Approval Package for:

APPLICATION NUMBER:
ANDA 076744

Name: Testosterone Gel
1%

Sponsor: Par Pharmaceuticals, Inc.

Approval Date: May 23, 2007
CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
ANDA 076744

CONTENTS

<table>
<thead>
<tr>
<th>Reviews / Information Included in this Review</th>
</tr>
</thead>
<tbody>
<tr>
<td>Approval Letter</td>
</tr>
<tr>
<td>Tentative Approval Letter</td>
</tr>
<tr>
<td>Labeling</td>
</tr>
<tr>
<td>Labeling Review(s)</td>
</tr>
<tr>
<td>Medical Review(s)</td>
</tr>
<tr>
<td>Chemistry Review(s)</td>
</tr>
<tr>
<td>Bioequivalence Review(s)</td>
</tr>
<tr>
<td>Statistical Review(s)</td>
</tr>
<tr>
<td>Microbiology Review(s)</td>
</tr>
<tr>
<td>Administrative &amp; Correspondence Documents</td>
</tr>
</tbody>
</table>
APPLICATION NUMBER:
ANDA 076744

APPROVAL LETTER
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
Beltville, 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
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,

[Signature]

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 8/24/04
HFD-620/S.Liu 8/24/04
HFD-617/W.Pamphile 8/23/04
HFD-613/R.Wu 8/24/04
HFD-613/J.Grace 8/24/04

F/T by wp 8/20/04
V:\FIRMSNZ\PADDOCK\LTRS&REV\76744.TA.doc

TENTATIVE APPROVAL

Robert Levent
10/27/2004

8/27/04
APPLICATION NUMBER:
ANDA 076744

LABELING
Testosterone gel treatment at 6 g/day and 10 g/day for 20 days produced significant improvement in mood, function, 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 partner of patients with testosterone gel treatment, as did the subjective scores for "testosterone duration of erection". Testosterone gel treatment at 5 g/day and 10 g/day produced positive effects on mood function, sexual enjoyment of sexual activity and quality of life, although indicating inferiority of the 5 g/day dose. The DHT concentrations increased in parallel with testosterone concentrations at 5 g/day and 10 g/day (P<0.05). However, the IDMT ratio stayed within the normal range, indicating normal or favorable metabolic physiology of the androgen. Serum estradiol (E2) concentrations increased in parallel with testosterone concentrations during treatment at 10 g/day but not at 5 g/day, and remained elevated throughout the treatment period but remained within the normal range. The testosterone gel treatment in men with hypergonadotropic hypogonadism, serum levels of LH and FSH fell within the normal range 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) at which the skin reddening was noted was determined for each subject. A single 24 (±1) hour application of duplicate patches containing 2 mg testosterone gel was applied to the upper inner arm of each subject on consecutive days (D1, D2, D3). On D1, each subject received five exposure times of ultraviolet light, each exposure being 50% greater than the previous one. Skin evaluation was made on D2, 24 h after patch removal. To assess the potential for control application sites to ultraviolet light did not produce increased inflammation relative to non-inflammatory application sites, including application sites to the back. Potential for Testosterone Transfer: The potential for dermal testosterone transfer following testosterone gel use was evaluated in a clinical study of testosterone gel use in 27 subjects with normal skin and 27 subjects with skin contact so that the labial partners gained maximum exposure to the testosterone gel application sites. Under these study conditions, all unprotected female partners had a sensitization reaction 2 times the baseline value at some time during the study. When a short cover the application sites, the transfer of testosterone from the males to the females partner was completely prevented.

INDICATIONS AND USAGE
Testosterone gel is indicated for replacement therapy in males for conditions associated with a deficiency or absence of physiological amounts of testosterone.

CONTRAINDICATIONS
Testosterone gel is 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 woman, and must not be used in women.

Pregnant women should avoid skin contact with testosterone gel application sites in men. In the event of skin contact, patient and/or the patient’s partner should wash their hands with soap and water as soon as possible. Testosterone gel 1% has been applied does come in direct contact with the skin of a pregnant woman, the skin of the pregnant area should be washed with soap and water immediately. In in vitro studies show that residual testosterone is removed from the skin surface by washing with soap.

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-ethyl testosterone (e.g., methyltestosterone) has been associated with various hepatic adverse effects (polycystic hepatic, hepatic neoplasms, etc.) and with the development of androgenic or estrogenic side effects (galactorrhea, gynecomastia, etc.). Polycystic hepatic changes and Papillary hepatic carcinoma were observed in the oral androgen group.

2. Androgens are responsible for the growth spurt of adolescence and for the onset of menstruation. When used in doses sufficient to produce an increase in appetite and protein anabolism, androgenic and glucocorticoid effects may be more apparent than the effects that are desired, i.e., androgenic and anabolic effects. When androgens are used in the treatment of anemia, the patient should be under the care of a physician with special experience in blood diseases, and the patient should be examined at least every six months by a hematologist to determine the patient's response to therapy and the patient's compliance with the regimen.

In conclusion, testosterone gel is an effective and safe treatment option for men with hypogonadism, with potential benefits in improving mood, sexual function, and quality of life. However, it is important to consider the potential risks and contraindications associated with its use.
studies show that
9.3% (15)
3.7% (6)
1.9% (3)
3.1% (5)
1.9% (3)
In diabetic patients, the metabolic effects of androgens may decrease blood glucose and,
Testosterone has been tested by subcutaneous injection and implantation in mice and
There are rare reports of hepatocellular carcinoma in patients receiving long-term oral
2.5% (4)
1.9% (3)
prostate cancer prior to initiation of testosterone replacement therapy.

Laboratory Tests
1. Hemoglobin and hematocrit levels should be checked periodically (to detect polycythemia) in
2. Liver function, prostatic specific antigen, cholesterol, and high-density lipoprotein should be

Drug Interactions
Oxyphenbutazone: Concurrent administration of oxyphenbutazone and androgens may result in ele-
Insulin: In diabetic patients, the metabolic effects of androgens may decrease blood glucose and,
Propranolol: In a published pharmacokinetic study of an injectable testosterone product, adminis-
Corticosteroids: The concurrent administration of testosterone with ACTH or corticosteroids may

Disability
Androgens may decrease levels of thyroxin-binding globulin, resulting in decreased total T4 serum

Drug Laboratory Test Interactions

Asthma 0% 1% 0%
Testosterone gel contains testosterone, a Schedule III controlled substance as defined by the

Pregnancy Category X (see CONTRAINDICATIONS): 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

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

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

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

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

Ovulations

Dosage and Administration
The recommended starting dose of testosterone gel is 5 g delivering 5 mg of testosterone systemi-
cally applied once-daily. Therapy should be increased to 7.5 g, 10 g, 12.5 g, or 15 g as needed. Therapy may be increased at 1-2 week intervals. Effective dosage may vary from patient to patient.

Overdose
No reports of testosterone gel overdose have been received. However, there is one report of acute

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

Disposal
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.

Table 4: Clinical Adverse Effects of Testosterone Gel

Table 5: Serum PSA Increases

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

NDC Number
5484-418-72 2.5 g per packet
5484-510-72 5 g per packet

Testosterone gel is supplied in unit-dose packets in cartons of 30. Each packet of 2.5 g or

Rashes

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Disposal
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.
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% treatment:

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 any application site(s). Repeat until the entire contents of the packet have been applied.

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

5. Apply testosterone gel 1% only to healthy, normal skin on your abdomen (stomach area), upper arm, 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 show 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:

- Penile 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].

Issued: 12/06

PI418-72-42-02
Testosterone Gel 1%
Contains
2.5 grams
Rx only
Use complete contents of foil packet.
Patient: Please read patient leaflet.
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 "prostatic" to read "prostatic"
      ii. Add as item 7: "7. GELS ARE FLAMMABLE. AVOID FIRE, FLAME OR SMOKING"
   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"

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/cdemnew/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.

[Signature]

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

<table>
<thead>
<tr>
<th>Establishment Name</th>
<th>Yes</th>
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<th>N.A.</th>
</tr>
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<tbody>
<tr>
<td>Different name than on acceptance to file letter?</td>
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### Error Prevention Analysis

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### Labeling

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### Labeling (continued)

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### Scoring:

Describe scoring configuration of RLD and applicant (page #) in the FTR

<table>
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<td>Is the scoring configuration different than the RLD?</td>
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<tr>
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<td></td>
</tr>
</tbody>
</table>

### Inactive Ingredients:

(FTR: List page # in application where inactives are listed)

<table>
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<td>X</td>
<td></td>
</tr>
<tr>
<td>Has the term &quot;other ingredients&quot; been used to protect a trade secret? If so, is claim supported?</td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Failure to list the coloring agents if the composition statement lists e.g., Cepacol, Opaspray?</td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Failure to list gelatin, coloring agents, antimicrobials for capsules in DESCRIPTION?</td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Failure to list dyes in imprinting inks? (Coloring agents e.g., iron oxides need not be listed)</td>
<td></td>
<td>X</td>
<td></td>
</tr>
</tbody>
</table>

### USP Issues:

(FTR: List USP/ANDA dispensing/storage recommendations)

<table>
<thead>
<tr>
<th></th>
<th>Yes</th>
<th>No</th>
<th>N.A.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Do container recommendations fail to meet or exceed USP/ANDA recommendations? If so, are the recommendations supported and is the difference acceptable?</td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Because of proposed packaging configuration or for any other reason, does this applicant meet fail to meet all of the unprotected conditions of use referenced by the RLD?</td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Does USP have labeling recommendations? If any, does ANDA meet them?</td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Is the product light sensitive? If so, is NDA and/or ANDA in a light resistant container?</td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>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.</td>
<td></td>
<td>X</td>
<td></td>
</tr>
</tbody>
</table>

### Bioequivalence Issues:

(Compare bioequivalency values: insert to study. List Cmax, Tmax, T 1/2 and date study)

<table>
<thead>
<tr>
<th></th>
<th>Yes</th>
<th>No</th>
<th>N.A.</th>
</tr>
</thead>
</table>

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.09.063.0035332; 80-0005-04; Issued 11/02
   - Patient Information: A.09.063.0035331; 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 68.9% to 67.0%. 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

<table>
<thead>
<tr>
<th></th>
<th></th>
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<th></th>
<th></th>
</tr>
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<tbody>
<tr>
<td>021015 001</td>
<td>0003804</td>
<td>AUG 30, 2020</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>U-459 (TESTOSTERONE REPLACEMENT THERAPY IN MALES FOR CONDITIONS ASSOCIATED WITH A DEFICIENCY OR ABSENCE OF ENDOGENOUS TESTOSTERONE)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Exclusivity Data

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>021015 001</td>
<td>001</td>
<td>NDF (NEW DOSAGE FORM)</td>
<td>MAR 28, 2003</td>
<td>Expired</td>
</tr>
</tbody>
</table>

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: -
   Test conditions: accelerated (40°C/75% RH) and controlled room temperature (25°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.
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]

   2.5 gram and 5 gram packet foil laminate:
8. PRODUCT DESCRIPTION:

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.

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>Pharmaceutical Function</th>
<th>% w/w</th>
<th>Concentration (mg/g)</th>
<th>Exhibit Batch/ Commercial Batch (kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Testosterone USP</td>
<td>Active</td>
<td>1.000</td>
<td>10.000</td>
<td>(b)(4)</td>
</tr>
<tr>
<td>Ethanol (Alcohol USP³)</td>
<td></td>
<td></td>
<td></td>
<td>(b)(4)</td>
</tr>
<tr>
<td>Purified Water USP</td>
<td></td>
<td></td>
<td></td>
<td>(b)(4)</td>
</tr>
<tr>
<td>Carbomer 940 NF</td>
<td></td>
<td></td>
<td></td>
<td>(b)(4)</td>
</tr>
<tr>
<td>Isopropyl Myristate NF</td>
<td></td>
<td></td>
<td></td>
<td>(b)(4)</td>
</tr>
<tr>
<td>Sodium Hydroxide NF</td>
<td></td>
<td></td>
<td></td>
<td>(b)(4)</td>
</tr>
</tbody>
</table>

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.


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: 1/22/004
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

<table>
<thead>
<tr>
<th>Patent Data</th>
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<tr>
<td>-----------</td>
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</tr>
<tr>
<td>Failure to list the coloring agents if the composition statement lists e.g., Opacode, Opaspray?</td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Failure to list gelatin, coloring agents, antimicrobials for capsules in DESCRIPTION?</td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Failure to list dyes in imprinting inks? (Coloring agents e.g., iron oxides need not be listed)</td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>USP issues: (FTR: List USP/ANDA dispensing/storage recommendations)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Do container recommendations fall to meet or exceed USP/ANDA recommendations? If so, are the recommendations supported and is the difference acceptable?</td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Because of proposed packaging configuration or for any other reason, does this applicant meet fail to meet all of the unregulated conditions of use referred to by the RLD?</td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Does USP have labeling recommendations? If any, does ANDA meet them?</td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Is the product light sensitive? If so, is NDA and/or ANDA in a light resistant container?</td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>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.</td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Bioequivalence Issues: (Compare bioequivalency values: insert to study. List Cmax, Tmax, T 1/2 and date study</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
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: A09.053.0039332; 80-0005-04; Issued 11/02
- Patient Information: A09.063.0039331; 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][b] to [b][4][b] 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

Patent and Exclusivity Search Results from query on 021015 001.

Patent Data
# represents patent information submitted prior to August 18, 2003

Exclusivity Data

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]

Manufacturing Facility (Vol A1.10, pg. 4023)
Paddock Laboratories, Inc.
3940 Quebec Ave N
Minneapolis, MN 55427

Storage Conditions:
NDA: Store at Controlled Room Temperature 20º-25ºC (68º-77ºF) (see USP).
ANDA: [redacted]
Test conditions: accelerated (40ºC/75% RH) and controlled room temperature (25ºC/60% RH)

Dispensing Recommendations:
NDA: None
ANDA: None

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]

2.5 gram and 5 gram packet foil laminate:
8. PRODUCT DESCRIPTION:
ANDA- Clear 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.

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<th>Concentration (mg/g)</th>
<th>Exhibit/Batch/CommercialBatch (kg)</th>
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<td>Active</td>
<td>1.000</td>
<td>10.000</td>
<td></td>
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<tr>
<td>Ethanol (Alcohol USP)</td>
<td></td>
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<tr>
<td>Purified Water USP</td>
<td></td>
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</tr>
<tr>
<td>Carbomer 940 NF</td>
<td></td>
<td></td>
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<tr>
<td>Isopropyl Myristate NF</td>
<td></td>
<td></td>
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<td></td>
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<td></td>
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</table>

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.


Date of Review: May 29, 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
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 AndroGe® (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 % to %. However, the total amount of alcohol in the formulation remains the same based on absolute alcohol content."

Other AndroGe supplements of interest:

- S-013 approved August 16, 2005...This supplement pertains to the final printed container and carton labels for AndroGe single pump and twin pump. 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.

<table>
<thead>
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<th>Patent Data</th>
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<tr>
<td># represents patent information submitted prior to August 18, 2003</td>
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<tbody>
<tr>
<td>Appliance No</td>
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<tr>
<td>021015 001</td>
</tr>
</tbody>
</table>

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
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]

   2.5 gram and 5 gram packet foil laminate:

8. PRODUCT DESCRIPTION:

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.

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>Pharmaceutical Function</th>
<th>% w/w</th>
<th>Concentration (mg/g)</th>
<th>Exhibit Batch/Commercial Batch (kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Testosterone USP</td>
<td>Active</td>
<td>1.000</td>
<td>10.000</td>
<td>(a) (4)</td>
</tr>
<tr>
<td>Ethanol (Alcohol USP²)</td>
<td></td>
<td></td>
<td></td>
<td>(b) (4)</td>
</tr>
<tr>
<td>Purified Water USP</td>
<td></td>
<td></td>
<td></td>
<td>(b) (4)</td>
</tr>
<tr>
<td>Carbomer 940 NF</td>
<td></td>
<td></td>
<td></td>
<td>(b) (4)</td>
</tr>
<tr>
<td>Isopropyl Myristate NF</td>
<td></td>
<td></td>
<td></td>
<td>(b) (4)</td>
</tr>
<tr>
<td>Sodium Hydroxide NF</td>
<td></td>
<td></td>
<td></td>
<td>(b) (4)</td>
</tr>
</tbody>
</table>

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.


Date of Review: April 11, 2007
Date of Submission: December 26, 2006
Primary Reviewer: Ruby Wu (for Postolito 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
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

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
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<th></th>
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<td>021016</td>
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<td>AUG 30, 2020</td>
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U-490 (TESTOSTERONE REPLACEMENT THERAPY IN MALES FOR CONDITIONS ASSOCIATED WITH A DEFICIENCY OR ABSENCE OF ENDOGENOUS TESTOSTERONE)

Exclusivity Data

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<td>NDF (NEW DOSAGE FORM)</td>
<td>FEB 28, 2003</td>
<td>Expired!</td>
</tr>
</tbody>
</table>
NOTES/QUESTIONS TO THE CHEMIST:

FOR THE RECORD:

1. MODEL LABELING - This review is based on the labeling of AndroGe® (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, information pertaining to the pump in the RLD labeling has been cut out.

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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**

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<td>U-490 (TESTOSTERONE REPLACEMENT THERAPY IN MALES FOR CONDITIONS ASSOCIATED WITH A DEFICIENCY OR ABSENCE OF ENDOGENOUS TESTOSTERONE )</td>
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Test conditions: accelerated (40\(^\circ\)C/75% RH) and controlled room temperature (25\(^\circ\)C/60% RH)

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   NDA: None
   ANDA: None

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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.

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

ANDA 76-744
V:\FIRMSNZ\PADDOCK\LTRS\REV\76744.ap2.L.doc
Review
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
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

Table of Contents .................................................................................................................. 2

Chemistry Review Data Sheet ............................................................................................... 3

The Executive Summary ......................................................................................................... 7

I. Recommendations ............................................................................................................... 7
   A. Recommendation and Conclusion on Approvability The ANDA is not approvable pending
      clarification of MINOR Chemistry issues. Labeling and Bioequivalence are pending. ........ 7
   B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk
      Management Steps, if Approvable N/A ........................................................................... 7

II. Summary of Chemistry Assessments ................................................................................. 7
    A. Description of the Drug Product(s) and Drug Substance(s) ........................................... 7
    B. Description of How the Drug Product is Intended to be Used ...................................... 7
    C. Basis for Approvability or Not-Approval Recommendation ......................................... 8

III. Administrative .................................................................................................................. 8
    A. Reviewer’s Signature ....................................................................................................... 8
    B. Endorsement Block ......................................................................................................... 8
    C. CC Block ....................................................................................................................... 8
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:

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6. SUBMISSION(S) BEING REVIEWED:

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<td>May 22, 2003</td>
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<td>May 21, 2003</td>
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7. NAME & ADDRESS OF APPLICANT:

<table>
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<tr>
<th>Name:</th>
<th>Paddock Laboratories, Inc.</th>
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<tbody>
<tr>
<td>Address:</td>
<td>3940 Quebec Avenue North</td>
</tr>
<tr>
<td></td>
<td>Minneapolis, MN 55427</td>
</tr>
<tr>
<td>Representative:</td>
<td>Patrick L. Johnson</td>
</tr>
<tr>
<td>Telephone / Fax:</td>
<td>763-546-4676 / 763-546-4842</td>
</tr>
</tbody>
</table>

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
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

![Chemical Structure](image)

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

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1 Action codes for DMF Table:
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Other codes indicate why the DMF was not reviewed, as follows:
2 – Type 1 DMF
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4 – Sufficient information in application
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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:

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18. STATUS:

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<td>Radiopharmaceutical</td>
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</table>

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:
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 ) 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
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  
[Signature]

B. Endorsement Block

HFD-627/K. Woodland/ KWoodland 10/24/03
HFD-620/Shing Liu, Ph.D./ SL Liu 9/7/03
HFD-617/Wanda Pamphile, Pharm.D./ WP 10/31/03
V:\FIRMSNZ\PADDOCK\LTRS&REV\76744.CR1.REV.DOC

C. CC Block
Chemistry Assessment Section

Deficiency Please fill 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. 

2. 

3. 

4. 

5. Regarding the drug product stability specifications, we have the following comments:
   a. Please revise 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 [REDACTED] 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,

\[\text{Signature}\]
Rashmikant M. Patel, Ph.D.
Director
Division of Chemistry I
Office of Generic Drugs
Center for Drug Evaluation and Research

10/30/03
cc: ANDA 76-744
    ANDA DUP 76-744
    DIV FILE
    Field Copy

Endorsements (Draft and Final with Dates):

HFD-627/K.Woodland/  K. Woodland  10/29/03
HFD-627/S.Liu, Ph.D./  S.H. Liu  10/30/03
HFD-617/W.Pamphile, Pharm.D./  W. Pamphile  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

Table of Contents .............................................................................................................. 2

Chemistry Review Data Sheet .............................................................................................. 3

The Executive Summary ....................................................................................................... 7

I. Recommendations ........................................................................................................... 7  
   A. Recommendation and Conclusion on Approvability ................................................. 7  
   B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable N/A .............................................................. 7

II. Summary of Chemistry Assessments .............................................................................. 7  
   A. Description of the Drug Product(s) and Drug Substance(s) ...................................... 7
   B. Description of How the Drug Product is Intended to be Used ................................... 7
   C. Basis for Approvability or Not-Approval Recommendation ...................................... 8

III. Administrative ................................................................................................................ 8  
   A. Reviewer’s Signature .................................................................................................. 8
   B. Endorsement Block .................................................................................................... 8
   C. CC Block .................................................................................................................... 8
Chemistry Review Data Sheet

1. ANDA 76-744

2. REVIEW #: 2

3. REVIEW DATE: February 24, 2003

4. REVIEWER: Kathy P. Woodland

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

Androst-4-en-3-one, 17-hydroxy-, (17beta)-, \( \text{C}_{19}\text{H}_{28}\text{O}_2 \), 288.429

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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)
### CHEMISTRY REVIEW

Chemistry Review Data Sheet

**B. Other Documents:**

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**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:

Minor Amendment
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 09) 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

Page 7 of 18
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

B. Endorsement Block

HFD-627/K. Woodland/2/27/04
HFD-620/Shing Liu, Ph.D./3/10/04
HFD-617/Wanda Pamphile, Pharm.D./

C. CC Block

Following this page, 6 pages withheld in full (b)(4)
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 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 the drug product stability acceptance criteria for the 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 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’Ambrogiio

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 the total impurity acceptance criteria for the drug product, and submit a revised drug product specification sheet accordingly.

2. Please the drug product stability acceptance criteria for 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,

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

3/16/04
cc: ANDA 76-744
    ANDA DUP 76-744
    DIV FILE
    Field Copy

Endorsements (Draft and Final with Dates):

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

F/T by: wp 3/11/04

Final Draft
V:\FIRMSN\Z\PADDOCK\LTRS&REV\76744.cr2.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

Table of Contents ........................................................................................................................................... 2

Chemistry Review Data Sheet ......................................................................................................................... 3

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III. Administrative .............................................................................................................................................. 8
   A. Reviewer’s Signature ................................................................................................................................. 8
   B. Endorsement Block .................................................................................................................................. 8
   C. CC Block .................................................................................................................................................. 8
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

7. NAME & ADDRESS OF APPLICANT:

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

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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
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 (3)(5)) 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

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/ KWoodland 9/22/04
HFD-620/Shing Liu, Ph.D./ 9/25/04
HFD-617/Wanda Pamphile, Pharm.D./ 9/28/04
V:\FIRMSNZ\PADDOCK\LTRS&REV\76744.CR3.DOC

C. CC Block

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

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

F/T by:

V:\FIRMSNZ\PADDOCK\LTRS&REV\76744.cr3.doc

**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:

- The procedure to [REDACTED] has been revised to specify the use of [REDACTED]. 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 [REDACTED] for all stability samples.
- The content uniformity procedure was revised; using [REDACTED] was removed. Content Uniformity testing will be performed using [REDACTED] of individual packets. A copy of the procedure was submitted.
- Sampling plan
The following methods were revised:
C. CC Block
ANDA 76-744

Testosterone Gel 1%

Par Pharmaceutical
(Formerly Paddock Laboratories, Inc)

Kathy P. Woodland
Division of Chemistry I
Team 5
Table of Contents

Table of Contents ........................................................................................................................................... 2

Chemistry Review Data Sheet......................................................................................................................... 3

The Executive Summary .................................................................................................................................. 7

I. Recommendations ....................................................................................................................................... 7
   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. ................................................................................................................................. 7
   B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable N/A ....................................................................................................................... 7

II. Summary of Chemistry Assessments ........................................................................................................ 7
    A. Description of the Drug Product(s) and Drug Substance(s) .................................................................. 7
    B. Description of How the Drug Product is Intended to be Used ............................................................... 7
    C. Basis for Approvability or Not-Approval Recommendation .................................................................. 8
1. ANDA 76-744

2. REVIEW #: 4

3. REVIEW DATE: March 8, 2007

4. REVIEWER: Kathy P. Woodland

5. PREVIOUS DOCUMENTS:

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7. NAME & ADDRESS OF APPLICANT:

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

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:

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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:

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<td>Radiopharmaceutical</td>
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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
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

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The product is to be stored at
C. Basis for Approvability or Not-Approval Recommendation

The ANDA is approvable. CMC, labeling, EER, and bio are acceptable.
The specified impurities are as follows: (page 4489-Table1) (the approximate relative retention times and relative response factors are given in the table)

<table>
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<tr>
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<th>Impurity Type</th>
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</table>

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.
CHEMISTRY REVIEW

Chemistry Assessment Section

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 \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
APPLICATION NUMBER:
ANDA 076744

BIOEQUIVALENCE REVIEW
DIVISION OF BIOEQUIVALENCE REVIEW

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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 (AUC\text{t} 0.99, 96.2-101.5; C\text{max} 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 lnAUC\text{t} and lnC\text{MAX} 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*treatment 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 lnC\text{max} and lnAUC\text{t} (n=18), but not lnAUC\text{infinity} (n=11 only for estimable AUC\text{infinity}). 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

I. Executive Summary ........................................................................................................ 1
II. Table of Contents .......................................................................................................... 2
III. Submission Summary .................................................................................................. 2
   A. Drug Product Information ......................................................................................... 2
   B. PK/PD Information ..................................................................................................... 3
   C. Contents of Submission ............................................................................................. 4
   D. Pre-Study Bioanalytical Method Validation ............................................................... 5
   E. In Vivo Studies ........................................................................................................... 5
      1. Single-dose Fasting Bioequivalence Study ............................................................... 5
      2. Single-dose Fed Bioequivalence Study .................................................................. 7
   F. Formulation ................................................................................................................ 7
   G. In Vitro Dissolution ..................................................................................................... 7
   H. Waiver Request(s) ...................................................................................................... 7
   I. Deficiency Comments .................................................................................................. 7
   J. Recommendations ....................................................................................................... 7
IV. Appendix ...................................................................................................................... 9
   A. Individual Study Reviews ......................................................................................... 9
      1. Single-dose Fasting Bioequivalence Study ............................................................... 9
      2. Single-dose Fed Bioequivalence Study .................................................................. 9
   B. Formulation Data ....................................................................................................... 19
   C. Dissolution Data ......................................................................................................... 20
   D. Consult Reviews ......................................................................................................... 20
   E. SAS Outputs ................................................................................................................ 21
   F. Additional Attachments ............................................................................................. 22

III. Submission Summary

A. Drug Product Information

Test Product
Reference Product

Paddock's Testosterone Gel, 1%
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 [3860], 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 (04/09/01) and 01-023 (04/23/01), Control Document Nos. 02-162 (03/22/02) and 02-284 (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**

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<tr>
<td>Waiver requests</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>BCS Waivers</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>Vasoconstrictor Studies</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>Clinical Endpoints</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>Failed Studies</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>Amendments</td>
<td>Yes</td>
<td>1 (Telephone Amendment to provide long-term stability data and weights of gel applied in the study)</td>
</tr>
</tbody>
</table>
D. Pre-Study Bioanalytical Method Validation

<table>
<thead>
<tr>
<th>Analyte name</th>
<th>Total Testosterone (Total testosterone is the same as free plus protein bound testosterone.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Internal Standard</td>
<td>0%</td>
</tr>
<tr>
<td>Method description</td>
<td>GC/MS</td>
</tr>
<tr>
<td>QC range</td>
<td>0.150 ng/mL, 0.750 ng/mL &amp; 3.50 ng/mL</td>
</tr>
<tr>
<td>Standard curve range</td>
<td>0.0500 - 10.0 ng/mL</td>
</tr>
<tr>
<td>Limit of quantitation</td>
<td>0.0500 ng/mL</td>
</tr>
<tr>
<td>Average recovery of Drug (%)</td>
<td>83.1%</td>
</tr>
<tr>
<td>Average Recovery of Int. Std (%)</td>
<td>75.9%</td>
</tr>
<tr>
<td>Intraday precision range (%CV)</td>
<td>1.95-7.34%</td>
</tr>
<tr>
<td>Intraday accuracy range (%)</td>
<td>93.0-97.3%</td>
</tr>
<tr>
<td>Interday precision range (%CV)</td>
<td>3.24-7.60%</td>
</tr>
<tr>
<td>Interday accuracy range (%)</td>
<td>96.6-107.2%</td>
</tr>
<tr>
<td>Bench-top stability (hrs)</td>
<td>24 hours</td>
</tr>
<tr>
<td>Stock stability (days)</td>
<td>87 days</td>
</tr>
<tr>
<td>Processed stability (hrs)</td>
<td>19 days</td>
</tr>
<tr>
<td>Freeze-thaw stability (cycles)</td>
<td>3 cycles</td>
</tr>
<tr>
<td>Long-term storage stability (days)</td>
<td>301 days</td>
</tr>
<tr>
<td>Dilution integrity</td>
<td>2-fold, 94.5%; 4-fold, 93.7%</td>
</tr>
<tr>
<td>Specificity</td>
<td>Acceptable for Total Testosterone</td>
</tr>
<tr>
<td>SOPs submitted</td>
<td>None</td>
</tr>
<tr>
<td>Bioanalytical method is acceptable</td>
<td>Yes</td>
</tr>
<tr>
<td>20% Chromatograms included (Y/N)</td>
<td>Yes</td>
</tr>
<tr>
<td>Random Selection of Serial Chrom</td>
<td>Yes</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Study Summary</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study No.</td>
</tr>
<tr>
<td>Study Design</td>
</tr>
<tr>
<td>No. of subjects enrolled</td>
</tr>
<tr>
<td>No. of subjects completing</td>
</tr>
<tr>
<td>No. of subjects analyzed</td>
</tr>
<tr>
<td>Subjects (Normal/Patients?)</td>
</tr>
<tr>
<td>Sex(es) included (how many?)</td>
</tr>
<tr>
<td>Test product</td>
</tr>
<tr>
<td>Reference product</td>
</tr>
<tr>
<td>Strength tested</td>
</tr>
<tr>
<td>Dose</td>
</tr>
</tbody>
</table>
*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

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Point Estimate</th>
<th>90% Confidence Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC₀-t</td>
<td>0.92</td>
<td>82.0-102.0</td>
</tr>
<tr>
<td>AUC∞</td>
<td>0.94</td>
<td>82.5-108.2</td>
</tr>
<tr>
<td>Cmax</td>
<td>0.93</td>
<td>81.4-105.6</td>
</tr>
</tbody>
</table>

### Summary of Statistical Analysis of All Evaluable Subjects
Uncorrected for Average Baseline (N=81)
Additional Information in Appendix and Table 7

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Point Estimate</th>
<th>90% Confidence Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC₀-t</td>
<td>0.99</td>
<td>96.2-101.5</td>
</tr>
<tr>
<td>Cmax</td>
<td>0.96</td>
<td>88.6-104.2</td>
</tr>
</tbody>
</table>

### Summary of Statistical Analysis of Group #5*
Corrected for Average Baseline (N=18)
Additional Information in Appendix and Table 7

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Point Estimate</th>
<th>90% Confidence Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC₀-t</td>
<td>0.95</td>
<td>83.5-109.1</td>
</tr>
<tr>
<td>AUC∞</td>
<td>0.95</td>
<td>75.2-121.2 (n=11)</td>
</tr>
<tr>
<td>Cmax</td>
<td>1.00</td>
<td>89.3-110.8</td>
</tr>
</tbody>
</table>

*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

<table>
<thead>
<tr>
<th>Reason why assay was repeated</th>
<th>Number of samples reanalyzed</th>
<th>Number of recalculated values used after reanalysis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Actual number</td>
<td>% of total assays</td>
</tr>
<tr>
<td></td>
<td>T</td>
<td>R</td>
</tr>
<tr>
<td>Confirmatory reassays</td>
<td>17</td>
<td>10</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Location in appendix</th>
<th>Inactive ingredients within IIG Limits (yes or no)</th>
<th>If no, list ingredients outside of limits</th>
<th>If a tablet, is the product scored? (yes or no)</th>
<th>If yes, which strengths are scored?</th>
<th>Is scoring of RLD the same as test? (yes or no)</th>
<th>Formulation is acceptable (yes or no)</th>
<th>If not acceptable, why?</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Yes</td>
<td></td>
<td>N/A</td>
<td></td>
<td>N/A</td>
<td>Yes</td>
<td></td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Strengths for which waivers requested</th>
<th>Regulation cited</th>
<th>Proportional to strength tested in vivo (yes or no)</th>
<th>Dissolution is acceptable (yes or no)</th>
<th>Waiver granted (yes or no)</th>
</tr>
</thead>
<tbody>
<tr>
<td>N/A</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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.

Hoainhson Nguyen, Review Team I, Date signed

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

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

HNguyen/03-01-04/Revised 06-08-04/v:\firmsnz\paddock\trs\rev\76744n0503.doc
IV. Appendix

A. Individual Study Reviews

1. Single-dose Fasting Bioequivalence Study

<table>
<thead>
<tr>
<th>Study Information</th>
<th>PDL-203</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study Title</td>
<td>A Multi-Site, Randomized, Single-Dose, Two-Way Crossover Relative Bioavailability Study of Testosterone Gel Formulations in Hypogonadal Men</td>
</tr>
<tr>
<td>Clinical Site</td>
<td>SFBC Ft. Myers, Fr. Myers, FL &amp; SFBC Anapharm, Quebec, Canada</td>
</tr>
<tr>
<td>Principal Investigator</td>
<td>Ira A. Zucker, M.D. &amp; Eric Bicrell, M.D.</td>
</tr>
</tbody>
</table>
| 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.

<table>
<thead>
<tr>
<th>Analytical Site</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Analytical Director</td>
<td>(b)(6)</td>
</tr>
<tr>
<td>Analysis Dates</td>
<td>02/28/03-05/07/03</td>
</tr>
<tr>
<td>Storage Period (no. of days from first sample to final analysis)</td>
<td>301 days</td>
</tr>
</tbody>
</table>
Treatment ID  
Test or Reference  
Product Name  
Manufacturer  
Batch/Lot No.  
Manufacture Date  
Expiration Date  
Strength  
Dosage Form  
Batch Size  
Potency  
Content Uniformity  
Formulation  
Dose Administered  
Route of Administration*  
A  
Test  
Testosterone Gel  
Paddock  
2044938  
Not provided  
12/03  
1%  
Gel  
\[88\%\]  
99.5%  
98.4% (RSD=0.9%)  
See Appendix Section B  
10 gm  
Topical  
B  
Reference  
AndroGel\textregistered\  
Unimed  
00688  
09/03  
1%  
Gel  
\[88\%\]  
97.4%  
99.3% (RSD=0.9%)  

*NOTE:  
- An adhesive, sterile, non-absorbent plastic drape (i.e., \[88\%\]) 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.

<table>
<thead>
<tr>
<th></th>
<th>Test</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean</td>
<td>9.709 gm (n=81)</td>
<td>9.615 gm (n=81)</td>
</tr>
<tr>
<td>CV %</td>
<td>1.85</td>
<td>1.94</td>
</tr>
</tbody>
</table>

- 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 reaction; 1=erythema; 2=erythema and edema; and 3= marked erythema and edema.

Table 1  Demographics of Study Subjects [N = 81]

<table>
<thead>
<tr>
<th>Age</th>
<th>Weight (kg)</th>
<th>Age Groups</th>
<th>Gender</th>
<th>Race Category</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Range</td>
<td>%</td>
<td>Sex</td>
<td>Male</td>
<td>100.0</td>
</tr>
<tr>
<td>Mean</td>
<td>55.80</td>
<td>0.0</td>
<td>8.6</td>
<td>Caucasian</td>
<td>88.6</td>
</tr>
<tr>
<td>SD</td>
<td>9.66</td>
<td>18-40</td>
<td>Female</td>
<td>Afr. Amer.</td>
<td>0.0</td>
</tr>
<tr>
<td>Range</td>
<td>36</td>
<td>41-64</td>
<td>65.4</td>
<td>Hispanic</td>
<td>11.4</td>
</tr>
<tr>
<td></td>
<td>70</td>
<td>65-75</td>
<td>25.9</td>
<td>Asian</td>
<td>0.0</td>
</tr>
<tr>
<td></td>
<td>121.8</td>
<td>&gt;75</td>
<td>0.0</td>
<td>Others</td>
<td>0.0</td>
</tr>
</tbody>
</table>

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

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

<table>
<thead>
<tr>
<th>Adverse Event Description</th>
<th># in Test Group</th>
<th># in Reference Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemorrhoids</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Flatulence</td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Constipation</td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Bruises on arms</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Low blood pressure</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Pain on bruised arm</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Sore throat</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Irregular Pulse</td>
<td></td>
<td>2</td>
</tr>
<tr>
<td>Dizziness</td>
<td></td>
<td>2</td>
</tr>
<tr>
<td>Itchiness on back</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Testicular Inflammation</td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Stuffy nose</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Heating at the dosing site</td>
<td></td>
<td>1</td>
</tr>
<tr>
<td><strong>Total:</strong></td>
<td><strong>54</strong></td>
<td><strong>47</strong></td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>QC Conc. (ng/mL)</th>
<th>Parent: Total Testosterone</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inter day Precision (% CV)</td>
<td>5.9</td>
</tr>
<tr>
<td>Inter day Accuracy (%)</td>
<td>96.1</td>
</tr>
<tr>
<td>Cal. Standards Conc. (ng/mL)</td>
<td>0.250, 0.500, 0.750, 1.00, 2.50, 5.00, 7.50, 10.0</td>
</tr>
<tr>
<td>Inter day Precision (% CV)</td>
<td>2.6-4.4</td>
</tr>
<tr>
<td>Inter day Accuracy (%)</td>
<td>91.9-106.5</td>
</tr>
<tr>
<td>Linearity Range (range of R² values)</td>
<td>0.250-10.0 (0.981-0.998)</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Units</th>
<th>Test Mean</th>
<th>%CV</th>
<th>Reference Mean</th>
<th>%CV</th>
<th>T/R</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC₀-t</td>
<td>Ng.hr/mL</td>
<td>98.27</td>
<td>45</td>
<td>100.0</td>
<td>42</td>
<td>0.98</td>
</tr>
<tr>
<td>AUC∞</td>
<td>Ng.hr/mL</td>
<td>108.4</td>
<td>49</td>
<td>122.7</td>
<td>39</td>
<td>0.88</td>
</tr>
<tr>
<td>Cmax</td>
<td>ng/mL</td>
<td>4.612</td>
<td>47</td>
<td>4.769</td>
<td>53</td>
<td>0.97</td>
</tr>
<tr>
<td>Tmax</td>
<td>Hrs</td>
<td>18.41</td>
<td>42</td>
<td>18.05</td>
<td>36</td>
<td>1.02</td>
</tr>
<tr>
<td>T1/2</td>
<td>Hrs</td>
<td>11.77</td>
<td>53</td>
<td>13.85</td>
<td>62</td>
<td>0.85</td>
</tr>
<tr>
<td>kel</td>
<td>Hrs⁻¹</td>
<td>0.07834</td>
<td>57</td>
<td>0.06841</td>
<td>55</td>
<td>1.14</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Test</th>
<th>Reference</th>
<th>T/R</th>
<th>90% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC₀-t</td>
<td>90.13</td>
<td>98.53</td>
<td>0.92</td>
<td>82.0-102.0</td>
</tr>
<tr>
<td>AUC∞</td>
<td>108.7</td>
<td>115.0</td>
<td>0.94</td>
<td>82.5-108.2</td>
</tr>
<tr>
<td>Cmax</td>
<td>4.070</td>
<td>4.390</td>
<td>0.93</td>
<td>81.4-105.6</td>
</tr>
</tbody>
</table>

Table 8 Additional Study Information

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Root mean square error, AUC₀-t</td>
<td>1.114567 (weight=group sample size)</td>
</tr>
<tr>
<td>Root mean square error, AUC∞</td>
<td>1.332627 (weight=group sample size)</td>
</tr>
<tr>
<td>Root mean square error, Cmax</td>
<td>0.856858 (weight=group sample size)</td>
</tr>
<tr>
<td>mean ratio AUC₀-t/AUC∞</td>
<td>T =0.9600 R =0.9436</td>
</tr>
<tr>
<td>Range of values, ratio AUC₀-t/AUC∞</td>
<td>T =0.8001-0.9982 R =0.7422-0.9999</td>
</tr>
</tbody>
</table>
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 T\text{max}: None
  c. first measurable drug concentration as C\text{max}: 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\textsuperscript{[b]}(c) 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 AUC(0-t), AUC∞, C\text{max} 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 InCmax and lnAUCt (n=18), but not InAUCinfinity (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:

<table>
<thead>
<tr>
<th>Root MSE</th>
<th>lnAUCt</th>
<th>lnCmax</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group #5</td>
<td>0.230273</td>
<td>0.185265</td>
</tr>
<tr>
<td>Group #7*</td>
<td>0.312100</td>
<td>0.368726</td>
</tr>
</tbody>
</table>

(*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-Infinitiy) 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

<table>
<thead>
<tr>
<th>Time</th>
<th>N</th>
<th>Mean</th>
<th>Coeff of Variation</th>
<th>Minimum</th>
<th>Maximum</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hour0</td>
<td>81</td>
<td>0.000</td>
<td>.</td>
<td>0.000</td>
<td>0.000</td>
</tr>
<tr>
<td>Hour1</td>
<td>81</td>
<td>1.492</td>
<td>72.997</td>
<td>0.000</td>
<td>6.540</td>
</tr>
<tr>
<td>Hour2</td>
<td>81</td>
<td>1.895</td>
<td>79.650</td>
<td>0.000</td>
<td>11.110</td>
</tr>
<tr>
<td>Hour3</td>
<td>81</td>
<td>2.177</td>
<td>68.741</td>
<td>0.547</td>
<td>10.280</td>
</tr>
<tr>
<td>Hour4</td>
<td>81</td>
<td>2.267</td>
<td>57.294</td>
<td>0.000</td>
<td>6.490</td>
</tr>
<tr>
<td>Hour6</td>
<td>81</td>
<td>1.759</td>
<td>83.137</td>
<td>0.067</td>
<td>9.226</td>
</tr>
<tr>
<td>Hour7</td>
<td>81</td>
<td>2.454</td>
<td>65.104</td>
<td>0.000</td>
<td>10.007</td>
</tr>
<tr>
<td>Hour8</td>
<td>81</td>
<td>2.241</td>
<td>53.445</td>
<td>0.000</td>
<td>5.320</td>
</tr>
<tr>
<td>Hour9</td>
<td>81</td>
<td>1.816</td>
<td>62.678</td>
<td>0.000</td>
<td>6.020</td>
</tr>
<tr>
<td>Hour10</td>
<td>81</td>
<td>1.981</td>
<td>64.881</td>
<td>0.000</td>
<td>6.313</td>
</tr>
<tr>
<td>Hour11</td>
<td>81</td>
<td>2.557</td>
<td>58.472</td>
<td>0.000</td>
<td>8.107</td>
</tr>
<tr>
<td>Hour12</td>
<td>81</td>
<td>3.374</td>
<td>54.449</td>
<td>0.773</td>
<td>11.507</td>
</tr>
<tr>
<td>Hour13</td>
<td>81</td>
<td>3.509</td>
<td>50.366</td>
<td>0.000</td>
<td>9.007</td>
</tr>
<tr>
<td>Hour14</td>
<td>81</td>
<td>3.421</td>
<td>45.581</td>
<td>0.777</td>
<td>10.070</td>
</tr>
<tr>
<td>Hour15</td>
<td>81</td>
<td>1.840</td>
<td>63.598</td>
<td>0.000</td>
<td>6.777</td>
</tr>
<tr>
<td>Hour16</td>
<td>81</td>
<td>1.026</td>
<td>74.482</td>
<td>0.000</td>
<td>4.037</td>
</tr>
<tr>
<td>Hour17</td>
<td>81</td>
<td>0.673</td>
<td>101.156</td>
<td>0.000</td>
<td>3.523</td>
</tr>
<tr>
<td>Hour18</td>
<td>81</td>
<td>0.762</td>
<td>90.327</td>
<td>0.000</td>
<td>3.247</td>
</tr>
<tr>
<td>Hour19</td>
<td>81</td>
<td>1.117</td>
<td>77.357</td>
<td>0.000</td>
<td>4.017</td>
</tr>
<tr>
<td>Hour20</td>
<td>81</td>
<td>0.174</td>
<td>205.205</td>
<td>0.000</td>
<td>1.657</td>
</tr>
<tr>
<td>Hour21</td>
<td>81</td>
<td>0.131</td>
<td>194.261</td>
<td>0.000</td>
<td>0.963</td>
</tr>
<tr>
<td>Hour22</td>
<td>81</td>
<td>0.102</td>
<td>203.484</td>
<td>0.000</td>
<td>1.193</td>
</tr>
</tbody>
</table>

### Reference Treatment

<table>
<thead>
<tr>
<th>Time</th>
<th>N</th>
<th>Mean</th>
<th>Coeff of Variation</th>
<th>Minimum</th>
<th>Maximum</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hour0</td>
<td>81</td>
<td>0.000</td>
<td>.</td>
<td>0.000</td>
<td>0.000</td>
</tr>
<tr>
<td>Hour1</td>
<td>81</td>
<td>1.331</td>
<td>66.315</td>
<td>0.003</td>
<td>3.990</td>
</tr>
<tr>
<td>Hour2</td>
<td>81</td>
<td>1.698</td>
<td>57.760</td>
<td>0.163</td>
<td>5.737</td>
</tr>
<tr>
<td>Hour3</td>
<td>81</td>
<td>2.024</td>
<td>62.736</td>
<td>0.000</td>
<td>8.493</td>
</tr>
<tr>
<td>Hour4</td>
<td>81</td>
<td>2.154</td>
<td>51.102</td>
<td>0.337</td>
<td>5.310</td>
</tr>
<tr>
<td>Hour5</td>
<td>81</td>
<td>1.758</td>
<td>67.352</td>
<td>0.000</td>
<td>5.780</td>
</tr>
<tr>
<td>Hour6</td>
<td>81</td>
<td>2.269</td>
<td>70.571</td>
<td>0.000</td>
<td>10.943</td>
</tr>
<tr>
<td>Hour7</td>
<td>81</td>
<td>2.059</td>
<td>46.875</td>
<td>0.450</td>
<td>5.013</td>
</tr>
<tr>
<td>Hour8</td>
<td>81</td>
<td>1.797</td>
<td>59.805</td>
<td>0.000</td>
<td>5.763</td>
</tr>
<tr>
<td>Hour9</td>
<td>81</td>
<td>1.979</td>
<td>59.776</td>
<td>0.110</td>
<td>6.244</td>
</tr>
<tr>
<td>Hour10</td>
<td>81</td>
<td>2.513</td>
<td>73.717</td>
<td>0.070</td>
<td>13.383</td>
</tr>
<tr>
<td>Hour11</td>
<td>81</td>
<td>3.246</td>
<td>56.704</td>
<td>0.000</td>
<td>8.540</td>
</tr>
<tr>
<td>Hour12</td>
<td>81</td>
<td>3.750</td>
<td>63.588</td>
<td>0.000</td>
<td>13.083</td>
</tr>
<tr>
<td>Hour13</td>
<td>81</td>
<td>3.380</td>
<td>46.057</td>
<td>0.000</td>
<td>11.370</td>
</tr>
<tr>
<td>Hour14</td>
<td>81</td>
<td>1.737</td>
<td>57.883</td>
<td>0.000</td>
<td>4.670</td>
</tr>
<tr>
<td>Hour15</td>
<td>81</td>
<td>1.126</td>
<td>62.805</td>
<td>0.000</td>
<td>3.230</td>
</tr>
<tr>
<td>Hour16</td>
<td>81</td>
<td>0.667</td>
<td>91.089</td>
<td>0.000</td>
<td>2.677</td>
</tr>
<tr>
<td>Hour17</td>
<td>81</td>
<td>0.850</td>
<td>84.406</td>
<td>0.000</td>
<td>3.187</td>
</tr>
<tr>
<td>Hour18</td>
<td>81</td>
<td>1.121</td>
<td>73.815</td>
<td>0.000</td>
<td>3.040</td>
</tr>
<tr>
<td>Hour19</td>
<td>81</td>
<td>0.186</td>
<td>250.393</td>
<td>0.000</td>
<td>3.447</td>
</tr>
<tr>
<td>Hour20</td>
<td>81</td>
<td>0.192</td>
<td>198.547</td>
<td>0.000</td>
<td>2.674</td>
</tr>
<tr>
<td>Hour21</td>
<td>81</td>
<td>0.158</td>
<td>170.848</td>
<td>0.000</td>
<td>1.374</td>
</tr>
</tbody>
</table>
Figure 1

Testosterone Mean Plasma Concentrations
Single Dose Fasting Study

Concentration (ng/mL)

Time (hr)
2. Single-dose Fed Bioequivalence Study  N/A

B. Formulation Data

<table>
<thead>
<tr>
<th>Ingredients</th>
<th>Amount per gm</th>
<th>w/w</th>
</tr>
</thead>
<tbody>
<tr>
<td>Testosterone USP</td>
<td>10.000</td>
<td>1.000</td>
</tr>
<tr>
<td>Ethanol (Alcohol USP)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Purified Water USP</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Carbomer 940 NF</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Isopropyl Myristate NF</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sodium Hydroxide NF</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
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, Huaxiang; Conner, Dale P; Li, Qian H
Subject: RE: Statistical Consult for ANDA 40-557 (Sicor's Methylprednisolone Acetate Injectable Suspension)

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

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)

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)

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

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

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

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

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

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

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

5. Analysis Based on All Evaluable Subjects (n=81) With Grp*Trt Term Retained in the Model (for Baseline-Uncorrected Total Testosterone)
6. Analysis of All Evaluable Subjects (n=81) Using Weight of Grp Sample Size (for Baseline-Uncorrected Total Testosterone)
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
HFD-652/ YHuang
HFD-617/ A. Sigler
HFD-650/ D. Conner

V:\FIRMSNZ\paddock\ltrs&rev\76744n0503.doc
Printed in final on / /

BIOEQUIVALENCE - ACCEPTABLE Submission date: 05-21-03 & 02-13-04

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

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

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

TEAM LEADER: Yih-Chain Huang  BRANCH: I
INITIAL: W  DATE: 6/15/04

DIRECTOR, DIVISION OF BIOEQUIVALENCE: DALE P. CONNER, Pharm. D.
INITIAL:  DATE: 6/18/04
CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
ANDA 076744

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS
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”.

RECEIVED  
MAY 22, 2003  
OGD / CDER
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.

[Signature]

Patrick L. Johnson  
Director of Regulatory Affairs

Enclosures
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

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: 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.

[Signature]

Patrick L. Johnson
Director of Regulatory Affairs

Enclosures
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)

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RECOMMENDATION:  □ COMPLETE  □ INCOMPLETE

Reviewed by:

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

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

Director, Division of Bioequivalence  Date: 6/25/03
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Additional Comments regarding the ANDA:
The RLD is Unimed Pharos' Androgel Topical Gel, 1% (NDA #21-015).

The following items are not provided in the submission:
1. Procedure 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

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<td>EC 1 YES On Cards YES Therapeutic Code 3020300</td>
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| Cover Letter | YES - cover letter | Table of Contents | YES |
|--------------|--------------------|-------------------|
| PART 3 Combination Product Category | 2 Prefilled Drug Del Dev/Sys |
| (Must be completed for 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
- 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. In-Vivo PK Study
  - 1. Study(ies) meet BE Criteria (90% CI or 80-125, Cmax, AUC)
  - 2. In-Vitro Dissolution
  - 3. Data Files (Computer Media) Submitted
- b. Adhesion Study
- c. Skin Irritation/Sensitization Study
# NASALLY ADMINISTERED DRUG PRODUCTS

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<td>b. Suspensions (Q1/Q2 sameness):</td>
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<td>2. In-Vivo BE Study with Clinical EndPoints</td>
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<td>a. Properly defined BE endpoints (eval. by Clinical Team)</td>
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<td>b. Summary results meet BE criteria (90% CI within +/- 20% or 80-120)</td>
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<td>c. Summary results indicate superiority of active treatments (test &amp; reference) over vehicle/placebo (p&lt;0.05) (eval. by Clinical Team)</td>
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# TOPOICAL CORTICOSTEROIDS (VASOCONSTICTOR STUDIES)

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<td>b. Pivotal Study (study meets BE criteria 90% CI or 80-125)</td>
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## 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
   c. COA(s) specifications and test results from drug substance mfr(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

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

4
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

Recommendation:

Date 6/30/03  ☑ FILE  ☐ REFUSE to RECEIVE

Supervisory Concurrence/Date: 

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 to 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
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 Leuprolide 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
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.


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.


15. Pull USP information. (USP yes no)

16. Final Grammar review on letter.

17. EES slip.


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
PEI 2127022

PADDOCK LABORATORIES INC
3940 QUEBEC AVE NORTH
MINNEAPOLIS, MN 55427

DMF No: 
AADA: 

Responsibilities: FINISHED DOSAGE MANUFACTURER

ofile: [Signature]
OAI Status: NONE

EMilestone Name Date Type Insp. Date Decision & Reason Creator
<table>
<thead>
<tr>
<th>EMilestone Name</th>
<th>Date</th>
<th>Type</th>
<th>Insp. Date</th>
<th>Decision &amp; Reason</th>
<th>Creator</th>
</tr>
</thead>
<tbody>
<tr>
<td>SUBMITTED TO OC</td>
<td>02-JUL-2003</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Paddock Laboratories, Inc.
Attention: Patrick L. Johnson
3940 Quebec Avenue North
Minneapolis, MN 55427

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 judgment 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,

[Signature]

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 01-Jul-03 date
HFD-615/SMiddleton, CSO date 03-Aug-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

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"):

RECEIVED
AUG 22 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.


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,

[Signature]

James R. Ferguson

Encl.
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"): 

RECEIVED
AUG 25 2003
OGDW/CPL
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.


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

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.

Patrick L. Johnson
Director of Regulatory Affairs
September 12, 2003

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
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:
1-827-5725
S. KIM
Project Manager (HFD-617) 30

1-827-5848
D. GILL
Team Leader (HFD-623) 30

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

Last Milestone: SUBMITTED TO DO

Milestone Date: 02-JUL-03

OAI Status: NONE

Establishment: CFN: FEI:

DMF No: 1390

Responsibilities:

Profile: CSN

Last Milestone: OC RECOMMENDATION

Milestone Date: 02-JUL-03

Decision: ACCEPTABLE

Reason: BASED ON PROFILE
Questions for DA re deficiencies.

-----Original Message-----
From: Patrick Johnson [mailto:PJohnson@paddocklabs.com]
Sent: Friday, November 21, 2003 2:29 PM
To: 'pamphilew@cdrer.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 [redacted] 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**

<table>
<thead>
<tr>
<th>Testosterone Impurity Profile</th>
<th>API Specification</th>
<th>Finished Product Specification</th>
<th>Stability Specification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Specified Impurities:</td>
<td>(b) 4(4)</td>
<td>(b) 4(4)</td>
<td>(b) 4(4)</td>
</tr>
<tr>
<td>Individual Unspecified Impurities:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total Impurities:</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
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.

[Signature]

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 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  
Wanda Pamphile

Orig: ANDA 76-744  
Cc: Division File  
Chem. I telecon binder  

\CDS013\OGDS11\FIRMSNZ\PADDOCK\TELECONS\76744.doc
January 29, 2004

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 3 0 2004
OGD/CDEH
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 (Study Code: GX020). Attached is a complete copy of the report for the ANDA file (Attachment 1).
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:

<table>
<thead>
<tr>
<th>Nominal concentration (ng/mL)</th>
<th>1.50</th>
<th>7.50</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Standard Curve No.</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>310d</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Calculated concentration (ng/mL)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>99</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Number</strong></td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td><strong>Mean</strong></td>
<td>1.51</td>
<td>6.97</td>
</tr>
<tr>
<td><strong>SDev</strong></td>
<td>0.0162</td>
<td>0.0455</td>
</tr>
<tr>
<td><strong>CV (%)</strong></td>
<td>1.1</td>
<td>0.7</td>
</tr>
<tr>
<td><strong>Bias (%)</strong></td>
<td>0.9</td>
<td>-7.0</td>
</tr>
</tbody>
</table>
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.

[Signature]

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  Sponsor: PADDOCK LABS
Org Code : 600  3940 QUEBEC AVE NORTH
Priority :  MINNEAPOLIS, MN  55427

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

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

FDA Contacts:  S. PARK
Project Manager (HFD-617)  30
1-827-5725

D. GILL
Team Leader (HFD-630)  30
1-827-5848

Overall Recommendation: ACCEPTABLE on 10-FEB-2004 by 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: FEI:

DMF No: AADA:

Responsibilities: CSN
OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 02-JUL-03
Decision: ACCEPTABLE
Reason: BASED ON PROFILE
April 8, 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 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 09 2004
OGD/CDER
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 [redacted].”

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 [redacted].”

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.

      [Signature]

      Wendy A. Saunders
      Senior Regulatory Affairs Analyst

      cc: desk copy for labeling reviewer, Ruby Wu
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.
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.

[Signature]

Wendy A. Saunders
Senior Regulatory Affairs Analyst

cc: desk copy for labeling reviewer, Ruby Wu
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 01 2004
OGD/CDER
CHEMISTRY

A. Deficiencies:

1. Please further [redacted] 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 [redacted]. In the January 29, 2004 amendment, it was [redacted] to NMT [redacted]. As requested by the Agency, Paddock is further [redacted] the specification to NMT [redacted]. 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 [redacted] the drug product stability acceptance criteria for [redacted] and total impurities. Also, please submit a revised drug product stability sheet.

<table>
<thead>
<tr>
<th>Impurity</th>
<th>Original ANDA</th>
<th>January 29, 2004 Amendment</th>
<th>June 30, 2004 (Current) Amendment</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The acceptance criteria for the drug product impurity stability specifications have been [redacted] 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 [redacted] impurities acceptance criteria, are provided in Attachment 3.
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.


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.
Mr. Gary Buehler  
Director, Office of Generic Drugs  
June 30, 2004  
Page 4

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.

[Signature]

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 [redacted]. 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 [redacted] 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 [redacted] 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 Saunders' substitute)

<table>
<thead>
<tr>
<th>DATE:</th>
<th>August 12, 2004</th>
</tr>
</thead>
<tbody>
<tr>
<td>ANDA NUMBER:</td>
<td>76-744</td>
</tr>
<tr>
<td>PRODUCT NAME:</td>
<td>Testosterone Gel 1%</td>
</tr>
<tr>
<td>INITIATED BY:</td>
<td>Firm_ Agency _X</td>
</tr>
<tr>
<td>FIRM NAME:</td>
<td>Paddock Laboratories, Inc. (Minnesota, MN 55427)</td>
</tr>
<tr>
<td>FIRM REPRESENTATIVE:</td>
<td>Todd Deleahant</td>
</tr>
<tr>
<td>TELEPHONE NUMBER:</td>
<td>763-732-0364</td>
</tr>
<tr>
<td>FDA REPRESENTATIVE:</td>
<td>Shing H. Liu, Ph.D. (Team Leader of Team 5)</td>
</tr>
</tbody>
</table>

**SIGNATURE**
Shing H. Liu

[Signature]

8/12/04

Orig: ANDA 76-744
Cc: Division File
    Chem. 1 telecon binder
13 August 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

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 [Redacted] 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.

[Signature]

Todd M. Delehant, PhD.
Regulatory Affairs Analyst
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 (HPD-617) 301-827-5725
D. GILL
Team Leader (HPD-630) 301-827-5848

Overall Recommendation: ACCEPTABLE on 10-FEB-2004 by J. D AMBROGIO (HPD-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: (9)(4) FEI: (9)(4) (9)(4)
Responsibilities:  

Profile: CSN  
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

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

A copy of the revised procedure is included in this submission (Attachment 1).

The procedure to has been revised to specify the use of . A copy of the revised method is included in this submission (Attachment 2).

The testosterone gel has been revised to specify the use of . A copy of the revised method is included in this submission (Attachment 3).
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, 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

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, PhD.
Regulatory Affairs Analyst

Attachments

RECEIVED
OCT 25 2004
OGD / CDER
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:
1. Martin Shimer
   Chief, Reg. Support Branch
   Contains GDEA certification: Yes □ No □  Determined of involvement? Yes □ No □
   (required if sub after 6/1/92)  Pediatric Exclusivity System
   Patent/Exclusivity Certification: Yes □ No □  Determined of involvement
   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 □  Date settled:
   Is applicant eligible for 180 day
   Generic Drugs Exclusivity for each strength: Yes □ No □
   Type of Letter: "To be issued within 45 days" 2/18/04
   Comments:
   Eligible for Tentative Approval only

2. Project Manager, Wanda Pamphile Team 5
   Review Support Branch
   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
   Date Patent/Exclusivity expires: 8-30-20  Date of Labeling Approv. Sum.: 6-3-04
   Citizens' Petition/Legal Case: Yes □ No □  Date of Sterility Assur. App.: NA
   (If YES, attach email from PM to CP coord)  Methods Val. Samples Pending Yes □ No □
   First Generic: Yes □ No □  JV 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
   Initials

REVIEWER:  FINAL ACTION
6. Vacant  
Deputy Dir., DLPS  
Para. IV Patent Cert. Yes  
Pending Legal Action: Yes  
Comments: Labeling found acceptable 6/3/04. CMC found acceptable 6/28/04. Methods validation was not requested. API is compendial. Drug product was not requested as it does not meet compendial criteria for IV. Bioequivalence study single/dose testing found acceptable 6/15/04. Short consult also completed. Biostudy sites have acceptable documentation histories. Office level bio endorsed 6/15/04.

7. Peter Rickman  
Director, DLPS  
Para. IV Patent Cert. Yes  
Pending Legal Action: Yes  
Comments: Labeling found acceptable 6/3/04. CMC found acceptable 6/28/04. Methods validation was not requested. API is compendial. Drug product was not requested as it does not meet compendial criteria for IV. Bioequivalence study single/dose testing found acceptable 6/15/04. Short consult also completed. Biostudy sites have acceptable documentation histories. Office level bio endorsed 6/15/04.

8. Robert L. West  
Deputy Director, OGD  
Para. IV Patent Cert. Yes  
Pending Legal Action: Yes  
Comments: Acceptable B5 dated 3/10/04. Date of B5 3/10/04. NOAA is asked (3/30/04) to provide Paddock's paragraph IV certification for the '894 patent (8/30/04). Paddock was ruled within the 45 day period. The 60 month statutory hold period expires on 11/7/06.  
This ANDA is recommended for tentative approval.

9. Gary Buehler  
Director, OGD  
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 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 V:\\CDS014\\DRUGAPP\\ directory.
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

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
September 26, 2006

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  
Sr. Director, Regulatory Affairs

RECEIVED  
SEP 28 2006  
OGD / CDER
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

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 jszoza@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
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
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

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
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
January 5, 2007

Copy 1
Copy 2
Copy 3 (Field)*

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

* Mr. Matthew Spataro
NYDO NDA/ANDA File Room
158-15 Liberty Avenue
Jamaica, New York 11433
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

RE: ANDA #76-744, Testosterone Gel 1%

Labeling Amendment

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 jszoza@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 Testosterone Gel Strength(s) 1%

APPROVAL ☐ TENTATIVE APPROVAL ☐ SUPPLEMENTAL APPROVAL (NEW STRENGTH) ☐ OTHER ☐

REVIEWER:

1. **Martin Shimer**
   Chief, Reg. Support Branch
   Contains GDEA certification: Yes ☒ No ☐ Determin. of Involvement? Yes ☒ No ☐
   (required if sub after 6/1/92)
   Pediatric Exclusivity System
   RLD = NDA#21-015
   Date 5/23/07
   Date Checked 5/23/07
   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 ☐
   Date of latest Labeling Review/Approval Summary
   Any filing status changes requiring addition Labeling Review Yes ☒ No ☐
   Type of Letter: Full Approval
   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**
   Team 5
   Review Support Branch
   Original Rec'd date 5-21-03
   Date Acceptable for Filing 5-22-03
   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 Parisse)
   Acceptable Bio review tabbed Yes ☒ No ☐
   Bio Review Filed in DFS: Yes ☒ No ☐
   Suitability Petition/Pediatric Waiver
   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 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  
   OGD Regulatory Counsel,  Post-MMA Language Included  
   Comments: N/A.  
   Date 5/23/07  
   Initials rlw/for

5. **Div. Dir./Deputy Dir.**  
   Chemistry Div. I II OR III  
   Comments: It was TAed on 10/27/04. There is no change in the section. Recommend AP.  
   Date 5/17/07  
   Initials RMP

6. **Frank Holcombe**  *(First Generics Only)*  
   Assoc. Dir. For Chemistry  
   Comments: (First generic drug review)  
   N/A. This ANDA was granted tentative approval on October 27, 2004. In addition, Watson's ANDA 76-737 for this drug product was approved on January 27, 2006.  
   Date 5/23/07  
   Initials rlw/for

7. **Vacant**  
   Deputy Dir., DLPS  
   RLD = Androgel 1%  
   Unimed Pharmaceuticals, Inc.  NDA 21-015  
   Date  
   Initials_____

8. **Peter Rickman**  
   Director, DLPS  
   Para.IV Patent Cert: Yes  
   Pending Legal Action: Yes  
   Petition: Yes  
   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.  
   Date 5/23/07  
   Initials rlw/for

OR

8. **Robert L. West**  
   Deputy Director, OGD  
   Para.IV Patent Cert: Yes  
   Pending Legal Action: Yes  
   Petition: Yes  
   Press Release Acceptable  
   Based upon the settlement agreement between Par and Unimed, this ANDA is recommended for final approval.  
   Date 5/23/07  
   Initials RLWest
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