CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

ANDA 076744

Name: Testosterone Gel 1%

Sponsor: Par Pharmaceuticals, Inc.

Approval Date: May 23, 2007

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APPLICATION NUMBER:

ANDA 076744

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APPLICATION NUMBER:

ANDA 076744

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville, MD 20857

ANDA 76-744

Par Pharmaceutical, Inc.
Attention: Julie Szozda
Senior Associate, Regulatory Affairs
One Ram Ridge Road
Spring Valley, NY 10977

Dear Madam:

This is in reference to your abbreviated new drug application (ANDA) dated May 21, 2003, submitted pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act (the Act), for Testosterone Gel, 1%, packaged in 2.5 gram and 5 gram Unit-Dose Packets.

Reference is also made to the tentative approval letter issued by this office on October 24, 2004, and to your amendments dated September 15, September 26, and December 26, 2006; and January 5, and May 3, 2007. We also acknowledge receipt of your correspondence dated December 13, 2006, regarding the licensing agreement between Par Pharmaceutical, Inc. and Unimed Pharmaceuticals, Inc. described below.

We have completed the review of this ANDA and have concluded that adequate information has been presented to demonstrate that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly the ANDA is approved, effective the date of this letter. The Division of Bioequivalence has determined your Testosterone Gel, 1%, to be bioequivalent and, therefore, therapeutically equivalent to the reference listed drug, AndroGel®, 1%, of Unimed Pharmaceuticals, Inc.

The reference listed drug (RLD) upon which you have based your ANDA, AndroGel®, 1% of Unimed Pharmaceuticals, Inc. (Unimed), is subject to a period of patent protection. As noted in the agency's publication titled Approved Drug Products with Therapeutic Equivalence Evaluations (the “Orange Book”), U.S. Patent No. 6,503,894 (the '894 patent), is scheduled to expire on August 30, 2020.

Your ANDA contains a paragraph IV certification to the '894 patent under section 505(j)(2)(A)(vii)(IV) of the Act stating that the patent is invalid, unenforceable, or will not be infringed by your manufacture, use, or sale of Testosterone Gel, 1%, under this ANDA. Section 505(j)(5)(B)(iii) of the act provides that approval of an ANDA shall be made effective immediately, unless an action was brought against Paddock Laboratories, Inc, the former owner of this ANDA, for infringement of the ‘894 patent. This action must have been brought against Paddock prior to the expiration of 45 days from the date the notice Paddock provided under section 505 (j)(2)(B)(i) was received by the NDA/patent holder(s). Paddock notified the agency that it complied with the requirements of section 505(j)(2)(B) of the Act, and that litigation was initiated against Paddock for infringement of '894 patent in the United States District Court for the Northern District of Georgia Atlanta Division [Unimed Pharmaceuticals, Inc., v. Paddock Laboratories, Inc.), Civil Action No. 1:03-CV-2503].

You have informed the agency that on September 13, 2006, Par Pharmaceutical, Inc. reached a settlement in its lawsuit with the NDA and patent holder, Unimed Pharmaceuticals, Inc. (Unimed), and also entered into a licensing agreement with Unimed. This settlement and licensing agreement, in addition to the relinquishment by Watson Laboratories Inc. of its entitlement to 180-day generic drug exclusivity for this drug product, provides a regulatory basis for approval of this ANDA.

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 application 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 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
5/23/2007 02:21:13 PM
for Gary Buehler

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 076744

TENTATIVE APPROVAL LETTER

ANDA 76-744

OCT 27 2004

Paddock Laboratories, Inc.
Attention: Todd M. Delehant, PhD.
3940 Quebec Avenue North
Minneapolis, MN 55427

Dear Sir:

This is in reference to your abbreviated new drug application (ANDA) dated May 21, 2003, submitted pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act (the Act), for Testosterone Gel, 1%.

Reference is also made to your amendments dated April 8, May 19, June 30, August 13, September 15, and October 22, 2004. We also acknowledge receipt of your correspondence dated September 5, and September 12, 2003, addressing the patent issue noted below.

We have completed the review of this abbreviated application, and based upon the information you have presented to date we have concluded that the drug is safe and effective for use as recommended in the submitted labeling. However, final approval of your application is blocked at this time by the ongoing patent litigation referenced below. Therefore, the application is **tentatively approved.** This determination is based upon information available to the agency at this time (i.e., information in your application and the status of current good manufacturing practices (cGMPs) of the facilities used in the manufacture and testing of the drug product). This determination is subject to change on the basis of new information that may come to our attention. This letter does not address notice issues related to the 180-day exclusivity provisions under section 505(j)(5)(B)(iv) of the Act.

The listed drug product (RLD) referenced in your application, AndroGel Topical Gel, 1% of Unimed Pharmaceuticals, Inc., is subject to a period of patent protection. As noted in the Agency's publication entitled Approved Drug Products with Therapeutic Equivalence Evaluations, the "Orange Book", U.S. patent 6,503,894 (the '894 patent) is due to expire on August 30, 2020. Your application contains a paragraph IV patent certification to the '894 patent under section 505(j)(2)(A)(vii)(IV) of the Act stating that the '894 patent is invalid and/or will not be infringed by Paddock's manufacture, use, or sale of Testosterone Gel, 1%, under this ANDA. Section 505(j)(5)(B)(iii) [1] of the Act provides that approval of an ANDA shall be made effective immediately, unless an action is brought against Paddock Laboratories, Inc. (Paddock) for infringement of the '894 patent that was the subject of the paragraph IV certification. This action must have been brought against Paddock prior to the expiration of 45 days from the date the notice you provided under paragraph (2)(B)(i) was received by the patent/NDA holder(s). You have notified the Agency that Paddock complied with the requirements of section 505 (j)(2)(B) of the Act, and that litigation is currently underway in the United States District Court for the Northern District of Georgia Atlanta Division involving your challenge to the '894 patent [Unimed Pharmaceuticals, Inc., v. Paddock Laboratories, Inc., Civil Action No. 1:03-CV-2503]. Therefore, final approval of this ANDA cannot be granted until:

1. a. the expiration of the 30-month period provided for in section 505(j)(5)(B)(iii) since the date of receipt of the 45-day notice required under section 505(j)(2)(B)(i), unless the court has extended or reduced the period because of the failure of either party to reasonably cooperate in expediting the action, or,

   b. the date of court decision [505(j)(5)(B)(iii) (I), (II), or (III)], or,

   c. the '894 patent has expired, and

[1] Because information on the '894 patent was submitted before August 18, 2003, this reference is to a section of the Act as in effect prior to December 8, 2003, when the Medicare Prescription Drug, Improvement and Modernization Act (MMA) (Public Law 108-173) was enacted. See MMA § 1101(c)(3).

2. The agency is assured there is no new information that would affect whether final approval should be granted.

In order to reactivate your application prior to final approval, please submit a "MINOR AMENDMENT - FINAL APPROVAL REQUESTED" 90 days prior to the date you believe that your application will be eligible for final approval. This amendment should provide:

1. A copy of an order or judgment, settlement agreement between the parties, or a licensing agreement between you and the patent holder, or any other relevant information, and

2. a. updated information related to final-printed labeling or chemistry, manufacturing and controls data, or any other change in the conditions outlined in this abbreviated application, or

   b. a statement that no such changes have been made to the application since the date of tentative approval.

In addition to the amendment requested above, the agency may request at any time prior to the final date of approval that you submit an additional amendment containing the requested information. Failure to submit either or, if requested, both amendments may result in rescission of the tentative approval status of your application, or may result in a delay in the issuance of the final approval letter.

Any significant changes in the conditions outlined in this abbreviated application as well as changes in the status of the manufacturing and testing facilities' compliance with current good manufacturing practices (cGMPs) are subject to agency review before final approval of the application will be made. Such changes should be categorized as representing either "major" or "minor" changes, and they will be reviewed according to OGD policy in effect at the time of receipt. The submission of multiple amendments prior to final approval may also result in a delay in the issuance of the final approval letter.

This drug product may not be marketed without final Agency approval under section 505 of the Act. The introduction or delivery for introduction into interstate commerce of this drug product before the final approval date is prohibited under section 501 of the Act and 21 U.S.C. 331 (d). Also, until the Agency issues the final approval letter, this drug product will not be deemed approved for marketing under 21 USC 355, and will not be listed in the "Orange Book".

The amendment to request final approval should be designated as a MINOR AMENDMENT in your cover letter. Before you submit the amendment, please contact Wanda Pamphile, Pharm.D., Project Manager, at (301) 827-5848, for further instructions.

Sincerely yours,

Robert Lewis for 10/27/2004

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

cc: ANDA 76-744
Division File
Field Copy
HFD-610/R. West
HFD-330
HFD-205

Endorsements:
HFD-620/K.Woodland K Woodland 8/24/04
HFD-620/S.Liu S.H. Liu 8/24/04
HFD-617/W.Pamphile WF 8/23/04
HFD-613/R.Wu
HFD-613/J.Grace 8/24/04

F/T by wp 8/20/04
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TENTATIVE APPROVAL

Robert Levis
10/27/2004

8/27/04

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 076744

LABELING

Testosterone Gel 1%

C III

Testosterone Gel 1%

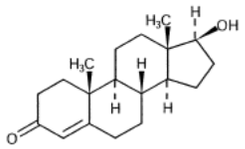
Rx only

DESCRIPTION

Testosterone gel 1% is a clear, colorless hydroalcoholic gel containing 1% testosterone. Testosterone gel provides continuous transdermal delivery of testosterone, the primary circulating endogenous androgen, for 24 hours following a single application to intact, clean, dry skin of the shoulders, upper arms and/or abdomen.

A daily application of testosterone gel 5 g, 7.5 g, or 10 g contains 50 mg, 75 mg, or 100 mg of testosterone, respectively, to be applied daily to the skin's surface. Approximately 10% of the applied testosterone dose is absorbed across skin of average permeability during a 24-hour period.

The active pharmacologic ingredient in testosterone gel is testosterone. Testosterone USP is a white to practically white crystalline powder chemically described as 17-beta hydroxyandrost-4-en-3-one.



Testosterone

$C_{19}H_{28}O_2$ MW 288.42

Inactive ingredients in testosterone gel are ethanol 68.9%, purified water, sodium hydroxide, carbomer 940 and isopropyl myristate; these ingredients are not pharmacologically active.

CLINICAL PHARMACOLOGY

Testosterone gel delivers physiologic amounts of testosterone, producing circulating testosterone concentrations that approximate normal levels (298 -1043 ng/dL) seen in healthy men.

Testosterone-General Androgen Effects:

Endogenous androgens, including testosterone and dihydrotestosterone (DHT), are responsible for the normal growth and development of the male sex organs and for maintenance of secondary sex characteristics. These effects include the growth and maturation of prostate, seminal vesicles, penis, and scrotum; the development of male hair distribution, such as facial, pubic, chest, and axillary hair; laryngeal enlargement, vocal chord thickening, alterations in body musculature, and fat distribution. Testosterone and DHT are necessary for the normal development of secondary sex characteristics. Male hypogonadism results from insufficient secretion of testosterone and is characterized by low serum testosterone concentrations. Symptoms associated with male hypogonadism include impotence and decreased sexual desire, fatigue and loss of energy, mood depression, regression of secondary sexual characteristics and osteoporosis. Hypogonadism is a risk factor for osteoporosis in men.

Drugs in the androgen class also promote retention of nitrogen, sodium, potassium, phosphorus, and decreased urinary excretion of calcium. Androgens have been reported to increase protein anabolism and decrease protein catabolism. Nitrogen balance is improved only when there is sufficient intake of calories and protein.

Androgens are responsible for the growth spurt of adolescence and for the eventual termination of linear growth brought about by fusion of the epiphyseal growth centers. In children, exogenous androgens accelerate linear growth rates but may cause a disproportionate advancement in bone maturation. Use over long periods may result in fusion of the epiphyseal growth centers and termination of the growth process. Androgens have been reported to stimulate the production of red blood cells by enhancing erythropoietin production.

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

There is a lack of substantial evidence that androgens are effective in accelerating fracture healing or in shortening post-surgical convalescence.

Pharmacokinetics

Absorption

Testosterone gel is a hydroalcoholic formulation that dries quickly when applied to the skin surface. The skin serves as a reservoir for the sustained release of testosterone into the systemic circulation. Approximately 10% of the testosterone dose applied on the skin surface from testosterone gel is absorbed into systemic circulation. Therefore, 5 g and 10 g of testosterone gel systemically deliver approximately 5 mg and 10 mg of testosterone, respectively. In a study with 10 g of testosterone gel all patients showed an increase in serum testosterone within 30 minutes, and eight of nine patients had a serum testosterone concentration within normal range by 4 hours after the initial application. Absorption of testosterone into the blood continues for the entire 24-hour dosing interval. Serum concentrations approximate the steady state level by the end of the first 24 hours and are at steady state by the second or third day of dosing.

With single daily applications of testosterone gel follow-up measurements 30, 90 and 180 days after starting treatment have confirmed that serum testosterone concentrations are generally maintained within the eugonadal range. Figure 1 summarizes the 24-hour pharmacokinetic profiles of testosterone for hypogonadal men (<300 ng/dL) maintained on 5 g or 10 g of testosterone gel, 1% for 30 days. The average (± SD) daily testosterone concentration produced by testosterone gel 10 g on Day 30 was 792 (± 294) ng/dL and by testosterone gel 5 g 566 (±262) ng/dL.

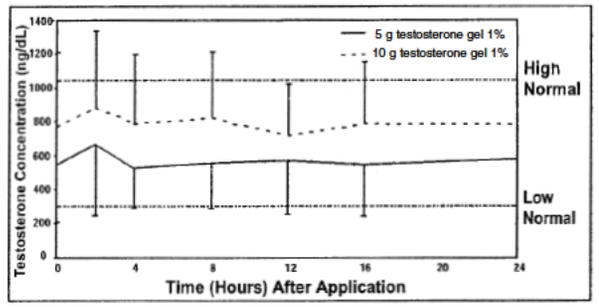


Figure 1. Mean (±SD) Steady State Serum Testosterone Concentrations on Day 30 in Patients Applying Testosterone Gel Once Daily

When testosterone gel treatment is discontinued after achieving steady state, serum testosterone levels remain in the normal range for 24 to 48 hours but return to their pretreatment levels by the fifth day after the last application.

Distribution

Circulating testosterone is chiefly bound in the serum to sex hormone-binding globulin (SHBG) and albumin. The albumin-bound fraction of testosterone easily dissociates from albumin and is presumed to be bioactive. The portion of testosterone bound to SHBG is not considered biologically active. The amount of SHBG in the serum and the total testosterone level will determine the distribution of bioactive and nonbioactive androgen. SHBG-binding capacity is high in prepubertal children, declines during puberty and adulthood, and increases again during the later decades of life. Approximately 40% of testosterone in plasma is bound to SHBG, 2% remains unbound (free) and the rest is bound to albumin and other proteins.

Metabolism

There is considerable variation in the half-life of testosterone as reported in the literature, ranging from 10 to 100 minutes. Testosterone is metabolized to various 17-keto steroids through two different pathways. The major active metabolites of testosterone are estradiol and DHT. DHT binds with greater affinity to SHBG than does testosterone. In many tissues, the activity of testosterone depends on its reduction to DHT, which binds to cytosol receptor proteins. The steroid-receptor complex is transported to the nucleus where it initiates transcription and cellular changes related to androgen action. In reproductive tissues, DHT is further metabolized to 3- α and 3- β androstanediol.

DHT concentrations increased in parallel with testosterone concentrations during testosterone gel treatment. After 180 days of treatment, mean DHT concentrations were within the normal range with 5 g testosterone gel and were about 7% above the normal range after a 10 g dose. The mean steady state DHT/T ratio during 180 days of testosterone gel treatment remained within normal limits (as determined by the analytical laboratory involved with this clinical trial) and ranged from 0.23 to 0.29 (5 g/day) and from 0.27 to 0.33 (10 g/day).

Excretion

About 90% of a dose of testosterone given intramuscularly is excreted in the urine as glucuronic and sulfuric acid conjugates of testosterone and its metabolites; about 6% of a dose is excreted in the feces, mostly in the unconjugated form. Inactivation of testosterone occurs primarily in the liver.

Special Populations

In patients treated with testosterone gel there are no observed differences in the average daily serum testosterone concentration at steady state based on age, cause of hypogonadism or body mass index. No formal studies were conducted involving patients with renal or hepatic insufficiencies.

Clinical Studies

Testosterone gel was evaluated in a multicenter, randomized, parallel-group, active-controlled, 180-day trial in 227 hypogonadal men. The study was conducted in 2 phases. During the Initial Treatment Period (Days 1-90), 73 patients were randomized to testosterone gel 5 g daily, 78 patients to testosterone gel 10 g daily, and 76 patients to a non-scrotal testosterone transdermal system. The study was double-blind for dose of testosterone gel but open-label for active control. Patients who were originally randomized to testosterone gel and who had single-sample serum testosterone levels above or below the normal range on Day 60 were titrated to 7.5 g daily on Day 91. During the Extended Treatment Period (Days 91-180), 51 patients continued on testosterone gel 5 g daily, 52 patients continued on testosterone gel 10 g daily, 41 patients continued on a non-scrotal testosterone transdermal system (5 mg daily), and 40 patients received testosterone gel 7.5 g daily. Upon completion of the initial study, 163 enrolled and 162 patients received treatment in an open-label extension study of testosterone gel for an additional period of up to 3 years.

Mean peak, trough and average serum testosterone concentrations within the normal range (298-1043 ng/dL) were achieved on the first day of treatment with doses of 5 g and 10 g. In patients continuing on testosterone gel 5 g and 10 g, these mean testosterone levels were maintained within the normal range for the 180-day duration of the original study. Figure 2 summarizes the 24-hour pharmacokinetic profiles of testosterone administered as testosterone gel for 30, 90 and 180 days. Testosterone concentrations were maintained as long as the patient continued to properly apply the prescribed testosterone gel treatment.

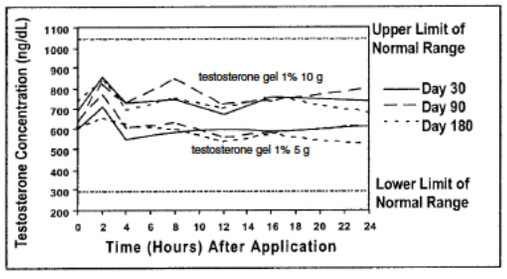


Figure 2. Mean Steady State Testosterone Concentrations in Patients with Once-Daily Testosterone Gel Therapy

Table 1 summarizes the mean testosterone concentrations on Treatment Day 180 for patients receiving 5 g, 7.5 g, or 10 g of testosterone gel. The 7.5 g dose produced mean concentrations intermediate to those produced by 5 g and 10 g of testosterone gel.

Table 1: Mean (±SD) Steady State Serum Testosterone Concentrations During Therapy (Day 180)

	5 g	7.5 g	10 g
	N = 44	N = 37	N = 48
C_{avg}	555 ± 225	601 ± 309	713 ± 209
C_{max}	830 ± 347	901 ± 471	1083 ± 434
C_{min}	371 ± 165	406 ± 220	485 ± 156

Of 129 hypogonadal men who were appropriately titrated with testosterone gel and who had sufficient data for analysis, 87% achieved an average serum testosterone level within the normal range on Treatment Day 180.

Testosterone gel 5 g/day and 10 g/day resulted in significant increases over time in total body mass and total body lean mass, while total body fat mass and the percent body fat decreased significantly. These changes were maintained for 180 days of treatment during the original study. Changes in the 7.5 g dose group were similar. Bone mineral density in both hip and spine increased significantly from Baseline to Day 180 with 10 g testosterone gel.

Testosterone gel treatment at 5 g/day and 10 g/day for 90 days produced significant improvement in libido (measured by sexual motivation, sexual activity and enjoyment of sexual activity as assessed by patient responses to a questionnaire). The degree of penile erection as subjectively estimated by the patients, increased with testosterone gel treatment, as did the subjective score for "satisfactory duration of erection". Testosterone gel treatment at 5 g/day and 10 g/day produced positive effects on mood and fatigue. Similar changes were seen after 180 days of treatment and in the group treated with the 7.5 g dose. DHT concentrations increased in parallel with testosterone concentrations at testosterone gel doses of 5 g/day and 10 g/day, but the DHT/T ratio stayed within the normal range, indicating enhanced availability of the major physiologically active androgen. Serum estradiol (E2) concentrations increased significantly within 30 days of starting treatment with testosterone gel 5 or 10 g/day and remained elevated throughout the treatment period but remained within the normal range for eugonadal men. Serum levels of SHBG decreased very slightly (1 to 11%) during testosterone gel treatment. In men with hypergonadotropic hypogonadism, serum levels of LH and FSH fell in a dose- and time- dependent manner during treatment with testosterone gel.

Potential for Phototoxicity:

The phototoxic potential of testosterone gel was evaluated in a double-blind, single-dose study in 27 subjects with photosensitive skin types. The Minimal Erythema Dose (MED) of ultraviolet radiation was determined for each subject. A single 24 (+1) hour application of duplicate patches containing test articles (placebo gel, testosterone gel, or saline) was made to naïve skin sites on Day 1. On Day 2, each subject received five exposure times of ultraviolet radiation, each exposure being 25% greater than the previous one. Skin evaluations were made on Days 2-5. Exposure of test and control article application sites to ultraviolet light did not produce increased inflammation relative to non-irradiated sites, indicating no phototoxic effect.

Potential for Testosterone Transfer:

The potential for dermal testosterone transfer following testosterone gel use was evaluated in a clinical study between males dosed with testosterone gel and their untreated female partners. Two to 12 hours after testosterone gel (10 g) application by the male subjects, the couples (N=38 couples) engaged in daily, 15-minute sessions of vigorous skin-to-skin contact so that the female partners gained maximum exposure to the testosterone gel application sites. Under these study conditions, all unprotected female partners had a serum testosterone concentration > 2 times the baseline value at some time during the study. When a shirt covered the application site(s), the transfer of testosterone from the males to the female partners was completely prevented.

INDICATIONS AND USAGE

Testosterone gel is indicated for replacement therapy in males for conditions associated with a deficiency or absence of endogenous testosterone:

1. Primary hypogonadism (congenital or acquired)-testicular failure due to cryptorchidism, bilateral torsion, orchitis, vanishing testis syndrome, orchiectomy, Klinefelter's syndrome, chemotherapy, or toxic damage from alcohol or heavy metals. These men usually have low serum testosterone levels and gonadotropins (FSH, LH) above the normal range.

2. Hypogonadotropic hypogonadism (congenital or acquired)-idiopathic gonadotropin or luteinizing hormone-releasing hormone (LHRH) deficiency or pituitary-hypothalamic injury from tumors, trauma, or radiation. These men have low testosterone serum levels but have gonadotropins in the normal or low range.

Testosterone gel has not been clinically evaluated in males under 18 years of age.

CONTRAINDICATIONS

Androgens are contraindicated in men with carcinoma of the breast or known or suspected carcinoma of the prostate.

Testosterone gel is not indicated for use in women, has not been evaluated in women, and must not be used in women.

Pregnant women should avoid skin contact with testosterone gel application sites in men. Testosterone may cause fetal harm. In the event that unwashed or unclothed skin to which testosterone gel 1% has been applied does come in direct contact with the skin of a pregnant woman, the general area of contact on the woman should be washed with soap and water as soon as possible. *In vitro* studies show that residual testosterone is removed from the skin surface by washing with soap and water.

Testosterone gel should not be used in patients with known hypersensitivity to any of its ingredients, including testosterone USP that is chemically synthesized from soy.

WARNINGS

1. Prolonged use of high doses of orally active 17-alpha-alkyl androgens (e.g., methyltestosterone) has been associated with serious hepatic adverse effects (peliosis hepatis, hepatic neoplasms, cholestatic hepatitis, and jaundice). Peliosis hepatis can be a life-threatening or fatal complication. Long-term therapy with testosterone enanthate, which elevates blood levels for prolonged periods, has produced multiple hepatic adenomas. Testosterone gel is not known to produce these adverse effects.
2. Geriatric patients treated with androgens may be at an increased risk for the development of prostatic hyperplasia and prostatic carcinoma.
3. Geriatric patients and other patients with clinical or demographic characteristics that are recognized to be associated with an increased risk of prostate cancer should be evaluated for the presence of prostate cancer prior to initiation of testosterone replacement therapy. In men receiving testosterone replacement therapy, surveillance for prostate cancer should be consistent with current practices for eugonadal men. Increases in serum PSA from baseline values were seen in approximately 18% of individuals in an open label study of 162 hypogonadal men treated with testosterone gel for up to 42 months. Most of these increases were seen within the first year of therapy. (see **ADVERSE REACTIONS** and **PRECAUTIONS: Carcinogenesis, Mutagenesis, Impairment of Fertility and Laboratory Tests).**
4. Edema with or without congestive heart failure may be a serious complication in patients with pre-existing cardiac, renal, or hepatic disease. In addition to discontinuation of the drug, diuretic therapy may be required.
5. Gynecomastia frequently develops and occasionally persists in patients being treated for hypogonadism.

6. The treatment of hypogonadal men with testosterone esters may potentiate sleep apnea in some patients, especially those with risk factors such as obesity or chronic lung diseases.
7. ALCOHOL BASED GELS ARE FLAMMABLE. AVOID FIRE, FLAME OR SMOKING UNTIL THE GEL HAS DRIED.

PRECAUTIONS

Transfer of testosterone to another person can occur when vigorous skin-to-skin contact is made with the application site (see **Clinical Studies**). The following precautions are recommended to minimize potential transfer of testosterone from testosterone gel-treated skin to another person:

- Patients should wash their hands immediately with soap and water after application of testosterone gel.
- Patients should cover the application site(s) with clothing after the gel has dried (e.g. a shirt).
- In the event that unwashed or unclothed skin to which testosterone gel has been applied does come in direct contact with the skin of another person, the general area of contact on the other person should be washed with soap and water as soon as possible. *In vitro* studies show that residual testosterone is removed from the skin surface by washing with soap and water.

Changes in body hair distribution, significant increase in acne, or other signs of virilization of the female partner should be brought to the attention of a physician.

General

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

- Too frequent or persistent erections of the penis.
- Any nausea, vomiting, changes in skin color, or ankle swelling.
- Breathing disturbances, including those associated with sleep.

Information for Patients

Advise patients to carefully read the information brochure that accompanies each carton of 30 testosterone gel single-use packets.

Advise patients of the following:

- Testosterone gel should not be applied to the scrotum.
- Testosterone gel should be applied once daily to clean dry skin.
- After application of testosterone gel, it is currently unknown for how long showering or swimming should be delayed. For optimal absorption of testosterone, it appears reasonable to wait at least 5-6 hours after application prior to showering or swimming. Nevertheless, showering or swimming after just 1 hour should have a minimal effect on the amount of testosterone gel absorbed if done very infrequently.
- SINCE ALCOHOL BASED GELS ARE FLAMMABLE, AVOID FIRE, FLAME OR SMOKING UNTIL THE GEL HAS DRIED.

Laboratory Tests

1. Hemoglobin and hematocrit levels should be checked periodically (to detect polycythemia) in patients on long-term androgen therapy.
2. Liver function, prostatic specific antigen, cholesterol, and high-density lipoprotein should be checked periodically.
3. To ensure proper dosing, serum testosterone concentrations should be measured (see **DOSAGE AND ADMINISTRATION**).

Drug Interactions

Oxyphenbutazone: Concurrent administration of oxyphenbutazone and androgens may result in elevated serum levels of oxyphenbutazone.
Insulin: In diabetic patients, the metabolic effects of androgens may decrease blood glucose and, therefore, insulin requirements.
Propranolol: In a published pharmacokinetic study of an injectable testosterone product, administration of testosterone cypionate led to an increased clearance of propranolol in the majority of men tested.
Corticosteroids: The concurrent administration of testosterone with ACTH or corticosteroids may enhance edema formation; thus, these drugs should be administered cautiously, particularly in patients with cardiac or hepatic disease.

Drug/Laboratory Test Interactions

Androgens may decrease levels of thyroxin-binding globulin, resulting in decreased total T4 serum levels and increased resin uptake of T3 and T4. Free thyroid hormone levels remain unchanged, however, and there is no clinical evidence of thyroid dysfunction.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Animal Data: Testosterone has been tested by subcutaneous injection and implantation in mice and rats. In mice, the implant induced cervical-uterine tumors, which metastasized in some cases. There is suggestive evidence that injection of testosterone into some strains of female mice increases their susceptibility to hepatoma. Testosterone is also known to increase the number of tumors and decrease the degree of differentiation of chemically induced carcinomas of the liver in rats.
Human Data: There are rare reports of hepatocellular carcinoma in patients receiving long-term oral therapy with androgens in high doses. Withdrawal of the drugs did not lead to regression of the tumors in all cases.

Geriatric patients treated with androgens may be at an increased risk for the development of prostatic hyperplasia and prostatic carcinoma.

Geriatric patients and other patients with clinical or demographic characteristics that are recognized to be associated with an increased risk of prostate cancer should be evaluated for the presence of prostate cancer prior to initiation of testosterone replacement therapy.

In men receiving testosterone replacement therapy, screening for prostate cancer should be consistent with current practices for eugonadal men. Increases in serum PSA from baseline values were reported in approximately 18% of individual patients treated for up to 42 months in an open-label safety study (see **ADVERSE REACTIONS).**

Pregnancy Category X (see **CONTRAINDICATIONS**)-Teratogenic Effects: Testosterone gel is not indicated for women and must not be used in women.

Nursing Mothers: Testosterone gel is not indicated for women and must not be used in women.

Pediatric Use: Safety and efficacy of testosterone gel in pediatric patients have not been established.

ADVERSE REACTIONS

In a controlled clinical study, 154 patients were treated with testosterone gel for up to 6 months (see **Clinical Studies**). Adverse Events possibly, probably or definitely related to the use of testosterone gel and reported by ≥1% of the patients are listed in Table 2.

Table 2: Adverse Events Possibly, Probably or Definitely Related to Use of Testosterone Gel in the 180-Day Controlled Clinical Trial

Adverse Event	Dose of Testosterone Gel		
	5 g n=77	7.5 g n=40	10 g n=78
Acne	1%	3%	8%
Alopecia	1%	0%	1%
Application Site Reaction	5%	3%	4%
Asthenia	0%	3%	1%
Depression	1%	0%	1%
Emotional Lability	0%	3%	3%
Gynecomastia	1%	0%	3%
Headache	4%	3%	0%
Hypertension	3%	0%	3%
Lab Test Abnormal*	6%	5%	3%
Libido Decreased	0%	3%	1%
Nervousness	0%	3%	1%
Pain Breast	1%	3%	1%
Prostate Disorder**	3%	3%	5%
Testis Disorder***	3%	0%	0%

**Lab test abnormal* occurred in nine patients with one or more of the following events: elevated hemoglobin or hematocrit, hyperlipidemia, elevated triglycerides, hypokalemia, decreased HDL, elevated glucose, elevated creatinine, or elevated total bilirubin.

** *Prostate disorders* included five patients with enlarged prostate, one patient with BPH, and one patient with elevated PSA results.

****Testis disorders* were reported from two patients: one patient with left varicocele and one patient with slight sensitivity of left testis.

The following adverse events possibly related to the use of testosterone gel occurred in fewer than 1% of patients: amnesia, anxiety, discolored hair, dizziness, dry skin, hirsutism, hostility, impaired urination, paresthesia, penis disorder, peripheral edema, sweating, and vasodilation.

In this clinical trial of testosterone gel, skin reactions at the site of application were reported with testosterone gel, but none was severe enough to require treatment or discontinuation of drug.

Six (4%) patients in this trial had adverse events that led to discontinuation of testosterone gel. These events included the following: cerebral hemorrhage, convulsion (neither of which were considered related to testosterone gel administration), depression, sadness, memory loss, elevated prostate specific antigen and hypertension. No testosterone gel patients discontinued due to skin reactions.

In an uncontrolled pharmacokinetic study of 10 patients, two had adverse events associated with testosterone gel; these were asthenia and depression in one patient and increased libido and hyperkinesia in the other. Among 17 patients in foreign clinical studies there was one instance each of acne, erythema and benign prostate adenoma associated with a 2.5% testosterone gel formulation applied dermally.

One hundred sixty-two (162) patients have received testosterone gel, 1% for up to 3 years in a long-term follow-up study for patients who completed the controlled clinical trial. Table 3 summarizes those adverse events possibly, probably or definitely related to the use of testosterone gel, 1% and reported by 2 or more subjects in at one treatment group.

Table 3: Incidence of Treatment-Emergent Adverse Events Possibly, Probably or Definitely Related to the Use of Testosterone Gel in the 3 Year Open-Label Extension Clinical Trial

Adverse Event Category/Classification	Treatment Group % (N=162)
Lab Test Abnormal+	9.3% (15)
Skin Dry	1.9% (3)
Application Site Reaction	5.6% (9)
Acne	3.1% (5)
Pruritus	1.9% (3)
Enlarged Prostate	11.7% (19)
Carcinoma of Prostate	1.2% (2)
Urinary Symptoms*	3.7% (6)
Testis Disorder**	1.9% (3)
Gynecomastia	2.5% (4)
Anemia	2.5% (4)

+*Lab test abnormal* occurred in fifteen patients with one or more of the following events: elevated AST, elevated ALT, elevated testosterone, elevated hemoglobin or hematocrit, elevated cholesterol, elevated cholesterol/LDL ratio, elevated triglycerides, elevated HDL, or elevated serum creatinine.

**Urinary symptoms* included nocturia, urinary hesitancy, urinary incontinence, urinary retention, urinary urgency and weak urinary stream.

*** Testis disorder* included three patients. There were two patients with a non-palpable testis and one patient with slight right testicular tenderness.

Two patients reported serious adverse events considered possibly related to treatment: deep vein thrombosis (DVT) and prostate disorder requiring a transurethral resection of the prostate (TURP). Nine patients discontinued treatment due to adverse events possibly related to treatment with testosterone gel, including two patients with application site reactions, one with kidney failure, and five with prostate disorders (including increase in serum PSA in 4 patients, and increase in PSA with prostate enlargement in a fifth patient). All patients who discontinued due to an increase in serum PSA did so by Day 357.

Increases in Serum PSA

During the initial 6-month study, the mean change in PSA values had a statistically significant increase of 0.26 ng/mL. Serum PSA was measured every 6 months thereafter. While there was no statistically significant increase in mean PSA from 6 months through 36 months of testosterone gel treatment for the overall group of 162 patients enrolled in the long-term extension study, there were increases in serum PSA seen in approximately 18% of individual patients. In the long-term extension study, the overall mean change from baseline in serum PSA values for the entire group was 0.11 ng/mL.

Twenty-nine (29) (18%) patients met the per-protocol criterion for increase in serum PSA value, defined as a value ≥2X the baseline value or any single absolute value ≥6 ng/mL. Twenty five of these patients met this criterion by virtue of a post-baseline value at lease twice the baseline value. In most of these cases (22/25), the maximum serum PSA value attained was ≤2 ng/mL. The first occurrence of a pre-specified, post-baseline increase in serum PSA was seen at or prior to Month 12 in most of the patients who met this criterion (23 of 29; 79%). Four patients met this criterion by having a serum PSA ≥6 ng/mL and in these, maximum serum PSA values were 6.2 ng/mL, 6.6 ng/mL, 6.7 ng/mL, and 10.7 ng/mL (in testosterone gel-treated patients). In two of these testosterone gel-treated patients, prostate cancer was detected on biopsy. The first patient's PSA levels were 4.7 ng/mL and 6.2 ng/mL at baseline and at Month 6/Final, respectively. The second patient's PSA levels were 4.2 ng/mL, 5.2 ng/mL, 5.8 ng/mL, and 6.6 ng/mL at baseline, Month 6, Month 12, and Final, respectively.

DRUG ABUSE AND DEPENDENCE

Testosterone gel contains testosterone, a Schedule III controlled substance as defined by the Anabolic Steroids Control Act.

Oral ingestion of testosterone gel will not result in clinically significant serum testosterone concentrations due to extensive first-pass metabolism.

OVERDOSAGE

No reports of testosterone gel overdose have been received. However, there is one report of acute overdosage by injection of testosterone enanthate: testosterone levels of up to 11,400 ng/dL were implicated in a cerebrovascular accident.

DOSAGE AND ADMINISTRATION

The recommended starting dose of testosterone gel is 5 g delivering 5 mg of testosterone systemically, applied once daily (preferably in the morning) to clean, dry, intact skin of the shoulders and upper arms and/or abdomen. Serum testosterone levels should be measured approximately 14 days after initiation of therapy to ensure proper dosing. If the serum testosterone concentration is below the normal range, or if the desired clinical response is not achieved, the daily testosterone gel dose may be increased from 5 g to 7.5 g and from 7.5 g to 10 g as instructed by the physician.

Testosterone gel is available in unit-dose packets.

Testosterone gel must not be applied to the genitals.

If using the packets, the entire contents should be squeezed into the palm of the hand and immediately applied to the application sites. Alternately, patients may squeeze a portion of the gel from the packet into the palm of the hand and apply to application sites. Repeat until the entire contents have been applied.

Application sites should be allowed to dry for a few minutes prior to dressing. Hands should be washed with soap and water after testosterone gel has been applied.

HOW SUPPLIED

Testosterone gel contains testosterone, a Schedule III controlled substance as defined by the Anabolic Steroids Control Act.

Testosterone gel is supplied in unit-dose aluminum foil packets in cartons of 30. Each packet of 2.5 g or 5 g gel contains 25 mg or 50 mg testosterone, respectively, and is supplied as follows:

NDC Number	Strength	Package Size
49884-418-72	1% (25 mg)	30 packets: 2.5 g per packet
49884-510-72	1% (50 mg)	30 packets: 5 g per packet

Keep testosterone gel out of the reach of children.

Storage

Store at 25°C (77°F); excursions permitted to 15° to 30°C (59° to 86°F) [see USP Controlled Room Temperature].

Disposal

Used testosterone gel packets should be discarded in household trash in a manner that prevents accidental application or ingestion by children or pets. In addition, any discarded gel should be thoroughly rinsed down the sink or discarded in the household trash in a manner that prevents accidental application or ingestion by children or pets.

Manufactured by:
Paddock Laboratories, Inc.
Minneapolis, MN 55427

Manufactured for:
Par Pharmaceutical Companies, Inc.
Spring Valley, NY 10977

Revised: 04/07 OS418-72-42-02

Patient Information and Instructions for Using

CIII Testosterone Gel 1%

Read this information carefully before using testosterone gel 1%. The following information about testosterone gel 1% should not take the place of your doctor's orders or recommendations. Your doctor will tell you exactly what dose to take, how to safely take it, and when to take it. Make sure you understand the benefits and risks of testosterone gel 1% before you use it. If you have any other questions about your testosterone gel 1% therapy, ask your doctor or pharmacist.

What is testosterone gel 1%?

Testosterone gel 1% is a clear, colorless gel medicine that delivers testosterone into your body through your skin. Once testosterone gel 1% is absorbed through your skin, it enters your bloodstream and helps your body reach normal testosterone levels. The type of testosterone delivered by testosterone gel 1% is the same as the testosterone produced in your body.

Your doctor has prescribed this therapy because your body is not making enough testosterone. The medical term for this condition is hypogonadism. Testosterone helps the body produce sperm and male sexual characteristics. Testosterone is also necessary for normal sexual function and sex drive.

Who should not take testosterone gel 1%?

Testosterone gel 1% **must not be used by women** or by those individuals with known hypersensitivity to any of its components, including individuals who are hypersensitive to testosterone that is chemically synthesized from soy. Pregnant women should avoid skin contact with testosterone gel 1% application sites in men. The active ingredient in testosterone gel 1% is testosterone. (See "Inactive Ingredients" at the end of this leaflet for a list of the other ingredients.) Testosterone may cause fetal harm.

You should not use testosterone gel 1% if you have any of the following conditions:

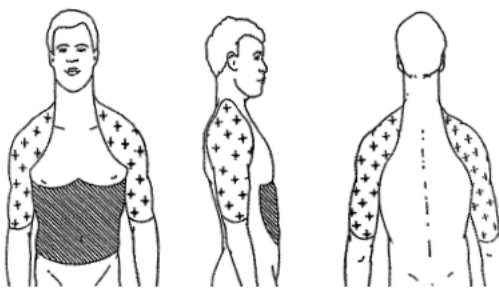
- prostate cancer (if your doctor knows for sure or suspects it)
- breast cancer (a rare condition for men)

How should I use testosterone gel 1% packets?

It is important that you read and follow these directions on how to use testosterone gel 1% properly.

1. **Apply testosterone gel 1% at the same time each day (preferably every morning).** You should apply your daily dose of gel every morning to clean, dry, intact skin. If you take a bath or shower in the morning, use testosterone gel 1% **after** your bath or shower. Your doctor will tell you how much testosterone gel 1% to use each day.
2. **Be sure your skin is completely dry.**
3. **Open the packet.** Open one testosterone gel 1% aluminum foil packet by folding the top edge at the perforation and tearing completely across the packet along the perforation.
4. **Remove the contents from the packet. Squeeze the contents into the palm of your hand.** Squeeze from the bottom of the packet toward the top. If you like, you may squeeze a portion of the gel from the packet into the palm of your hand and apply to application site(s). **Repeat until the entire contents of the packet have been applied.**

Men should apply gel to starred (upper arm/shoulders) or shaded (abdomen) areas only.



5. **Apply testosterone gel 1% only to healthy, normal skin on your abdomen (stomach area), shoulders, or upper arms.** In this way your body will absorb the right amount of testosterone. **Never apply testosterone gel 1% to your genitals (penis or scrotum) or to skin with open sores, wounds, or irritation.**
6. **Wash your hands with soap and water right away after application to reduce the chance that the medicine will spread from your hands to other people.**
7. **Let testosterone gel 1% dry for a few minutes before you dress.** This prevents your clothing from wiping the gel off your skin. It ensures that your body will absorb the correct amount of testosterone.
8. **Allow gel to dry completely before smoking or going near an open flame.**
9. **Wait 5 to 6 hours before showering or swimming.** To ensure that the greatest amount of testosterone gel 1% is absorbed into your system, you should wait 5 to 6 hours after application before showering or swimming. Once in a while, you may shower or swim as soon as 1 hour after applying testosterone gel 1%. If done infrequently, this will have little effect on the amount of testosterone gel 1% that is absorbed by your body.
10. **Maintain normal activities.** Once your hands are washed and the application site is covered with clothing, there is little risk of transferring testosterone to someone else's skin due to bodily contact. If, however, you expect direct skin contact with someone else, you should wash your application site(s) with soap and water before that encounter. This will reduce the chance that the medicine will transfer to the other person.

What to do if someone else is exposed to testosterone gel 1%.
If someone else is exposed to testosterone gel 1% either by direct contact with the gel itself or indirectly because of contact with your treated skin, that person should wash the area of contact with soap and water as soon as possible. The longer the gel is in contact with the skin before washing, the greater is the chance that some testosterone will be absorbed by the other person. This is especially important for women (especially pregnant women) and children. They have naturally low levels of testosterone and could be harmed by it.

What to do if you get testosterone gel 1% in your eyes.
If you get testosterone gel 1% in your eyes, rinse your eyes right away with warm clean water to flush out any testosterone gel 1%. Seek medical attention if needed.

What to do if you miss a dose.
If you miss a dose, do not double your next dose the next day to catch up. If your next dose is less than 12 hours away, it is best just to wait. Do not take the skipped dose. If it is more than 12 hours until your next dose, take the dose you missed. Resume your normal dosing the next day.

What should I avoid while using testosterone gel 1%?
It is important that you do not spread the medicine to others, especially women and children. Be sure to wash your hands after applying testosterone gel 1%. Do not allow other persons to contact your skin where you have applied testosterone gel 1%, especially pregnant or nursing women. **Testosterone may harm the developing baby. ALCOHOL BASED GELS ARE FLAMMABLE. AVOID FIRE, FLAME OR SMOKING UNTIL THE GEL HAS DRIED.**

What are the possible side effects of testosterone gel 1%?
Testosterone gel 1% may cause the following side effects:
- breast development and breast discomfort
- extra fluid in the body. This may cause serious problems for patients with heart, kidney, or liver damage.
- sleep disturbance called "sleep apnea." This is more likely in patients who are overweight or who have lung disease.
- prostate enlargement, sometimes accompanied by difficulty urinating
- emotional problems like depression
- changes in blood levels of cholesterol. This may be monitored and prevented by periodic blood tests.

Tell your doctor if you develop any of the following side effects:
- penis erections that are too frequent or continue too long
- nausea, vomiting, yellow or darker skin (jaundice), or ankle swelling
- breathing problems, including problems breathing while sleeping
- difficulty urinating
- any side effect that concerns you

Tell your doctor about other medicines you are taking. Testosterone gel 1% may affect how these medicines work, and you may need to have your doses adjusted.

Tell your doctor if your female partner develops changes in hair distribution, increases in acne or other signs of masculinity.

Older patients may be at increased risk of developing enlarged prostate or prostate cancer. This also may be monitored by periodic blood tests and prostate exams.

Disposal
Used testosterone gel 1% packets should be discarded in the household trash in a manner that prevents accidental application or ingestion by children or pets. In addition, any discarded gel should be thoroughly rinsed down the sink or discarded in the household trash in a manner that prevents accidental application or ingestion by children or pets.

Other Information
Never share your testosterone gel 1% with anyone. Every patient is different. Your doctor has prescribed testosterone gel 1% specifically for your needs. Use testosterone gel 1% only for the condition for which it was prescribed. Medicines are sometimes prescribed for purposes other than those described in a patient information leaflet. If you have any questions or concerns about your testosterone gel 1% treatment, ask your health care provider or pharmacist. They can answer your questions and give you the printed information about testosterone gel 1% that is written for health professionals.

Keep testosterone gel 1% out of the reach of children.

Inactive Ingredients:
Ethanol, purified water, sodium hydroxide, Carbomer 940 and isopropyl myristate.

Store at 25°C (77°F); excursions permitted to 15° to 30°C (59° to 86°F) [see USP Controlled Room Temperature].

Manufactured by:
Paddock Laboratories, Inc.
Minneapolis, MN 55427
Manufactured for:
Par Pharmaceutical Companies, Inc.
Spring Valley, NY 10977

Issued: 12/06 PI418-72-42-02


TEAR HERE
NDC 49884-418-48
CIII
Testosterone
Gel 1%
Contains
2.5 grams
Rx only
Use complete contents of foil packet.
Patient:
Please read patient leaflet.
PAR
PHARMACEUTICAL
PAR
PHARMACEUTICAL
3 49884-418-48 9
N
Par Pharmaceutical Cos., Inc.
Spring Valley, NY 10977
For
Paddock Laboratories, Inc.
Minneapolis, MN 55427
Manufactured by:
PO41848-1-02
11/06
Keep out of reach of children; this package is not child-resistant.
For topical use only.
Store at 25°C (77°F); excursions permitted to 15° to 30°C (59° to 86°F) [see USP Controlled Room Temperature].

TEAR HERE

NDC 49884-510-63

CIII

Testosterone Gel 1%

Contains

5 grams

Rx only

Use complete contents of foil packet.

Patient:
Please read patient leaflet.

PAR PHARMACEUTICAL

PAR PHARMACEUTICAL

N 49884-510-63

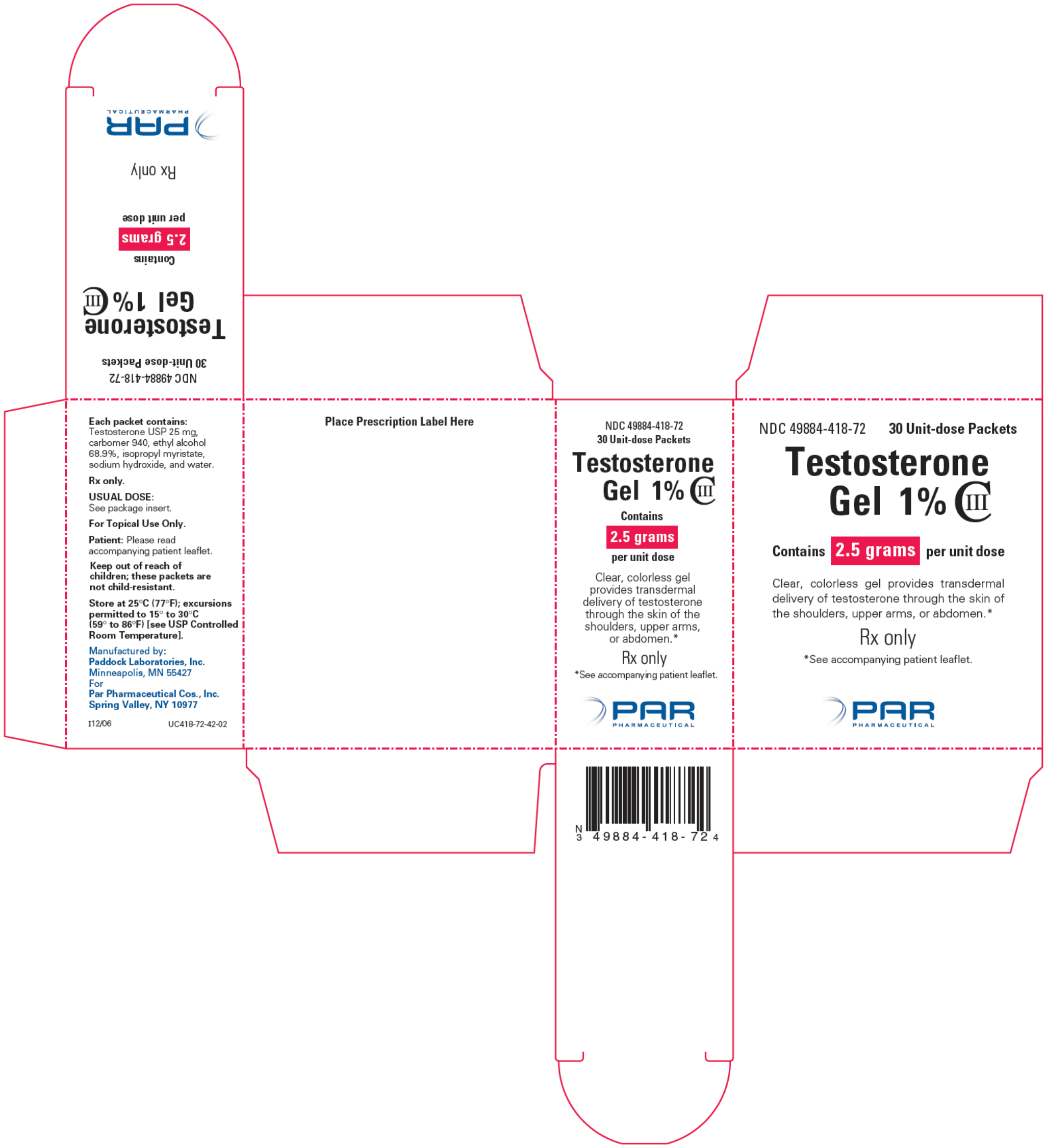
Manufactured by:
Paddock Laboratories, Inc.
Minneapolis, MN 55427
For
Par Pharmaceutical Cos., Inc.
Spring Valley, NY 10977

11 2/06 P051 0-63-1-02

Store at 25°C (77°F); excursions permitted to 15° to 30°C (59° to 86°F) [see USP Controlled Room Temperature].

For topical use only.

Keep out of reach of children; this package is not child-resistant


PHARMACEUTICAL
Rx only
Contains
2.5 grams
per unit dose
Testosterone
Gel 1% C III
NDC 49884-418-72
30 Unit-dose Packets
Each packet contains:
Testosterone USP 25 mg, carbomer 940, ethyl alcohol 68.9%, isopropyl myristate, sodium hydroxide, and water.
Rx only.
USUAL DOSE:
See package insert.
For Topical Use Only.
Patient: Please read accompanying patient leaflet.
Keep out of reach of children; these packets are not child-resistant.
Store at 25°C (77°F); excursions permitted to 15° to 30°C (59° to 86°F) [see USP Controlled Room Temperature].
Manufactured by:
Paddock Laboratories, Inc.
Minneapolis, MN 55427
For
Par Pharmaceutical Cos., Inc.
Spring Valley, NY 10977
I12/06
UC418-72-42-02
Place Prescription Label Here
NDC 49884-418-72
30 Unit-dose Packets
Testosterone
Gel 1% C III
Contains
2.5 grams
per unit dose
Clear, colorless gel provides transdermal delivery of testosterone through the skin of the shoulders, upper arms, or abdomen.*
Rx only
*See accompanying patient leaflet.
PAR PHARMACEUTICAL
N 3 49884-418-72 4
NDC 49884-418-72 30 Unit-dose Packets
Testosterone
Gel 1% C III
Contains 2.5 grams per unit dose
Clear, colorless gel provides transdermal delivery of testosterone through the skin of the shoulders, upper arms, or abdomen.*
Rx only
*See accompanying patient leaflet.
PAR PHARMACEUTICAL

PHARMACEUTICAL

Rx only

Contains
5 grams
per unit dose

Testosterone Gel 1% CIII

30 Unit-dose Packets
NDC 49884-510-72

Each packet contains:
Testosterone USP 50 mg, carbomer 940, ethyl alcohol 68.9%, isopropyl myristate, sodium hydroxide, and water.

Rx only.

USUAL DOSE:
See package insert.

For Topical Use Only.

Patient: Please read accompanying patient leaflet.

Keep out of reach of children; these packets are not child-resistant.

Store at 25°C (77°F); excursions permitted to 15° to 30°C (59° to 86°F) [see USP Controlled Room Temperature].

Manufactured by:
Paddock Laboratories, Inc.
Minneapolis, MN 55427
For
Par Pharmaceutical Cos., Inc.
Spring Valley, NY 10977

I12/06 UC510-72-42-02

Place Prescription Label Here

NDC 49884-510-72
30 Unit-dose Packets

Testosterone Gel 1% CIII

Contains
5 grams
per unit dose

Clear, colorless gel provides transdermal delivery of testosterone through the skin of the shoulders, upper arms, or abdomen.*

Rx only

*See accompanying patient leaflet.

PAR PHARMACEUTICAL

N 3 49884-510-72 5

NDC 49884-510-72 **30 Unit-dose Packets**

Testosterone Gel 1% CIII

Contains **5 grams** **per unit dose**

Clear, colorless gel provides transdermal delivery of testosterone through the skin of the shoulders, upper arms, or abdomen.*

Rx only

*See accompanying patient leaflet.

PAR PHARMACEUTICAL

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 076744

LABELING REVIEWS

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

ANDA Number: 76-744
Date of Submission: May 21, 2003 (Original Submission)
Applicant's Name: Paddock Laboratories, Inc.
Established Name: Testosterone Gel, 1%

Labeling Deficiencies:

1. CONTAINER (2.5 g and 5 g unit-dose foil packets)
   a. We encourage the use of boxing, contrasting colors, or other means to differentiate the 2.5 g packet from the 5 g packet.
   b. Describe the location where the expiration date will be printed/stamped.

2. CARTON (30 x unit-dose packets)
   Refer to comment 1.a.

3. PHYSICIAN INSERT
   a. We encourage you to relocate the phrase "Rx only" from the HOW SUPPLIED section, to a location just under the TITLE of the package insert.
   b. Please note that USAN names are common nouns and should be treated as such in a text of labeling (i.e., lower case). Upper case may be used when the USAN name stands alone on labels or in the title of the package insert.
   c. Throughout your insert, revise "5 G", "7.5 G", and "10 G" to read "5 g", "7.5 g", and "10 g" respectively
   d. Throughout your insert, revise "testosterone gel 1%" to read "testosterone gel" if it comes immediately before a number (e.g., DESCRIPTION, Second paragraph, first sentence)
   e. WARNINGS
      i. Item 2: revise "pro-static" to read "prostatic"
      ii. Add as item 7: "7. GELS ARE FLAMMABLE. AVOID FIRE, FLAME OR SMOKING (b) (4) ."
   f. PRECAUTIONS
      i. First paragraph, third bullet, second sentence: italicize "*In vitro*"
      ii. Advise patients of the following, add as the fourth bullet: "• Since gels are flammable, avoid fire, flame or smoking (b) (4) "

4. PATIENT INFORMATION AND INSTRUCTIONS FOR USING
   a. Refer to comment 3.b.
   b. Please refer to the attached mocked-up copy of the patient leaflet for more labeling revision requests.

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

Prior to approval, it may be necessary to revise your labeling subsequent to approved changes for the reference listed drug. In order to keep ANDA labeling current, we suggest that you subscribe to the daily or weekly updates of new documents posted on the CDER web site at the following address -

http://www.fda.gov/cder/cdernew/listserv.html

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.

Wm. Peter Rickman
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

Attachment: Mocked-up copy of your insert labeling

Following this page, 4 pages withheld in full (b)(4)- draft labeling

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.		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?	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. 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:

FOR THE RECORD:

1. MODEL LABELING - This review is based on the labeling of AndroGel® (testosterone gel) by Unimed Pharmaceuticals NDA 21-015/S-008 approved 9/17/03
   - Physician Insert: A.09.063.0039332; 80-0005-04; Issued 11/02
   - Patient Information: A.09.063.0039331; 85-0004-02; Issued 11/02

   Please note that in innovator changed the alcohol content % label claim from 68.9% to 67.0%. Based in the Chemistry memo in DFS dated July 30, 2003, "The drug product specification was updated to reflect the change in the alcohol used in the manufacturing from (b) (4) to (b) (4). However, the total amount of alcohol in the formulation remains the same based on absolute alcohol content."

   Drug Substance is USP: Packaging and storage— Preserve in well-closed containers
   Testosterone Gel is not USP

2. PATENTS AND EXCLUSIVITIES

Patent and Exclusivity Search Results from query on 021015 001.

Patent Data

 # represents patent information submitted prior to August 18, 2003

Appl No	Prod No	Patent No	Patent Expiration	Use Code	How Filed	Labeling Impact
021015	001	#6503894	AUG 30,2020	U-490 (TESTOSTERONE REPLACEMENT THERAPY IN MALES FOR CONDITIONS ASSOCIATED WITH A DEFICIENCY OR ABSENCE OF ENDOGENOUS TESTOSTERONE)	IV	None

Exclusivity Data

Appl No	Prod No	Exclusivity Code	Exclusivity Expiration	
021015	001	NDF (NEW DOSAGE FORM)	FEB 28,2003	Expired!

The firm's statements are accurate. [Vol. A1.1, pg. 19-17]
Notice of filing of legal action Case 1: 03-CV-2503 [Vol. A2.1, September 5, 2003 amendment]

3. MANUFACTURING FACILITY (Vol A1.10, pg. 4023)
   Paddock Laboratories, Inc.
   3940 Quebec Ave N
   Minneapolis, MN 55427

4. STORAGE CONDITIONS:
   NDA: Store at Controlled Room Temperature 20°-25°C (68°-77°F) (see USP).
   ANDA: - (b) (4)
   Test conditions: accelerated (40^0C/75% RH) and controlled room temperature (25^0C/60% RH)

5. DISPENSING RECOMMENDATIONS:
   NDA: None
   ANDA: None

6. PRODUCT LINE:
   The innovator: unit-dose aluminum foil packets in cartons of 30. Each packet of 2.5 g or 5.0 g gel contains 25 mg or 50 mg testosterone respectively.
   The applicant's product will be packaged in unit-dose foil laminate packets containing 2.5 grams or 5 grams (equivalent to 25 mg or 50 mg of testosterone, respectively) per packet. Thirty unit-dose packets will be packaged per shelf carton. [Vol. A1.1, pg. 4279]

7. CONTAINER/CLOSURE SYSTEM: [Vol. A1.10, pg. 4324]
   2.5 gram and 5 gram packet foil laminate:

8. PRODUCT DESCRIPTION:
ANDA- Clear [redacted] gel (Vol. A1.10, pg. 4418-9)

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 3847.

Ingredient	Pharmaceutical Function	% w/w	Concentration (mg/g)	ExhibitBatch/ CommercialBatch (kg/ [redacted]
Testosterone USP	Active	1.000	10.000	[redacted]
Ethanol(Alcohol USP[a])	[redacted]			
Purified Water USP				
Carbomer 940 NF				
Isopropyl Myristate NF				
Sodium Hydroxide NF				

[redacted] Paddock provided an ingredient comparison table (p. 3843) to show that, based on their information, their formulation is Q1/Q2 to the innovator's formulation.

10. BIOEQUIVALENCE: pending as of January 8, 2004.

Date of Review: January 15, 2003 Date of Submission: May 21, 2003

Primary Reviewer: Ruby Wu (for Debbie Catterson) Date: 1/15/04

Team Leader: John Grace Date: 1/22/2004

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cc: ANDA 76-744
DUP/DIVISION FILE
HFD-613/RWu for DCatterson/JGrace (no cc)
V:\FIRMSNZ\PADDOCK\LTRS&REV\76744.na1.L.doc
Review

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

ANDA Number: 76-744
Date of Submission: April 8, 2004 and May 19, 2004 (Amendments-FPL)
Applicant's Name: Paddock Laboratories, Inc.
Established Name: Testosterone Gel, 1%

APPROVAL SUMMARY:

Do you have 12 Final Printed Labels and Labeling? Yes

1. CONTAINER (2.5 g and 5 g unit-dose foil packets)
   Satisfactory in final print as of the April 8, 2004 submission [Vol. A2.1]

2. CARTON (30 x unit-dose packets)
   Satisfactory in final print as of the May 19, 2004 submission [Vol. T90402 (will be placed in A2.1 or A3.1)]

3. PHYSICIAN INSERT
   Satisfactory in final print as of the May 19, 2004 submission [Vol. T90402; Revised February 2004]

4. PATIENT INFORMATION AND INSTRUCTIONS FOR USING
   Satisfactory in final print as of the May 19, 2004 submission [Vol. T90402; Revised February 2004]

5. Revisions needed post-approval: No

BASIS OF APPROVAL:
Was this approval based upon a petition? No
What is the RLD on the 356(h) form: AndroGel®
NDA Number: 21-015
NDA Drug Name: testosterone gel
NDA Firm: Unimed Pharmaceuticals
Date of Approval of NDA Insert and supplement: NDA 21-015/S-008 approved 9/17/03
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

Appl No	Prod No	Patent No	Patent Expiration	Use Code	How Filed	Labeling Impact
021015	001	#6503894	AUG 30,2020	U-490 (TESTOSTERONE REPLACEMENT THERAPY IN MALES FOR CONDITIONS ASSOCIATED WITH A DEFICIENCY OR ABSENCE OF ENDOGENOUS TESTOSTERONE)	IV	None

Exclusivity Data

Appl No	Prod No	Exclusivity Code	Exclusivity Expiration	
021015	001	NDF (NEW DOSAGE FORM)	FEB 28,2003	Expired!

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.		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?	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. 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:

FOR THE RECORD:

1. MODEL LABELING - This review is based on the labeling of AndroGel® (testosterone gel) by Unimed Pharmaceuticals NDA 21-015/S-008 approved 9/17/03
   - Physician Insert: A.09.063.0039332; 80-0005-04; Issued 11/02
   - Patient Information: A.09.063.0039331; 85-0004-02; Issued 11/02

   Please note that the innovator changed the alcohol content % label claim from 68.9% to 67.0%. Based on the Chemistry memo in DFS dated July 30, 2003, "The drug product specification was updated to reflect the change in the alcohol used in the manufacturing from (b) (4) to (b) (4) However, the total amount of alcohol in the formulation remains the same based on absolute alcohol content."

   Drug Substance is USP: Packaging and storage— Preserve in well-closed containers
   Testosterone Gel is not USP

2. PATENTS AND EXCLUSIVITIES

Patent and Exclusivity Search Results from query on 021015 001.

Patent Data

 # represents patent information submitted prior to August 18, 2003

Appl No	Prod No	Patent No	Patent Expiration	Use Code	How Filed	Labeling Impact
021015	001	#6503894	AUG 30,2020	U-490 (TESTOSTERONE REPLACEMENT THERAPY IN MALES FOR CONDITIONS ASSOCIATED WITH A DEFICIENCY OR ABSENCE OF ENDOGENOUS TESTOSTERONE)	IV	None

Exclusivity Data

Appl No	Prod No	Exclusivity Code	Exclusivity Expiration	
021015	001	NDF (NEW DOSAGE FORM)	FEB 28,2003	Expired

The firm's statements are accurate. [Vol. A1.1, pg. 19-17]
Notice of filing of legal action Case 1: 03-CV-2503 [Vol. A2.1, September 5, 2003 amendment]

3. MANUFACTURING FACILITY (Vol A1.10, pg. 4023)
   Paddock Laboratories, Inc.
   3940 Quebec Ave N
   Minneapolis, MN 55427

4. STORAGE CONDITIONS:
   NDA: Store at Controlled Room Temperature 20°-25°C (68°-77°F) (see USP).
   ANDA: - (b) (4)
   Test conditions: accelerated (40^0C/75% RH) and controlled room temperature (25^0C/60% RH)

5. DISPENSING RECOMMENDATIONS:
   NDA: None
   ANDA: None

6. PRODUCT LINE:
   The innovator: unit-dose aluminum foil packets in cartons of 30. Each packet of 2.5 g or 5.0 g gel contains 25 mg or 50 mg testosterone respectively.
   The applicant's product will be packaged in unit-dose foil laminate packets containing 2.5 grams or 5 grams (equivalent to 25 mg or 50 mg of testosterone, respectively) per packet. Thirty unit-dose packets will be packaged per shelf carton. [Vol. A1.1, pg. 4279]

7. CONTAINER/CLOSURE SYSTEM: [Vol. A1.10, pg. 4324]
   2.5 gram and 5 gram packet foil laminate:

8. PRODUCT DESCRIPTION:
ANDA- Clear [redacted] gel (Vol. A1.10, pg. 4418-9)

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 3847.

Ingredient	Pharmaceutical Function	% w/w	Concentration (mg/g)	ExhibitBatch/ CommercialBatch (kg/ [redacted])
Testosterone USP	Active	1.000	10.000	[redacted]
Ethanol(Alcohol USP[a])	[redacted]			
Purified Water USP				
Carbomer 940 NF				
Isopropyl Myristate NF				
Sodium Hydroxide NF				

[redacted] Paddock provided an ingredient comparison table (p. 3843) to show that, based on their information, their formulation is Q1/Q2 to the innovator's formulation.

10. BIOEQUIVALENCE: pending as of May 24, 2004.

Date of Review: May 26, 2004 Date of Submission: April 8, 2004 and May 19, 2004

Primary Reviewer: Ruby Wu (for Debbie Catterson) Date: 5/26/04

Team Leader: John Grace Date: 6/3/04

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cc: ANDA 76-744
DUP/DIVISION FILE
HFD-613/RWu for DCatterson/JGrace (no cc)
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Review

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

ANDA Number: 76-744

Date of Submission: December 26, 2006 (Amendment)

Applicant's Name: Par Pharmaceuticals (transferred from Paddock Laboratories, Inc.)

Established Name: Testosterone Gel, 1%

Labeling Deficiencies:

1. CONTAINER (2.5 g and 5 g unit-dose foil packets)
   Satisfactory in final print as of the December 26, 2006 e-amendment.

2. CARTON (30 x unit-dose packets)
   Satisfactory in final print as of the December 26, 2006 e-amendment.

3. PHYSICIAN INSERT
   Due to changes in the insert labeling for the reference listed drug, (AndroGel® (testosterone gel) by Unimed Pharmaceuticals NDA 21-015/S-011 approved August 11, 2005.), please revise your labeling to be in accord with the attached labeling. You are not seeking approval for the drug product in metered-dose pumps. Therefore, please do not include information pertaining to the pumps in your insert.

4. PATIENT INFORMATION AND INSTRUCTIONS FOR USING
   Satisfactory in final print as of the December 26, 2006 e-amendment.

Revise your labeling, as instructed above, and submit final printed labeling electronically according to the guidance for industry titled Providing Regulatory Submissions in Electronic Format – ANDA.

Prior to approval, it may be necessary to revise your labeling subsequent to approved changes for the reference listed drug. In order to keep ANDA labeling current, we suggest that you subscribe to the daily or weekly updates of new documents posted on the CDER web site at the following address - http://www.fda.gov/cder/cdernew/listserv.html

To facilitate review of your next submission, and in accordance with 21 CFR 314.94(a)(8)(iv), please provide a side-by-side comparison of your proposed labeling with the enclosed copy of the reference listed drug's labeling with all differences annotated and explained.

Attachment: RLD insert labeling

NOTES/QUESTIONS TO THE CHEMIST:

FOR THE RECORD:

1. MODEL LABELING - This review is based on the labeling of AndroGel® (testosterone gel) by Unimed Pharmaceuticals NDA 21-015/S-011 approved August 11, 2005. The letter states the physician insert is approved and asked the firm to submit FPL. However, the letter asks the firm to submit proposed draft patient information leaflet. Therefore, I only asked Par to revise the physician insert. Par may revise their patient information leaflet after it has been approved for the RLD. Par's ANDA does not provide for the Pump configuration. Therefore, info pertaining to the pump in the RLD labeling has been carved out.

   Please note that in innovator changed the alcohol content % label claim from 68.9% to 67.0%. Based in the Chemistry memo in DFS dated July 30, 2003, "The drug product specification was updated to reflect the change in the alcohol used in the manufacturing from (b) (4) to (b) (4) However, the total amount of alcohol in the formulation remains the same based on absolute alcohol content."

   Other AndroGel supplements of interest:

   - *S-013 approved August 16, 2005...This supplement pertains to the final printed container and carton labels for AndroGel single pump and twinpump. Par does not have this packaging configuration. Therefore this supplement will not affect Par's labels and labeling.*
   - *S-010 Prior Approval Supplement is a Chemistry, Manufacturing and Controls NDA supplement that provides for new container systems of 88 g and 44 g multi-dose pumps, which was approved on September 26, 2003. This supplement contains the proposed container labels and carton labels for the multi-dose pumps.*
   - *S-010 Final Printed Label contains the approved Package Insert and Patient Package Insert. Note that Final Printed Labels for the container and carton were not included.*

   Drug Substance is USP: Packaging and storage— Packaging and storage— Preserve in well-closed containers. Store at 25, excursions permitted between 15 and 30.
   Testosterone Gel is not USP (checked 4/11/07)

   ANDA tentatively approved October 27, 2004. In the December 26, 2006 submission, firm provided revised labeling to reflect transfer of ownership from Paddock to Par.

2. PATENTS AND EXCLUSIVITIES

Patent and Exclusivity Search Results from query on 021015 001.

Patent Data

 # represents patent information submitted prior to August 18, 2003

Appl No	Prod No	Patent No	Patent Expiration	Use Code	How Filed	Labeling Impact
021015	001	#6503894	AUG 30,2020	U-490 (TESTOSTERONE REPLACEMENT THERAPY IN MALES FOR CONDITIONS ASSOCIATED WITH A DEFICIENCY OR ABSENCE OF ENDOGENOUS TESTOSTERONE)	IV	None

Exclusivity Data

Appl No	Prod No	Exclusivity Code	Exclusivity Expiration	
021015	001	NDF (NEW DOSAGE FORM)	FEB 28,2003	Expired!

The firm's statements are accurate. [Vol. A1.1, pg. 19-17]
Notice of filing of legal action Case 1: 03-CV-2503 [Vol. A2.1, September 5, 2003 amendment]

3. MANUFACTURING FACILITY (Vol A1.10, pg. 4023)
   Paddock Laboratories, Inc.
   3940 Quebec Ave N
   Minneapolis, MN 55427

4. STORAGE CONDITIONS:
   NDA: Store at Controlled Room Temperature 20°-25°C (68°-77°F) (see USP).
   ANDA: - Store at 25°C (77°F); excursions permitted to 15° to 30°C (59° to 86°F) [see USP Controlled

Room Temperature].
Test conditions: accelerated (40^0C/75% RH) and controlled room temperature (25^0C/60% RH)

5. DISPENSING RECOMMENDATIONS:
   NDA: None
   ANDA: None

6. PRODUCT LINE:
   The innovator: unit-dose aluminum foil packets in cartons of 30. Each packet of 2.5 g or 5.0 g gel contains 25 mg or 50 mg testosterone respectively AND in non-aerosol, metered-dose pump. Each individual packaged 88 g Pump is capable of dispensing 75 g or 60 metered 1.25 g doses.

   The applicant's product will be packaged in unit-dose foil laminate packets containing 2.5 grams or 5 grams (equivalent to 25 mg or 50 mg of testosterone, respectively) per packet. Thirty unit-dose packets will be packaged per shelf carton. [Vol. A1.1, pg. 4279]

7. CONTAINER/CLOSURE SYSTEM: [Vol. A1.10, pg. 4324]
   2.5 gram and 5 gram packet foil laminate:

8. PRODUCT DESCRIPTION:
   ANDA- Clear (b) (4) gel (Vol. A1.10, pg. 4418-9)

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 3847.

Ingredient	Pharmaceutical Function	% w/w	Concentration (mg/g)	ExhibitBatch/ CommercialBatch (kg/ (b) (4)
Testosterone USP	Active	1.000	10.000	(b) (4)
Ethanol(Alcohol USP[a])	(b) (4)			
Purified Water USP				
Carbomer 940 NF				
Isopropyl Myristate NF				
Sodium Hydroxide NF				

(b) (4)

. Paddock provided an ingredient comparison table (p. 3843) to show that, based on their information, their formulation is Q1/Q2 to the innovator's formulation.

10. BIOEQUIVALENCE: 08-SEP-04: No bio issues. Submitted standard language to firm in AC letter. Firm verbalized understanding. BIO AC / AS

Date of Review: April 11, 2007 Date of Submission: December 26, 2006
Primary Reviewer: Ruby Wu (for Postelle Birch)
Team Leader: John Grace

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

/s/

Ruby Wu
4/11/2007 12:21:18 PM
MEDICAL OFFICER

John Grace
4/12/2007 10:57:41 AM
MEDICAL OFFICER

This review supersedes the approval summary signed off 6/3/04

APPROVAL SUMMARY

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

ANDA Number: 76-744

Date of Submission: May 3, 2007 (Amendment)

Applicant's Name: Par Pharmaceuticals (transferred from Paddock Laboratories, Inc.)

Established Name: Testosterone Gel, 1%

APPROVAL SUMMARY:

Do you have 12 Final Printed Labels and Labeling? Yes

1. CONTAINER (2.5 g and 5 g unit-dose foil packets)
   Satisfactory in final print as of the December 26, 2006 e-amendment.

2. CARTON (30 x unit-dose packets)
   Satisfactory in final print as of the December 26, 2006 e-amendment.

3. PHYSICIAN INSERT
   Satisfactory in final print as of the May 3, 2007 e-amendment.

4. PATIENT INFORMATION AND INSTRUCTIONS FOR USING
   Satisfactory in final print as of the December 26, 2006 e-amendment.

5. Revisions needed post-approval: No

BASIS OF APPROVAL:
Was this approval based upon a petition? No
What is the RLD on the 356(h) form: AndroGel®
NDA Number: 21-015
NDA Drug Name: testosterone gel
NDA Firm: Unimed Pharmaceuticals
Date of Approval of NDA Insert and supplement: NDA 21-015/S-011 approved August 11, 2005
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

Appl No	Prod No	Patent No	Patent Expiration	Use Code	How Filed	Labeling Impact
021015	001	#6503894	AUG 30,2020	U-490 (TESTOSTERONE REPLACEMENT THERAPY IN MALES FOR CONDITIONS ASSOCIATED WITH A DEFICIENCY OR ABSENCE OF ENDOGENOUS TESTOSTERONE)	IV	None

Exclusivity Data

Appl No	Prod No	Exclusivity Code	Exclusivity Expiration	
021015	001	NDF (NEW DOSAGE FORM)	FEB 28,2003	Expired!

NOTES/QUESTIONS TO THE CHEMIST:

FOR THE RECORD:

1. MODEL LABELING - This review is based on the labeling of AndroGel® (testosterone gel) by Unimed Pharmaceuticals NDA 21-015/S-011 approved August 11, 2005. The letter states the physician insert is approved and asked the firm to submit FPL. However, the letter asks the firm to submit proposed draft patient information leaflet. Therefore, I only asked Par to revise the physician insert. Par may revise their patient information leaflet after it has been approved for the RLD. Par's ANDA does not provide for the Pump configuration. Therefore, info pertaining to the pump in the RLD labeling has been carved out.

   Please note that in innovator changed the alcohol content % label claim from 68.9% to 67.0%. Based in the Chemistry memo in DFS dated July 30, 2003, "The drug product specification was updated to reflect the change in the alcohol used in the manufacturing from (b) (4) to (b) (4) However, the total amount of alcohol in the formulation remains the same based on absolute alcohol content."

   Other AndroGel supplements of interest:

   - *S-013 approved August 16, 2005...This supplement pertains to the final printed container and carton labels for AndroGel single pump and twinpump. Par does not have this packaging configuration. Therefore this supplement will not affect Par's labels and labeling.*
   - *S-010 Prior Approval Supplement is a Chemistry, Manufacturing and Controls NDA supplement that provides for new container systems of 88 g and 44 g multi-dose pumps, which was approved on September 26, 2003. This supplement contains the proposed container labels and carton labels for the multi-dose pumps.*
   - *S-010 Final Printed Label contains the approved Package Insert and Patient Package Insert. Note that Final Printed Labels for the container and carton were not included.*

   Drug Substance is USP: Packaging and storage— Packaging and storage— Preserve in well-closed containers. Store at 25, excursions permitted between 15 and 30.
   Testosterone Gel is not USP (checked 5/8/07)

   ANDA tentatively approved October 27, 2004. In the December 26, 2006 submission, firm provided revised labeling to reflect transfer of ownership from Paddock to Par.

2. PATENTS AND EXCLUSIVITIES

Patent and Exclusivity Search Results from query on 021015 001.

Patent Data

 # represents patent information submitted prior to August 18, 2003

Appl No	Prod No	Patent No	Patent Expiration	Use Code	How Filed	Labeling Impact
021015	001	#6503894	AUG 30,2020	U-490 (TESTOSTERONE REPLACEMENT THERAPY IN MALES FOR CONDITIONS ASSOCIATED WITH A DEFICIENCY OR ABSENCE OF ENDOGENOUS TESTOSTERONE)	IV	None

Exclusivity Data

Appl No	Prod No	Exclusivity Code	Exclusivity Expiration	
021015	001	NDF (NEW DOSAGE FORM)	FEB 28,2003	Expired!

The firm's statements are accurate. [Vol. A1.1, pg. 19-17]
Notice of filing of legal action Case 1: 03-CV-2503 [Vol. A2.1, September 5, 2003 amendment]

3. MANUFACTURING FACILITY (Vol A1.10, pg. 4023)
   Paddock Laboratories, Inc.
   3940 Quebec Ave N
   Minneapolis, MN 55427

4. STORAGE CONDITIONS:
   NDA: Store at Controlled Room Temperature 20°-25°C (68°-77°F) (see USP).
   ANDA: - Store at 25°C (77°F); excursions permitted to 15° to 30°C (59° to 86°F) [see USP Controlled

Room Temperature].
Test conditions: accelerated (40^{0}C/75% RH) and controlled room temperature (25^{0}C/60% RH)

5. DISPENSING RECOMMENDATIONS:
   NDA: None
   ANDA: None

6. PRODUCT LINE:
   The innovator: unit-dose aluminum foil packets in cartons of 30. Each packet of 2.5 g or 5.0 g gel contains 25 mg or 50 mg testosterone respectively AND in non-aerosol, metered-dose pump. Each individual packaged 88 g Pump is capable of dispensing 75 g or 60 metered 1.25 g doses.

   The applicant's product will be packaged in unit-dose foil laminate packets containing 2.5 grams or 5 grams (equivalent to 25 mg or 50 mg of testosterone, respectively) per packet. Thirty unit-dose packets will be packaged per shelf carton. [Vol. A1.1, pg. 4279]

7. CONTAINER/CLOSURE SYSTEM: [Vol. A1.10, pg. 4324]
   2.5 gram and 5 gram packet foil laminate:

8. PRODUCT DESCRIPTION:
   ANDA- Clear (b) (4) gel (Vol. A1.10, pg. 4418-9)

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 3847.

Ingredient	Pharmaceutical Function	% w/w	Concentration (mg/g)	ExhibitBatch/ CommercialBatch (kg/ (b) (4)
Testosterone USP	Active	1.000	10.000	(b) (4)
Ethanol(Alcohol USP[a])	(b) (4)			
Purified Water USP				
Carbomer 940 NF				
Isopropyl Myristate NF				
Sodium Hydroxide NF				

(b) (4)

. Paddock provided an ingredient comparison table (p. 3843) to show that, based on their information, their formulation is Q1/Q2 to the innovator's formulation.

10. BIOEQUIVALENCE: 08-SEP-04: No bio issues. Submitted standard language to firm in AC letter. Firm verbalized understanding. BIO AC / AS

Date of Review: May 8, 2007 Date of Submission: May 3, 2007
Primary Reviewer: Ruby Wu (for Postelle Birch)
Team Leader: John Grace

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

/s/

Ruby Wu
5/8/2007 03:55:35 PM
MEDICAL OFFICER

John Grace
5/9/2007 12:09:58 PM
MEDICAL OFFICER

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 076744

CHEMISTRY REVIEWS

ANDA 76-744

Testosterone Gel 1%

Paddock Laboratories, Inc.

Kathy P. Woodland
Division of Chemistry I
Team 5

Table of Contents

Chemistry Review Data Sheet

1. ANDA 76-744

2. REVIEW #: 1

3. REVIEW DATE: September 10, 2003

4. REVIEWER: Kathy P. Woodland

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
None	

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
New Correspondence	September 12, 2003
New Correspondence	September 5, 2003
New Correspondence	August 22, 2003
New Correspondence	July 22, 2003
Acknowledgment letter	July 2, 2003
New Correspondence	June 17, 2003
Acceptable for filing	May 22, 2003
Original Submission	May 21, 2003

7. NAME & ADDRESS OF APPLICANT:

Name:	Paddock Laboratories, Inc.
Address:	3940 Quebec Avenue North Minneapolis, MN 55427
Representative:	Patrick L. Johnson
Telephone / Fax:	763-546-4676 / 763-546-4842

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name:	None
b) Non-Proprietary Name (USAN):	Testosterone

9. LEGAL BASIS FOR SUBMISSION:

Reference Product: Androgel
Manufacturer: Unimed Pharmaceuticals, Inc. (NDA 21-015)
Unimed Pharmaceuticals currently has an unexpired patent, US Patent No. 6503894 (Expires 30 Aug 2020). Exclusivity Data: No unexpired exclusivities. Paddock Laboratories has submitted a Paragraph IV certification claiming that the patent is invalid or will not be infringed by the proposed drug product.

10. PHARMACOLOGICAL CATEGORY:

Testosterone replacement therapy in males for conditions associated with a deficiency or absence of endogenous testosterone.

11. DOSAGE FORM: Gel

12. STRENGTH/POTENCY: 1%

13. ROUTE OF ADMINISTRATION: Topical

14. Rx/OTC DISPENSED: __x_Rx ___OTC

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

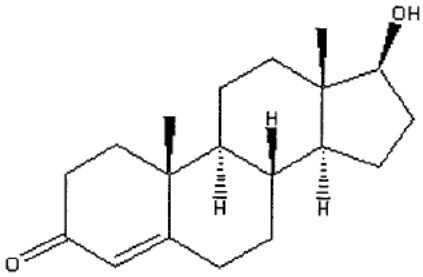
_____SPOTS product – Form Completed

___x__Not a SPOTS product

Chemistry Review Data Sheet

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

Androst-4-en-3-one, 17-hydroxy-, (17beta)-, $C_{19}H_{28}O_2$, 288.429



17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	II		(b) (4)	3	Adequate	10/15/2003	Reviewed by R.Trimmer
	III			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:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
None		

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	N/A		
EES	Pending		
Methods Validation	N/A		
Labeling	Pending		
Bioequivalence	Pending		
EA	N/A		
Radiopharmaceutical	N/A		

19. ORDER OF REVIEW

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

Executive Summary Section

The Chemistry Review for ANDA 76-744

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability The ANDA is not approvable pending clarification of MINOR Chemistry issues. Labeling, EES, and Bioequivalence are pending.

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

II. Summary of Chemistry Assessments

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

*The drug substance Testosterone is USP. The drug product Testosterone Gel 1% is non-USP.
The product will be packaged in unit-dose foil laminate packets containing 2.5 grams or 5 grams (equivalent to 25 mg or 50 mg of testosterone, respectively) per packet. Thirty unit-dose packets will be packaged per shelf carton.

*The DMF associated with this application (DMF (b) (4)) is adequate to support the ANDA.

*Paddock Laboratories, Inc. has developed their own in-house methods for the drug substance: assay, impurities, and residual solvents. Method validations for each of the methods were submitted.

*Paddock Laboratories, Inc. has developed their own in-house methods for the drug product; assay, impurities, and alcohol content. Method validations for each of the methods were submitted.

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

The recommended starting dose of Testosterone Gel 1% is 5 G delivering 5 mg of Testosterone systemically, applied once daily (preferably in the morning) to clean, dry, intact skin of the shoulders and upper arms and/or abdomen. Upon opening the packet(s), the entire contents should be squeezed into the palm of the hand and immediately applied to the application sites.

The product is to be stored at (b) (4)

C. Basis for Approvability or Not-Approval Recommendation

The ANDA is not approvable at this time for the following reasons:

Minor Chemistry issues
Pending Labeling
Pending Bioequivalence
Pending EES

III. Administrative

A. Reviewer's Signature Kathy P. Woodland

B. Endorsement Block

HFD-627/K.Woodland/ KWoodland 10/24/03
HFD-620/Shing Liu,Ph.D./ S.H.Liu 10/27/03
HFD-617/Wanda Pamphile,Pharm.D./ WP 10/30/03
V:\FIRMSNZ\PADDOCK\LTRS&REV\76744.CR1.REV.DOC

C. CC Block

Following this page, 8 pages withheld in full (b)(4)

Deficiency Please (b) (4) the acceptance criteria for Impurities for drug product stability. The limit for impurities should be the same as those established for the drug product at release except for those that increase with time.
Deficiency Please explain "other specified impurities" in your specifications.
Deficiency Please revise the drug product stability test "container weight check" to "% weight loss".
Deficiency Please submit a revised drug product stability sheet.

30. MICROBIOLOGY N/A

31. SAMPLES AND RESULTS/METHODS VALIDATION STATUS

The drug substance is USP. The drug product is non-USP but does not require a method validation based on the current OGD guideline for method validation.

32. LABELING Pending review

33. ESTABLISHMENT INSPECTION Pending

34. BIOEQUIVALENCE Pending review

35. ENVIRONMENTAL IMPACT CONSIDERATIONS/CATEGORICAL EXCLUSION:

Paddock has claimed a categorical exclusion from the requirement to submit an Environmental Assessment and a statement certifying that Paddock is in compliance with Federal, State, and local environmental laws and regulations.

36. CHEMISTRY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 76-744 APPLICANT: Paddock Laboratories, Inc.

DRUG PRODUCT: Testosterone Gel, 1%

The deficiencies presented below represent MINOR deficiencies.

A. Deficiencies:

1. (b) (4)
2.
3.
4.

5. Regarding the drug product stability specifications, we have the following comments:
   a. Please (b) (4) the acceptance criteria for Impurities. The limit for impurities should be the same as those established for the drug product at release except for those that increase with time.
   b. Please revise the test "container weight check" to "% weight loss".
   c. Please explain "other specified impurities" in your specifications.
   d. Please submit a revised drug product stability sheet.

6. You have identified (b) (4) as an impurity. Please clarify.

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

1. The firms referenced in your ANDA application relative to the manufacturing and testing of the product must be in compliance with cGMP's at the time of approval.

2. The USP methods for the drug substance are the regulatory methods and they will prevail in the event of any dispute.

3. Your bioequivalence information is pending review. Deficiencies, if any, will be communicated separately.

4. Your labeling information is pending review. Deficiencies, if any, will be communicated separately.

5. Please provide all available long-term stability data to update your studies.

Sincerely yours,

Shrujhon Patel for 10/30/03

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

cc: ANDA 76-744
ANDA DUP 76-744
DIV FILE
Field Copy

Endorsements (Draft and Final with Dates):

HFD-627/K.Woodland/ K Woodland 10/24/03
HFD-627/S.Liu, Ph.D./ S.H. Liu 10/30/03
HFD-617/W.Pamphile, Pharm.D./ WP 10/30/03

F/T by:

V:\FIRMSNZ\PADDOCK\LTRS&REV\76744.cr1.rev.doc

TYPE OF LETTER: NOT APPROVABLE - MINOR

ANDA 76-744

Testosterone Gel 1%

Paddock Laboratories, Inc.

Kathy P. Woodland
Division of Chemistry I
Team 5

Table of Contents

Chemistry Review Data Sheet

1. ANDA 76-744

2. REVIEW #: 2

3. REVIEW DATE: February 24, 2003

4. REVIEWER: Kathy P. Woodland

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
New Correspondence	September 12, 2003
New Correspondence	September 5, 2003
New Correspondence	August 22, 2003
New Correspondence	July 22, 2003
Acknowledgment letter	July 2, 2003
New Correspondence	June 17, 2003
Acceptable for filing	May 22, 2003
Original Submission	May 21, 2003

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Amendment	January 29, 2004

7. NAME & ADDRESS OF APPLICANT:

Name:	Paddock Laboratories, Inc.
Address:	3940 Quebec Avenue North Minneapolis, MN 55427
Representative:	Daniel W. Rockcliffe
Telephone / Fax:	763-546-0364 / 763-546-4842

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name:	None
b) Non-Proprietary Name (USAN):	Testosterone

9. LEGAL BASIS FOR SUBMISSION:

   See Review #1

10. PHARMACOLOGICAL CATEGORY:

    Testosterone replacement therapy in males for conditions associated with a deficiency or absence of endogenous testosterone.

11. DOSAGE FORM: Gel

12. STRENGTH/POTENCY: 1%

13. ROUTE OF ADMINISTRATION: Topical

14. Rx/OTC DISPENSED: __x_Rx ___OTC

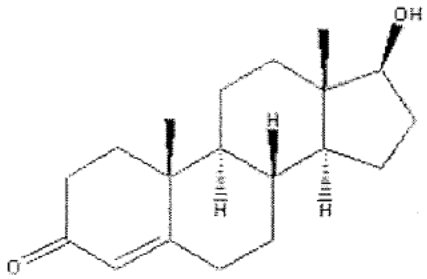
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

    _____SPOTS product – Form Completed

    ___x___Not a SPOTS product

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

Androst-4-en-3-one, 17-hydroxy-, (17beta)-, $C_{19}H_{28}O_2$, 288.429



17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	II	(b) (4)		3	Adequate	10/15/2003	Reviewed by R.Trimmer
	III			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:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
None		

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	N/A		
EES	Acceptable	2-10-04	J. D'Ambrogio
Methods Validation	N/A		
Labeling	Deficient	1/22/04	R. Wu
Bioequivalence	Pending-review		
EA	N/A		
Radiopharmaceutical	N/A		

19. ORDER OF REVIEW

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

Executive Summary Section

The Chemistry Review for ANDA 76-744

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability The ANDA is not approvable pending clarification of MINOR chemistry issues. Labeling is deficient, and Bioequivalence is pending.

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

II. Summary of Chemistry Assessments

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

*The drug substance Testosterone is USP. The drug product Testosterone Gel 1% is non-USP.
The product will be packaged in unit-dose foil laminate packets containing 2.5 grams or 5 grams (equivalent to 25 mg or 50 mg of testosterone, respectively) per packet. Thirty unit-dose packets will be packaged per shelf carton.

*The DMF associated with this application (DMF (b) (4)) is adequate to support the ANDA and there have been no updates since the last review.

*Paddock Laboratories, Inc. has developed their own in-house methods for the drug substance: assay, impurities, and residual solvents. Method validations for each of the methods were submitted and found acceptable.

*Paddock Laboratories, Inc. has developed their own in-house methods for the drug product; assay, impurities, and alcohol content. Method validations for each of the methods were submitted and found acceptable.

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

The recommended starting dose of Testosterone Gel 1% is 5 G delivering 5 mg of Testosterone systemically, applied once daily (preferably in the morning) to clean, dry, intact skin of the shoulders and upper arms and/or abdomen. Upon opening the packet(s), the entire contents should be squeezed into the palm of the hand and immediately applied to the application sites.

The product is to be stored at (b) (4)

C. Basis for Approvability or Not-Approval Recommendation

The ANDA is not approvable at this time for the following reasons:

Minor Chemistry issues
Labeling is deficient
Pending Bioequivalence

III. Administrative

A. Reviewer's Signature

/s/ K. Woodland

B. Endorsement Block

/s/ K. Woodland 2/11/04
S.H. Liu 3/11/04
HFD-627/K.Woodland/2/27/04
HFD-620/Shing Liu,Ph.D./3/10/04
HFD-617/Wanda Pamphile,Pharm.D./ 3/11/04
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C. CC Block

Following this page, 6 pages withheld in full (b)(4)

Individual Unspecified: NMT (b) (4)
Total Impurities: NMT

b. "other individual specified impurities" are impurities that have been identified in drug substance or drug product under stress conditions and separated under chromatographic conditions described in procedure #1586. For the drug substance, it will be identified by (b) (4) and monitored.

c. The "container weight check" has been revised to "container weight change (%)".

d. A revised drug product stability sheet was submitted.

Conclusion

a. Not Satisfactory **New Deficiency** Please (b) (4) the drug product stability acceptance criteria for the (b) (4) and Total Impurities.

b. Satisfactory The definition is acceptable.

c. Satisfactory The revision to "container weight change (%)" is acceptable.

d. Not Satisfactory **New Deficiency** Please submit a revised drug product stability sheet.

Updated stability data was submitted: controlled room temperature (b) (4) months. All data was within the proposed specifications.

30. MICROBIOLOGY N/A

31. SAMPLES AND RESULTS/METHODS VALIDATION STATUS

The drug substance is USP. The drug product is non-USP but does not require a method validation based on the current OGD guideline for method validation.

32. LABELING deficient on 1/22/04 by R. Wu

33. ESTABLISHMENT INSPECTION Acceptable on 2/10/04 by J. D'Ambrogio

34. BIOEQUIVALENCE Pending review

35. ENVIRONMENTAL IMPACT CONSIDERATIONS/CATEGORICAL EXCLUSION:

Paddock has claimed a categorical exclusion from the requirement to submit an Environmental Assessment and a statement certifying that Paddock is in compliance with Federal, State, and local environmental laws and regulations.

In addition to responding to the deficiencies the applicant has noted and acknowledged the following comments in their response:

1. The firms referenced in their ANDA application relative to the manufacturing and testing of the product must be in compliance with cGMP's at the time of approval.

2. The USP methods for the drug substance are the regulatory methods and they will prevail in the event of any dispute.

3. Their bioequivalence information is pending review. Deficiencies, if any, will be communicated separately.

4. Their labeling information is pending review. Deficiencies, if any, will be communicated separately.

5. Provided all available long-term stability data to update their studies.

36. CHEMISTRY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 76-744 APPLICANT: Paddock Laboratories, Inc.

DRUG PRODUCT: Testosterone Gel, 1%

The deficiencies presented below represent MINOR deficiencies.

A. Deficiencies:

1. Please further (b) (4) the total impurity acceptance criteria for the drug product, and submit a revised drug product specification sheet accordingly.

2. Please (b) (4) the drug product stability acceptance criteria for (b) (4) and total impurities. Also, please submit a revised drug product stability sheet.

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 long-term stability data to update your studies.

2. Labeling deficiencies were faxed to you on January 22, 2004. Please respond to the labeling deficiencies.

Sincerely yours,

Ahuja Hon Jain for 3/11/04

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

cc: ANDA 76-744
ANDA DUP 76-744
DIV FILE
Field Copy

Endorsements (Draft and Final with Dates): /s/ for K Woodland 3/11/04

HFD-627/K.Woodland/ 2/27/04
HFD-627/S.Liu, Ph.D./ S-H. Liu 3/11/04
HFD-617/W.Pamphile, Pharm.D./ WP 3/11/04

F/T by: wp 3/11/04

Final Draft
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TYPE OF LETTER: NOT APPROVABLE - MINOR

ANDA 76-744

Testosterone Gel 1%

Paddock Laboratories, Inc.

Kathy P. Woodland
Division of Chemistry I
Team 5

Table of Contents

Chemistry Review Data Sheet

1. ANDA 76-744

2. REVIEW #: 3

3. REVIEW DATE: July 30, 2004
   Revised August 16, 2004
   Revised September 22, 2004

4. REVIEWER: Kathy P. Woodland

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
New Correspondence	September 12, 2003
New Correspondence	September 5, 2003
New Correspondence	August 22, 2003
New Correspondence	July 22, 2003
Acknowledgment letter	July 2, 2003
New Correspondence	June 17, 2003
Acceptable for filing	May 22, 2003
Original Submission	May 21, 2003
Amendment	January 29, 2004
Amendment (labeling)	April 8, 2004
Amendment (labeling)	April 19, 2004

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Amendment	June 30, 2004
Telephone Amendment	August 13, 2004
T-con	September 2, 2004
Telephone Amendment	September 15, 2004
Telephone Amendment	October 22, 2004

7. NAME & ADDRESS OF APPLICANT:

Name:	Paddock Laboratories, Inc.
Address:	3940 Quebec Avenue North Minneapolis, MN 55427
Representative:	Daniel W. Rockcliffe

Chemistry Review Data Sheet

Telephone / Fax: 763-546-0364 / 763-546-4842

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: None
b) Non-Proprietary Name (USAN): Testosterone

9. LEGAL BASIS FOR SUBMISSION:

See Review #1

10. PHARMACOLOGICAL CATEGORY:

Testosterone replacement therapy in males for conditions associated with a deficiency or absence of endogenous testosterone.

11. DOSAGE FORM: Gel

12. STRENGTH/POTENCY: 1%

13. ROUTE OF ADMINISTRATION: Topical

14. Rx/OTC DISPENSED: __x_Rx ___OTC

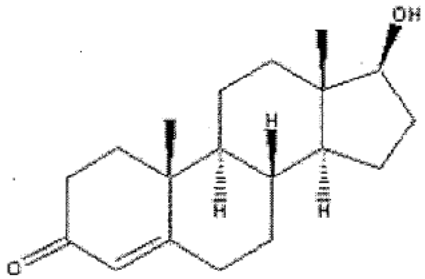
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

_____SPOTS product – Form Completed

___x___Not a SPOTS product

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

Androst-4-en-3-one, 17-hydroxy-, (17beta)-, $C_{19}H_{28}O_2$, 288.429



17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	II	(b) (4)		3	Adequate	6/23/04	Reviewed by M. Darj
	III			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:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
None		

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	N/A		
EES	Acceptable	2-10-04	J. D'Ambrogio
Methods Validation	N/A		
Labeling	Acceptable	6/3/04	R. Wu
Bioequivalence	Acceptable	6/15/04	H. Nguyen
EA	N/A		
Radiopharmaceutical	N/A		

19. ORDER OF REVIEW

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

Executive Summary Section

The Chemistry Review for ANDA 76-744

The Executive Summary

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 N/A

II. Summary of Chemistry Assessments

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

*The drug substance Testosterone is USP. The drug product Testosterone Gel 1% is non-USP.
The product will be packaged in unit-dose foil laminate packets containing 2.5 grams or 5 grams (equivalent to 25 mg or 50 mg of testosterone, respectively) per packet. Thirty unit-dose packets will be packaged per shelf carton.

*The DMF associated with this application (DMF (b) (4)) is adequate to support the ANDA and there have been no updates since the last review.

*Paddock Laboratories, Inc. has developed their own in-house methods for the drug substance: assay, impurities, and residual solvents. Method validations for each of the methods were submitted and found acceptable.

*Paddock Laboratories, Inc. has developed their own in-house methods for the drug product; assay, impurities, and alcohol content. Method validations for each of the methods were submitted and found acceptable.

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

The recommended starting dose of Testosterone Gel 1% is 5 G delivering 5 mg of Testosterone systemically, applied once daily (preferably in the morning) to clean, dry, intact skin of the shoulders and upper arms and/or abdomen. Upon opening the packet(s), the entire contents should be squeezed into the palm of the hand and immediately applied to the application sites.

The product is to be stored at (b) (4)

C. Basis for Approvability or Not-Approval Recommendation

The ANDA is approvable. CMC, labeling, EER, and bio are acceptable.

III. Administrative

A. Reviewer's Signature Kathy P. Woodland

B. Endorsement Block

HFD-627/K.Woodland/ K Woodland 9/22/04
HFD-620/Shing Liu,Ph.D./ S.H. Liu 9/28/04
HFD-617/Wanda Pamphile,Pharm.D./ WP 9/28/04
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C. CC Block

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Response as per T-con 8/12/04. To address the new deficiency, a T-con was made. The specifications were revised as follows (same as release). They are satisfactory.

Test	Acceptance Criteria
Impurity Profile (b) (4)	
	NMT (b) (4)
	NMT
	NMT
	NMT
	NMT
	NMT
	NMT
Total Impurities:	NMT

Updated stability data was submitted: controlled room temperature 24 months. All data was within the proposed specifications.

30. MICROBIOLOGY N/A

31. SAMPLES AND RESULTS/METHODS VALIDATION STATUS

The drug substance is USP. The drug product is non-USP but does not require a method validation based on the current OGD guideline for method validation.

32. LABELING Acceptable on 6/3/04 by R. Wu

33. ESTABLISHMENT INSPECTION Acceptable on 2/10/04 by J. D'Ambrogio

34. BIOEQUIVALENCE Acceptable on 6/15/04 by H.Nguyen

35. ENVIRONMENTAL IMPACT CONSIDERATIONS/CATEGORICAL EXCLUSION:

Paddock has claimed a categorical exclusion from the requirement to submit an Environmental Assessment and a statement certifying that Paddock is in compliance with Federal, State, and local environmental laws and regulations.

In addition to responding to the deficiencies the applicant has noted and acknowledged the following:

1. The applicant provided full term (24 month) stability data for Lot# 2044939 (2.5g), 2044938 (5 g) in Attachment 7. The data is satisfactory.

2. The applicant responded to the Labeling deficiencies on 4/8/04 and 5/19/04.

cc: ANDA 76-744
ANDA DUP 76-744
DIV FILE
Field Copy

Endorsements (Draft and Final with Dates):

HFD-627/K.Woodland/ K.Woodland 9/22/04
HFD-627/S.Liu, Ph.D./ S.H.Liu 9/28/04
HFD-617/W.Pamphile, Pharm.D./ WP 9/28/04

F/T by:

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TYPE OF LETTER: APPROVABLE

Addendum to ANDA 76-744 Chemistry Review # 3

Telephone Amendment to ANDA 76-744 in response to the chemistry deficiency communicated on September 2, 2004 for Testosterone Gel 1%

On September 2, 2004 there was a T-con between Radhika Rajagopalan, Ph.D. and Paddock. Sampling details were discussed. The content uniformity procedure was defective, the firm didn't use the entire contents of the pouch. The assay and alcohol procedure needed duplicate runs. The procedures should be revised indicating how many assay runs are done.

Per the September 15, 2004 Telephone Amendment the following were revised:

- (b) (4)
- The procedure to (b) (4) has been revised to specify the use of (b) (4) (b) (4). The revised method was submitted.
- The stability protocols have been revised for the 2.5 g package size and the 5 g package size. Gel tests will be performed (b) (4) for all stability samples
- The content uniformity procedure was revised; using (b) (4) was removed. Content Uniformity testing will be performed using (b) (4) of individual packets. A copy of the procedure was submitted.
- Sampling plan

(b) (4)

The following methods were revised:

(b) (4)

HFD-627/K.Woodland/ KWoodland 9/28/04
HFD-620/Shing Liu,Ph.D./ S.H.Liu 9/22/04
HFD-617/Wanda Pamphile,Pharm.D./ [illegible] 9/28/04
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C. CC Block

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ANDA 76-744

Testosterone Gel 1%

Par Pharmaceutical
(Formerly Paddock Laboratories, Inc)

Kathy P. Woodland
Division of Chemistry I
Team 5

Table of Contents

Chemistry Review Data Sheet

1. ANDA 76-744

2. REVIEW #: 4

3. REVIEW DATE: March 8, 2007

4. REVIEWER: Kathy P. Woodland

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
New Correspondence	September 12, 2003
New Correspondence	September 5, 2003
New Correspondence	August 22, 2003
New Correspondence	July 22, 2003
Acknowledgment letter	July 2, 2003
New Correspondence	June 17, 2003
Acceptable for filing	May 22, 2003
Original Submission	May 21, 2003
Amendment	January 29, 2004
Amendment (labeling)	April 8, 2004
Amendment (labeling)	May 19, 2004
Amendment	June 30, 2004
Telephone Amendment	August 13, 2004
T-con	September 2, 2004
Telephone Amendment	September 15, 2004
Telephone Amendment	October 22, 2004

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Amendment	December 26, 2006
Amendment (Gratuitous)	January 5, 2007

7. NAME & ADDRESS OF APPLICANT:

Name:	Par Pharmaceutical (Formerly Paddock Laboratories, Inc.)
Address:	One Ram Ridge Road Spring Valley, New York 10977

Chemistry Review Data Sheet

Representative: Janis A. Picurro

Telephone / Fax: 845-425-7100/ 845-639-5201

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: None
b) Non-Proprietary Name (USAN): Testosterone Gel 1%

9. LEGAL BASIS FOR SUBMISSION:

See Review #1

10. PHARMACOLOGICAL CATEGORY:

Testosterone replacement therapy in males for conditions associated with a deficiency or absence of endogenous testosterone.

11. DOSAGE FORM: Gel

12. STRENGTH/POTENCY: 1%

13. ROUTE OF ADMINISTRATION: Topical

14. Rx/OTC DISPENSED: __x_Rx ___OTC

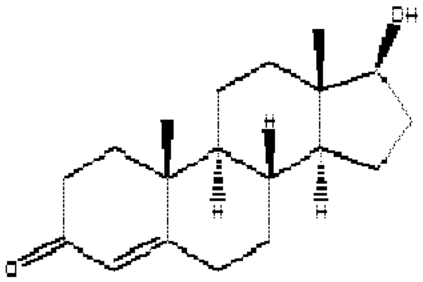
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

_____SPOTS product – Form Completed

___x___Not a SPOTS product

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

Androst-4-en-3-one, 17-hydroxy-, (17beta)-, $C_{19}H_{28}O_2$, 288.429



17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	II		(b) (4)	1	Adequate	3/8/2007	Reviewed by K.Woodland
	III			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:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
None		

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	N/A		
EES	Acceptable	4/24/07	S. Furguson
Methods Validation	N/A		
Labeling	Acceptable	5/9/07	R. Wu
Bioequivalence	Acceptable	6/15/04	H. Nguyen
EA	N/A		
Radiopharmaceutical	N/A		

19. ORDER OF REVIEW

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

Chemistry Assessment Section

The Chemistry Review for ANDA 76-744

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability The ANDA was Tentatively Approved on October 27, 2004. There were no changes made in the CMC since the TA. The ANDA is approvable.

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

II. Summary of Chemistry Assessments

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

*The drug substance Testosterone is USP. The drug product Testosterone Gel 1% is non-USP.
The product will be packaged in unit-dose foil laminate packets containing 2.5 grams or 5 grams (equivalent to 25 mg or 50 mg of testosterone, respectively) per packet. Thirty unit-dose packets will be packaged per shelf carton.

*The DMF associated with this application (DMF (b) (4) is adequate to support the ANDA and there have been no updates since the last review.

*Par Pharmaceutical (Formerly Paddock Laboratories, Inc.) has developed their own in-house methods for the drug substance: assay, impurities, and residual solvents. Method validations for each of the methods were submitted and found acceptable.

* Par Pharmaceutical (Formerly Paddock Laboratories, Inc. has developed their own in-house methods for the drug product; assay, impurities, and alcohol content. Method validations for each of the methods were submitted and found acceptable.

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

The recommended starting dose of Testosterone Gel 1% is 5 G delivering 5 mg of Testosterone systemically, applied once daily (preferably in the morning) to clean, dry, intact skin of the shoulders and upper arms and/or abdomen. Upon opening the packet(s), the entire contents should be squeezed into the palm of the hand and immediately applied to the application sites.

The product is to be stored at (b) (4)

C. Basis for Approvability or Not-Approval Recommendation

The ANDA is approvable. CMC, labeling, EER, and bio are acceptable.

Following this page, 3 pages withheld in full (b)(4)

Test	Acceptance Criteria	Method No.
(b) (4)	(b) (4)	
		1588
		57
Container weight change (%)		1471

The specified impurities are as follows: (page 4489-Table1) (the approximate relative retention times and relative response factors are given in the table)

Specified Impurity	Impurity Type
(b) (4)	

Unspecified impurities are any detectable peak not listed in Table 1

Updated stability data was submitted: controlled room temperature 24 months. All data was within the proposed specifications.

30. MICROBIOLOGY N/A

31. SAMPLES AND RESULTS/METHODS VALIDATION STATUS

The drug substance is USP. The drug product is non-USP but does not require a method validation based on the current OGD guideline for method validation.

32. LABELING Acceptable on 5/9/07 by R. Wu

33. ESTABLISHMENT INSPECTION Acceptable on 4/24/07 by S. Furguson

34. BIOEQUIVALENCE Acceptable on 6/15/04 by H.Nguyen

35. ENVIRONMENTAL IMPACT CONSIDERATIONS/CATEGORICAL EXCLUSION:

Paddock has claimed a categorical exclusion from the requirement to submit an Environmental Assessment and a statement certifying that Paddock is in compliance with Federal, State, and local environmental laws and regulations.

cc: ANDA 76-744
ANDA DUP 76-744
DIV FILE
Field Copy

Endorsements (Draft and Final with Dates):

HFD-620/K.Woodland/
HFD-620/R.Bykadi, Ph.D./ 3/10/07/
HFD-617/B.Danso, Pharm.D./5-10-07

F/T by:

V:\Chemistry Division I\Team 5\Final Version For DFS\76744cr4.doc

TYPE OF LETTER: APPROVABLE

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

/s/

Kathy P. Woodland
5/18/2007 10:33:28 AM
CHEMIST

Gururaj Bykadi
5/21/2007 06:46:05 AM
CHEMIST

Benjamin Danso
5/31/2007 11:11:13 AM
CSO

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 076744

BIOEQUIVALENCE REVIEW

1.1

DIVISION OF BIOEQUIVALENCE REVIEW

ANDA No.	76-744
Drug Product Name	Testosterone Gel
Strength	1%
Applicant Name	Paddock Laboratories, Inc.
Address	Minneapolis, MN
Submission Date(s)	May 21, 2003
Amendment Date(s)	February 19, 2004 (Telephone)
Reviewer	Hoainhon Nguyen
First Generic	Yes
File Location	**V:\firmsnz\paddock\ltrs&rev\76744n0503.doc**

I. Executive Summary

The firm has submitted a single-dose, 2-way crossover fasting bioequivalence study comparing the test product, Testosterone Gel, 1%, with the RLD product, Unimed Pharmaceuticals' AndroGel® (testosterone gel) 1%. The fasting study was performed in 81 male hypogonadal patients at a dose of approximately 2x5 gm and resulted in acceptable data (point-estimate, 90% CI) that demonstrate BE in the fasted state (AUCt 0.99, 96.2-101.5; Cmax 0.96, 88.6-104.2). It should be noted that the study was conducted in 7 groups and 2 sites, and the group*treatment term for lnAUCt and lnCMAX was found statistically significant. Various additional analyses were done, using weight of group sample size (with group*treatment term removed), excluding subjects from Site 2, retaining group*trt term, using baseline-uncorrected data and analyzing each group separately. The results of all analyses showed that the study met the confidence interval criteria except for the analyses of Groups #1, 2, 3, 4, 6 and 7 alone, where the study power was evidently insufficient (the number of subjects was low for Groups # 1, 2, 3, 4 and 6 (n=5 to n=12) or the intrasubject variability, measured by root MSE, was high for Group #7 (n=26)). Analysis of Group #5(n=18) alone showed the study results passed the 90% confidence interval criteria for lnCmax and lnAUCt (n=18), but not lnAUCinfinity (n=11 only for estimable AUCinfinity). Although the number of subjects in Group #5 was smaller compared with Group #7, the intrasubject variability for Group #5 (recruited at Site 1, USA) was significantly lower, compared with that of Group #7 (recruited at Site 2, Canada). Based on the results of the above-mentioned analyses, the fasting study is considered acceptable.

The firm did not submit *in vitro* testing results for the test product. Currently there was no FDA-recommended release method for the drug product. The firm is recommended to develop an *in vitro* testing method and conduct *in vitro* testing for the test product for stability and quality control programs in the future.

The application is acceptable with no deficiencies.

II. Table of Contents

III. Submission Summary

A. Drug Product Information

Test Product	Paddock's Testosterone Gel, 1%
Reference Product	AndroGel® (testosterone gel) 1%. The Orange Book staff confirmed that the 2.5 g and 5 g unit doses of AndroGel® are considered as one strength, i.e., 1% (See the review of Control Document No. 02-284 ((b) (4) ; 05/15/02)
RLD Manufacturer	Unimed Pharmaceuticals
NDA No.	21-015
RLD Approval Date	02/28/2000
Indication	AndroGel® is indicated for replacement therapy in males for conditions associated with a deficiency or absence of endogenous testosterone: Primary hypogonadism (congenital or acquired) and hypogonadotropic hypogonadism (congenital or acquired). These men have low testosterone serum levels but have gonadotropins in the normal or low range.

B. PK/PD Information (PDR 2004)

Bioavailability	10%
Food Effect	N/A
Tmax	2 hours
Metabolism	Metabolized to various 17-keto steroids. The major active metabolites are estradiol and dihydrotestosterone (DHT).
Excretion	About 90% of a dose of testosterone given intramuscularly is excreted in the urine as glucuronic and sulfuric acid conjugates of testosterone and its metabolites; about 6% of a dose is excreted in the feces, mostly in the unconjugated form. Inactivation of testosterone occurs primarily in the liver.
Distribution	Circulating testosterone is chiefly bound in the serum to sex hormone-binding globulin (SHBG) and albumin. The albumin-bound fraction of testosterone easily dissociates from albumin and is presumed to be bioactive. The portion of testosterone bound to SHBG is not considered biologically active. The amount of SHBG in the serum and the total testosterone level will determine the distribution of bioactive and nonbioactive androgen. SHBG-binding capacity is high in prepubertal children, declines during puberty and adulthood, and increases again during the later decades of life. Approximately 40% of testosterone in plasma is bound to SHBG, 2% remains unbound (free) and the rest is bound to albumin and other proteins.
Half-life	10-100 minutes
Relevant OGD or DBE History	**Protocol Nos. 01-019 ((b) (4) 04/09/01) and 01-023 ((b) (4) ; 04/23/01), Control Document Nos. 02-162 ((b) (4) ; 03/22/02) and 02-284 ((b) (4) (b) (4) ; 05/15/02):** The DBE recommended the following concerning the bioequivalence requirements for the drug product:

- A single-dose, two-way crossover fasting bioequivalence study in hypogonadal male volunteers, not in female volunteers.
- Measurement of testosterone only in plasma. Measurement of the metabolite DHT is not necessary for an ANDA.
- Individual post-dose concentrations should be corrected for endogenous circadian testosterone levels at corresponding time points. The baseline corrected and uncorrected data and statistical analyses should be submitted to the Agency.
- Cumulative skin irritation and skin sensitization studies are not necessary for this product. However, irritation/sensitization occurring during the study

should be recorded and submitted, preferably in a summary table.

Relevant NDA Information

- Analytical methods used for studies of NDA's of testosterone gels (NDA Nos. 21-015 (AndroGel®), 21-463 (Fortigel®) and 21-454 (Testim™) measured total and free testosterone as well as DHT (mostly RIA methods, with free testosterone measured by equilibrium dialysis). However, extensive PK analyses were performed on total testosterone concentrations. (Total testosterone is the same as free plus protein (albumin) bound testosterone.)
- For NDA 21-015 (AndroGel®), baseline total testosterone levels were measured for 24 hours predose and the mean baseline total testosterone levels range from 1.88 ng/mL (CMIN) to 3.33 ng/mL (CMAX) during this predose period. The CMIN baseline levels were found at approximately 12 hours predose (evening) and CMAX baseline levels were found at approximately 24 hours and 0 hour predose (morning). In hypogonadal male volunteers, the baseline total testosterone levels were averaged at 1.67 ng/mL.
- No *in vitro* testing method and data were reported for the RLD product, AndroGel® (NDA 21-015). However, an *in vitro* testing method was developed for Fortigel® (NDA 21-463) using procedure derived from the SUPAC-CMC-7 Guidance with Franz diffusion cells.

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	No	
Vasoconstrictor Studies	No	
Clinical Endpoints	No	
Failed Studies	No	
Amendments	Yes	1(Telephone Amendment to provide long-term stability data and weights of gel applied in the study)

D. Pre-Study Bioanalytical Method Validation

	Parent
Analyte name	Total Testosterone (Total testosterone is the same as free plus protein bound testosterone.)
Internal Standard	(b) (4)
Method description	GC/MS
QC range	0.150 ng/mL, 0.750 ng/mL & 3.50 ng/mL
Standard curve range	0.0500 - 10.0 ng/mL
Limit of quantitation	0.0500 ng/mL
Average recovery of Drug (%)	83.1%
Average Recovery of Int. Std (%)	75.9%
Intraday precision range (%CV)	1.95-7.34%
Intraday accuracy range (%)	93.0-97.3%
Interday precision range (%CV)	3.24-7.60%
Interday accuracy range (%)	96.6-107.2%
Bench-top stability (hrs)	24 hours
Stock stability (days)	87 days
Processed stability (hrs)	19 days
Freeze-thaw stability (cycles)	3 cycles
Long-term storage stability (days)	301 days
Dilution integrity	2-fold, 94.5%; 4-fold, 93.7%
Specificity	Acceptable for Total Testosterone
SOPs submitted	None
Bioanalytical method is acceptable	Yes
20% Chromatograms included (Y/N)	Yes
Random Selection of Serial Chrom	Yes

NOTE: Although the analytical method also measures metabolite DHT simultaneously and the prestudy method validation for DHT was provided, DHT was not measured and/or reported in the actual study. Therefore, the validation data for DHT are not reviewed here.

E. In Vivo Studies

1. Single-dose Fasting Bioequivalence Study

Study Summary	
Study No.	PDL-203
Study Design	Multi-site, randomized, single-dose, two-way crossover
No. of subjects enrolled	88 (6 dosing groups at Site 1, 1 dosing group at Site 2)
No. of subjects completing	87
No. of subjects analyzed	81*
Subjects (Normal/Patients?)	Hypogonadal patients
Sex(es) included (how many?)	Male: 81 Female: 0
Test product	Paddock's Testoterone Gel, 1%
Reference product	AndroGel® (testosterone gel), 1%
Strength tested	1%
Dose	10 gm

*NOTE: Of 87 completing subjects, there were 81 subjects who met the inclusion criteria for the mean pre-dose value in each period (<3.45 ng/mL) and were used in the study analysis.

Summary of Statistical Analysis of All Evaluable Subjects Corrected for Average Baseline (N=81) Additional Information in Appendix and Table 7		
Parameter	**Point Estimate**	**90% Confidence Interval**
AUC0-t	0.92	82.0-102.0
AUC∞	0.94	82.5-108.2
Cmax	0.93	81.4-105.6

Summary of Statistical Analysis of All Evaluable Subjects Uncorrected for Average Baseline (N=81) Additional Information in Appendix and Table 7		
Parameter	**Point Estimate**	**90% Confidence Interval**
AUC0-t	0.99	96.2-101.5
Cmax	0.96	88.6-104.2

Summary of Statistical Analysis of Group #5* Corrected for Average Baseline (N=18) Additional Information in Appendix and Table 7		
Parameter	**Point Estimate**	**90% Confidence Interval**
AUC0-t	0.95	83.5-109.1
AUC∞	0.95	75.2-121.2 (n=11)
Cmax	1.00	89.3-110.8

*NOTE: The original statistical analysis of 81 subjects resulted in statistically significant group*treatment term. Additional statistical analyses were carried out including separate analysis of each of the 7 groups of subjects. See the SAS output of all statistical analyses in the review Appendix.

Reanalysis of Study Samples (for Other Than Analytical Reasons) Additional information in Appendix								
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**
Confirmatory reassays	**17**	**10**	**0.20**	**0.12**	**16**	**10**	**0.19**	**0.12**

Did use of recalculated plasma concentration data change study outcome? The firm stated that *"Based on FDA's current position on samples reanalyzed as PK repeats, the results of this study were evaluated using only the original values for any samples that*

were reassayed for confirmatory reasons." This statement has been verified by the reviewer to be correct.

Comments on Fasting Study: The fasting study is acceptable. See additional comments under Comments section.

2. Single-dose Fed Bioequivalence Study N/A

F. Formulation

Location in appendix	Section B, Page 19
Inactive ingredients within IIG Limits (yes or no)	**Yes**
If no, list ingredients outside of limits	
If a tablet, is the product scored? (yes or no)	**N/A**
If yes, which strengths are scored?	
Is scoring of RLD the same as test? (yes or no)	**N/A**
Formulation is acceptable (yes or no)	**Yes**
If not acceptable, why?	

G. In Vitro Dissolution The firm did not submit *in vitro* testing results for the test product. Currently there was no FDA-recommended release method for the drug product. The firm is recommended to develop an *in vitro* testing method and conduct *in vitro* testing for the test product for stability and quality control programs in the future.

H. Waiver Request(s) N/A

Strengths for which waivers requested	N/A
Regulation cited	
Proportional to strength tested in vivo (yes or no)	
Dissolution is acceptable (yes or no)	
Waiver granted (yes or no)	

I. Deficiency Comments None

J. Recommendations

1. The single-dose, fasting bioequivalence study conducted by Paddock Laboratories on the test product, Testosterone Gel, 1%, lot # 2044938, comparing it with the reference product, Unimed Pharmaceuticals' AndroGel® (testosterone gel) 1%, lot #00688 has been found **acceptable** by the Division of Bioequivalence. The test product, Paddock's Testosterone Gel, 1%, is deemed bioequivalent to the reference product, Unimed Pharmaceuticals' AndroGel® (testosterone gel) 1%.

2. The firm is recommended to develop an *in vitro* testing method and conduct *in vitro* testing for the test product for stability and quality control programs in the future.

6/15/04

Hoainhon Nguyen, Review Team I, Date signed

6/15/2004

Yih Chain Huang, Ph.D., Team Leader, Review Team I, Date signed

6/15/04

Dale P. Conner, Pharm. D.
Director, Division of Bioequivalence
Office of Generic Drugs

HNguyen/03-01-04/Revised 06-08-04/v:\firmsnz\paddock\ltrs&rev\76744n0503.doc

IV. Appendix

A. Individual Study Reviews

1. Single-dose Fasting Bioequivalence Study

Study Information	
Study Number	PDL-203
Study Title	A Multi-Site, Randomized, Single-Dose, Two-Way Crossover Relative Bioavailability Study of Testosterone Gel Formulations in Hypogonadal Men
Clinical Site	SFBC Ft. Myers, Fr. Myers, FL & SFBC Anapharm, Quebec, Canada
Principal Investigator	Ira A. Zucker, M.D. & Eric Bicrell, M.D.
Study/Dosing Dates	Group I: 10/26/02 & 11/02/02 (Subjects #101-109 (n=8*)) Group II: 11/13/02 & 11/20/02 (Subjects #110-115 (n=5*)) Group III: 11/23/02 & 11/30/02 (Subjects #116-127 (n=12)) Group IV: 12/28/02 & 01/04/03 (Subjects #128-132 (n=5)) Group V: 03/15/03 & 03/22/03 (Subjects #133-150 (n=18)) Group VI: 04/05/03 & 04/12/03 (Subjects #151-158 (n=7*)) Group VII:03/22/03 & 03/29/03 (Subjects #201-230 (n=26*)) Subjects from Groups I-VI were recruited between 10/16/02-04/02/03 at SFBCFM (Florida, USA) and subjects from Group VII were recruited between 03/01/03-03/21/03 at SFBC Anapharm (Quebec, Canada). The sample analysis started on 02/28/03 (before Group V was dosed). Last sample of Group IV (Subject #132) was analyzed on 04/08/03 (after Group V was dosed). Samples from Group V were analyzed between 04/10/03-04/15/03 (after Group VI was dosed). Samples from Group VII were analyzed between 04/15/03-04/28/03 before the samples of Group VI were analyzed (between 04/28/03-04/29/03) but after Group VI was dosed. It did not appear that these groups were added on based on the statistical analysis of previous groups. The use of multiple groups appeared due to the availability of hypogonadal male subjects. *NOTE: Without dropout subjects and subjects who did not meet the inclusion criteria.
Analytical Site	(b) (4)
Analytical Director	(b) (6)
Analysis Dates	02/28/03-05/07/03
Storage Period (no. of days from first sample to final analysis)	301 days

Treatment ID	A	B
Test or Reference	Test	Reference
Product Name	Testosterone Gel	AndroGel®
Manufacturer	Paddock	Unimed
Batch/Lot No.	2044938	00688
Manufacture Date	Not provided	
Expiration Date	12/03	09/03
Strength	1%	1%
Dosage Form	Gel	Gel
Batch Size	(b) (4)	
Potency	99.5%	97.4%
Content Uniformity	98.4% (RSD=0.9%)	99.3% (RSD=0.9%)
Formulation	See Appendix Section B	
Dose Administered	10 gm	10 gm
Route of Administration*	Topical	

***NOTE:**

- An adhesive, sterile, non-absorbent plastic drape (i.e., (b) (4)) was placed above the antecubital space of each arm.
- Packets containing the drug were placed in individual plastic bags and the bags were closed and weighed. At dosing, the individual packets were removed from the bag and the gel was squeezed away from the end of the packet to be opened. The ends of the packets were removed and returned to the bag, and the gel was squeezed from the packets onto the shoulders and upper arms. The emptied packets were returned to the plastic bag and the bag was re-weighed. The individual applying the drug donned a pre-weighed rubber glove. The drug was distributed evenly throughout the area by hand and the glove was then removed and reweighed.

The weights of gel were averaged for each treatment as shown below.

	Test	**Reference**
Mean	9.709 gm (n=81)	9.615 gm (n=81)
CV%	1.85	1.94

- Approximately 10 gm (2 packets) of study drug was applied to the area of each subject. As soon as the gel dries (approximately 30 minutes), the plastic drape was removed carefully and the subjects wore a short sleeve scrub top.
- Immediately following collection of the 24 hour blood sample, the subjects showered so as to remove any residual, unabsorbed study drugs, and wore a clean shirt.

No. of Sequences	2
No. of Periods	2
No. of Treatments	2
No. of Groups	7
Washout Period	7 days
Randomization Scheme	Yes
Blood Sampling Times	-15 (±2), -8, 0, 1, 2, 3, 4, 6, 8, 10, 12, 14, 16, 18, 20, 24, 28, 32, 36, 40, 48, 60, 72 and 96 hours postdose.
Blood Volume Collected/Sample	10 mL/sample
Blood Sample Processing/Storage	Blood samples were collected in heparin-containing evacuated tubes, centrifuged and harvested for plasma which was stored at -20°C until shipping to the analytical laboratory.
IRB Approval	Yes
Informed Consent	Yes
Subjects Demographics	See Table 1
Length of Fasting	Approximately 10 hours predose to 4 hours postdose.
Length of Confinement	Approximately 13 hours predose to 48 hours postdose
Safety Monitoring*	Blood pressure, heart rate, respiratory rate and body temperature were measured at predose, 2, 4 and 6 hours postdose.

***NOTE:** The application site was examined and recordings were made for signs of erythema and edema just prior to and 4, 12, 24 and 48 hours post-application. Erythema and edema would be considered adverse events and evaluated by a dermatologist. These reactions would be scored using the International Contact Dermatitis Research Group system, where: 0=no reation; 1=erythema; 2=erythema and edema; and 3= marked erythema and edema.

Table 1 Demographics of Study Subjects [N = 81]

Age		Weight (kg)		Age Groups		Gender		Race	
				Range	%	Sex	%	Category	%
				<18	0.0			Caucasian	88.6
Mean	55.80	Mean	91.04	18-40	8.6	Male	100.0	Afr. Amer.	0.0
SD	9.66	SD	13.76	41-64	65.4	Female	0.0	Hispanic	11.4
Range	36	Range	62.7	65-75	25.9			Asian	0.0
	70		121.8	>75	0.0			Others	0.0

Study Results

Table 2 Dropout Information*

Subject No	103
Reason	Withdrew consent and failed to return for Period II
Period	II
Replacement	No

*NOTE: In addition to Subject #103, Subjects #112, 151, 206, 208, 213 and 216 were excluded from the statistical analyses as their mean predose values for Period I and/or Period II did not meet the inclusion criteria of <3.45 ng/mL as specified in the protocol.

Was there a difference in side effects for the test versus the reference? There was no clear difference in side effects for the test versus the reference product. The severity of the adverse effects ranged from mild to moderate, with one severe reaction (headache for Subject #118 during Reference treatment).

Table 3 Study Adverse Events

Adverse Event Description	# in Test Group	# in Reference Group
Hypertension	2	1
Headache	8	9
Vomiting	1	
Bowel movement with blood		1
Back spasms	1	
Muscle soreness		1
Lightheadedness	1	
Sinus allergy congestion	1	
Soreness at saline lock site	1	
Right elbow pain		1
Cold symptoms	1	
Swollen hands due to previous auto accident		1
Stiff neck	1	
Migraine	2	1
High blood pressure	11	4
Swollen testicles		1
Pain on buttock		2
Pain on calves		2
Dry skin	1	
Hot flushes	1	
Heartburn		1
Shoulder pain		1
Pimples on face	1	
Redness on forehead	1	
Tachycardia	1	
Burning sensation of left thumb		1
Muscle cramp on left calf		3
Itching in muscles	1	
Pimple on right arm		1
Bradycardia	2	1
Back pain	2	2
Pressure on the testicles		1
Bruised right elbow		1
General muscle stiffness	1	1

Table 4 Study Adverse Events (Continued)

Adverse Event Description	# in Test Group	# in Reference Group
Hemorrhoids	1	
Flatulence		1
Constipation		1
Bruises on arms	2	
Low blood pressure	2	
Pain on bruised arm	1	
Sore throat	1	
Irregular Pulse		2
Dizziness		2
Itchiness on back	3	1
Testicular Inflammation		1
Stuffy nose	1	1
Heating at the dosing site		1
Total:	**54**	**47**

Comments: *(on adverse events)* None

Was there a difference in protocol deviations for the test versus the reference? None of the protocol deviations appeared to compromise the integrity of the study. Blood sampling time deviations did not affect the study results since actual sampling times were used in the study result calculation and analysis.

Table 5 Assay Validation – Within Study

	Parent: Total Testosterone		
QC Conc. (ng/mL)	0.400 (n=176)	2.00(n=177)	8.00(n=177)
Inter day Precision (%CV)	5.9	5.1	5.5
Inter day Accuracy (%)	96.1	100.5	89.9
Cal. Standards Conc. (ng/mL)	0.250, 0.500, 0.750, 1.00, 2.50, 5.00, 7.50, 10.0		
Inter day Precision (%CV)	2.6-4.4		
Inter day Accuracy (%)	91.9-106.5		
Linearity Range (range of R^2 values)	0.250-10.0 (0.981-0.998)		

Chromatograms: Any interfering peaks? No.

SOP's dealing with analytical repeats of study samples: None provided.

Comments on repeat assays. The firm followed the current DBE's practice on samples reassayed for PK reasons or confirmatory reasons: only original values for these samples were used in the study result calculation and analysis. The reviewer agrees with the firm's approach.

Comments on Within-Study Validation: None

Conclusion: Analytical method is acceptable.

Table 6 Arithmetic Mean Pharmacokinetic Parameters - Corrected for Average Baseline (N=81)

NOTE: Average Total Testosterone Baseline Levels:

Test Treatment: 2.29 ng/mL (CV%=30; range: 0.49 - 3.32 ng/mL)
Reference Treatment: 2.25 ng/mL (CV%=30; range: 0.24 - 3.44 ng/mL)

The baseline sampling times were -15, -8 and 0 hour predose. Usually, -24, -12 and 0 hour predose sampling times are selected for circadian baseline levels. Based on the baseline data collected for a PK study submitted for the RLD product (NDA 20-015 submission dated 04/29/99), at approximately -15 to -12 hours predose (evening) minimum testosterone levels were observed and approximately -24 hours and 0 hour predose (morning), maximum testosterone levels were observed. Therefore, the baseline sampling times as chosen in this study are considered acceptable for approximating the range of the baseline testosterone levels.

Mean plasma concentrations are presented in Table 9 and Figure 1

Parameter	Units	Test		Reference		T/R
		Mean	%CV	Mean	% CV	
AUC_{0-t}	Ng.hr/mL	98.27	45	100.0	42	0.98
AUC_{∞}	Ng.hr/mL	108.4	49	122.7	39	0.88
C_{max}	Ng/mL	4.612	47	4.769	53	0.97
T_{max}	Hrs	18.41	42	18.05	36	1.02
$T_{1/2}$	Hrs	11.77	53	13.85	62	0.85
kel	Hrs^{-1}	0.07834	57	0.06841	55	1.14

Table 7 Least Squares Geometric Means and 90% Confidence Intervals (N=81)

Parameter	Test	Reference	T/R	90% CI
AUC_{0-t}	90.13	98.53	0.92	82.0-102.0
AUC_{∞}	108.7	115.0	0.94	82.5-108.2
C_{max}	4.070	4.390	0.93	81.4-105.6

Table 8 Additional Study Information

Root mean square error, AUC_{0-t}	1.114567 (weight=group sample size)	
Root mean square error, AUC_{∞}	1.332627 (weight=group sample size)	
Root mean square error, C_{max}	0.856858 (weight=group sample size)	
mean ratio AUC_{0-t}/AUC_{∞}	T =0.9600	R =0.9436
Range of values, ratio AUC_{0-t}/AUC_{∞}	T =0.8001-0.9982	R =0.7422-0.9999

Comments: (on pharmacokinetic analysis)

- kel and AUC∞ were determined for how many subjects: 40 subjects for Test treatment; 38 subjects for Reference treatment. The reviewer agrees with the firm's decision where KEL could not be calculated.
- Indicate the number of subjects with the following:
  a. measurable drug concentrations at 0 hr: None
  b. first scheduled post-dose sampling time as Tmax: None
  c. first measurable drug concentration as Cmax: None

- Did pharmacokinetic parameters and 90% confidence intervals calculated by the reviewer agree with firm's calculations? The firm did not calculate using the same model. Both the firm and reviewer found grp*trt interaction term significant (for LAUC(0-t) (p=0.0443) and LCMAX (p=0.0173)). The firm attributed the significant interaction term to Subject #111 (*"as removing this subject removed the significance for the interaction term for LCMAX (p=0.1784)"*). The firm analyzed the study results with the grp*trt interaction term removed from the model.

  Following the recommendations given by the Agency's statistician concerning statistical analysis of studies with more than one group included, ***the reviewer used weights of group sample sizes in the analysis when removing grp*trt term from the model***. (See the Consult Review in the Appendix for the detailed discussion of the analysis method for ANDA [redacted] (b) (4) which also had more than one groups in the bio study.). See discussion of additional analyses for grp*trt significant effect at the end of this section.

- Were there statistically significant sequence or period effects? The per (grp) term was found significant for LAUC(0-t) (p=0.0117), LCMAX (p=0.0263) and LAUC(0-Infinity) (p=0.0467). However, the period effect is generally thought not to affect the integrity of the study. In addition, the term per(grp) was retained in the model used to calculate the 90% confidence interval for LAUC's and LCMAX.

- Are the 90% confidence intervals for AUC0-t, AUC∞, Cmax within the acceptable limits of 80-125%. Yes

- **Statistical Analysis for Group Effect:** If the subjects were dosed as more than one group, comment on the statistical analysis for group effect? Following the recommendations of the Agency's statistician, the following model was used for analysis of the study which had 7 groups and 2 sites: Model Y=grp seq grp*seq subj(grp*seq) per(grp) trt grp*trt, where grp, seq, per and trt were class variables. Since the grp*trt term was found significant for LAUC(0-t) and LCMAX, the following additional analyses were performed (See the SAS output of these analyses on pages 22-24):

  1. **With grp*trt term removed and weights of group sample sizes used in the analysis (See the results summarized above.):** The 90%

confidence interval for LAUC's and LCMAX was within the acceptable limits.

2. **With Group #7 (of 26 subjects) removed since Group #7 was the only group from Site 2:** The 90% confidence interval for LAUC's and LCMAX was within the acceptable limits.. However, since ***the grp*trt term remained significant for LCMAX (p=0.0422) after the removal of Group #7***, weights of group sample sizes were used in the analysis of the remaining 6 groups (without grp*trt term included). The 90% confidence interval for LAUC's and LCMAX was within acceptable limits based on this analysis.

3. **Separate analyses of each of 7 groups:** The confidence interval criteria was not met for the analyses of Groups #1, 2, 3, 4, 6 and 7 alone, where the study power was evidently insufficient (the number of subjects was low for Groups # 1, 2, 3, 4 and 6 (n=5 to n=12) or the intrasubject variability, measured by root MSE, was high for Group #7 (n=26)). Analysis of Group #5(n=18) alone showed the study results passed the 90% confidence interval criteria for lnCmax and lnAUCt (n=18), but not lnAUCinfinity (n=11 only for estimable AUCinfinity). Although the number of subjects in Group #5 was smaller compared with Group #7, the intrasubject variability for Group #5 (recruited at Site 1, USA) was significantly lower, compared with that of Group #7 (recruited at Site 2, Canada) for lnAUCt and lnCmax:

	Root MSE	
	lnAUCt	lnCmax
Group #5	0.230273	0.185265
Group #7*	0.312100	0.368726

(***NOTE:** n=13 only for estimable AUCinfinity for Group #7. Similarly, n=11 for estimable AUCinfinity for Group #5. Therefore, Root MSE was not evaluated for lnAUCinfinity)

4. **Based on the analysis of all evaluable subjects (n=81), with grp*trt term retained in the model**, the 90% confidence interval for LAUC(0-t) and LCMAX was within the acceptable limits. (Least Squares Means for LAUC(0-Infinity) were non-estimatable.)

5. **Based on baseline-uncorrected total testosterone for all evaluable subjects (n=81) with grp*trt term retained**: The 90% confidence interval for LAUC(0-t) and LCMAX was within the acceptable limits.

6. **Based on baseline-uncorrected total testosterone for all evaluable subjects (n=81) using weight of group sample size:** The 90% confidence interval for LAUC's and LCMAX was within the acceptable limits.

Conclusion: Based on the results of the analyses above, the single-dose fasting bioequivalence study is considered acceptable.

Table 9 Mean Baseline-Corrected Testosterone Plasma Concentrations (ng/mL) Single-Dose Fasting Bioequivalence Study

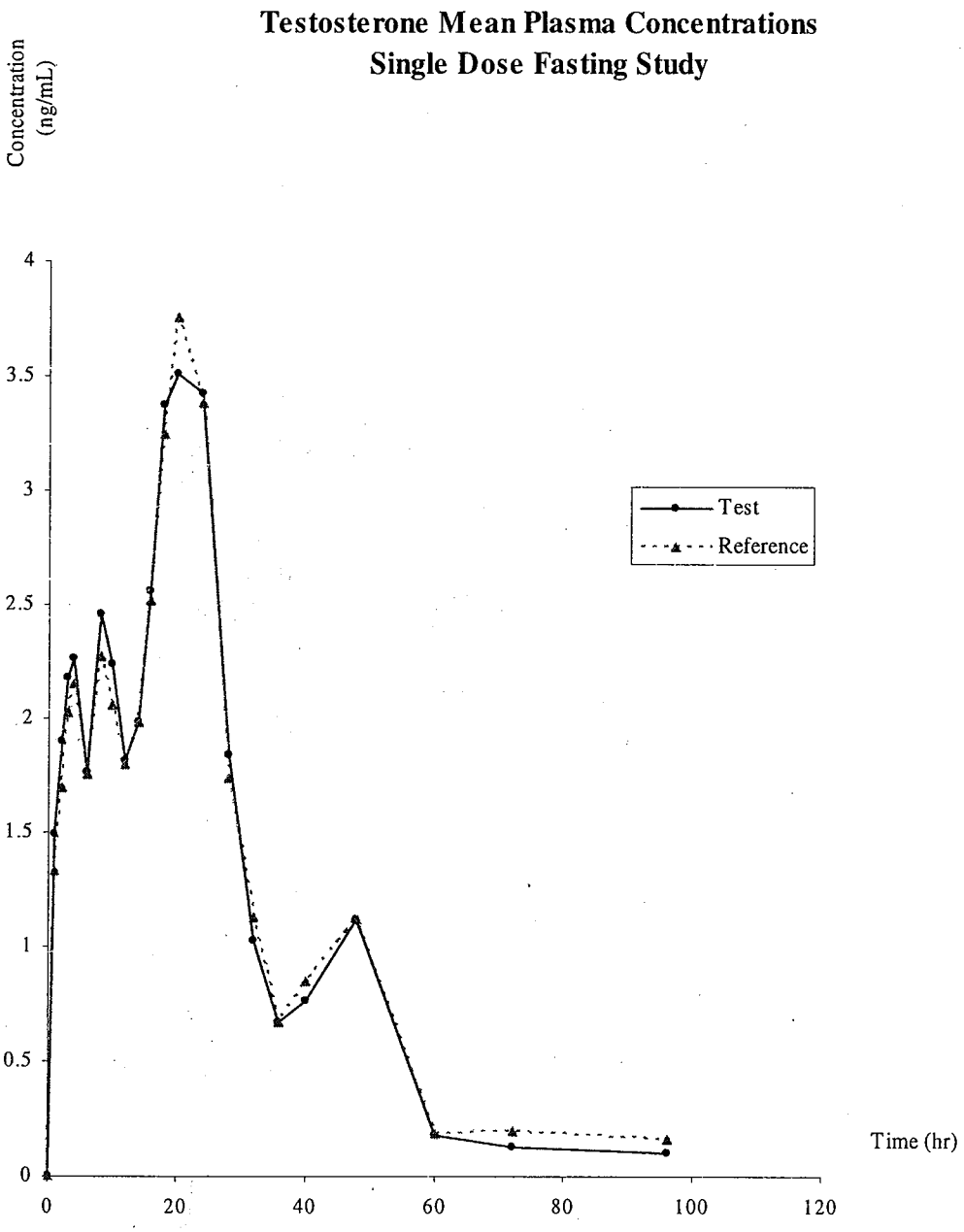
Test Treatment

Time	N	Mean	Coeff of Variation	Minimum	Maximum
Hour0	81	0.000	.	0.000	0.000
Hour1	81	1.492	72.997	0.000	6.540
Hour2	81	1.895	79.650	0.000	11.110
Hour3	81	2.177	68.741	0.547	10.280
Hour4	81	2.267	57.294	0.000	6.490
Hour6	81	1.759	83.137	0.067	9.226
Hour8	81	2.454	65.104	0.000	10.007
Hour10	81	2.241	53.445	0.000	5.320
Hour12	81	1.816	62.678	0.000	6.020
Hour14	81	1.981	64.881	0.000	6.313
Hour16	81	2.557	58.472	0.000	8.107
Hour18	81	3.374	54.449	0.773	11.507
Hour20	81	3.509	50.366	0.000	9.007
Hour24	81	3.421	45.581	0.777	10.070
Hour28	81	1.840	63.598	0.000	6.777
Hour32	81	1.026	74.482	0.000	4.037
Hour36	81	0.673	101.156	0.000	3.523
Hour40	81	0.762	90.327	0.000	3.247
Hour48	81	1.117	77.357	0.000	4.017
Hour60	81	0.174	205.205	0.000	1.657
Hour72	81	0.131	194.261	0.000	0.963
Hour96	81	0.102	203.484	0.000	1.193

Reference Treatment

Time	N	Mean	Coeff of Variation	Minimum	Maximum
Hour0	81	0.000	.	0.000	0.000
Hour1	81	1.331	66.315	0.003	3.990
Hour2	81	1.698	57.760	0.163	5.737
Hour3	81	2.024	62.736	0.000	8.493
Hour4	81	2.154	51.102	0.337	5.310
Hour6	81	1.758	67.352	0.000	5.780
Hour8	81	2.269	70.571	0.000	10.943
Hour10	81	2.059	46.875	0.450	5.013
Hour12	81	1.797	59.805	0.000	5.763
Hour14	81	1.979	59.776	0.110	6.244
Hour16	81	2.513	73.717	0.070	13.383
Hour18	81	3.246	56.704	0.000	8.540
Hour20	81	3.750	63.588	0.000	13.083
Hour24	81	3.380	46.057	0.000	11.370
Hour28	81	1.737	57.883	0.000	4.670
Hour32	81	1.126	62.805	0.000	3.230
Hour36	81	0.667	91.089	0.000	2.677
Hour40	81	0.850	84.406	0.000	3.187
Hour48	81	1.121	73.815	0.000	3.040
Hour60	81	0.186	250.393	0.000	3.447
Hour72	81	0.192	198.547	0.000	2.674
Hour96	81	0.158	170.848	0.000	1.374

Figure 1


Testosterone Mean Plasma Concentrations
Single Dose Fasting Study
Concentration (ng/mL)
4
3.5
3
2.5
2
1.5
1
0.5
0
0
20
40
60
80
100
120
Time (hr)
Test
Reference

2. Single-dose Fed Bioequivalence Study N/A

B. Formulation Data

Ingredients	Amount per gm	% w/w
Testosterone USP	10.000	1.000
Ethanol (Alcohol USP)	[redacted]	(b) (4)
Purified Water USP		
Carbomer 940 NF		
Isopropyl Myristate NF		
Sodium Hydroxide NF		
[redacted]		(b) (4)

C. Dissolution Data N/A (The firm did not submit *in vitro* release testing for the test product.)

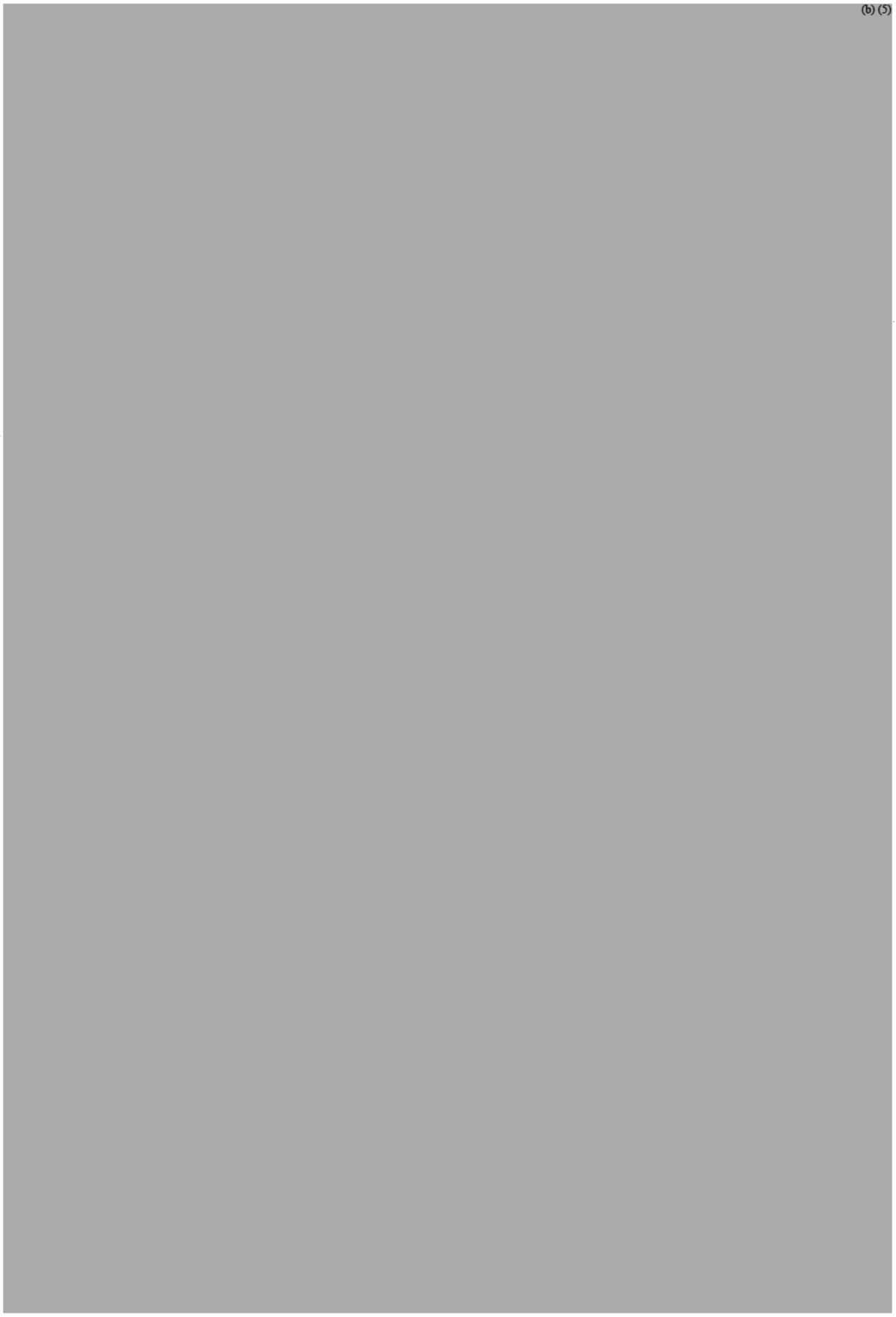
D. Consult Reviews Statistical Consult for Analysis of Group Effect (The consult response was from ANDA 40-557 and addressed similar issues concerning analyzing bioequivalence studies with more than one group included.)

From: Schuirmann, Donald J
Sent: Tuesday, October 28, 2003 11:02 AM
To: Nguyen, Hoainhon T
Cc: Machado, Stella G; Huang, Yih Chain; Li, Huaixiang; Conner, Dale P; Li, Qian H
Subject: RE: Statistical Consult for ANDA 40-557 (Sicor's Methylprednisolone Acetate Injectable Suspension)

Hoai,

(b) (5)

[redacted]


(b) (5)

(b) (5)

[redacted]

E. SAS Output: Analysis Based on All Evaluable Subjects (n=81) Using Weight of Group Sample Size (Baseline-Corrected Total Testosterone)

C:\Data\
REVIEWS\76744fa

F. Additional Attachments SAS Outputs for Additional Analyses

1. Analysis Based on All Evaluable Subjects (n=81) and With Grp*Trt Interaction Term Retained in the Model (for Baseline-Corrected Total Testosterone)

C:\Data\
REVIEWS\76744a

2. Analysis Based on 6 Groups of Evaluable Subjects (n=55) From Site 1 (Group #7 excluded) and With Grp*Trt Interaction Term Retained (for Baseline-Corrected Total Testosterone)

C:\Data\
REVIEWS\76744a

3. Analysis Based on 6 Groups of Evaluable Subjects (n=55) From 1 Site (Group #7 Excluded), With Grp*Trt Term Removed and Using Weight of Group Sample Size (for Baseline-Corrected Total Testosterone)

C:\Data\
REVIEWS\76744a

4. **Separate Analyses of Each of 7 Groups:**
   a) **Based on Group #1 Alone (n=8) From Site 1 (for Baseline-Corrected Total Testosterone)**

76744FASTGRP1
ONLY.lst

   b) **Based on Group #2 Alone (n=5) From Site 1 (for Baseline-Corrected Total Testosterone)**

76744FASTGRP2
ONLY.lst

   c) **Based on Group #3 Alone (n=12) From Site 1 (for Baseline-Corrected Total Testosterone)**

76744FASTGRP3
ONLY.lst

   d) **Based on Group #4 Alone (n=5) From Site 1 (for Baseline-Corrected Total Testosterone)**

76744FASTGRP4
ONLY.lst

   e) **Based on Group #5 Alone (n=18) From Site 1 (for Baseline-Corrected Total Testosterone)**

76744FASTGRP5
ONLY.lst

   f) **Based on Group #6 Alone (n=7) From Site 1 (for Baseline-Corrected Total Testosterone)**

76744FASTGRP6
ONLY.lst

   g) **Based on Group #7 Alone (n=26) From Site 2 (for Baseline-Corrected Total Testosterone)**

76744FASTGRP7
ONLY.lst

5. **Analysis Based on All Evaluable Subjects (n=81) With Grp*Trt Term Retained in the Model (for Baseline-Uncorrected Total Testosterone)**

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REVIEWS\76744a

6. Analysis of All Evaluable Subjects (n=81) Using Weight of Grp Sample Size (for Baseline-Uncorrected Total Testosterone)

C:\Data\
REVIEWS\76744a

BIOEQUIVALENCE COMMENTS

ANDA: 76-744 APPLICANT: Paddock Laboratories

DRUG PRODUCT: Testosterone Gel, 1%

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

We recommend that you develop an *in vitro* testing method and conduct *in vitro* testing for the test product in the future.

In future applications, please include the address of the laboratories conducting the dissolution testing in the bioequivalence section of the ANDA.

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

CC:ANDA 76-744
ANDA DUPLICATE
DIVISION FILE
FIELD COPY
HFD-652/ Bio Secretary - Bio Drug File
HFD-652/ HNguyen
HFD-652/ YHuang

Endorsements: (Final with Dates)
HFD-652/ HNguyen DNC
HFD-652/ YHuang 6/15/2004
HFD-617/ A. Sigler
HFD-650/ D. Conner 6/15/04

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Printed in final on / /

BIOEQUIVALENCY - ACCEPTABLE Submission date: 05-21-03 ~~& 02-19-04~~

1. FASTING STUDY (STF) OIC Strength: 1%
Clinical: SFBC Ft. Myers, Fr. Myers, FL & SFBC Anapharm, Quebec, Canada
Outcome: AC
Analytical: [redacted] (b)(4)

2. STUDY AMENDMENT (STA) (Long-term stability data; weights of gel applied in the study)
Strength: 1%
Outcome: AC

OUTCOME DECISIONS: **IC** - Incomplete **UN** - Unacceptable (fatal flaw)
AC - Acceptable **NC** - No credit

OFFICE OF GENERIC DRUGS
DIVISION OF BIOEQUIVALENCE

ANDA # : 76-744 SPONSOR : Paddock Laboratories
DRUG AND DOSAGE FORM : Testosterone Gel
STRENGTH(S) : 1%
TYPES OF STUDIES : Fasting Study
CINICAL STUDY SITE(S) : SFBC Ft. Myers, Fr. Myers, FL & SFBC Anapharm, Quebec, Canada
ANALYTICAL SITE(S) : (b) (4)

STUDY SUMMARY : Acceptable
DISSOLUTION : N/A
WAIVER REQUEST: N/A

DSI INSPECTION STATUS

Inspection needed: No	Inspection status:	Inspection results:
First Generic YES New facility _____ For cause _____ Other _____	Inspection requested: (date) Inspection completed: (date)	

PRIMARY REVIEWER : Hoainhon Nguyen BRANCH : I
INITIAL : HNC DATE : 6/15/04

TEAM LEADER : Yih-Chain Huang BRANCH : I
INITIAL : YCH DATE : 6/15/2004

DIRECTOR, DIVISION OF BIOEQUIVALENCE : DALE P. CONNER, Pharm. D.
INITIAL : DPC DATE : 6/15/04

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 076744

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

6/30/03 Ack for filing 505(j)(2)(A) S. Middleton

Concur Martin Hahn 1 July 2003

Concur. 01-JUL-2003 Murray M. Lumpkin

May 21, 2003

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: Testosterone Gel 1%
2.5 gram and 5 gram Packets
Initial Abbreviated New Drug Application (ANDA)

Dear Staff:

Paddock Laboratories, Inc. (Paddock Laboratories) is submitting this original abbreviated new drug application (ANDA), pursuant to Section 505(j) of the Federal Food, Drug and Cosmetic Act, seeking approval to market Paddock Laboratories' Testosterone Gel 1%. Paddock Laboratories Testosterone Gel 1% is bioequivalent to the approved, reference listed drug, AndroGel® (testosterone gel) 1% the subject of NDA 21-015 held by Unimed Pharmaceuticals, Inc.

A multi-site, randomized, single-dose, two-way crossover relative bioavailability study in fasted, hypogonadal men was conducted in support of this application. The study was managed by SFBC Ft. Myers, Inc., Ft. Myers, Florida on behalf of Paddock Laboratories. The study report and supporting documentation are contained in the bioequivalence section of this application.

The enclosed ANDA consists of 11 volumes. Paddock Laboratories is filing an archival copy (in blue folders) that contains all the information required in the ANDA, a technical review copy (in red folders) containing all the information in the archival copy with the exception of the bioequivalence section (Section VI.), and a bioequivalence review copy (in an orange folder) containing all information in the archival copy from the beginning of the ANDA through Section VII Components and Composition Statements. An additional two (2) copies of Section XV Analytical Methods is also provided since the proposed drug product is not subject to a USP monograph.

The enclosed ANDA has been organized according to the Agency's February 1999 Guidance for Industry – "Organization of an ANDA".

3940 Quebec Avenue N, Minneapolis, MN 55427 • 800.328.5113 • 763.546.4676 • Fax:763.546.4842 • www.paddocklabs.com

Paddock Laboratories hereby commits to resolution of any issues identified in the methods validation process after approval.

The drug product which is the subject of this Abbreviated New Drug Application, Testosterone Gel 1%, is not subjected to sterilization processes. Therefore, no sterilization information is included in this application.

We certify that, concurrently with filing this ANDA, a true copy of the technical sections of the ANDA (including a copy of the Form FDA 356h and a certification that the contents are a true copy of those filed with the Office of Generic Drugs) was sent to our local district office.

Please direct any written, telephone or fax communication regarding this application to:

Patrick Johnson
Director of Regulatory Affairs
Paddock Laboratories, Inc.
3940 Quebec Avenue North
Minneapolis, Minnesota 55427
Telephone: (763) 546-4676
Fax: (763) 546-4842

Sincerely,

Paddock Laboratories, Inc.

Patrick L. Johnson
Director of Regulatory Affairs

Enclosures

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE : June 16, 2003

TO : Director
Division of Bioequivalence (HFD-650)

FROM : Acting Chief, Regulatory Support Branch
Office of Generic Drugs (HFD-615)

SUBJECT: Examination of the bioequivalence study submitted with an ANDA for Testosterone Gel, 1%, to determine if the application is substantially complete for filing and/or granting exclusivity pursuant to USC 355(4)(B)(iv).

Paddock Laboratories, Inc. has submitted ANDA 76-744 for Testosterone Gel, 1%. The ANDA contains a certification pursuant to 21 USC 355 (j)(2)(A)(vii)(iv) stating that patent(s) for the reference listed drug will not be infringed by the manufacturing or sale of the proposed product. Also it is a first generic. In order to accept an ANDA that contains a first generic, the Agency must formally review and make a determination that the application is substantially complete. Included in this review is a determination that the bioequivalence study is complete, and could establish that the product is bioequivalent.

Please evaluate whether the study submitted by Paddock on May 22, 2003 for its Testosterone product satisfies the statutory requirements of "completeness" so that the ANDA may be filed.

A "complete" bioavailability or bioequivalence study is defined as one that conforms with an appropriate FDA guidance or is reasonable in design and purports to demonstrate that the proposed drug is bioequivalent to the "listed drug".

June 17, 2003

MAJ. S. Middleton 7/18/03

NEW CORRESP

AMENDMENT

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

(Additional Documents Requested)

NC

Re: ANDA 76-744, Testosterone Gel 1%

Dear Staff:

As requested by Ms. Saundra Middleton, CSO, FDA/CDER/OPS/DLPS, during a telephone conversation on June 16, 2003, the following additional items for the above referenced Abbreviated New Drug Application are enclosed:

1. cGMP Certification - Original signed document to replace copy (Page 4027 of original application).
2. Debarment Certification - Original signed document revised to remove the word "knowingly" as requested (Page 5011 of original application).
3. Two (2) floppy disks, each providing a copy of the SAS datasets for the bioequivalence study (Study No. PDL-203)

The documents included in this amendment serve as replacements for those provided in the original application.

Please direct any written, telephone or fax communication regarding this application to the attention of the undersigned at Paddock Laboratories, Inc., 3940 Quebec Avenue North, Minneapolis, Minnesota 55427, Telephone: (763) 546-4676, Fax: (763) 546-4842.

Sincerely,

Paddock Laboratories, Inc.

Patrick L. Johnson
Director of Regulatory Affairs

RECEIVED
JUN 18 2003
OGD / CDER

Enclosures

JUN 25 2003

BIOEQUIVALENCE CHECKLIST for First Generic ANDA
FOR APPLICATION COMPLETENESS

ANDA# 76-744 **FIRM NAME** **Paddock Laboratories, Inc.**

DRUG NAME Testosterone

DOSAGE FORM **Gel, 1%**
SUBJ: Request for examination of: Bioequivalence Study

Requested by: _____ Date: _____
Chief, Regulatory Support Team, (HFD-615)

	Summary of Findings by Division of Bioequivalence
☒	**Study meets statutory requirements**
☐	**Study does NOT meet statutory requirements**
	Reason:
☐ N/A	**Waiver meets statutory requirements**
☐	**Waiver does NOT meet statutory requirements**
	Reason:

RECOMMENDATION: ☒ **COMPLETE** ☐ **INCOMPLETE**

Reviewed by:

Zakaria Wahba Zakaria Wahba Date: 6/24/03
Reviewer

Gur-Jai Pal Singh Gurjai Pal Singh Date: 6-25-03
Team Leader

Director, Division of Bioequivalence Date: 6/25/03

Item Verified:	YES	NO	Required Amount	Amount Sent	Comments
Protocol	☒	☐			
Assay Methodology	☒	☐			
Procedure SOP	☐	☒			
Methods Validation	☒	☐			
Study Results Ln/Lin	☒	☐			
Adverse Events	☒	☐			
IRB Approval	☒	☐			
Dissolution Data	☐	☒			N/A
Pre-screening of Patients	☒	☐			
Chromatograms	☒	☐			
Consent Forms	☒	☐			
Composition	☒	☐			
Summary of Study	☒	☐			
Individual Data & Graphs, Linear & Ln	☒	☐			
PK/PD Data Disk Submitted)	☒	☐			on the EDR database
Randomization Schedule	☒	☐			
Protocol Deviations	☒	☐			
Clinical Site	☒	☐			
Analytical Site	☒	☐			
Study Investigators	☒	☐			

Medical Records	☒	☐			
Clinical Raw Data	☒	☐			
Test Article Inventory	☐	☒			
BIO Batch Size	☒	☐			
Assay of Active Content Drug	☒	☐			
Content Uniformity	☒	☐			
Date of Manufacture	☒	☐			
Exp. Date of RLD	☒	☐			
BioStudy Lot Numbers	☒	☐			
Statistics	☒	☐			
Summary results provided by the firm indicate studies pass BE criteria	☒	☐			
Waiver requests for other strengths / supporting data	☐	☒			N/A

Additional Comments regarding the ANDA:
The RLD is Unimed Pharms' Androgel Topical Gel, 1% (NDA #21-015).

The following items are not provided in the submission:
1. Prodedure SOP.
2. Test article inventory.

ANDA CHECKLIST
FOR COMPLETENESS and ACCEPTABILITY of an APPLICATION

ANDA#: 76-744 **FIRM NAME** PADDOCK LABORATORIES, INC.

RELATED APPLICATION(S): _____ **First Generic Product Received?** NA

DRUG NAME: TESTOSTERONE
DOSAGE FORM: GEL, 1%

Random Queue: Random 4 Chem Team Leader: Gill, Dave PM: Kim, Sarah

Labeling Reviewer: Catterson, Debbie Micro Review: NA Clinical Review: HIXON

Letter Date MAY 21, 2003	**Received Date** MAY 22, 2003
Comments EC 1 YES **On Cards YES** **androgens/anabolic steroids**	**Therapeutic Code 3020300**
Methods Validation Package (3 copies) (Required for Non-USP drugs) YES	(Not Applicable to Electronically Archived Submissions)
Archival and Review copies Field Copy Certification (Original Signature) YES	(Not Applicable to Electronically Archived Submissions)
Cover Letter YES - cover letter	**Table of Contents YES**
PART 3 Combination Product Category 2 Prefilled Drug Del Dev/Sys (Must be completedfor ALL Original Applications) Refer to the Part 3 Combination Algorithm	

ACCEPTABLE

Sec. I	**Signed and Completed Application Form (356h)** (Statement regarding Rx/OTC Status) YES	☒
Sec. II	**Basis for Submission** **NDA: 21-015** RLD: ANDROGEL Firm: UNIMED PHARMS ANDA suitability petition required? If yes, consult needed for pediatric study requirement.	☒
Sec. III	**Patent Certification** 1. Paragraph: IV - pg. 16 2. Expiration of Patent: AUGUST 30, 2020 A. Pediatric Exclusivity Submitted? B. Pediatric Exclusivity Tracking System checked? **Exclusivity Statement YES - 17**	☒

Sec. IV	**Comparison between Generic Drug and RLD-505(j)(2)(A)** 1. Conditions of use YES 2. Active ingredients YES 3. Route of administration YES 4. Dosage Form YES 5. Strength YES	☒
Sec. V	**Labeling** (Mult Copies N/A for E-Submissions) 1. 4 copies of draft (each strength and container) or 12 copies of FPL YES 2. 1 RLD label and 1 RLD container label YES 3. 1 side by side labeling comparison with all differences annotated and explained YES 4. Was a proprietary name request submitted? NO (If yes, send email to Labeling Rvwr indicating such.)	☒
Sec. VI	**Bioavailability/Bioequivalence** **1. Financial Certification** (Form FDA 3454) **and Disclosure Statement** (Form 3455) YES - pg. 173 **2. Request for Waiver of In-Vivo Study(ies):** N/A **3. Formulation data same?** (Comparison of all Strengths) (Ophthalmics, Otics, Topicals Perenterals) **4. Lot Numbers of Products used in BE Study(ies):** 2044937 **5. Study Type:** (Continue with the appropriate study type box below)	☒
Study Type	**IN-VIVO PK STUDY(IES)** (i.e., fasting/fed/sprinkle) a. Study(ies) meets BE criteria (90% CI or 80-125, Cmax, AUC) b. Data Files (Computer Media) Submitted c. In-Vitro Dissolution	☐
Study Type	**IN-VIVO BE STUDY with CLINICAL ENDPOINTS CLINICAL STU AND HIXON** a. Properly defined BE endpoints (eval. by Clinical Team) NO - does not need to be looked at per K. Scardina b. Summary results meet BE criteria (90% CI within +/- 20% or 80-120) pg. 222 c. Summary results indicate superiority of active treatments (test & reference) over vehicle/placebo ($p<0.05$) (eval. by Clinical Team) d. Data Files (Computer Media) Submitted YES - 6/16/03	☒
Study Type	**TRANSDERMAL DELIVERY SYSTEMS** a. <u>In-Vivo PK Study</u> 1. Study(ies) meet BE Criteria (90% CI or 80-125, Cmax, AUC) 2. In-Vitro Dissolution 3. Data Files (Computer Media) Submitted b. <u>Adhesion Study</u> c. <u>Skin Irritation/Sensitization Study</u>	☐

Study Type	**NASALLY ADMINISTERED DRUG PRODUCTS** a. Solutions (Q1/Q2 sameness): 1. In-Vitro Studies (Dose/Spray Content Uniformity, Droplet/Drug Particle Size Distrib., Spray Pattern, Plume Geometry, Priming & Repriming, Tail Off Profile) b. Suspensions (Q1/Q2 sameness): 1. In-Vivo PK Study a. Study(ies) meets BE Criteria (90% CI or 80-125, Cmax, AUC) b. Data Files (Computer Media) Submitted 2. In-Vivo BE Study with Clinical EndPoints a. Properly defined BE endpoints (eval. by Clinical Team) b. Summary results meet BE criteria (90% CI within +/- 20% or 80-120) c. Summary results indicate superiority of active treatments (test & reference) over vehicle/placebo ($p<0.05$) (eval. by Clinical Team) d. Data Files (Computer Media) Submitted 3. In-Vitro Studies (Dose/Spray Content Uniformity, Droplet/Drug Particle Size Distrib., Spray Pattern, Plume Geometry, Priming & Repriming, Tail Off Profile)	☐
Study Type	**TOPICAL CORTICOSTEROIDS (VASOCONSTRICTOR STUDIES)** a. Pilot Study (determination of ED50) b. Pivotal Study (study meets BE criteria 90%CI or 80-125)	☐
Sec. VII	**Components and Composition Statements** 1. Unit composition and batch formulation YES 2. Inactive ingredients as appropriate YES - see sheets attached	☒
Sec. VIII	**Raw Materials Controls** 1. **Active Ingredients** a. Addresses of bulk manufacturers YES b. Type II DMF authorization letters or synthesis YES - (b) (4) c. COA(s) specifications and test results from drug substance mfgr(s) YES d. Applicant certificate of analysis YES e. Testing specifications and data from drug product manufacturer(s) YES f. Spectra and chromatograms for reference standards and test samples YES g. CFN numbers (b) (4) 2. **Inactive Ingredients** a. Source of inactive ingredients identified pg. 3932 b. Testing specifications (including identification and characterization) YES c. Suppliers' COA (specifications and test results) YES d. Applicant certificate of analysis YES	☒
Sec.IX	**Description of Manufacturing Facility** 1. Full Address(es)of the Facility(ies) YES 2. CGMP Certification YES - not original (see amendment dated June 16, 2003) 3. CFN numbers 2127022	☒

Sec. X	**Outside Firms Including Contract Testing Laboratories** 1. Full Address YES 2. Functions YES 3. CGMP Certification/GLP YES 4. CFN numbers YES	☒
Sec. XI	**Manufacturing and Processing Instructions** 1. Description of the Manufacturing Process (including MicrobiologicalValidation, if Appropriate) YES 2. Master Production Batch Record(s) for largest intended production runs (no more than 10x pilot batch) with equipment specified YES 3.If sterile product: Aseptic fill / Terminal sterilization 4.Filter validation (if aseptic fill) 5. Reprocessing Statement YES - pg. 4125	☒
Sec. XII	**In-Process Controls** 1. Copy of Executed Batch Record with Equipment Specified, including Packaging Records (Packaging and Labeling Procedures), Batch Reconciliation and Label Reconciliation YES 2. In-process Controls - Specifications and data YES MASTER EXHIBIT MADE FILLED (b) (4)	☒
Sec. XIII	**Container** 1. Summary of Container/Closure System (if new resin, provide data) YES 2. Components Specification and Test Data (Type III DMF References) YES 3. Packaging Configuration and Sizes YES 4. Container/Closure Testing YES 5. Source of supply and suppliers address YES	☒
Sec. XIV	**Controls for the Finished Dosage Form** 1. Testing Specifications and Data YES 2. Certificate of Analysis for Finished Dosage Form YES - pg. 4418	☒
Sec. XV	**Stability of Finished Dosage Form** 1. Protocol submitted YES 2. Post Approval Commitments YES 3. Expiration Dating Period YES - 24 months 4. Stability Data Submitted YES a. 3 month accelerated stability data YES b. Batch numbers on stability records the same as the test batch YES	☒
Sec. XVI	**Samples** - Statement of Availability and Identification of: 1. Drug Substance YES 2. Finished Dosage Form YES 3. Same lot numbers YES	☒
Sec. XVII	**Environmental Impact Analysis Statement** YES	☒

Sec. XVIII	**GDEA (Generic Drug Enforcement Act)/Other:** 1. Letter of Authorization (U.S. Agent [if needed, countersignature on 356h]) YES 2. Debarment Certification (original signature) YES - pg. 5011 (see amendment dated June 16, 2003) 3. List of Convictions statement (original signature)	☒

Reviewing CSO/CST **Saundra Middleton** Saundra J. Middleton **Date 6/30/03**	**Recommendation:** ☒ **FILE** ☐ **REFUSE to RECEIVE**
Supervisory Concurrence/Date: [signature]	**Date:** 1 July 2003
Duplicate copy sent to bio: (Hold if RF and send when acceptable)	
Duplicate copy to **HFD-** for consult: Type:	

ADDITIONAL COMMENTS REGARDING THE ANDA:

Although not first, this ANDA was looked at by DBE for completeness and found complete. The reason this was sent t DBE was that there was reason to believe that 76-737 submitted by Watson may be incomplete since healthy volunteers were given Leuprolide Injection before dosing (see e-mail from K. Scardina attached). ANDA 76-737 was found complete by DBE on 6/25/03.

The DBE stated that the Paddock lacks the the following for the bioequivalence study results:

☐ **Procedure SOP**
☐ **Test article inventory**

6/16/03

Paddock was asked to remove the word "knowingly" from their debarment certification and provide orginal certification for cGMP certificate.

OGD Template Revised 05/12/2003

Middleton, Saundra T

FYI

From: Scardina, Krista
Sent: Monday, June 16, 2003 4:06 PM
To: Middleton, Saundra T
Subject: FW: Testosterone Gel

FYI

This email is regarding Arianne's application (Watson). Please see below.

Krista
-----Original Message-----
From: Sanchez, Aida L
Sent: Monday, June 16, 2003 3:48 PM
To: Scardina, Krista
Subject: RE: Testosterone Gel

Krista:

We should be reviewing that. Ask Reg Support to send it to Aaron. Thanks,

Lizzie

> -----Original Message-----
> **From:** Scardina, Krista
> **Sent:** Tuesday, June 10, 2003 4:15 PM
> **To:** Conner, Dale P; Davit, Barbara M
> **Cc:** Hixon, Dena R; Sanchez, Aida L; Scardina, Krista
> **Subject:** Testosterone Gel
>
> Hello all.
>
> I received a first generic filing review for Testosterone gel, 1% from Watson. From all other correspondence and history I have dug up on this product, a pk study is feasible in healthy males because blood levels are measurable.
>
> However, Watson did a study enrolling 80 HEALTHY males. The volunteers were first suppressed with an IM injection of 7.5 mg of Leuprolide (Lupron Depot). 24 days later, a second screening measurement of serum testosterone was collected to confirm complete testosterone suppression (< 200ng/dl) . After confirmation that the total testosterone concentration was < 200ng/dl, a second IM injection of 7.5 mg of Leuprolide injection was administered. Seven days after the second injection, the first testosterone treatment period began. There were two treatment periods, each lasting for 3 days. The treatment periods were separated by a 7 day washout period. The duration of the entire study was 2 months.
>
> This is very troubling to me. Is it necessary to give healthy volunteers Leurprolide injections and second, how does this affect a BE study? I am not sure where to go from here, but being it is a pk study, you all should probably look at the filing review. Please let me know what you think and I can send you the jackets jackets if needed.
>
> Thanks for your input.
>
> Krista

ANDA 76-744 Final Check List for Branch Chief

✓ 1) Check letter date and stamp date of ANDA vs. drafted letter.

✓ 2) Check for gross errors in letter.

✓ 3) Check that correct letter format is used. (PIV vs. Other acknowledgment)

✓ 4) Check address and contact person on letter vs. 356(h).

✓ 5) Check for any t-cons and verify date and correspondence date.

✓ 6) Check Patent Certification information in entered in COMIS (by Margo) vs. Actual certification. If multiple patent certifications, should be based on PIV if applicable or latest expiring patent.

✓ 7) Check for any comments or problems raised by reviewer on Check List.

✓ 8) Sign Check List.

✓ 9) Check electronic Orange Book to verify current patent information.

✓ 10) Review 356 (h). Check NDA number and RLD for correct reference.

✓ 11) Review Basis for Submission.

✓ 12) Review Patent Certifications and Exclusivity Statement. (If an expiration of an exclusivity has occurred make a note to the Labeling reviewer.

✓ 13) Review Comparison between Generic Drug and RLD for: condition of use, active ingredients, route of administration, dosage form and strength. Check Components and Composition.

✓ 14) Sign cover letter 505 (J)(2)(A) OK, date, and full signature.

✓ 15) Pull USP information. (USP ____yes ✓ no)

_____ 16) Final Grammar review on letter.

_____ 17) EES slip.

_____ 18) Document in record book.

Signature_____ date_____

ESTABLISHMENT EVALUATION REQUEST

DETAIL REPORT

Application:	ANDA 76744/000	Action Goal:	
Stamp:	22-MAY-2003	District Goal:	22-APR-2004
Regulatory Due:		Brand Name:	
Applicant:	PADDOCK LABS	Estab. Name:	TESTOSTERONE
	3940 QUEBEC AVE NORTH	Generic Name:	
	MINNEAPOLIS, MN 55427		
Priority:		Dosage Form:	(GEL)
Org Code:	600	Strength:	1 %

Application Comment:

FDA Contacts:	S. KIM	(HFD-400)	301-827-0513	, Project Manager
	D. GILL	(HFD-623)	301-827-5848	, Team Leader

Overall Recommendation: ----------

Establishment: CFN 2127022 FEI 2127022
PADDOCK LABORATORIES INC
3940 QUEBEC AVE NORTH
MINNEAPOLIS, MN 55427

DMF No: AADA:

Responsibilities: FINISHED DOSAGE MANUFACTURER

ofile: ~~TCM~~ "OIN" Should be SM OAI Status: NONE

EMilestone Name	Date	Type	Insp. Date	Decision & Reason	Creator
---	---	---	---	---	---

SUBMITTED TO OC 02-JUL-2003 MIDDLETONS

Establishment: CFN [redacted] FEI [redacted]

[redacted]

DMF No: [redacted] AADA:

Responsibilities: [redacted]

Profile: CSN OAI Status: NONE

EMilestone Name	Date	Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	02-JUL-2003				MIDDLETONS

ANDA 76-744

Paddock Laboratories, Inc.
Attention: Patrick L. Johnson
3940 Quebec Avenue North
Minneapolis, MN 55427

JUL 2 2003

Dear Sir:

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

Reference is made to the telephone conversation dated June 16, 2003 and your correspondence dated June 16, 2003.

NAME OF DRUG: Testosterone Gel, 1%

DATE OF APPLICATION: May 21, 2003

DATE (RECEIVED) ACCEPTABLE FOR FILING: May 22, 2003

You have filed a Paragraph IV patent certification, in accordance with 21 CFR 314.94(a)(12)(i)(A)(4) and Section 505(j)(2)(A)(vii)(IV) of the Act. Please be aware that you need to comply with the notice requirements, as outlined below. In order to facilitate review of this application, we suggest that you follow the outlined procedures below:

CONTENTS OF THE NOTICE

You must cite section 505(j)(2)(B)(ii) of the Act in the notice and should include, but not be limited to, the information as described in 21 CFR 314.95(c).

SENDING THE NOTICE

In accordance with 21 CFR 314.95(a):

- Send notice by U.S. registered or certified mail with return receipt requested to each of the following:

  1) Each owner of the patent or the representative designated by the owner to receive the notice;

2) The holder of the approved application under section 505(b) of the Act for the listed drug claimed by the patent and for which the applicant is seeking approval.

3) An applicant may rely on another form of documentation only if FDA has agreed to such documentation in advance.

DOCUMENTATION OF NOTIFICATION/RECEIPT OF NOTICE

You must submit an amendment to this application with the following:

- In accordance with 21 CFR 314.95(b), provide a statement certifying that the notice has been provided to each person identified under 314.95(a) and that notice met the content requirements under 314.95(c).

- In accordance with 21 CFR 314.95(e), provide documentation of receipt of notice by providing a copy of the return receipt or a letter acknowledging receipt by each person provided the notice.

- A designation on the exterior of the envelope and above the body of the cover letter should clearly state "PATENT AMENDMENT". This amendment should be submitted to your application as soon as documentation of receipt by the patent owner and patent holder is received.

DOCUMENTATION OF LITIGATION/SETTLEMENT OUTCOME

You are requested to submit an amendment to this application that is plainly marked on the cover sheet A PATENT AMENDMENT with the following:

- If litigation occurs within the 45-day period as provided for in section 505(j)(4)(B)(iii) of the Act, we ask that you provide a copy of the pertinent notification.

- Although 21 CFR 314.95(f) states that the FDA will presume the notice to be complete and sufficient, we ask that if you are not sued within the 45-day period, that you provide a letter immediately after the 45 day period elapses, stating that no legal action was taken by each person provided notice.

You must submit a copy of a court order or judgement or a settlement agreement between the parties, whichever is applicable, or a licensing agreement between you and the patent holder, or any other relevant information. We ask that this information be submitted promptly to the application.

If you have further questions you may contact Gregg Davis, Chief, Regulatory Support Branch, at (301) 827-5862.

In the interim, please submit the following for the bioequivalence study results:

- Procedure SOP
- Test article inventory

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

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

Should you have questions concerning this application, contact:

Sarah Kim
Project Manager
(301) 827-5848

Sincerely yours,

Gregory S. Davis for

Wm Peter Rickman
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

cc: ANDA 76-744
DUP/Jacket
Division File
Field Copy
HFD-610/R.West
HFD-610/P.Rickman
HFD-92
HFD-615/M.Bennett
HFD-600/

Endorsement: HFD-615/GDavis, Chief, RSB G Davis 01-JUL-2003 date
HFD-615/SMiddleton, CSO S Middleton date 6/30/03
Word File
V:/FIRMSNZ\PADDOCK\LTRS&REV\76744.ACK
FT/
ANDA Acknowledgment Letter!

August 22, 2003

BY EXPRESS MAIL, HAND DELIVERY AND FACSIMILE

Office of Generic Drugs (HFD-600)
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II, Room 150
7500 Standish Place
Rockville, MD 20855

NEW CORRESP
NC

Mayer, Brown, Rowe & Maw LLP
190 South La Salle Street
Chicago, Illinois 60603-3441

Main Tel (312) 782-0600
Main Fax (312) 701-7711
www.mayerbrownrowe.com

James R. Ferguson
Direct Tel (312) 701-7282
Direct Fax (312) 706-8421
jferguson@mayerbrownrowe.com

Re: ANDA No. 76-744 (Paddock Laboratories, Inc.)

NOTICE OF FILING OF LEGAL ACTION

Unimed Pharmaceuticals, Inc. ("Unimed") hereby notifies the FDA as required by 21 C.F.R. 314.107(f)(2) that a legal action for patent infringement has been filed by Unimed within 45 days of Unimed's receipt of the notice of certification letter for the above-referenced Abbreviated New Drug Application (the "ANDA"):

(NC)

NEW CORRESP

RECEIVED
AUG 2 2 2003
OGD/CDER

1. The ANDA application number is 76-744.

2. The name of the ANDA applicant is Paddock Laboratories, Inc. ("Paddock").

3. The established name of the drug product is Androgel® (1% testosterone gel), which is the subject of Unimed's NDA No. 021015.

4. Unimed received Paddock's notice of certification letter under §505(j)(2)(B)(ii) of the Federal Food, Drug and Cosmetic Act on July 11, 2003.

5. Under 21 C.F.R. 314.107(f)(1), the 45-day period begins on July 12, 2003 and ends on August 25, 2003.

6. Unimed certifies that an action for patent infringement under 35 U.S.C. §271(e)(2)-(4) was filed on August 21, 2003, in the Northern District of Georgia, Eastern Division, and is entitled "Unimed Pharmaceuticals, Inc. v. Paddock Laboratories, Inc., Case No. 1:03-cv-2503." A file-stamped copy of Unimed's Complaint is attached hereto.

7. Because Unimed has filed a legal action for patent infringement within the 45-day time period and has properly notified the FDA of the filing of the action, ANDA No. 76-744 may not be approved, pursuant to 21 U.S.C. §355(j)(5)(B)(iii), until either the expiration of the 30 month period, or such other time set forth therein.

Very truly yours,

James R. Ferguson

Encl.

MAYER
BROWN
ROWE
& MAW

Mayer, Brown, Rowe & Maw LLP
190 South La Salle Street
Chicago, Illinois 60603-3441

Main Tel (312) 782-0600
Main Fax (312) 701-7711
www.mayerbrownrowe.com

James R. Ferguson
Direct Tel (312) 701-7282
Direct Fax (312) 706-8421
jferguson@mayerbrownrowe.com

NAI
CmBium
9/5/03

NEW CORRESP
NC

August 22, 2003

BY EXPRESS MAIL AND FACSIMILE

Office of Generic Drugs (HFD-600)
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II, Room 150
7500 Standish Place
Rockville, MD 20855

Re: ANDA No. 76-744 (Paddock Laboratories, Inc.)

NOTICE OF FILING OF LEGAL ACTION
(FIRST AMENDED COMPLAINT)

Unimed Pharmaceuticals, Inc. ("Unimed") hereby notifies the FDA as required by 21 C.F.R. 314.107(f)(2) that a legal action for patent infringement has been filed by Unimed within 45 days of Unimed's receipt of the notice of certification letter for the above-referenced Abbreviated New Drug Application (the "ANDA"):

1. The ANDA application number is 76-744.

2. The name of the ANDA applicant is Paddock Laboratories, Inc. ("Paddock").

3. The established name of the drug product is Androgel® (1% testosterone gel), which is the subject of Unimed's NDA No. 021015.

4. Unimed received Paddock's notice of certification letter under §505(j)(2)(B)(ii) of the Federal Food, Drug and Cosmetic Act on July 11, 2003.

5. Under 21 C.F.R. 314.107(f)(1), the 45-day period begins on July 12, 2003 and ends on August 25, 2003.

6. Unimed certifies that a First Amended Complaint was filed on August 22, 2003, in the Northern District of Georgia, Atlanta Division, in the action for patent infringement under 35 U.S.C. §271(e)(2)-(4) entitled "Unimed Pharmaceuticals, Inc. and Laboratories Besins Iscovesco v. Paddock Laboratories, Inc., Case No. 1:03-cv-2503." A signed copy of Unimed's Amended Complaint is attached hereto. A file-stamped copy will be provided upon request.

7. Because Unimed has filed a legal action for patent infringement within the 45-day time period and has properly notified the FDA of the filing of the action, ANDA No. 76-744 may not be approved, pursuant to 21 U.S.C. §355(j)(5)(B)(iii), until either the expiration of the 30 month period, or such other time set forth therein.

Very truly yours,

James R. Ferguson

Encl.

September 5, 2003

Food and Drug Administration
Office of Generic Drugs (HFD-600)
Center for Drug Evaluation and Research
Metro Park North 2
7500 Standish Place, Room 150
Rockville, Maryland 20855

NEW CORRESP
NC

RE: ANDA 76-744
Testosterone Gel 1%

PATENT AMENDMENT

Dear Staff:

Reference is made to our abbreviated new drug application dated May 21, 2003 for Testosterone Gel 1%.

In accordance with 21 CFR 314.107(f)(2), Paddock Laboratories is hereby amending ANDA 76-744 with the following:

ANDA: 76-744

Applicant: Paddock Laboratories, Inc.

Name of Drug Product: Testosterone Gel 1%

Certification: Paddock Laboratories hereby certifies that within 45 days of receipt of the Patent Certification Notice, Unimed Pharmaceuticals, Inc. and Laboratories Besins Iscovesco initiated a patent infringement action against Paddock Laboratories relative to United States Patent No. 6,503,894. The action was filed in U.S. District Court, Northern District of Georgia, Atlanta Division on August 22, 2003 and designated Case Number 1:03-CV-2503.

This concludes our Patent Amendment to ANDA 76-744 for Testosterone Gel 1%. If you have any questions or require additional information regarding the above matter, please do not hesitate to contact us.

Very truly yours,

PADDOCK LABORATORIES, INC.

SEP 17 2003

Patrick L. Johnson
Director of Regulatory Affairs

September 12, 2003

NEW CORRESP
NC

Food and Drug Administration
Office of Generic Drugs
Center for Drug Evaluation and Research
Metro Park North 2
7500 Standish Place, Room 150
Rockville, Maryland 20855

RE: ANDA 76-744
Testosterone Gel 1%

PATENT AMENDMENT (UPDATE)

Dear Staff:

Reference is made to our abbreviated new drug application dated May 21, 2003 for Testosterone Gel, 1%.

In conjunction with the referenced ANDA, a Paragraph IV patent certification was filed relative to United States Patent No. 6,503,894 in accordance with 21 CFR 314.94(a)(12)(i)(A)(4) and Section 505(j)(2)(A)(vii)(IV) of the Act.

In accordance with the above, Paddock Laboratories, Inc. is amending ANDA 76-744 with the following:

In accordance with 21 CFR 314.95(b), Paddock is certifying that notice has been provided to each person identified under 314.95(a) and the notice met the content requirements under 314.95(c). A photostatic copy of the Patent Certification Notices is enclosed for your reference.

In accordance with 21 CFR 314.95(e), Paddock is providing documentation of receipt of notice by providing a photostatic copy of the certified mail return receipt acknowledging receipt by each person provided the notice.

This concludes our Patent Amendment to ANDA 76-744 for Testosterone Gel, 1%. If you have any questions or require additional information regarding the above matter, please do not hesitate to contact us.

Very truly yours,

PADDOCK LABORATORIES, INC.

Patrick L. Johnson
Director of Regulatory Affairs
/encls

RECEIVED
SEP 16 2003

FDA CDER EES

ESTABLISHMENT EVALUATION REQUEST

SUMMARY REPORT

Application : ANDA 76744/000

Org Code : 600

Priority :

Sponsor: PADDOCK LABS

3940 QUEBEC AVE NORTH

MINNEAPOLIS, MN 55427

Stamp Date : 22-MAY-2003

PDUFA Date :

Action Goal :

District Goal: 22-APR-2004

Brand Name :

Estab. Name: TESTOSTERONE

Generic Name:

Dosage Form: (GEL)

Strength : 1 %

FDA Contacts: S. KIM Project Manager (HFD-617) 301-827-5725

D. GILL Team Leader (HFD-623) 301-827-5848

--Overall Recommendation: ---

✓

Establishment : CFN : 2127022 FEI : 2127022

PADDOCK LABORATORIES INC

3940 QUEBEC AVE NORTH

MINNEAPOLIS, MN 55427

DMF No: AADA:

Responsibilities: FINISHED DOSAGE MANUFACTURER

Profile : OIN OAI Status: NONE

Last Milestone: SUBMITTED TO DO

Milestone Date: 02-JUL-03

:

:

Establishment : CFN : [redacted] (b)(4) FEI : [redacted] (b)(4)

[redacted] (b)(4)

DMF No: 1390 AADA:

Responsibilities: [redacted] (b)(4)

Profile : CSN OAI Status: NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 02-JUL-03

Decision : ACCEPTABLE

Reason : BASED ON PROFILE

Liu, Shing Hou

From: Pamphile, Wanda
Sent: Friday, November 21, 2003 3:07 PM
Woodland Outlaw, Kathy P; Liu, Shing Hou
Subject: FW: ANDA 76-744 Clarification of Chemistry Deficiencies

Questions for
DA re deficienc.

-----Original Message-----
From: Patrick Johnson [mailto:PJohnson@paddocklabs.com]
Sent: Friday, November 21, 2003 2:29 PM
To: 'pamphilew@cder.fda.gov'
Subject: ANDA 76-744 Clarification of Chemistry Deficiencies

Wanda,

Attached is the request for clarification of several statements made in the
Chemistry deficiency letter dated 10/31/03 for ANDA 76-744, Testosterone Gel
1%.

I will send the original by FedEx to your attention.

Please call me if you or the Chemistry reviewer have any questions.

Best regards,
Patrick

Patrick L. Johnson
Director of Regulatory Affairs
Paddock Laboratories, Inc.
3940 Quebec Ave N
Minneapolis MN 55427
Tel. 763-732-0393
Fax 763-546-4842
e-mail pjohnson@paddocklabs.com

<<Questions for FDA re deficiencies.pdf>>

November 21, 2003

Office of Generic Drugs, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855

RE: ANDA 76-744, Testosterone Gel 1%
Request for Clarification of Chemistry Deficiencies (Dated October 31, 2003)

Dear Staff:

In order to provide complete and comprehensive responses to the deficiencies recently received for this ANDA, Paddock Laboratories is seeking clarification of several of the statements included in the deficiency communication.

Deficiency A.2.a. "Please include the individual known specified impurities in the specifications for drug substance release..."

Paddock has included Specified Impurities as (b) (4) identified impurities and individual, not identified, specified impurities in the category *Other Individual Specified Impurities*, where each result is listed separately by relative retention time if an impurity peak is detected (see Table 1 below). The *Other Individual Specified Impurities* are also listed separately in the Inspection Report for the finished product when all of the testing is complete. Is further explanation required?

Table 1. Impurity Specifications and Reporting

Testosterone Impurity Profile	API Specification	Finished Product Specification	Stability Specification
Specified Impurities:			
(b) (4)	(b) (4)		
Individual Unspecified Impurities:			
Total Impurities:			

Paddock Laboratories, Inc.
3940 Quebec Avenue N, Minneapolis, MN 55427 • 800.328.5113 • 763.546.4676 • Fax:763.546.4842 • www.paddocklabs.com

Deficiencies A.3.d and A.5.c "Please explain 'other specified impurities' in your specifications." (for drug product release and stability specifications, respectively).

Individual specified impurities not listed separately are reported in the Inspection Plan individually in the category *Other Individual Specified Impurities*. Each result is listed separately by relative retention time if an impurity peak is detected. Is further explanation in the inspection plan or in the reporting required?

We look forward to your response. If you have any questions regarding the information provided please contact me at 763-732-0393.

Sincerely,

Paddock Laboratories, Inc.

Patrick L. Johnson
Director of Regulatory Affairs

RECORD OF TELEPHONE CONVERSATION

Reference is made to deficiency letter dated October 31, 2003. In the letter dated November 21, 2003, Paddock Laboratories requested clarification for the following deficiencies:

2.Regarding the drug substance, we have the following comments:

A. Please include the individual known specified impurities in the specifications for drug substance release and justify the proposed limits. Please refer to page 3933 in your submission.

3.Regarding the drug product specifications, we have the following comments:

D. Please explain "other specified impurities" in your specifications.

5.Regarding the drug product stability specifications, we have the following comments:

C. Please explain "other specified impurities" in your specifications.

Shing told Johnson that the deficiencies were cited because we thought Paddock Laboratories knew the identity of the "Other Individual Specified Impurities." In the November 21 letter, Paddock provided a table to list the impurity specifications and stated that "Specified Impurities" included (b) (4) identified impurities and individual, not identified, specified impurities. Shing commented that "not identified" implies "unknown", then how can an unknown impurity be specified"? Johnson said they should have used proper terms as stated in the Impurity Guidance.

Shing suggested that they add a footnote underneath the aforementioned table to explain that individual specified impurities not listed separately in the table are reported in the Inspection Plan individually in the category "Other Individual Specified Impurities", and that each result is listed separately by relative retention time if an impurity peak is detected. Shing stated that when the ANDA moves towards approval in the future, the division level/office level reviewer(s) will not raise the question as to "how an unknown impurity is called specified impurity."

DATE:
November 25, 2003

ANDA NUMBER:
76-744

PRODUCT NAME:
Testosterone Gel 1%

INITIATED BY:

Firm__X__ Agency__

FIRM NAME:
Paddock Laboratories, Inc.

FIRM REPRESENTATIVE:
Patrick L. Johnson

TELEPHONE NUMBER:
763-732-0393

FDA REPRESENTATIVE:
Shing Liu, Ph.D.
Wanda Pamphile, Ph.D.

SIGNATURE
Shing Liu S.H.Liu 11/26/03
Wanda Pamphile WP 11/26/03

Orig: ANDA 76-744
Cc: Division File
Chem. I telecon binder
\\CDS013\OGDS11\FIRMSNZ\PADDOCK\TELECONS\76744.doc

2.1

PADDOCK LABORATORIES

1978 2003 25 years

January 29, 2004

ORIG AMENDMENT
N/AM

Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II, HFD-600
7500 Standish Place, Room 150
Rockville, MD 20855-2773

Re: MINOR AMENDMENT to ANDA 76-744 in Response to the Deficiency Letter dated October 31 2003 for Testosterone Gel, 1%

Dear Staff:

Please accept this Minor Amendment to Paddock Laboratories' pending abbreviated new drug application for Testosterone Gel, 1%, ANDA 76-744, May 21, 2003, submitted pursuant to Section 505(j) of the Federal Food, Drug and Cosmetic Act. This amendment provides our responses to the October 31, 2003 deficiency letter.

Review and archival copies are included in this submission. A third copy has been sent to the Minneapolis District Office (field copy). Paddock Laboratories, Inc., does hereby certify that the submitted field copy is a true copy of the technical section of this application [21 CFR 314.94(d)(5)].

Please contact me at 763-732-0364 (telephone) or 763-546-4842 (fax) if you have any questions or need additional information.

Sincerely,

Daniel W. Rockcliffe
Regulatory Affairs Analyst

RECEIVED
JAN 30 2004
OGD/CDER

February 19, 2004

Dale Connor, Pharm. D.
Director, Division of Bioequivalence
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855

Re: ANDA 76-744, Testosterone Gel, 1%
Telephone Amendment to Provide Long-Term Frozen Stability of Testosterone in Plasma and Individual Subject Data Regarding Amount of Testosterone Applied

Dear Dr. Connor,

Reference is made to Paddock Laboratories, Inc.'s (Paddock) pending ANDA 76-744 for the above referenced drug product accepted for filing on May 22, 2003. Reference is also made to the February 3, 2004 telephone communication with Aaron Sigler, Division of Bioequivalence (DBE) Project Manager, in which Dr. Sigler requested long-term frozen stability of testosterone in plasma and individual subject data regarding the amount of testosterone applied during the clinical study.

The DBE requests are provided in bold print with Paddock's response following accordingly.

1. **Please provide long-term stability data for the Testosterone Gel in frozen plasma for a storage period of at least 193 days.**

   The following information summarizes the long-term stability for Testosterone in frozen plasma for 310 days and as such, covers the length of time any subject sample was stored frozen prior to analysis. This information is taken from page 10 of the Amendment 1 to the Validation Study Report ((b) (4) Study Code: GX020). Attached is a complete copy of the report for the ANDA file (Attachment 1).

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Long term stability:

For the determination of the long-term stability of Testosterone in plasma, 5 sets of validation samples were extracted and measured together with the freshly prepared calibration curve no. 99 (prepared on April 22, 2003). The validation samples were QC samples of study MA171 prepared on June 17, 2002 with a nominal concentration of 1.5 ng/mL and 7.5 ng/mL, which were stored at -20°C ± 5°C.

No significant deviations in the measured concentrations were observed. Therefore, Testosterone could be assumed as stable in the matrix at -20°C ± 5°C for at least 310 days.

The following table provides statistics for the long-term stability for Testosterone in frozen plasma:

	Nominal concentration (ng/mL)	
Standard Curve No.	**1.50**	**7.50**
310d	**Calculated concentration (ng/mL)**	
99	(b) (4)	
Number	**5**	**5**
Mean	**1.51**	**6.97**
SDev	**0.0162**	**0.0455**
CV (%)	**1.1**	**0.7**
Bias (%)	**0.9**	**-7.0**

The amendment also describes the results from additional validation experiments not performed for the original validation done in 1997 to bring the validation up to current standards. Specifically this includes stock solution stability and internal standard recovery. In addition, this amendment also validated the performance of a gas chromatography column from an alternative manufacturer used in the analysis of the study samples as well as validates the performance of the assay over a modified linear range compared to the original validation.

2. **Please provide individual subject data for the amount of testosterone applied to each subject, including the weights of the bag containing the drug packet and glove used to apply the drug product, weighed before and after application and the mean weights for each treatment with the CV percentage.**

   Requested data is provided in Attachment 2.

As stated in the Agency's February 3, 2004 telephone communication, this amendment is being submitted via telefax as a TELEPHONE AMENDMENT. A hard copy of this amendment is also being submitted in duplicate, as an archival and a review copy for incorporation into our file.

Paddock requests that all information in this file be treated as confidential within the meaning of 21 CFR 314.430 and that no information from the file be publicly released, through FOI or any other means, without the written consent of an authorized person from Paddock to a member of your Office.

If there are any questions regarding the information provided, please contact me by telephone at (763) 732-0415 or by fax at (763) 546-4842.

Sincerely,

PADDOCK LABORATORIES, INC.

Wendy A. Saunders
Senior Regulatory Affairs Analyst

telefax: Aaron Sigler, Pharm. D., Project Manager, Division of Bioequivalence

ESTABLISHMENT EVALUATION REQUEST

SUMMARY REPORT

Application : ANDA 76744/000
Org Code : 600
Priority :

Sponsor: PADDOCK LABS
3940 QUEBEC AVE NORTH
MINNEAPOLIS, MN 55427

Stamp Date : 22-MAY-2003
PDUFA Date :
Action Goal :
District Goal: 22-APR-2004

Brand Name :
Estab. Name: TESTOSTERONE
Generic Name:
Dosage Form: (GEL)
Strength : 1 %

FDA Contacts: S. PARK Project Manager (HFD-617) 301-827-5725

D. GILL Team Leader (HFD-630) 301-827-5848

Overall Recommendation: ACCEPTABLE on 10-FEB-2004by J. D AMBROGIO(HFD-322) 301-827-9049

Establishment : CFN : 2127022 FEI : 2127022
PADDOCK LABORATORIES INC
3940 QUEBEC AVE NORTH
MINNEAPOLIS, MN 55427

DMF No: AADA:

Responsibilities: FINISHED DOSAGE MANUFACTURER

Profile : OIN OAI Status: NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 10-FEB-04

Decision : ACCEPTABLE

Reason : DISTRICT RECOMMENDATION

Establishment : CFN : (b) (4) FEI : (b) (4)

(b) (4)

DMF No: (b) (4) AADA:

Responsibilities: (b) (4)

Profile : CSN OAI Status: NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 02-JUL-03

Decision : ACCEPTABLE

Reason : BASED ON PROFILE

April 8, 2004

ORIG AMENDMENT
AF

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, Room 150
7500 Standish Place
Rockville, MD 20855-2773

RE: ANDA 76-744; Testosterone Gel, 1%
LABELING AMENDMENT Responding to the Agency's January 22, 2004 Labeling Deficiency Letter

Dear Mr. Buehler,

Reference is made to Paddock Laboratories, Inc. (Paddock) pending ANDA 76-744 for the above referenced drug product.

Reference is also made to the Agency's January 22, 2004 labeling deficiency letter. A copy of the letter is provided as Attachment 1 for the reviewer's convenience.

In response to the deficiency letter, this amendment is submitted herewith to the above referenced ANDA. This amendment has been designated as a LABELING AMENDMENT. Each deficiency item is shown in bold print and has been addressed in the sequence presented in the deficiency letter.

RECEIVED
APR 0 9 2004
OGD / CDER

Paddock Laboratories, Inc.
3940 Quebec Avenue N, Minneapolis, MN 55427 • 800.328.5113 • 763.546.4676 • Fax:763.546.4842 • www.paddocklabs.com

LABELING

1. **CONTAINER (2.5 g and 5 g unit-dose foil packets)**

   a. **We encourage the use of boxing, contrasting colors. Or other means to differentiate the 2.5 g packet from the 5 g packet.**

   Paddock has differentiated the two packets by use of colors and boxing.

   b. **Describe the location where the expiration date will be printed/stamped.**

   The Expiration Date will be printed below the Lot Number on the backside of the packet.

2. **CARTON (30 x unit-dose packets)**

   a. **Refer to comment 1.a.**

   Paddock has differentiated the two cartons by use of colors and boxing.

3. **PHYSICIAN INSERT**

   a. **We encourage you to relocate the phrase "Rx only" from the HOW SUPPLIED section, to a location just under the TITLE of the package insert.**

   Paddock has relocated the "**Rx only**" just under the TITLE of the package insert.

   b. **Please note that USAN names are common nouns and should be treated as such in a text of labeling (i.e., lower case). Upper case may be used when the USAN name stands alone on labels or in the title of the package insert.**

   Paddock has changed the USAN name from upper case to lower case throughout the package insert, where appropriate.

   c. **Throughout your insert, revise "5 G", "7.5 G", and "10 G" to read "5 g", "7.5 g", and "10 g" respectively.**

   Throughout the package insert, Paddock has revised the gram abbreviation as appropriate.

3. **PHYSICIAN INSERT, Continued**

b. **Throughout your insert, revise "testosterone gel 1%" to read "testosterone gel" if it comes immediately before a number (e.g., DESCRIPTION, Second paragraph, first sentence).**

Throughout the package insert, the "1%" has been deleted from "testosterone gel" when "1%" comes immediately before a number.

c. **WARNINGS**

i. **Item 2: revise "pro-static" to read "prostatic".**

Paddock has deleted the hyphen from "prostatic" in the **WARNINGS** section.

ii. **Add as item 7: "7. GELS ARE FLAMMABLE. AVOID FIRE, FLAME OR SMOKING (b) (4)."**

Paddock has incorporated the above flammability statement in the **WARNINGS** section.

f. **PRECAUTIONS**

i. **First paragraph, third bullet, second sentence: italicize "*In vitro*"**

Paddock has italicized "In vitro" in the **PRECAUTIONS** section.

ii. **Advise patients of the following, add as the fourth bullet "• Since gels are flammable, avoid fire, flame or smoking (b) (4)."**

Paddock has incorporated the above flammability statement in the **PRECAUTIONS** section.

4. **PATIENT INFORMATION AND INSTRUCTIONS FOR USING**

a. **Refer to comment 3.b.**

Paddock has changed the USAN name from upper case to lower case throughout the package insert, where appropriate.

4. **PATIENT INFORMATION AND INSTRUCTIONS FOR USING, Continued**

   a. **Please refer to the attached mocked-up copy of the patient leaflet for more labeling revision requests.**

      Paddock has re-aligned the paragraphs and incorporated the flammability statements as appropriate.

Twelve copies of final printed labeling are provided in Attachment 2.

Paddock acknowledges that it may be necessary to revise our labeling prior to approval if there are subsequent approved labeling changes to the reference listed drug.

To facilitate review of this amendment, and in accordance with 21 CFR 314.94(a)(8)(iv), a side-by-side comparison of the revised, proposed package insert labeling (Revised February 2004) to the labeling submitted in the original application (Revised April 2003), is provided in Attachment 3.

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 our written consent to an authorized member of your office.

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), we hereby certify that a field copy of this amendment, dated April 8, 2004, has been submitted to the Minneapolis District Office for their review. This third (field) copy is a "true" copy of this amendment.

Should you have any questions or comments regarding this amendment, please contact me at (763) 732-0415 (telephone) or (763) 546-4842 (fax).

Sincerely,

PADDOCK LABORATORIES, INC.

Wendy A. Saunders
Senior Regulatory Affairs Analyst

cc: desk copy for labeling reviewer, Ruby Wu

ORIGINAL

May 19, 2004

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, Room 150
7500 Standish Place
Rockville, MD 20855-2773

RE: ANDA 76-744; Testosterone Gel, 1%
LABELING AMENDMENT Responding to the Agency's April 22, 2004 Telephone Communication

Dear Mr. Buehler,

Reference is made to Paddock Laboratories, Inc. (Paddock) pending ANDA 76-744 for the above referenced drug product.

Reference is also made to Paddock's Labeling Amendment submitted April 8, 2004 and to the April 22, 2004 telephone communication with Ruby Wu, labeling reviewer. In the telephone communication, it was requested that Paddock resubmit the 2.5 g and 5 g cartons due to the font legibility of the established name, scheduled drug insignia and corporate logo. In addition, it was requested that Paddock resubmit the package inserts as two-sided documents. Therefore, twelve copies of final printed labeling (true color, true size) for the revised cartons and inserts are provided on the following pages. Please be aware that no changes have been made to the labeling text or format.

In response to the telephone communication, this amendment is submitted herewith to the above referenced ANDA. This amendment has been designated as a LABELING AMENDMENT.

Paddock acknowledges that it may be necessary to revise our labeling prior to approval if there are subsequent approved labeling changes to the reference listed drug.

3940 Quebec Avenue N, Minneapolis, MN 55427 • 800.328.5113 • 763.546.4676 • Fax:763.546.4842 • www.paddocklabs.com

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 our written consent to an authorized member of your office.

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), we hereby certify that a field copy of this amendment, dated May 19, 2004, has been submitted to the Minneapolis District Office for their review. This third (field) copy is a "true" copy of this amendment.

Should you have any questions or comments regarding this amendment, please contact me at (763) 732-0415 (telephone) or (763) 546-4842 (fax).

Sincerely,

PADDOCK LABORATORIES, INC.

Wendy A. Saunders
Senior Regulatory Affairs Analyst

cc: desk copy for labeling reviewer, Ruby Wu

ORIGINAL

ORIG AMENDMENT

N | AM

June 30, 2004

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, Room 150
7500 Standish Place
Rockville, MD 20855-2773

RE: ANDA 76-744; Testosterone Gel 1%
MINOR AMENDMENT Responding to the Agency's March 11, 2004 Deficiency Letter

CHEMISTRY INFORMATION INCLUDED

Dear Mr. Buehler,

Reference is made to Paddock Laboratories, Inc. (Paddock) pending ANDA 76-744 for the above referenced drug product.

Reference is also made to Paddock's January 29, 2004 amendment and the Agency's March 11, 2004 deficiency letter. The Agency's letter is provided in Attachment 1.

In response to the deficiency letter, this amendment is submitted herewith to the above referenced ANDA. This amendment has been designated as a MINOR AMENDMENT. Each deficiency item is shown in bold print and has been addressed in the sequence presented in the deficiency letter.

RECEIVED
JUL 0 1 2004
OGD / CDER

Paddock Laboratories, Inc.
3940 Quebec Avenue N, Minneapolis, MN 55427 • 800.328.5113 • 763.546.4676 • Fax:763.546.4842 • www.paddocklabs.com

CHEMISTRY

A. Deficiencies:

1. **Please further (b) (4) the total impurity acceptance criteria for the drug product, and submit a revised drug product specification sheet accordingly.**

   In the original ANDA, Paddock proposed a drug product total impurity specification of NMT (b) (4). In the January 29, 2004 amendment, it was (b) (4) to NMT (b) (4). As requested by the Agency, Paddock is further (b) (4) the specification to NMT (b) (4). The drug product specification sheets (2.5 g and 5 g Inspection Plans) have been revised accordingly and are provided in Attachment 2. Also included in Attachment 2 are updated Certificates of Analysis (COAs) for Paddock Lot No.'s 2044939 (2.5 g) and 2044938 (5 g).

2. **Please (b) (4) the drug product stability acceptance criteria for (b) (4) and total impurities. Also, please submit a revised drug product stability sheet.**

	Proposed Stability Specifications		
Impurity	**Original ANDA**	**January 29, 2004 Amendment**	**June 30, 2004 (Current) Amendment**
(b) (4)			

The acceptance criteria for the drug product impurity stability specifications have been (b) (4) as appropriate. Please see the above table for the revised proposed specifications. The updated Product Stability Protocols, Protocol No.'s 5202530-07 (2.5 g) and 5205030-06 (5 g), containing the proposed (b) (4) impurities acceptance criteria, are provided in Attachment 3.

(b) (4)

(b) (4)

[redacted]

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 long-term stability data to update your studies.**

   The updated Testosterone Gel 1% long-term drug stability data (Stability Results Summary) for Paddock Lot No.'s 2044939 (2.5 g), 2044938 (5 g) can be found in Attachment 7. The stability data includes testing through 24 months. No stability issues or degradation trends are apparent. The completed stability data for Innovator Lot No.'s 00661 (2.5 g) and 00688 (5 g) was submitted in the January 29, 2004 amendment.

2. **Labeling deficiencies were faxed to you on January 22, 2004. Please respond to the labeling deficiencies.**

   Paddock responded to the January 22, 2004 labeling deficiency letter in labeling amendments dated April 8, 2004 and May 19, 2004.

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 our written consent to an authorized member of your office.

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), we hereby certify that a field copy of this amendment, dated June 30, 2004, has been submitted to the Minneapolis District Office for their review. This third (field) copy is a "true" copy of this amendment.

Should you have any questions or comments regarding this amendment, please contact me at (763) 732-0415 (telephone) or (763) 546-4842 (fax).

Sincerely,

PADDOCK LABORATORIES, INC.

Wendy A. Saunders
Senior Regulatory Affairs Analyst

Attachments

RECORD OF TELEPHONE CONVERSATION

Background Information:
Labeling, bio and EER of the ANDA are acceptable. The only remaining issue prior to approval is the specifications for stability. In the 06/30/04 MINOR amendment, the firm's proposed limits for *Impurity Profile for Testosterone Gel* are still (b) (4). However, the firm's full term (24 months) CRT stability data (submitted in the 06/30/04 amendment) showed that the drug product at expiry can meet the Impurities specifications proposed for Paddock's drug product release (which are considered acceptable per current OGD Guidelines, and are consistent with the limits proposed by another ANDA of the same drug product in the approval matrix).

Telephone Conversation:
Shing Liu called Wendy Saunders (who is in charge of the ANDA) on 08/10/04 at 11:45 am (MN time 10:45 am) and left a message in her voice mail. Liu found out the following day that Saunders was on (b) (6) leave and the operator directed Liu to another person (Ron) who did not return Liu's call. Instead, David Rosenberg called on 08/12/04, who then asked Todd Deleahant to call Liu. Finally, Liu talked to Deleahant at 11:25 am 08/12/04 (Thursday).

Liu: Please (b) (4) the Impurities specifications for stability. The specifications for release are acceptable. You may use the same impurities specifications for your stability protocol. Your full term stability data showed that your product will meet the specifications. If you agree, please submit a telephone amendment to include revised stability protocol.

Deleahant: We will look into this issue and submit a telephone amendment.

Liu: Please fax your amendment to my attention followed by a hard copy.

(Note: Deleahant has been with the firm only for a few months. He is Wendy Sauders' substitute)

DATE:
August 12, 2004

ANDA NUMBER:
76-744

PRODUCT NAME:
Testosterone Gel 1%

INITIATED BY:

Firm__ Agency __X

FIRM NAME:
Paddock Laboratories, Inc.
(Minnesota, MN 55427)

FIRM REPRESENTATIVE:
Todd Deleahant

TELEPHONE NUMBER:
763-732-0364

FDA REPRESENTATIVE:
Shing H. Liu, Ph.D.
(Team Leader of Team 5)

SIGNATURE
Shing H. Liu
8/12/04

Orig: ANDA 76-744
Cc: Division File
Chem. I telecon binder
V:\FIRMSNZ\PADDOCK\TELECONS\76744.tcon.081004.liu.doc

13 August 2004

ORIG AMENDMENT

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

N/Am

Re: TELEPHONE AMENDMENT to ANDA 76-744 in response to the chemistry deficiency communicated 12 August 2004 for Testosterone Gel 1%

Dear Staff:

Please accept this Telephone Amendment to Paddock Laboratories' pending application for Testosterone Gel 1%, ANDA 76-744, dated 22 May 2003 submitted pursuant to Section 505(j) of the Federal Food, Drug and Cosmetic Act. This amendment provides our responses to the 12 August 2004 Telephone Deficiency.

The stability specification limits for Impurity Profile for Testosterone Gel have been revised to be (b) (4) Copies of the revised Product Stability Protocol Forms are included in this submission (Attachment 1 and Attachment 2).

This response is initially being sent via facsimile to the chemistry reviewer, hard copies will be mailed the same day. A field copy has been sent to the Minneapolis District Office. Paddock Laboratories, Inc., does hereby certify that the submitted field copy is a true copy of the technical section of this application [21 CFR 314.96(1)].

Please contact me by telephone at 763-732-0364 or by fax at 763-546-4842 if you have any questions or need additional information.

Sincerely,

PADDOCK LABORATORIES, INC.

Todd M. Delehant, PhD.
Regulatory Affairs Analyst

RECEIVED
AUG 16 2004
OGD / CDER

3940 Quebec Avenue N, Minneapolis, MN 55427 • 800.328.5113 • 763.546.4676 • Fax:763.546.4842 • www.paddocklabs.com

Verified 10/21/2004 Request

ESTABLISHMENT EVALUATION REQUEST

SUMMARY REPORT

Application : ANDA 76744/000
Org Code : 600
Priority :

Sponsor: PADDOCK LABS
3940 QUEBEC AVE NORTH
MINNEAPOLIS, MN 55427

Stamp Date : 22-MAY-2003
PDUFA Date :
Action Goal :
District Goal: 22-APR-2004

Brand Name :
Estab. Name: TESTOSTERONE
Generic Name:
Dosage Form: (GEL)
Strength : 1 %

FDA Contacts: S. PARK Project Manager (HFD-617) 301-827-5725
D. GILL Team Leader (HFD-630) 301-827-5848

Overall Recommendation: ACCEPTABLE on 10-FEB-2004by J. D AMBROGIO(HFD-322) 301-827-9049

Establishment : CFN : 2127022 FEI : 2127022
PADDOCK LABORATORIES INC
3940 QUEBEC AVE NORTH
MINNEAPOLIS, MN 55427

DMF No: AADA:

Responsibilities: FINISHED DOSAGE MANUFACTURER

Profile : OIN OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 10-FEB-04
Decision : ACCEPTABLE
Reason : DISTRICT RECOMMENDATION

Establishment : CFN : (b) (4) FEI : (b) (4)
(b) (4)

(b) (4)

DMF No: (b) (4) AADA:

Responsibilities: (b) (4)

Profile : CSN OAI Status: NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 02-JUL-03

Decision : ACCEPTABLE

Reason : BASED ON PROFILE

15 September 2004

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

ORIG AMENDMENT
N 1 AM

Re: TELEPHONE AMENDMENT to ANDA 76-744 in response to the chemistry deficiency communicated 02 September 2004 for Testosterone Gel 1%

Dear Staff:

Please accept this Telephone Amendment to Paddock Laboratories' pending application for Testosterone Gel 1%, ANDA 76-744, dated 22 May 2003 submitted pursuant to Section 505(j) of the Federal Food, Drug and Cosmetic Act. This amendment provides our responses to the 02 September 2004 Telephone Deficiency.

Sampling Explanation

(b) (4) [redacted]. A copy of the revised procedure is included in this submission (Attachment 1).

The procedure to (b) (4) [redacted] has been revised to specify the use of (b) (4) [redacted]. A copy of the revised method is included in this submission (Attachment 2).

The testosterone gel (b) (4) [redacted] has been revised to specify the use of (b) (4) [redacted]. A copy of the revised method is included in this submission (Attachment 3).

RECEIVED
SEP 16 2004
OGD/CDER

Paddock Laboratories, Inc.
3940 Quebec Avenue N, Minneapolis, MN 55427 • 800.328.5113 • 763.546.4676 • Fax:763.546.4842 • www.paddocklabs.com

Pooling of Samples and Preparation of Samples (b) (4)

(b) (4)

Clarification of Content Uniformity Procedure

The content uniformity procedure (A.P. No. 1374) has been revised and a copy is included in this submission (Attachment 6). Section 6.1.2 was removed from the procedure which allowed for using (b) (4). The procedure has been updated to Paddock Laboratories, Inc. current document format as well.

This response is initially being sent via facsimile to the reviewer, hard copies will be mailed the same day. A field copy has been sent to the Minneapolis District Office. Paddock Laboratories, Inc., does hereby certify that the submitted field copy is a true copy of the technical section of this application [21 CFR 314.96(b)].

Paddock Laboratories, Inc. requests that all information in this file be treated as confidential within the meaning of 21 CFR 314.430 and that no information from the file be publicly released without the written consent of an authorized person from Paddock Laboratories, Inc.

Please contact me by telephone at (763) 732-0364 or by facsimile at (763) 546-4842 if you have any questions or need additional information.

Sincerely,

PADDOCK LABORATORIES, INC.

Todd M. Delehant

Todd M. Delehant, PhD.
Regulatory Affairs Analyst

22 October 2004

Mr. Gary Buehler
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

ORIG AMENDMENT
N/AM

Re: TELEPHONE AMENDMENT to ANDA 76-744 in response to the chemistry deficiency communicated 12 October 2004 for Testosterone Gel 1%

CHEMISTRY INFORMATION

Dear Mr. Buehler:

Please accept this Telephone Amendment to Paddock Laboratories' pending application for Testosterone Gel 1%, ANDA 76-744, dated 22 May 2003 submitted pursuant to Section 505(j) of the Federal Food, Drug and Cosmetic Act. This amendment provides our responses to the 12 October 2004 Telephone Deficiency.

This response is initially being sent via facsimile to the reviewer, hard copies will be mailed the same day. A field copy has been sent to the Minneapolis District Office. Paddock Laboratories, Inc., does hereby certify that the submitted field copy is a true copy of the technical section of this application [21 CFR 314.96(b)].

Paddock Laboratories, Inc. requests that all information in this file be treated as confidential within the meaning of 21 CFR 314.430 and that no information from the file be publicly released without the written consent of an authorized person from Paddock Laboratories, Inc.

Please contact me by telephone at (763) 732-0364 or by facsimile at (763) 546-4842 if you have any questions or need additional information.

Sincerely,

PADDOCK LABORATORIES, INC.

Todd M. Delehant

Todd M. Delehant, PhD.
Regulatory Affairs Analyst

RECEIVED
OCT 25 2004
OGD / CDER

Attachments

OGD APPROVAL ROUTING SUMMARY

ANDA # 76-714 Applicant **Paddock Laboratories, Inc.**
Drug **Testosterone Gel** Strength(s) 1 %

APPROVAL ☐ TENTATIVE APPROVAL ☑ SUPPLEMENTAL APPROVAL (NEW STRENGTH) ☐ OTHER ☐

REVIEWER:	DRAFT Package	FINAL Package
1. Martin Shimer Chief, Reg. Support Branch	Date 19 Aug 2004 Initials MMS	Date 10/27/04 for Initials Rew

Contains GDEA certification: Yes ☑ No ☐ Determ. of Involvement? Yes ☐ No ☒
(required if sub after 6/1/92) Pediatric Exclusivity System
RLD = NDA# 21-015
Patent/Exclusivity Certification: Yes ☑ No ☐ Date Checked 10/27/04
If Para. IV Certification- did applicant Nothing Submitted ☒
Notify patent holder/NDA holder Yes ☑ No ☐ Written request issued ☐
Was applicant sued w/in 45 days: Yes ☑ No ☐ Study Submitted ☐
Has case been settled: Yes ☐ No ☑ Date settled:
Is applicant eligible for 180 day
Generic Drugs Exclusivity for each strength: Yes ☐ No ☐ (not yet determined)
Type of Letter: PII to 8/04 → sued w/in 45 days → 30 month stay = 1/7/2006
Comments:
Eligible for Tentative Approval only

2. Project Manager, **Wanda Pamphile** Team 5 Review Support Branch	Date 8-18-04 Initials WP	Date 8-24-04 Initials WP

Original Rec'd date 5-21-03 EER Status Pending ☐ Acceptable ☒ OAI ☐
Date Acceptable for Filing 5-22-03 Date of EER Status 2-10-04
Patent Certification (type) IV Date of Office Bio Review 6-15-04
Date Patent/Exclus.expires 8-30-20 Date of Labeling Approv. Sum 6-3-04
Citizens' Petition/Legal Case Yes ☐ No ☒ Date of Sterility Assur. App. N/A
(If YES, attach email from PM to CP coord) Methods Val. Samples Pending Yes ☐ No ☒
First Generic Yes ☐ No ☐ MV Commitment Rcd. from Firm Yes ☒ No ☐
Acceptable Bio reviews tabbed Yes ☒ No ☐ Modified-release dosage form: Yes ☐ No ☒
Suitability Petition/Pediatric Waiver Interim Dissol. Specs in AP Ltr: Yes ☐
Pediatric Waiver Request Accepted ☐ Rejected ☐ Pending ☐

Previously reviewed and tentatively approved ☐ Date _____
Previously reviewed and CGMP def. /NA Minor issued ☐ Date _____
Comments:

3. David Read **(PP IVs Only)** Pre-MMA Language included ☐ OGD Regulatory Counsel, Post-MMA Language Included ☐ Comments:	Date _____ Initials _____

4. Div. Dir./Deputy Dir. Chemistry Div. I II OR III Comments:	Date 8/27/04 Initials PS

CMC OK
SUBS
release method for PAS only per Bria

REVIEWER: FINAL ACTION

5. Frank Holcombe **First Generics Only** Date 10/26/04
Assoc. Dir. For Chemistry Initials
Comments: (First generic drug review) SATISFACTORY

6. Vacant RLD= Androgel 1% NDA 21-015
Deputy Dir., DLPS Date
Unimed Pharmaceuticals, Inc. Initials

7. Peter Rickman Date 10/27/04
Director, DLPS Initials
Para.IV Patent Cert: Yes ☐ No ☐; Pending Legal Action: Yes ☐ No ☐; Petition: Yes ☐ No ☐
Comments: Labeling (PR) found acceptable 6/3/04. CMC found acceptable 9/28/04. Methods validation was not requested - API is compendial, drug product was not requested as it does not meet current criteria for OR I.V. Bioequivalence study (single dose, fasting) found acceptable 6/15/04. Stat consult also completed. Biostudy sites have acceptable OSI inspectional histories. Office-level bio endorsed 6/15/04. Concur w/ rec't for

8. Robert L. West Date 10/27/2004
Deputy Director, OGD Initials
Para.IV Patent Cert: Yes ☒ No ☐; Pending Legal Action: Yes ☒ No ☐; Petition: Yes ☐ No ☐
Comments: Acceptable EES dated 2/10/04 (Verified 10/27/04). No O.A.I. alerts noted. Paddock made a paragraph IV certification to the '894 patent (8/30/20). Paddock was sued within the 45-day period. The 30-month statutory hold period expires on 1/7/06.
This ANDA is recommended for tentative approval.

9. Gary Buehler Date 10/27/04
Director, OGD Initials
Comments: Tentative
First Generic Approval ☒ PD or Clinical for BE ☐ Special Scientific or Reg.Issue ☐

10. Project Manager, **Wanda Pamphile**
Team 5
Review Support Branch Date 10/27/04
N/A Date PETS checked for first generic drug (just prior to notification to firm) Initials
Applicant notification:
1:49 Time notified of approval by phone 1:53 Time approval letter faxed
FDA Notification:
10/27/04 Date e-mail message sent to "CDER-OGDAPPROVALS" distribution list.
10/27/04 Date Approval letter copied to \\CDS014\DRUGAPP\ directory.

File V:/division/dlps/approvrou8.doc

September 15, 2006

Mr. Gary Buehler
Director, Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Document Control Room
Metro Park North 4 (HFD-600)
7519 Standish Place
Rockville, MD 20855

XS

RE: ANDA 76-744; Testosterone Gel, 1%

TRANSFER OF OWNERSHIP

Dear Mr. Buehler,

Pursuant to 21 CFR 314.72(a)(1), this letter serves as notice that all rights to the above referenced application have been transferred from Paddock Laboratories, Inc. to Par Pharmaceutical Companies, Inc. This letter also serves to revise the authorized contact individual for the above referenced application. The current contact person listed in the ANDA is Wendy Saunders, Director of Regulatory Affairs, Paddock Laboratories, Inc.

All future correspondence and contact pertaining to this application should be directed to:

Michelle Bonomi-Huvala
Sr. Director, Regulatory Affairs
Par Pharmaceutical
One Ram Ridge Road
Spring Valley, NY 10977
Telephone: 845-639-5120
Fax: 845-639-5201
mbonomi@parpharm.com

Sincerely,

PADDOCK LABORATORIES, INC.

Wendy A. Saunders
Director of Regulatory Affairs

RECEIVED
SEP 29 2006
OGD / CDER

PAR PHARMACEUTICAL

Par Pharmaceutical, Inc.
One Ram Ridge Road
Spring Valley, NY 10977
tel 845 425 7100
fax 845 425 7907
www.parpharm.com

September 26, 2006

XS

Gary Buehler, Director
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North 2
7500 Standish Place
Rockville, Maryland 20855

RE: ANDA 76-744
Testosterone Gel, 1%
Change in Ownership of Application

Dear Mr. Buehler:

Pursuant to 21 CFR §314.72 (a)(1) Paddock Laboratories, Inc. notified the FDA of a change in ownership of ANDA 76-744 for Testosterone Gel 1% on September 15, 2006. All rights to ANDA 76-744 were transferred from Paddock Laboratories to Par Pharmaceutical, effective September 13, 2006.

In accordance with 21 CFR §314.72 (a)(2) Par Pharmaceutical, as the new owner, submits an executed application form FDA 356h reflecting the change in ownership of ANDA 76-744 from Paddock Laboratories to Par Pharmaceutical.

Par commits to all agreements, promises, and conditions made by Paddock Laboratories and contained in ANDA 76-744. Par has received a complete copy of the subject application and will advise the FDA about any subsequent changes in the conditions of the application.

If you have any questions or require additional information, please do not hesitate to contact me directly by phone at (845) 639-5120 or email, mbonomi@parpharm.com. In my absence please contact Janis Picurro, Director, at (845) 639-5121 or jpicurro@parpharm.com.

Sincerely,
PAR PHARMACEUTICAL, INC.

Michelle Bonomi-Huvala

Michelle Bonomi-Huvala
Sr. Director, Regulatory Affairs

PAR PHARMACEUTICAL

Par Pharmaceutical, Inc.
One Ram Ridge Road
Spring Valley, NY 10977
tel 845 425 7100
fax 845 425 7907
www.parpharm.com

Copy 1 ✓
Copy 2
Copy 3 (Field)*

December 13, 2006

Martin Shimer, Branch Chief, Regulatory Support Branch
Food and Drug Administration
Office of Generic Drugs
Center for Drug Evaluation and Research
Metro Park North II
7500 Standish Place, Room 150
Rockville, Maryland 20855

ORIGINAL

Patent Amendment

RE: ANDA 76-744, Testosterone Gel, 1%

Dear Mr. Shimer:

Reference is made to our abbreviated new drug application for Testosterone Gel 1% which Par acquired from Paddock Laboratories, Inc.

Par Pharmaceutical, Inc. has also acquired a licensing agreement with the patent owner, Unimed Laboratories. Par is amending the application with this updated Paragraph IV License certification in accordance with 21 CFR 314.94 (a)(12)(i)(A)(v). A copy of the Paragraph IV License certification is enclosed together with the relevant agreement documents.

We certify that the field copy of this Patent Amendment was submitted to the New York District Office.

This concludes our Patent Amendment to ANDA 76-744. If additional information is required, please do not hesitate to contact me directly at (845) 639-5128 or by e-mail at *jszozda@parpharm.com.*

Sincerely,
PAR PHARMACEUTICAL, INC.

Julie Szozda
Senior Associate, Regulatory Affairs

*Mr. Matthew Spataro
NYDO NDA/ANDA File Room
Food and Drug Administration
158-15 Liberty Avenue
Jamaica, New York 11433

RECEIVED
DEC 14 2006
OGD / CDER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville, MD 20857

ANDA 76-744

Par Pharmaceutical
Attention: Michelle Bonomi-Huvala
One Ram Ridge Road
Spring Valley, NY 10977

Dear Madam:

We acknowledge receipt of your communication dated September 26, 2006, submitted as required by the provisions of Regulation 21 CFR 314.72(a) and Section 505(k) of the Federal Food, Drug and Cosmetic Act for the abbreviated new drug application (ANDA) for Testosterone Gel, 1%.

Your letter details the transfer of ownership of the ANDA from Paddock Laboratories, Inc. to Par Pharmaceutical.

Pursuant to 21 CFR 314.72(b), the new owner shall advise FDA about any change in the conditions of the pending application.

The material submitted is being retained as part of your application.

Sincerely yours,

{See appended electronic signature page}

William P. Rickman
Director
Division of Labeling and Program Support
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/

Timothy W. Ames
12/14/2006 04:02:01 PM
Signing off for Wm Peter Rickman

PAR PHARMACEUTICAL

Par Pharmaceutical, Inc.
One Ram Ridge Road
Spring Valley, NY 10977
tel 845 425 7100
fax 845 425 7907
www.parpharm.com

Copy 1 ✓
Copy 2
Copy 3 (Field)*

ORIGINAL

December 26, 2006

Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North 2
7500 Standish Place, Room 150
Rockville, Maryland 20855

ORIG AMENDMENT
N-000-AM

Minor Amendment - Final Approval Requested

RE: ANDA #76-744, Testosterone Gel 1%

Dear: Sir/Madam:

Reference is made to the Agency's Tentative Approval letter pertaining to our abbreviated new drug application and all subsequent amendments relative to Testosterone Gel 1%. A copy of the 10/27/04 Tentative Approval letter and the 12/14/06 transfer of ownership of the application acknowledgement letter are provided for reference.

In accordance with the 11/14/06 request by Dr. Benjamin Danso, Project Manager, FDA, we herewith submit this minor amendment via facsimile and hard copy to reactivate our application, ANDA 76-744, and request final approval.

Our labeling has been updated in accordance to the labeling changes for the reference listed drug approved on 08/2005 and to reflect the transfer of ownership of the ANDA to PAR. Final printed labeling is provided in final print in pdf and MS Word format on the enclosed CD ROM. In addition, a side-by-side comparison of our proposed labeling with the previously submitted labeling with all differences annotated and explained is included on the enclosed CD ROM. Subsequent to the Agency's, letters, there have been no changes to this application.

We certify that the field copy of this minor amendment-final approval requested was submitted to the FDA New York District Office.

This concludes our minor amendment to our abbreviated new drug application for Testosterone Gel 1%, ANDA 76-744. If you have any questions, please don't hesitate to contact me at (845) 639-5128 or by e-mail at *jszozda@parpharm.com.*

Sincerely,
PAR PHARMACEUTICAL

Julie Szozda

Julie Szozda
Senior Associate, Regulatory Affairs

Enc.

*Mr. Matthew Spataro
NYDO NDA/ANDA File Room
Food and Drug Administration
158-15 Liberty Avenue
Jamaica, New York 11433

RECEIVED
DEC 27 2006
OGD / CDER

PAR PHARMACEUTICAL

Par Pharmaceutical, Inc.
One Ram Ridge Road
Spring Valley, NY 10977
tel 845 425 7100
fax 845 425 7907
www.parpharm.com

January 5, 2007

ORIGINAL

Copy 1 ✓
Copy 2
Copy 3 (Field)*

ORIG AMENDMENT
N-AA

Via Facsimile and Overnight Mail
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North 2, Room 150
7500 Standish Place
Rockville, Maryland 20855

RE: ANDA 76-744, Testosterone Gel 1%

Gratuitous Amendment to our December 26, 2006 Submission

Dear Staff:

In accordance Dr. Benjamin Danso's request of January 5, 2007 we herewith submit this gratuitous amendment to our December 26, 2006 request for final approval to advise the Agency that there were no chemistry, manufacturing and controls changes to our application subsequent to the Agency's tentative approval letter dated October 27, 2004. Final printed labeling was submitted with our December 26th minor amendment.

We acknowledge that Testosterone Gel 1% may not be marketed without final Agency approval and introduction or delivery into interstate commerce of the drug products will not occur before the effective date of approval of this application.

We certify that the field copy of this gratuitous amendment was submitted to the FDA New York District Office.

This concludes our amendment to our abbreviated new drug application for Testosterone Gel %, ANDA 76-744. If you have any questions regarding the above, please do not hesitate to contact us.

Sincerely,
PAR PHARMACEUTICAL, INC.

Janis A. Picurro
Director, Regulatory Affairs

RECEIVED
JAN 0 8 2007
CGD / CDER

* Mr. Matthew Spataro
NYDO NDA/ANDA File Room
158-15 Liberty Avenue
Jamaica, New York 11433

PAR PHARMACEUTICAL

Par Pharmaceutical, Inc.
One Ram Ridge Road
Spring Valley, NY 10977
tel 845 425 7100
fax 845 425 7907
www.parpharm.com

Copy 1
Copy 2

May 3, 2007

Ruby (Chi-Ann) Wu
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North 2
7500 Standish Place, Room 150
Rockville, Maryland 20855

Labeling Amendment

RE: ANDA #76-744, Testosterone Gel 1%

Dear Ms Wu:

Reference is made to the Agency's facsimile of April 12, 2007 requesting that our package insert labeling for Testosterone Gel 1% be updated to be in line with the changes in the reference listed drug, AndroGel.

In accordance with the Agency's request, we herewith submit this labeling amendment to ANDA 76-744.

Our package insert has been updated according to the Agency's instructions. Final printed labeling is provided electronically in pdf and MSWord format on the enclosed CD Rom. To facilitate review, a side-by-side comparison of the final printed proposed with the reference listed drug labeling with all differences annotated and explained is also provided on the enclosed CD Rom. The final printed containers, cartons and patient information and instructions for using leaflet submitted on December 26, 2006 are satisfactory as indicated in the April 12, 2007.

This concludes our labeling amendment to our abbreviated new drug application for Testosterone Gel 1%. If you have any questions, please don't hesitate to contact me at (845) 639-5128 or by e-mail at *jszozda@parpharm.com.*

Sincerely,
PAR PHARMACEUTICAL, INC.

Julie Szozda
Submissions Manager, Regulatory Affairs

Enc.

OGD APPROVAL ROUTING SUMMARY

ANDA # 76-744 Applicant Par Pharmaceutical, Inc.
Drug Testasterone Gel Strength(s)1%

APPROVAL ☒ TENTATIVE APPROVAL ☐ SUPPLEMENTAL APPROVAL (NEW STRENGTH) ☐ OTHER ☐

REVIEWER:	**DRAFT Package**	**FINAL Package**
1. **Martin Shimer** Chief, Reg. Support Branch	Date15 May 2007 Initials MHS	Date5/23/07 Initials rlw/for

Contains GDEA certification: Yes ☒ No ☐ (required if sub after 6/1/92)
Patent/Exclusivity Certification: Yes ☒ No ☐
If Para. IV Certification- did applicant Notify patent holder/NDA holder Yes ☒ No ☐
Was applicant sued w/in 45 days: Yes ☒ No ☐
Has case been settled: Yes ☒ No ☐
Is applicant eligible for 180 day Generic Drugs Exclusivity for each strength: Yes ☐ No ☒
Date of latest Labeling Review/Approval Summary _____
Any filing status changes requiring addition Labeling Review Yes ☐ No ☒
Type of Letter:Full Approval

Determ. of Involvement? Yes ☐ No ☒
Pediatric Exclusivity System
RLD =_____ NDA#21-015
Date Checked 5/23/07
Nothing Submitted ☒
Written request issued ☐
Study Submitted ☐
Date settled:

Comments:Firm submitted PIV cert to the '894 patent. Par notified and was sued within 45 days triggering a 30 month stay of approval. This stay was effectively ended once Par and Unimed entered into a settlement and licensing agreement ending the ongoing litigation. Watson ANDA 76-737 had been eligible for 180 day exclusivity. However, on 10/31/2006 Watson relinquished their eligibility to this exclusivity clearing the way for all subsequent PIV filers. This ANDA is eligible for Full Approval.

2. Project Manager, Ben Danso Team5 Review Support Branch	Date4-10-07 Initials BD	Date 5-10-07 Initials _____

Original Rec'd date5-21-03
Date Acceptable for Filing5-22-03
Patent Certification (type)P4
Date Patent/Exclus.expires 8-30-2020
Citizens' Petition/Legal Case Yes☐ No ☒ (If YES, attach email from PM to CP coord)
First Generic Yes ☐ No ☒
Priority Approval Yes ☐ No ☒ (If yes, prepare Draft Press Release, Email it to Cecelia Parise)
Acceptable Bio review tabbed Yes ☒ No ☐
Bio Review Filed in DFS: Yes ☐ No ☒
Suitability Petition/Pediatric Waiver

EER Status Pending ☐ Acceptable ☒ OAI ☐
Date of EER Status 4-24-07
Date of Office Bio Review 6-15-04
Date of Labeling Approv. Sum 5-9-07
Date of Sterility Assur. App.
Methods Val. Samples Pending Yes ☐ No ☒
MV Commitment Rcd. from Firm Yes ☐ No ☐
Modified-release dosage form: Yes ☐ No ☐
Interim Dissol. Specs in AP Ltr: Yes ☐

Pediatric Waiver Request Accepted ☐ Rejected ☐ Pending ☐
Previously reviewed and tentatively approved ☒ Date 10-27-04
Previously reviewed and CGMP def. /NA Minor issued ☐ Date _____
Comments:

3. Labeling Endorsement Reviewer:		Labeling Team Leader:
Date_____ Name/Initials_____		Date Thu 5/17/2007 1:07 PM Name/Initials Grace, John F

Comments:
concur

From: Wu, Ruby (Chi-Ann)
Sent: Thursday, May 17, 2007 12:00 PM
To: Danso, Benjamin; Grace, John F
Subject: RE: ANDA 76-744 (PAR's TESTOSTERONE)

I checked OB, DSS and USP. Drug product not subject to a USP monograph.

Labeling AP summary signed off 5/9/07 remains acceptable.

Ruby

4. David Read **(PP IVs Only)** Pre-MMA Language included ☐ Date 5/23/07
OGD Regulatory Counsel, Post-MMA Language Included ☐ Initials rlw/for
Comments:N/A.

5. Div. Dir./Deputy Dir. Date 5/17/07
Chemistry Div. I II OR III Initials RMP
Comments:It was TAed on 10/27/04.There is no change in the section. Recommend AP.

6. Frank Holcombe **First Generics Only** Date 5/23/07
Assoc. Dir. For Chemistry Initials rlw/for
Comments: (First generic drug review)
N/A. This ANDa was granted tentative approval on Oct0ber 27, 2004. In addition, Watson's ANDA 76-737 for this drug product was approved on January 27, 2006.

7. Vacant Date _____
Deputy Dir., DLPS Initials _____
RLD = Androgel 1%
Unimed Pharmaceuticals, Inc. NDA 21-015

8. Peter Rickman Date 5/23/07
Director, DLPS Initials rlw/for
Para.IV Patent Cert: Yes☐ No☐;Pending Legal Action: Yes ☐No ☐;Petition: Yes☐ No☐
Comments:This ANDA was tentatively approved on October 27, 2004. Refer to the administrative sign off form completed at that time. Final approval was blocked because of the 30-month stay in effect as a result of Par's (formerly Paddock's) challenge of the '894 patent. Ownership of this ANDA was transferred from Paddock to Par Pharmaceutical Inc. in 2006. On December 13, 2006, Par provided documentation of a licensing agreement with the patent holder (Unimed). This licensing agreement allows Par to market testosterone gel effective the earliest of August 31, 2015, or upon the date any other generic product referencing Androgel or an authorized generic of Androgel is offered for sale in the U.S. On December 26, 2006, Par submitted a minor amendment to request final approval based upon the licensing agreement. Par stated that no changes had been made to the CMC section of the ANDA since the date of the tentative approval. Updated FPL was also submitted on 5/3/07.

FPL found acceptable for final approval 5/9/07 (DFS).

CMC found acceptable for approval (Chemistry Review #4) 5/18/07. Methods validation was not requested.

OR

8. Robert L. West Date 5/23/07
Deputy Director, OGD Initials RLWest
Para.IV Patent Cert: Yes☐ No☒; Pending Legal Action: Yes☐ No☒; Petition: Yes☐ No☒
Press Release Acceptable ☐
Comments:Acceptable EES dated 4/24/07 (Verified 5/23/07). No "OAI" Alerts noted.

Based upon the settlement agreement between Par and Unimed, this ANDA is recommended for final approval.

9. Gary Buehler — Date 5/23/07
Director, OGD — Initials rlw/for
Comments:
First Generic Approval ☐ PD or Clinical for BE ☐ Special Scientific or Reg.Issue ☐
Press Release Acceptable ☐

10. Project Manager, Team Ben Danso — Date _____
Review Support Branch — Initials _____

_____Date PETS checked for first generic drug (just prior to notification to firm)

Applicant notification:
_____Time notified of approval by phone
_____Time approval letter faxed

FDA Notification:
_____Date e-mail message sent to "CDER-OGDAPPROVALS" distribution list.
_____Date Approval letter copied to \\CDS014\DRUGAPP\ directory.

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

/s/

Benjamin Danso
6/5/2007 12:20:37 PM