunity for a hearing.

SPECIAL INSTRUCTIONS:

Chemistry comments provided.

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, OR PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW.

If received by someone other than the addressee or a person authorized to deliver this document to the addressee, you are hereby notified that any disclosure, dissemination, copying, or other action to the content of this communication is not authorized. If you have received this document in error, please immediately notify us by telephone and return it to us by mail at the above address.

Law

APR 14 2005

36. CHEMISTRY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 76-761

APPLICANT: Upsher-Smith Laboratories, Inc.

DRUG PRODUCT: Oxandrolone Tablets USP, 2.5mg

The deficiencies presented below represent MINOR deficiencies.

A. Deficiencies:

1. The Drug Master File (DMF) for Oxandrolone, USP remains deficient. The deficiencies have been transmitted to the DMF holder. Please do not respond to this deficiency letter until you have received notification from the DMF holder that the deficiencies have been addressed.
2. Please demonstrate that Oxandrolone drug substance will not convert to other forms upon long term storage. Also, we recommend addition of a test (e.g. or etc.) to the drug substance release and stability for every batch. Please consult with your drug substance manufacturer.
3. Please tighten your drug product specifications for Total Impurities both for release and stability based on observed results. Alternatively, justify the acceptance criteria by comparison with reference listed drug.

Sincerely yours,

DS Gillo

for Vilayat A. Sayeed, Ph.D.
Director
Division of Chemistry III
Office of Generic Drugs
Center for Drug Evaluation and Research

UPSHER-SMITH LABORATORIES, INC.
6701 Evenstad Drive
Maple Grove, MN 55369
TELEPHONE: (763) 315-2000
FAX: (763) 315-2260

FAX

TO: Sarah Park

FAX: (301) 827-9274

FROM: Kimberly Oakins
Regulatory Affairs Specialist

DATE: May 13, 2005

RE: ANDA 76-761, _____ (Oxandrolone Tablets, USP) 2.5 mg
Request for Agency's concurrence on Proposed Acceptance Criteria for
Total Related Substances in the Drug Product in Response to Agency's
April 14, 2005 Minor Deficiency Letter

NUMBER OF PAGES (INCLUDING COVER PAGE): 2

Dear Ms. Park:

In a deficiency letter dated April 14, 2005, the Agency requested that the drug product specification for Total Impurities for both release and stability be tightened. The deficiency letter specifically states:

Tighten your drug product specifications for Total Impurities both for release and stability based on observed results. Alternatively, justify the acceptance criteria by comparison with reference-listed drug.

Currently, the proposed specification is _____ Provided on the following page is a justification for revising the specification from _____ to _____

Upsher-Smith is requesting the Agency's concurrence with the proposed drug product Total Impurity specification of _____. If the Agency disagrees with this proposal, we are requesting a teleconference at your earliest convenience to discuss the topic further.

If you have any questions or concerns, please feel free to contact me at (763) _____

Best regards,

Kimberly Oakins

Kimberly C. Oakins
Regulatory Affairs Specialist

The pages in this facsimile are for the sole use of the individual and entity to whom they are addressed. They may contain information that is privileged, confidential and exempt from disclosure under applicable law. If you are not the intended recipient or the employee or agent responsible for delivering this transmission to the intended recipient, be aware that any disclosure, duplication, distribution, review or use of the contents of this transmission are strictly prohibited. If you have received this transmission in error, please notify this firm immediately by collect call so that we may retrieve this transmission or have it destroyed.

Justification for Proposed Drug Product Total Impurity Specification

Data from the biot and ongoing stability studies were reviewed to determine appropriate revised specifications for total (specified and unspecified) impurities in the drug product. Data has been obtained through the stability interval in all four packaging configurations (5-count bottle, 100-count bottle, 1000-count bottle and unit dose packaging).

Based on the 24-months of real time data collected in all packaging configurations, Upsher-Smith proposes to revise the total (specified and unspecified) impurities from NMT 0.1% to NMT 0.2% for finished product and stability. Although no significant increase or adverse trending was observed, the data demonstrates a slight upward trend in total impurities. The specification of 0.1% was established taking into consideration the following factors: Using regression statistics, the 95% confidence band is at 0.1% for the 100-count bottle and approaches 0.2% for the other three (3) packaging configurations. This is based on one manufacturing lot packaged into four configurations. It does not take into account manufacturing variability. In addition the related substance test method has variability due to the poor aqueous solubility of the drug substance and the difficult detection characteristics of the drug substance due to a weak absorption. The test method utilizes a detection wavelength of 254 nm. Analysis at this low wavelength has the potential for random peak interferences. In addition to the low wavelength, a sample concentration step is used for the method to assure detection with appropriate limits. The method validation precision studies, which included spiking oxandrolone into placebo 20 times, resulted in an RSD of 10%. This in itself could contribute to 10% variation in total related substance results.

In conclusion due to the limited amount of data (i.e., one manufacturing lot) upon which the specification is based and the difficult nature of the test method, the 0.2% limit represents a reasonable total related substance specification to establish at this time.

UPSHER-SMITH

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ORIG AMENDMENT
N/A
AA

May 21, 2005

FEDERAL EXPRESS

**Chemistry Unsolicited
Amendment**

Mr. Gary Buehler
Director, Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855

**RE: ANDA 76-761; (Oxandrolone Tablets, USP) 2.5 mg
UNSOLICITED AMENDMENT Providing Data in Support of a Proposed
Revision to the Drug Product Total Related Compound Acceptance Criteria
in response to the Agency's April 14, 2005 Minor Deficiency Letter**

Dear Mr. Buehler:

Reference is made to the Upsher-Smith Laboratories, Inc. (Upsher-Smith) pending ANDA 76-761 for the above referenced product.

Reference is made to the April 14, 2005 Minor Deficiency Letter requesting that the drug product total related compound specification for release and stability be tightened based on observed results.

Reference is also made to the May 13, 2005 facsimile submitted to the Agency providing justification for a proposed drug product total related compound specification of . A copy of the May 13, 2005 facsimile is provided in **Attachment 1**.

On May 18, Upsher-Smith received phone call from Mike Darj, Chemist, requesting that we provide data in support of the proposed drug product total related compound specification of . Provided in **Attachment 2** is stability data obtained from all 4 package configurations (5-count bottle, 100-count bottle, 1000-count bottle and 100-count unit dose package). Provided in **Attachment 3** is a SLIM regression statistics.

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MAY 23 2005

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Upsher-Smith Laboratories, Inc.

ANDA 76-761

(Oxandrolone Tablets, USP) 2.5 mg

report using the 95% confidence interval which supports the proposed specification of

Upsher-Smith is requesting the Agency's concurrence with the proposed drug product total related compound specification of . If the Agency disagrees with this proposal, Upsher-Smith is requesting a teleconference as soon as possible to discuss the topic further.

We request that all information related to this application be treated as confidential within the meaning of 21 CFR 314.430, and that no information, except as provided in 21 CFR 314.430 be released without Upsher-Smith's written consent to an authorized member of the Office of Generic Drugs.

This amendment is being submitted in duplicate as an archival and a review copy, for incorporation into our file.

As required per 21 CFR 314.96(b), Upsher-Smith hereby certifies that a field copy of this amendment, dated May 21, 2005, has been submitted to the Minneapolis District Office for their review. This third (field) copy is a "true" copy of this amendment.

If there are any questions or comments regarding this amendment, please contact me at (763) 

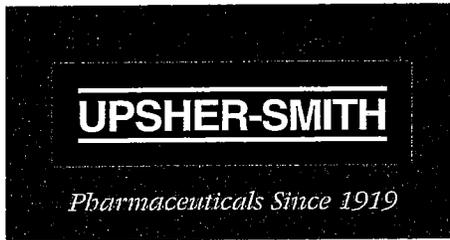
Sincerely,

UPSHER-SMITH LABORATORIES, INC.



Kimberly C. Oakins
Regulatory Affairs Specialist

Enclosures



ORIG AMENDMENT

N / AM

ES added
6/17/05
S. Park

June 6, 2005

FEDERAL EXPRESS

Mr. Gary Buehler
Acting Director, Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855

**MINOR
CHEMISTRY
AMENDMENT**

**RE: ANDA 76-761; ^M (Oxandrolone Tablets, USP) 2.5 mg
MINOR CHEMISTRY AMENDMENT responding to the Agency's April 14, 2005
Chemistry Deficiency Letter**

Dear Mr. Buehler:

Reference is made to the Upsher-Smith Laboratories, Inc. (Upsher-Smith) pending ANDA 76-761 for the above referenced product.

Reference is also made to the Agency's April 14, 2005 MINOR Chemistry Deficiency Letter. A copy of the MINOR deficiency Letter is provided in **Attachment 1**.

Reference is also made to facsimiles submitted to the Agency on May 13, 2005 (**Attachment 2**) and May 21, 2005 (cover letter provided in **Attachment 3**).

This amendment is submitted herewith to the above referenced ANDA to address the Chemistry comments noted. This amendment has been designated as a MINOR AMENDMENT. The following deficiency items, shown in bold print, have been addressed in the order presented in the deficiency letter.

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JUN 07 2005

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UPsher-SMITH LABORATORIES, INC.
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CORPORATE 763-315-2000 FAX 763-315-2001
SALES & DISTRIBUTION 1-800-654-2299 SALES FAX 763-315-2244
www.upsher-smith.com

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Chemistry Deficiencies:

1. The Drug Master File (DMF) [redacted] for Oxandrolone, USP remains deficient. The deficiencies have been transmitted to the DMF holder. Please do not respond to this deficiency letter until you have received notification from the DMF holder that the deficiencies have been addressed.

In response to a deficiency letter dated April 14, 2005 [redacted] submitted an amendment to DMF # [redacted] for Oxandrolone, USP on May 23, 2005. A copy of the cover letter is provided in Attachment 4.

2. Please demonstrate that Oxandrolone drug substance will not convert to other [redacted] forms upon long-term storage. Also, we recommend addition of a [redacted] test (e.g., [redacted] or etc.) to the drug substance release and stability for every batch. Please consult with your drug substance manufacturer.

Please refer to [redacted] amendment to DMF # [redacted], submitted to the Agency on May 23, 2005 for discussion regarding demonstration that the Oxandrolone drug substance will not convert to other [redacted] forms upon long-term storage. [redacted] has incorporated a [redacted] test to the drug substance release and stability testing for every batch. In addition, Pharmaceutics International Inc. (PII) has incorporated a [redacted] test to the drug substance release testing of every batch. PII will use an [redacted] scan of the drug substance lot used in the biolot provided by [redacted] as the reference scan. Methodology and acceptance criteria utilized by both [redacted] and PII is consistent with USP/NF <941> [redacted]. A copy of the revised PII drug substance release specification is provided in Attachment 5.

As a result of the addition of [redacted] testing for the drug substance, [redacted] is being added as an analytical testing site to perform [redacted] testing for the drug substance only. [redacted] is located at the following address:

Telephone [redacted]

The FDA registration number for [redacted] is [redacted]. A letter providing GMP and debarment certification is provided in Attachment 6.

3. Please tighten your drug product specification for Total Impurities both for release and stability based on observed results. Alternatively, justify the acceptance criteria by comparison with the reference listed drug.

In the original ANDA, Upsher-Smith proposed a Total Impurity (Degradation Product) specification of ~~_____~~. In the November 20, 2003 deficiency letter, the Agency requested that the Total Impurities (Degradation Products) specification for both release and stability be lowered. In our April 16, 2004 response, Upsher-Smith proposed a ~~_____~~ Total Impurity (Degradation Products) acceptance criterion, based on the limited data available at the time.

In the April 14, 2004 deficiency letter, the Agency again requested that the Total Impurity (Degradation Products) specification for both release and stability be lowered. On May 13, 2005, Upsher-Smith submitted a meeting request (**Attachment 2**) to discuss the Total Impurity (Degradation Products) acceptance criteria, proposing a ~~_____~~ limit. On May 18, 2005, Mike Darj, Chemist FDA, requested ~~_____~~ stability data and a ~~_____~~ regression statistics report. An amendment was submitted on May 21, 2005, providing the requested data. (A copy of the cover letter is provided in **Attachment 3**.) On May 26, 2005, Sarah Park, Project Manager FDA, stated that the Agency would not grant our meeting request due to the amount of data provided. She indicated the Agency would review the data provided to support the proposed specification as part of our official deficiency response.

Subsequently, Upsher-Smith has re-reviewed the available data, and is proposing a ~~_____~~ Total Impurity (Degradation Products) acceptance criterion for drug product release and stability. Provided in **Attachment 7** is a revised justification for the proposed specification, ~~_____~~ stability data, and a copy of the ~~_____~~ regression statistics report in support of the proposed acceptance criterion of ~~_____~~.

Copies of the revised PII finished product release specification, PII finished product stability specification, and the Upsher-Smith finished product release specifications (one per packaging configuration) are provided in **Attachment 8**. Please note that, consistent with Mike Darj's May 18, 2005 request, terminology has been changed from "related compounds" to "degradation products."

If the Agency does not concur with the proposed acceptance criterion of ~~_____~~ Upsher-Smith is requesting a teleconference with the Agency to discuss and resolve this issue and avoid another subsequent deficiency, further delaying approval and patient access to quality, low-cost generic alternatives to the innovator product.

We request that all information related to this application be treated as confidential within the meaning of 21 CFR 314.430, and that no information, except as provided in 21 CFR

Upsher-Smith Laboratories, Inc.

ANDA 76-761

(Oxandrolone Tablets, USP) 2.5 mg

314.430 be released without Upsher-Smith's written consent to an authorized member of the Office of Generic Drugs.

This amendment is being submitted in duplicate as an archival and a review copy, for incorporation into our file.

As required per 21 CFR 314.96(b), Upsher-Smith hereby certifies that a field copy of this amendment, dated June 6, 2005, has been submitted to the Minneapolis District Office for their review. This third (field) copy is a "true" copy of this amendment.

If there are any questions or comments regarding this amendment, please contact me at (763)

Sincerely,

UPSHER-SMITH LABORATORIES, INC.



Kimberly C. Oakins
Regulatory Affairs Specialist

Enclosures

UPSHER-SMITH LABORATORIES, INC.
6701 Evenstad Drive
Maple Grove, MN 55369
TELEPHONE: (763) 315-2000
FAX: (763) 315-2260

FAX

TO: Jeanne Skanchy
FAX: (301) 827-9274
FROM: Kimberly Oakins
Regulatory Affairs Specialist
DATE: September 14, 2006
RE: ANDA 76-761, Oxandrolone Tablets, USP 2.5 mg
AMENDMENT responding to the Agency's request for post-
approval commitment to submit changes in compliance with
USP

NUMBER OF PAGES (INCLUDING COVER PAGE): 6

Dear Ms. Skanchy:

Per your request on September 14, 2006, please find a faxed copy of the amendment submitted to the Agency for the above reference application, ANDA 76-761, Oxandrolone Tablets, USP 2.5 mg.

If you have any questions or comments regarding this submission, please contact me at (763)

Best regards,

Kimberly Oakins

Kimberly Oakins
Regulatory Affairs Specialist

The pages in this facsimile are for the sole use of the individual and entity to whom they are addressed. They may contain information that is privileged, confidential and exempt from disclosure under applicable law. If you are not the intended recipient or the employee or agent responsible for delivering this transmission to the intended recipient, be aware that any disclosure, duplication, distribution, review or use of the contents of this transmission are strictly prohibited. If you have received this transmission in error, please notify this firm immediately by collect call so that we may retrieve this transmission or have it destroyed.



DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

Form Approved: OMB No. 0910-0338
Expiration Date: August 31, 2005
See OMB Statement on page 2.

**APPLICATION TO MARKET A NEW DRUG, BIOLOGIC,
OR AN ANTIBIOTIC DRUG FOR HUMAN USE**
(Title 21, Code of Federal Regulations, Parts 314 & 601)

FOR FDA USE ONLY

APPLICATION NUMBER

APPLICANT INFORMATION

NAME OF APPLICANT Upsher-Smith Laboratories, Inc	DATE OF SUBMISSION 9/16/06
TELEPHONE NO. (Include Area Code) 763-315-2000	FACSIMILE (FAX) Number (Include Area Code) 763-258-5578
APPLICANT ADDRESS (Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued): 6701 Evenstad Drive Maple Grove, MN 55369	AUTHORIZED U.S. AGENT NAME & ADDRESS (Number, Street, City, State, ZIP Code, telephone & FAX number) IF APPLICABLE N/A

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER (If previously issued) 76-761	
ESTABLISHED NAME (e.g., Proper name, USP/USAN name) Oxandrolone Tablets, USP	PROPRIETARY NAME (trade name) IF ANY N/A
CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME (If any) Oxandrolone	CODE NAME (If any) N/A
DOSAGE FORM: Immediate-release Tablet	STRENGTHS: 2.5 mg
ROUTE OF ADMINISTRATION: Oral	
(PROPOSED) INDICATION(S) FOR USE: Adjunctive therapy to promote weight gain	

APPLICATION DESCRIPTION

APPLICATION TYPE (check one) NEW DRUG APPLICATION (CDA, 21 CFR 314.50) ABBREVIATED NEW DRUG APPLICATION (ANDA, 21 CFR 314.94) BIOLOGICS LICENSE APPLICATION (BLA, 21 CFR Part 601)

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

IF AN ANDA, OR 505(b)(2), IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION

Name of Drug Oxandrin® Tablets Holder of Approved Application Savient Pharmaceuticals

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

IF A SUBMISSION OF PARTIAL APPLICATION, PROVIDE LETTER DATE OF AGREEMENT TO PARTIAL SUBMISSION: _____

IF A SUPPLEMENT, IDENTIFY THE APPROPRIATE CATEGORY CBE CBE-30 Prior Approval (PA)

REASON FOR SUBMISSION
Amendment regarding post-approval commitment to submit changes in compliance with USP

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

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

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

Refer to ANDA

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

Refer to ANDA

This application contains the following items: (Check all that apply)

<input type="checkbox"/>	1. Index
<input type="checkbox"/>	2. Labeling (check one) <input type="checkbox"/> Draft Labeling <input type="checkbox"/> Final Printed Labeling
<input type="checkbox"/>	3. Summary (21 CFR 314.50 (c))
<input checked="" type="checkbox"/>	4. Chemistry section
<input checked="" type="checkbox"/>	A. Chemistry, manufacturing, and controls information (e.g., 21 CFR 314.50(d)(1); 21 CFR 601.2)
<input type="checkbox"/>	B. Samples (21 CFR 314.50 (e)(1); 21 CFR 601.2 (a)) (Submit only upon FDA's request)
<input type="checkbox"/>	C. Methods validation package (e.g., 21 CFR 314.50(e)(2)(i); 21 CFR 601.2)
<input type="checkbox"/>	5. Nonclinical pharmacology and toxicology section (e.g., 21 CFR 314.50(d)(2); 21 CFR 601.2)
<input type="checkbox"/>	6. Human pharmacokinetics and bioavailability section (e.g., 21 CFR 314.50(d)(3); 21 CFR 601.2)
<input type="checkbox"/>	7. Clinical Microbiology (e.g., 21 CFR 314.50(d)(4))
<input type="checkbox"/>	8. Clinical data section (e.g., 21 CFR 314.50(d)(5); 21 CFR 601.2)
<input type="checkbox"/>	9. Safety update report (e.g., 21 CFR 314.50(d)(5)(vi)(b); 21 CFR 601.2)
<input type="checkbox"/>	10. Statistical section (e.g., 21 CFR 314.50(d)(6); 21 CFR 601.2)
<input type="checkbox"/>	11. Case report tabulations (e.g., 21 CFR 314.50(f)(1); 21 CFR 601.2)
<input type="checkbox"/>	12. Case report forms (e.g., 21 CFR 314.50 (f)(2); 21 CFR 601.2)
<input type="checkbox"/>	13. Patent information on any patent which claims the drug (21 U.S.C. 355(b) or (c))
<input type="checkbox"/>	14. A patent certification with respect to any patent which claims the drug (21 U.S.C. 355 (b)(2) or (j)(2)(A))
<input type="checkbox"/>	15. Establishment description (21 CFR Part 600, if applicable)
<input type="checkbox"/>	16. Debarment certification (FD&C Act 306 (k)(1))
<input checked="" type="checkbox"/>	17. Field copy certification (21 CFR 314.50 (l)(3))
<input type="checkbox"/>	18. User Fee Cover Sheet (Form FDA 3397)
<input type="checkbox"/>	19. Financial Information (21 CFR Part 54)
<input type="checkbox"/>	20. OTHER (Specify)

CERTIFICATION

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

1. Good manufacturing practice regulations in 21 CFR Parts 210, 211 or applicable regulations, Parts 606, and/or 820.
2. Biological establishment standards in 21 CFR Part 600.
3. Labeling regulations in 21 CFR Parts 201, 606, 610, 660, and/or 809.
4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR Part 202.
5. Regulations on making changes in application in FD&C Act section 306A, 21 CFR 314.71, 314.72, 314.97, 314.99, and 601.12.
6. Regulations on Reports in 21 CFR 314.80, 314.81, 600.80, and 600.81.
7. Local, state and Federal environmental impact laws.

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

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

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

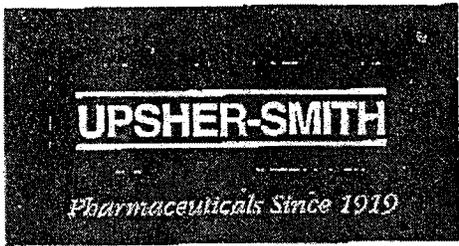
SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT <i>Kimberly C. Oakins</i>	TYPED NAME AND TITLE Kimberly C. Oakins	DATE: 9/14/06
ADDRESS (Street, City, State, and ZIP Code) 6701 Evenstad Drive, Maple Grove, MN 55369		Telephone Number (763) 315-2000

Public reporting burden for this collection of information is estimated to average 24 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Department of Health and Human Services
Food and Drug Administration
CDER, HFD-99
1401 Rockville Pike
Rockville, MD 20852-1448

Food and Drug Administration
CDER (HFD-94)
12229 Wilkins Avenue
Rockville, MD 20852

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



September 14, 2006

FEDERAL EXPRESS/FACSIMILE

**AMENDMENT
IN RESPONSE
TO FDA
REQUEST**

Mr. Gary Buehler
Director, Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

**RE: ANDA 76-761; Oxandrolone Tablets, USP, 2.5 mg
AMENDMENT responding to the Agency's request for post-approval
commitment to submit changes in compliance with USP**

Dear Mr. Buehler:

Reference is made to the Upsher-Smith Laboratories, Inc. (Upsher-Smith) pending ANDA 76-761 for the above referenced product.

Upsher-Smith Laboratories, Inc. acknowledges that any changes made to the USP monograph for the above reference product will be submitted to the application post-approval.

Specifically, Upsher-Smith Laboratories, Inc. commits to submitting a revised drug substance specification for Oxandrolone, USP via an Annual Report post-approval to incorporate the assay specification of 98.0-102.0%, published in USP 24, Supplement 2.

We request that information related to this application be treated as confidential within the meaning of 21 CFR 314.430, and that no information, except as provided in 21 CFR 314.430, be released without our written consent to an authorized member of the Office of Generic Drugs.

This amendment is being submitted in duplicate as an archival and a review copy, for incorporation into our file.

UPSHER-SMITH LABORATORIES, INC.
5701 EVENSTAD DRIVE, MAPLE GROVE, MN USA 55369-6026
CORPORATE 763-315-2000 FAX 763-315-2001
SALES & DISTRIBUTION 1-800-654-2299 SALES FAX 763-315-2244
www.upsheer-smith.com

7 18 991 ON

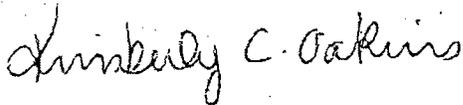
Excellence Through Innovation

MA9919 9002 161 285
SEP 14 2006 9:38AM

Pursuant to 21 CFR 314.96(b), we hereby certify that a field copy of this application has been submitted to the Minneapolis District Office for their review. Upsher-Smith certifies the field copy is a complete and true copy of the technical information provided in this application.

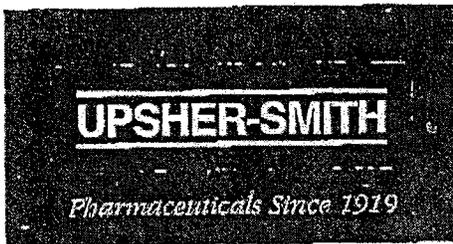
If you have any questions or comments regarding this submission, please contact me at (763) _____

Sincerely,
UPSHER-SMITH LABORATORIES, INC.



Kimberly C. Oakins
Regulatory Affairs Specialist

Enclosures



September 14, 2006

CERTIFIED MAIL/RETURN RECEIPT REQUESTED

W. Charles Becoat
Director
Minneapolis District Office
Food and Drug Administration
212 3rd Avenue South
Minneapolis, MN 55401-1912

**RE: ANDA 76-761; Oxandrolone Tablets, USP, 2.5 mg
AMENDMENT responding to the Agency's request for post-approval
commitment to submit changes in compliance with USP**

Dear Mr. Becoat:

As required per 21 CFR 314.94(d)(5), please find enclosed the District FDA copy of this Amendment, dated September 14, 2006, for the above referenced drug product

If you have any questions or comments regarding this submission, please contact me at (763) —

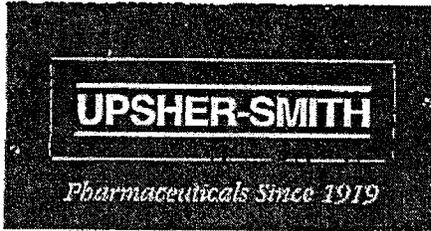
Sincerely,

UPsher-SMITH LABORATORIES, INC.

Kimberly C. Oakins
Regulatory Affairs Specialist

Enclosures

UPsher-SMITH LABORATORIES, INC.
6701 EVENSTAD DRIVE, MAPLE GROVE, MN USA 55369-6026
CORPORATE 763-315-2000 FAX 763-315-2001
SALES & DISTRIBUTION 1-800-654-2299 SALES FAX 763-315-2244
www.upsher-smith.com



November 16, 2006

VIA FEDERAL EXPRESS/FACSIMILE

Mr. Gary Buehler
 Director, Office of Generic Drugs
 Center for Drug Evaluation and Research
 Food and Drug Administration
 Document Control Room
 Metro Park North II
 7500 Standish Place, Room 150
 Rockville, MD 20855-2773

<p>Telephone Amendment</p> <p>CMC and Labeling</p>
--

RE: ANDA 76-761; Oxandrolone Tablets, USP, 2.5 mg
Amendment responding to Agency's telephone deficiency received November 16

Dear Mr. Buehler:

Reference is made to Upsher-Smith Laboratories, Inc. (Upsher-Smith) pending ANDA 76-761 for the above reference product. Reference is also made to the telephone deficiency communication received from Jeanne Skanchy on November 16, 2006.

The USP monograph for Oxandrolone was revised and published in USP29/NF24 Supplement 2, effective August 1, 2006. The assay acceptance criteria were revised to 98.0-102.0%. Although previous concurrence was obtained to implement this change post-approval, the Agency requested that we implement this USP change prior to approval. In addition, the assay determination by titration was removed from the monograph. Provided in **Attachment 1** contains a revised specification for Oxandrolone, USP which incorporates these changes to the assay specification to be consistent with the USP monograph.

The USP assay test method was also revised in Supplement 2 for Oxandrolone. _____, the manufacturer of oxandrolone, performed a comparison of the USP HPLC method versus the currently proposed HPLC test method SOP T231 (same as PII test TM 04-0168). The methods were found to be equivalent. A copy of _____ Validation Test Report TPR5 is provided in **Attachment 2**. Upsher-Smith proposes to maintain TM-04-0168 as an alternate regulatory analytical test method. Upsher-Smith acknowledges that USP methods are the regulatory methods, and in case of any dispute, USP methods should be used.

ANDA 76-761 Oxandrolone Tablet, USP 2.5 mg
Telephone Amendment
November 16, 2006

Additionally, the Agency requested that Upsher-Smith revise the package insert to remove reference to _____, which will not be official until Upsher-Smith receives FDA approval. The package insert has been revised to state "USP Dissolution Test Pending". Final printed labeling for the package insert is provided electronically on a virus-free CD immediately following this cover letter. The software used to determine that the disc is virus-free was Symantec AntiVirus, Program Version 10.0.2.2020, Scan Engine 61.3.0.18, Virus Definition File Version 11/15/2006 rev. 18. A courtesy hard copy of the package insert is provided in **Attachment 3**.

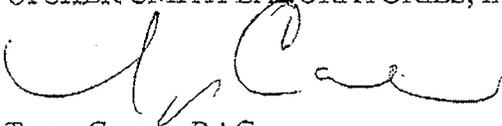
We request that information related to this application be treated as confidential within the meaning of 21 CFR 314.430, and that no information, except as provided in 21 CFR 314.430, be released without our written consent to an authorized member of the Office of Generic Drugs.

This amendment is being submitted in duplicate as an archival and a review copy for incorporation into our file.

Pursuant to 21 CFR 314.96(b), we hereby certify that a field copy of this amendment has been submitted to the Minneapolis District Office for their review. Upsher-Smith certifies the field copy is a complete and true copy of the technical information provided in this application.

If you have any questions or comments regarding this submission, please contact Kim Oakins at (763) _____

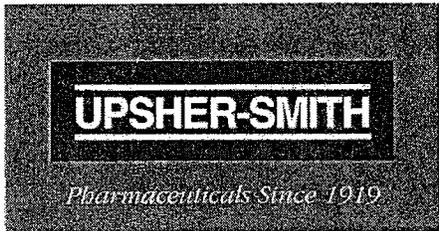
Sincerely,
UPSHER-SMITH LABORATORIES, INC.



Tanya Carone, RAC
Associate Manager, New Product Regulatory Affairs

Attachments

AS-1



ORIG AMENDMENT

N-000-AA

October 10, 2006

FEDERAL EXPRESS

**GRATUITOUS
AMENDMENT**

Mr. Gary Buehler
Director, Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855

RECEIVED
OCT 11 2006
OGD / CDER

RE: **ANDA 76-761; Oxandrolone Tablets, USP 2.5 mg**
GRATUITOUS AMENDMENT to remove the proprietary name

Dear Mr. Buehler:

Reference is made to the Upsher-Smith Laboratories, Inc. (Upsher-Smith) pending ANDA 76-761 for the above referenced product.

Upsher-Smith is hereby requesting the removal of ' ' as the proprietary name for the above referenced product.

We request that all information related to this application be treated as confidential within the meaning of 21 CFR 314.430, and that no information, except as provided in 21 CFR 314.430 be released without Upsher-Smith's written consent to an authorized member of the Office of Generic Drugs.

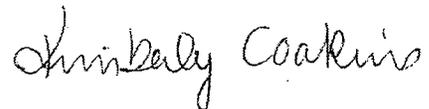
This amendment is being submitted in duplicate as an archival and a review copy, for incorporation into our file.

Upsher-Smith Laboratories, Inc.
ANDA 76-761
Oxandrolone Tablets, USP 2.5 mg

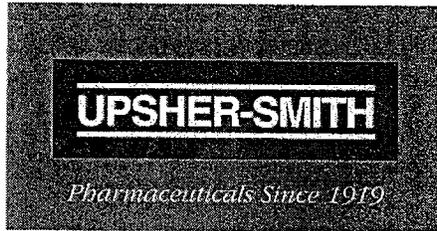
If there are any questions or comments regarding this amendment, please contact me at
(763) _____

Sincerely,

UPSHER-SMITH LABORATORIES, INC.

A handwritten signature in cursive script that reads "Kimberly C. Oakins".

Kimberly C. Oakins
Regulatory Affairs Specialist



ORIGINAL

FEDERAL EXPRESS

November 8, 2006

Mr. Gary Buehler, R.Ph.
Director, Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II, Room 150
7500 Standish Place
Rockville, MD 20855

*Amendment to Pending
ANDA*

ORIG AMENDMENT
N/AF

**RE: ANDA 76-761 Oxandrolone Tablets, USP 2.5 mg
Amendment to Pending ANDA – Final Printed Labeling**

Dear Mr. Buehler:

Reference is made to the Upsher-Smith Laboratories, Inc. (Upsher-Smith) pending ANDA 76-761 for the above referenced product.

The package insert has been revised to incorporate changes provided in a labeling template sent to Upsher-Smith from FDA via email on November 3, 2006. A copy of the November 3, 2006 email is provided in **Attachment 1**.

A side-by-side comparison of the previously submitted labeling (revision 0204) for Oxandrolone Tablets, USP 2.5 mg with the revised labeling (revision 0906) is provided with all differences annotated and explained. (**Attachment 2**).

In addition to the changes made to the package insert, the proprietary name was also removed from all of the labeling components. A Gratuitous Amendment was submitted to the Agency on October 10, 2006, indicating the removal of the proprietary name " — ". Final printed labeling for all components are provided both electronically on a CD located immediately following the cover letter and in courtesy paper copies (**Attachment 3**).

RECEIVED

NOV 09 2006
OGD / ODER

UPSHER-SMITH LABORATORIES, INC.
6701 EVENSTAD DRIVE, MAPLE GROVE, MN USA 55369-8026
CORPORATE 763-315-2000 FAX 763-315-2001
SALES & DISTRIBUTION 1-800-654-2299 SALES FAX 763-315-2244
www.upshe-smith.com

Excellence Through Innovation

November 8, 2006

The following items are provided in support of this Amendment:

- A copy of the labeling template sent from FDA to USL on November 3, 2006 (**Attachment 1**).
- A side-by-side comparison of the previously submitted package insert (revision 0204) for Oxandrolone Tablets, USP 2.5 mg with the revised package insert (revision 0906) is provided with all differences annotated and explained. (**Attachment 2**).
- Final printed labeling for Oxandrolone Tablets, USP, 2.5 mg. These labeling components are provided electronically on a virus-free CD, consuming approximately 600 KB of storage space. The software used to determine that the disc is virus-free was Symantec AntiVirus, Program Version 10.0.2.2020, Scan Engine 61.3.0.18, Virus Definition File Version 11/7/2006 rev. 19. The following files are contained on the CD:

Label Description	File name
100 count unit dose carton	2.5mgudcarton.pdf
5 count bottle	2.5mg5bottle.pdf
100 count bottle	2.5mg100bottle.pdf
1000 count bottle	2.5mg1000bottle.pdf
Unit Dose Blister	2.5mgblister.pdf
Package Insert	pi.pdf

The CD is provided in a protective sleeve immediately following this cover letter. A courtesy paper copy of the final printed labeling is provided in **Attachment 3**.

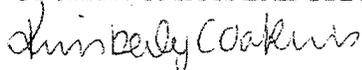
We request that information related to this application be treated as confidential within the meaning of 21 CFR 314.430, and that no information, except as provided in 21 CFR 314.430, be released without our written consent to an authorized member of the Office of Generic Drugs.

This amendment is being submitted in duplicate as an archival and a review copy, for incorporation into our file

If there are any questions regarding the information provided in this submission, please contact me at (763) _____

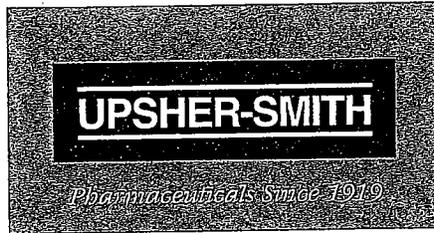
Sincerely,

UPSHER-SMITH LABORATORIES, INC.



Kimberly C. Oakins
Associate Manager Marketed Products Regulatory Affairs

attachments



November 29, 2006

VIA FEDERAL EXPRESS/FACSIMILE

Mr. Gary Buehler
Director, Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

*Amendment to Pending
ANDA*

**RE: ANDA 76-761; Oxandrolone Tablets, USP, 2.5 mg
Amendment responding to Agency's telephone fax received November 29, 2006**

Dear Mr. Buehler:

Reference is made to Upsher-Smith Laboratories, Inc. (Upsher-Smith) pending ANDA 76-761 for the above reference product.

The package insert has been revised to incorporate changes provided from the labeling deficiency sent to Upsher-Smith from FDA via telephone fax on November 29, 2006. A copy of the telephone fax is provided in **Attachment 1**.

A side-by-side comparison of the previously submitted labeling (revision 1106) for Oxandrolone Tablets, USP 2.5 mg with the revised labeling (revision 1106A) is provided with the differences annotated and explained in **Attachment 2**.

Final printed labeling for the package insert is provided electronically on a virus-free CD immediately following this cover letter and in courtesy paper copies. The software used to determine that the disc is virus-free was Symantec AntiVirus, Program Version 10.0.2.2020, Scan Engine 61.3.0.18, Virus Definition File Version 11/28/2006 rev. 18. A courtesy hard copy of the package insert is provided in **Attachment 3**.

We request that information related to this application be treated as confidential within the meaning of 21 CFR 314.430, and that no information, except as provided in 21 CFR 314.430, be released without our written consent to an authorized member of the Office of Generic Drugs.

UPSHER-SMITH LABORATORIES, INC.
6701 EVENSTAD DRIVE, MAPLE GROVE, MN USA 55369-6026
CORPORATE 763-315-2000 FAX 763-315-2001
SALES & DISTRIBUTION 1-800-654-2299 SALES FAX 763-315-2244
www.upsher-smith.com

Excellence Through Innovation

ANDA 76-761
Oxandrolone Tablet, USP 2.5 mg
Amendment to Pending ANDA

November 29, 2006

This amendment is being submitted in duplicate as an archival and a review copy for incorporation into our file.

If you have any questions or comments regarding this submission, please contact me at (763)

Sincerely,
UPSHER-SMITH LABORATORIES, INC.

Kimberly C. Oakins

Kimberly C. Oakins
Associate Manager, Marketed Products Regulatory Affairs

Attachments

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

Form Approved: OMB No. 0910-0338
Expiration Date: September 30, 2008
See OMB Statement on page 2.

**APPLICATION TO MARKET A NEW DRUG, BIOLOGIC,
OR AN ANTIBIOTIC DRUG FOR HUMAN USE**
(Title 21, Code of Federal Regulations, Parts 314 & 601)

FOR FDA USE ONLY

APPLICATION NUMBER

APPLICANT INFORMATION

NAME OF APPLICANT Upsher-Smith Laboratories, Inc.	DATE OF SUBMISSION 11/29/06
TELEPHONE NO. (Include Area Code) 763-315-2000	FACSIMILE (FAX) Number (Include Area Code) 763-258-5578
APPLICANT ADDRESS (Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued): 6701 Evenstad Drive Maple Grove, MN 55369	AUTHORIZED U.S. AGENT NAME & ADDRESS (Number, Street, City, State, ZIP Code, telephone & FAX number) IF APPLICABLE

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER (If previously issued) 76-761		
ESTABLISHED NAME (e.g., Proper name, USP/USAN name) Oxandrolone Tablets, USP	PROPRIETARY NAME (trade name) IF ANY NA	
CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME (If any) 17β-hydroxy-17α-methyl-2-oxa-5α-androstan-3-one	CODE NAME (If any) NA	
DOSAGE FORM: Tablets	STRENGTHS: 2.5 mg	ROUTE OF ADMINISTRATION: Oral
(PROPOSED) INDICATION(S) FOR USE: Adjunctive therapy to offset protein catabolism associated with prolonged administration of corticosteroids, and for relief of bone pain frequently accompanying osteoporosis.		

APPLICATION DESCRIPTION

APPLICATION TYPE (check one) <input type="checkbox"/> NEW DRUG APPLICATION (CDA, 21 CFR 314.50) <input checked="" type="checkbox"/> ABBREVIATED NEW DRUG APPLICATION (ANDA, 21 CFR 314.94) <input type="checkbox"/> BIOLOGICS LICENSE APPLICATION (BLA, 21 CFR Part 601)
IF AN NDA, IDENTIFY THE APPROPRIATE TYPE <input type="checkbox"/> 505 (b)(1) <input type="checkbox"/> 505 (b)(2)
IF AN ANDA, OR 505(b)(2), IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION Name of Drug <u>Oxandrin Tabletsr</u> Holder of Approved Application <u>Savient Pharmaceutical Inc.</u>
TYPE OF SUBMISSION (check one) <input type="checkbox"/> ORIGINAL APPLICATION <input type="checkbox"/> AMENDMENT TO APENDING APPLICATION <input type="checkbox"/> RESUBMISSION <input type="checkbox"/> PRESUBMISSION <input type="checkbox"/> ANNUAL REPORT <input type="checkbox"/> ESTABLISHMENT DESCRIPTION SUPPLEMENT <input type="checkbox"/> EFFICACY SUPPLEMENT <input type="checkbox"/> LABELING SUPPLEMENT <input type="checkbox"/> CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT <input type="checkbox"/> OTHER
IF A SUBMISSION OF PARTIAL APPLICATION, PROVIDE LETTER DATE OF AGREEMENT TO PARTIAL SUBMISSION: _____
IF A SUPPLEMENT, IDENTIFY THE APPROPRIATE CATEGORY <input type="checkbox"/> CBE <input type="checkbox"/> CBE-30 <input type="checkbox"/> Prior Approval (PA)
REASON FOR SUBMISSION Providing final printed labeling per November 29, 2006 FDA telephone fax.
PROPOSED MARKETING STATUS (check one) <input checked="" type="checkbox"/> PRESCRIPTION PRODUCT (Rx) <input type="checkbox"/> OVER THE COUNTER PRODUCT (OTC)
NUMBER OF VOLUMES SUBMITTED <u>1</u> THIS APPLICATION IS <input type="checkbox"/> PAPER <input checked="" type="checkbox"/> PAPER AND ELECTRONIC <input type="checkbox"/> ELECTRONIC
ESTABLISHMENT INFORMATION (Full establishment information should be provided in the body of the Application.) Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g. Final dosage form, Stability testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready. Refer to ANDA

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

Refer to ANDA

This application contains the following items: (Check all that apply)

<input type="checkbox"/>	1. Index
<input checked="" type="checkbox"/>	2. Labeling (check one) <input type="checkbox"/> Draft Labeling <input checked="" type="checkbox"/> Final Printed Labeling
<input type="checkbox"/>	3. Summary (21 CFR 314.50 (c))
<input type="checkbox"/>	4. Chemistry section
<input type="checkbox"/>	A. Chemistry, manufacturing, and controls information (e.g., 21 CFR 314.50(d)(1); 21 CFR 601.2)
<input type="checkbox"/>	B. Samples (21 CFR 314.50 (e)(1); 21 CFR 601.2 (a)) (Submit only upon FDA's request)
<input type="checkbox"/>	C. Methods validation package (e.g., 21 CFR 314.50(e)(2)(i); 21 CFR 601.2)
<input type="checkbox"/>	5. Nonclinical pharmacology and toxicology section (e.g., 21 CFR 314.50(d)(2); 21 CFR 601.2)
<input type="checkbox"/>	6. Human pharmacokinetics and bioavailability section (e.g., 21 CFR 314.50(d)(3); 21 CFR 601.2)
<input type="checkbox"/>	7. Clinical Microbiology (e.g., 21 CFR 314.50(d)(4))
<input type="checkbox"/>	8. Clinical data section (e.g., 21 CFR 314.50(d)(5); 21 CFR 601.2)
<input type="checkbox"/>	9. Safety update report (e.g., 21 CFR 314.50(d)(5)(vi)(b); 21 CFR 601.2)
<input type="checkbox"/>	10. Statistical section (e.g., 21 CFR 314.50(d)(6); 21 CFR 601.2)
<input type="checkbox"/>	11. Case report tabulations (e.g., 21 CFR 314.50(f)(1); 21 CFR 601.2)
<input type="checkbox"/>	12. Case report forms (e.g., 21 CFR 314.50 (f)(2); 21 CFR 601.2)
<input type="checkbox"/>	13. Patent information on any patent which claims the drug (21 U.S.C. 355(b) or (c))
<input type="checkbox"/>	14. A patent certification with respect to any patent which claims the drug (21 U.S.C. 355 (b)(2) or (j)(2)(A))
<input type="checkbox"/>	15. Establishment description (21 CFR Part 600, if applicable)
<input type="checkbox"/>	16. Debarment certification (FD&C Act 306 (k)(1))
<input type="checkbox"/>	17. Field copy certification (21 CFR 314.50 (l)(3))
<input type="checkbox"/>	18. User Fee Cover Sheet (Form FDA 3397)
<input type="checkbox"/>	19. Financial Information (21 CFR Part 54)
<input type="checkbox"/>	20. OTHER (Specify)

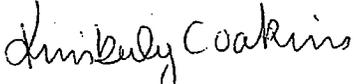
CERTIFICATION

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

1. Good manufacturing practice regulations in 21 CFR Parts 210, 211 or applicable regulations, Parts 606, and/or 820.
2. Biological establishment standards in 21 CFR Part 600.
3. Labeling regulations in 21 CFR Parts 201, 606, 610, 660, and/or 809.
4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR Part 202.
5. Regulations on making changes in application in FD&C Act section 506A, 21 CFR 314.71, 314.72, 314.97, 314.99, and 601.12.
6. Regulations on Reports in 21 CFR 314.80, 314.81, 600.80, and 600.81.
7. Local, state and Federal environmental impact laws.

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

The data and information in this submission have been reviewed and, to the best of my knowledge are certified to be true and accurate.
Warning: A willfully false statement is a criminal offense, U.S. Code, title 18, section 1001.

SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT 	TYPED NAME AND TITLE Kimberly C. Oakins Associate Manager, Marketed Products Regulatory Affairs	DATE: 11/29/06
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ADDRESS (Street, City, State, and ZIP Code) 701 Evenstad Drive, Maple Grove, MN 55369	Telephone Number (763) 315-2000
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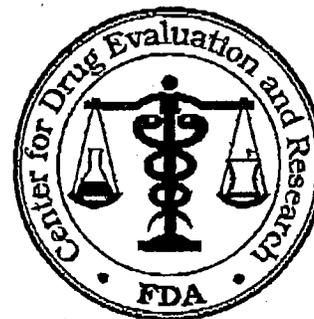
Public reporting burden for this collection of information is estimated to average 24 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Attachment 1

Telephone Fax

ANDA 76-761

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place
Rockville, MD 20855-2773
301-827-0507



TO: Upsher Smith Laboratories

TEL: —

ATTN: Mark Robbins

FAX: —

FROM: Wm Peter Rickman

This facsimile is in reference to your abbreviated new drug application submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Oxandrolone Tablets, USP
Pages (including cover): 2

SPECIAL INSTRUCTIONS:

Labeling Comments

Per conversation, please see attached label with mark-ups.

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, OR PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW.

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1 PAGE WITHHELD IN FULL

Attachment 2

8 PAGES WITHHELD IN FULL

Attachmen + 3

Oxandrolone Tablets,
USP 2.5 mg



Oxandrolone Tablets,
USP 2.5 mg

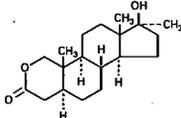


Oxandrolone Tablets, USP

Rx only

DESCRIPTION

Oxandrolone Tablets, USP contain 2.5 mg of the anabolic steroid oxandrolone. Oxandrolone is 17 β -hydroxy-17 α -methyl-2-oxa-5 α -androstane-3-one with the following structural formula:



Molecular Weight: 306.44

Molecular Formula: C₁₉H₃₀O₃

Inactive ingredients include anhydrous lactose, hypromellose, magnesium stearate, and pregelatinized starch.

USP Dissolution Test Pending.

CLINICAL PHARMACOLOGY

Anabolic steroids are synthetic derivatives of testosterone. Certain clinical effects and adverse reactions demonstrate the androgenic properties of this class of drugs. Complete dissociation of anabolic and androgenic effects has not been achieved. The actions of anabolic steroids are therefore similar to those of male sex hormones with the possibility of causing serious disturbances of growth and sexual development if given to young children. Anabolic steroids suppress the gonadotropic functions of the pituitary and may exert a direct effect upon the testes.

During exogenous administration of anabolic androgens, endogenous testosterone release is inhibited through inhibition of pituitary luteinizing hormone (LH). At large doses, spermatogenesis may be suppressed through feedback inhibition of pituitary follicle-stimulating hormone (FSH).

Anabolic steroids have been reported to increase low-density lipoproteins and decrease high-density lipoproteins. These levels revert to normal on discontinuation of treatment.

INDICATIONS AND USAGE

Oxandrolone Tablets, USP are indicated as adjunctive therapy to offset the protein catabolism associated with prolonged administration of corticosteroids, and for the relief of the bone pain frequently accompanying osteoporosis (see **DOSE AND ADMINISTRATION**).

DRUG ABUSE AND DEPENDENCE

Oxandrolone is classified as a controlled substance under the Anabolic Steroids Control Act of 1990 and has been assigned to Schedule III (non-narcotic).

CONTRAINDICATIONS

1. Known or suspected carcinoma of the prostate or the male breast.
2. Carcinoma of the breast in females with hypercalcaemia (androgenic anabolic steroids may stimulate osteolytic bone resorption).
3. Pregnancy, because of possible masculinization of the fetus. Oxandrolone has been shown to cause embryotoxicity, fetotoxicity, infertility, and masculinization of female animal offspring when given in doses 9 times the human dose.
4. Nephrosis, the nephrotic phase of nephritis.
5. Hypercalcaemia.

WARNINGS

PELIOUSIS HEPATIS, A CONDITION IN WHICH LIVER AND SOMETIMES SPLENIC TISSUE IS REPLACED WITH BLOOD-FILLED CYSTS, HAS BEEN REPORTED IN PATIENTS RECEIVING ANDROGENIC ANABOLIC STEROID THERAPY. THESE CYSTS ARE SOMETIMES PRESENT WITH MINIMAL HEPATIC DYSFUNCTION, BUT AT OTHER TIMES THEY HAVE BEEN ASSOCIATED WITH LIVER FAILURE. THEY ARE OFTEN NOT RECOGNIZED UNTIL LIFE-THREATENING LIVER FAILURE OR INTRA-ABDOMINAL HEMORRHAGE DEVELOPS. WITHDRAWAL OF DRUG USUALLY RESULTS IN COMPLETE DISAPPEARANCE OF LESIONS.

LIVER CELL TUMORS ARE ALSO REPORTED. MOST OF THESE TUMORS ARE BENIGN AND ANDROGEN-DEPENDENT, BUT FATAL MALIGNANT TUMORS HAVE BEEN REPORTED. WITHDRAWAL OF DRUG OFTEN RESULTS IN REGRESSION OR CESSATION OF PROGRESSION OF THE TUMOR. HOWEVER, HEPATIC TUMORS ASSOCIATED WITH ANDROGENS OR ANABOLIC STEROIDS ARE MUCH MORE VASCULAR THAN OTHER HEPATIC TUMORS AND MAY BE SILENT UNTIL LIFE-THREATENING INTRA-ABDOMINAL HEMORRHAGE DEVELOPS. BLOOD LIPID CHANGES THAT ARE KNOWN TO BE ASSOCIATED WITH INCREASED RISK OF ATHEROSCLEROSIS ARE SEEN IN PATIENTS TREATED WITH ANDROGENS OR ANABOLIC STEROIDS. THESE CHANGES INCLUDE DECREASED HIGH-DENSITY LIPOPROTEINS AND SOMETIMES INCREASED LOW-DENSITY LIPOPROTEINS. THE CHANGES MAY BE VERY MARKED AND COULD HAVE A SERIOUS IMPACT ON THE RISK OF ATHEROSCLEROSIS AND CORONARY ARTERY DISEASE.

Cholestatic hepatitis and jaundice may occur with 17-alpha-alkylated androgens at a relatively low dose. If cholestatic hepatitis with jaundice appears or if liver function tests become abnormal, oxandrolone should be discontinued and the etiology should be determined. Drug-induced jaundice is reversible when the medication is discontinued.

In patients with breast cancer, anabolic steroid therapy may cause hypercalcaemia by stimulating osteolysis. Oxandrolone therapy should be discontinued if hypercalcaemia occurs.

Edema with or without congestive heart failure may be a serious complication in patients with pre-existing cardiac, renal, or hepatic disease. Concomitant administration of adrenal cortical steroid or ACTH may increase the edema.

In children, androgen therapy may accelerate bone maturation without producing compensatory gain in linear growth. This adverse effect results in compromised adult height. The younger the child, the greater the risk of compromising final mature height. The effect on bone maturation should be monitored by assessing bone age of the left wrist and hand every 6 months (see **PRECAUTIONS, Laboratory Tests**).

Geriatric patients treated with androgenic anabolic steroids may be at an increased risk for the development of prostatic hypertrophy and prostatic carcinoma.

ANABOLIC STEROIDS HAVE NOT BEEN SHOWN TO ENHANCE ATHLETIC ABILITY.

PRECAUTIONS

Concurrent dosing of oxandrolone and warfarin may result in unexpectedly large increases in the International Normalized Ratio (INR) or prothrombin time (PT). When oxandrolone is prescribed to patients being treated with warfarin, doses of warfarin may need to be decreased significantly to maintain the desirable INR level and diminish the risk of potentially serious bleeding. (See **PRECAUTIONS, Drug Interactions).**

General

Women should be observed for signs of virilization (deepening of the voice, hirsutism, acne, clitoromegaly).

Discontinuation of drug therapy at the time of evidence of mild virilism is necessary to prevent irreversible virilization. Some virilizing changes in women are irreversible even after prompt discontinuance of therapy and are not prevented by concomitant use of estrogens. Menstrual irregularities may also occur.

Anabolic steroids may cause suppression of clotting factors II, V, VII, and X, and an increase in prothrombin time.

Information for Patients

The physician should instruct patients to report immediately any use of warfarin and any bleeding.

The physician should instruct patients to report any of the following side effects of androgens:

- Males:** Too frequent or persistent erections of the penis, appearance or aggravation of acne.
Females: Hoarseness, acne, changes in menstrual periods, or more facial hair.
All patients: Nausea, vomiting, changes in skin color, or ankle swelling.

Geriatric Use:

Certain geriatric use information is protected by marketing exclusivity.

Laboratory Tests

Women with disseminated breast carcinoma should have frequent determination of urine and serum calcium levels during the course of therapy (see **WARNINGS**).

Because of the hepatotoxicity associated with the use of 17-alpha-alkylated androgens, liver function tests should be obtained periodically.

Periodic (every 6 months) x-ray examinations of bone age should be made during treatment of children to determine the rate of bone maturation and the effects of androgen therapy on the epiphyseal centers.

Androgenic anabolic steroids have been reported to increase low-density lipoproteins and decrease high-density lipoproteins. Therefore, caution is required when administering these agents to patients with a history of cardiovascular disease or who are at risk for cardiovascular disease. Serum determination of lipid levels should be performed periodically and therapy adjusted accordingly.

Hemoglobin and hematocrit should be checked periodically for polycythemia in patients who are receiving high doses of anabolic steroids.

Drug Interactions

Anticoagulants:

Anabolic steroids may increase sensitivity to oral anticoagulants. Dosage of the anticoagulant may have to be decreased in order to maintain desired prothrombin time. Patients receiving oral anticoagulant therapy require close monitoring, especially when anabolic steroids are started or stopped.

Warfarin: A multiodose study of oxandrolone, given as 5 or 10 mg BID in 15 healthy subjects concurrently treated with warfarin, resulted in a mean increase in S-warfarin half-life from 26 to 48 hours and AUC from 4.55 to 12.08 ng-hr/mL; similar increases in R-warfarin half-life and AUC were also detected. Microscopic hematuria (9/15) and gingival bleeding (1/15) were also observed. A 5.5-fold decrease in the mean warfarin dose from 6.13 mg/day to 1.13 mg/day (approximately 80-85% reduction of warfarin dose), was necessary to maintain a target INR of 1.5. When oxandrolone therapy is initiated in a patient already receiving treatment with warfarin, the INR or prothrombin time (PT) should be monitored closely and the dose of warfarin adjusted as necessary until a stable target INR or PT has been achieved.

Furthermore, in patients receiving both drugs, careful monitoring of the INR or PT, and adjustment of the warfarin dosage if indicated are recommended when the oxandrolone dose is changed or discontinued. Patients should be closely monitored for signs and symptoms of occult bleeding.

Oral Hypoglycemic Agents:

Oxandrolone may inhibit the metabolism of oral hypoglycemic agents.

Adrenal Steroids or ACTH:

In patients with edema, concomitant administration with adrenal cortical steroids or ACTH may increase the edema.

Drug/Laboratory Test Interactions

Anabolic steroids may decrease levels of thyroxine-binding globulin, resulting in decreased total T₄ serum levels and increased resin uptake of T₃ and T₄. Free thyroid hormone levels remain unchanged. In addition, a decrease in PBI and radioactive iodine uptake may occur.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Animal Data:

Oxandrolone has not been tested in laboratory animals for carcinogenic or mutagenic effects. In 2-year chronic oral rat studies, a dose-related reduction of spermatogenesis and decreased organ weights (testes, prostate, seminal vesicles, ovaries, uterus, adrenals, and pituitary) were shown.

Human Data:

Liver cell tumors have been reported in patients receiving long-term therapy with androgenic anabolic steroids in high doses (see **WARNINGS**). Withdrawal of the drugs did not lead to regression of the tumors in all cases.

Geriatric patients treated with androgenic anabolic steroids may be at an increased risk for the development of prostatic hypertrophy and prostatic carcinoma.

Pregnancy

Teratogenic effects – Pregnancy Category X (see **CONTRAINDICATIONS**).

Nursing Mothers

It is not known whether anabolic steroids are excreted in human milk. Because of the potential of serious adverse reactions in nursing infants from oxandrolone, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use

Anabolic agents may accelerate epiphyseal maturation more rapidly than linear growth in children and the effect may continue for 6 months after the drug has been stopped. Therefore, therapy should be monitored by x-ray studies at 6-month intervals in order to avoid the risk of compromising adult height. Androgenic anabolic steroid therapy should be used very cautiously in children and only by specialists who are aware of the effects on bone maturation (see **WARNINGS**).

ADVERSE REACTIONS

Patients with moderate to severe COPD or COPD patients who are unresponsive to bronchodilators should be monitored closely for COPD exacerbation and fluid retention.

The following adverse reactions have been associated with use of anabolic steroids:

Hepatic

Cholestatic jaundice with, rarely, hepatic necrosis and death. Hepatocellular neoplasms and peliosis hepatitis with long-term therapy (see **WARNINGS**). Reversible changes in liver function tests also occur including increased bromsulphthalein (BSP) retention, changes in alkaline phosphatase and increases in serum bilirubin, aspartate aminotransferase (AST, SGOT) and alanine aminotransferase (ALT, SGPT).

In Males

Prepubertal: Phallic enlargement and increased frequency or persistence of erections.

Postpubertal: Inhibition of testicular function, testicular atrophy and oligospermia, impotence, chronic priapism, epididymitis, and bladder irritability.

In Females

Clitoral enlargement, menstrual irregularities.

CNS: Habituation, excitation, insomnia, depression, and changes in libido.

Hematologic: Bleeding in patients on concomitant oral anticoagulant therapy.

Breast: Gynecomastia.

Larynx: Deepening of the voice in females.

Hair: Hirsutism and male pattern baldness in females.

Skin: Acne (especially in females and prepubertal males).

Skeletal: Premature closure of epiphyses in children (see **PRECAUTIONS, Pediatric Use**).

Fluid and Electrolytes: Edema, retention of serum electrolytes (sodium chloride, potassium, phosphate, calcium).

Metabolic/Endocrine: Decreased glucose tolerance (see **PRECAUTIONS, Laboratory Tests**), increased creatinine excretion, increased serum levels of creatinine phosphokinase (CPK). Masculinization of the fetus. Inhibition of gonadotropin secretion.

OVERDOSAGE

No symptoms or signs associated with overdosage have been reported. It is possible that sodium and water retention may occur.

The oral LD50 of oxandrolone in mice and dogs is greater than 5,000 mg/kg. No specific antidote is known, but gastric lavage may be used.

DOSE AND ADMINISTRATION

Therapy with anabolic steroids is adjunctive to and not a replacement for conventional therapy. The duration of therapy with Oxandrolone Tablets, USP will depend on the response of the patient and the possible appearance of adverse reactions. Therapy should be intermittent.

Adults

The response of individuals to anabolic steroids varies. The daily adult dosage is 2.5 mg given in 2 to 4 divided doses. The desired response may be achieved with as little as 2.5 mg or as much as 20 mg daily. A course of therapy of 2 to 4 weeks is usually adequate. This may be repeated intermittently as indicated.

Children

For children the total daily dosage of Oxandrolone Tablets, USP is ≤ 0.1 mg per kilogram body weight or ≤ 0.045 mg per pound of body weight. This may be repeated intermittently as indicated.

HOW SUPPLIED

Oxandrolone Tablets, USP 2.5 mg are oval, white, scored, uncoated tablets, debossed with "2.5" on one side and "U" to the left and "S" to the right of the score on the other side. Oxandrolone Tablets, USP are available in bottles of 100 tablets (NDC 0245-0271-1), bottles of 1000 tablets (NDC 0245-0271-10) and in unit dose cartons of 100 tablets (10 cards containing 10 tablets each) (NDC 0245-0271-01).

Store at 20-25°C (68-77°F). Excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature]. Dispense in a light, light-resistant container with a child-resistant closure as defined in the USP.

Keep out of reach of children.

Manufactured by
UPsher-SMITH LABORATORIES, INC.
Minneapolis, MN 55447

by: Pharmaceuticals International, Inc.
Hunt Valley, MD 21031

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40-27100-05

Revised 1106A