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APPLICATION NUMBER:
203098Orig1s000

MEDICAL REVIEW(S)

CLINICAL REVIEW

Application Type	NDA, 505(b)(2)
Application Number(s)	203,098
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Division / Office	Division of Reproductive and Urologic Products
Reviewer Name(s)	Donald McNellis, MD
Review Completion Date	January 29, 2013
Established Name	Testosterone Gel
(Proposed) Trade Name	None
Therapeutic Class	Testosterone replacement
Applicant	Perrigo Israel Pharma Ltd.
Formulation(s)	Gel for transdermal use
Dosing Regimen	Once daily
Indication(s)	Male hypogonadism
Intended Population(s)	Males \geq 18 years of age with hypogonadism

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Table of Contents

1	RECOMMENDATIONS/RISK BENEFIT ASSESSMENT	3
1.1	Recommendation on Regulatory Action	3
1.2	Risk Benefit Assessment.....	3
1.3	Recommendations for Postmarket Risk Evaluation and Mitigation Strategies ...	4
1.4	Recommendations for Postmarket Requirements and Commitments	4
2	INTRODUCTION AND REGULATORY BACKGROUND	4
2.1	Product Information	4
2.2	Tables of Currently Available Treatments for Proposed Indications	5
2.3	Availability of Proposed Active Ingredient in the United States	7
2.4	Important Safety Issues with Consideration to Related Drugs.....	7
2.5	Summary of Presubmission Regulatory Activity Related to Submission	7
2.6	Other Relevant Background Information	9
3.1	Submission Quality and Integrity	10
3.2	Compliance with Good Clinical Practices	10
3.3	Financial Disclosures.....	11
4	SIGNIFICANT EFFICACY/SAFETY ISSUES RELATED TO OTHER REVIEW DISCIPLINES	11
4.1	Chemistry Manufacturing and Controls	11
4.2	Clinical Microbiology.....	11
4.3	Preclinical Pharmacology/Toxicology	11
4.4	Clinical Pharmacology.....	12
4.4.1	Mechanism of Action.....	12
4.5	Office of Scientific Investigations	12
5	SOURCES OF CLINICAL DATA.....	13
	Tables of Studies/Clinical Trials.....	13
5.2	Review Strategy	14
5.3	Discussion of Individual Studies/Clinical Trials.....	15
5.3.1	Bioequivalence Trial – 03-0415-001.....	15
5.3.2	Skin Sensitization Study - DS102308.....	17
5.3.3	Skin Irritation Study – DS310208	21
5.3.4	Residual Testosterone After Washing – Study PRG-806	24
5.3.5	Testosterone Transfer – Study M1IU09001	27
6	REVIEW OF BIOEQUIVALENCE.....	30
6.1	Bioequivalence Study.....	30
6.1.1	GCP and GLP Certification	30
6.1.2	Demographics.....	30
6.1.3	Subject Disposition.....	31
6.1.4	Pharmacokinetic Procedures	32

6.1.5	Statistical Analyses	32
6.1.6	Results	32
6.1.7	Bioequivalence Conclusions	33
7	REVIEW OF SAFETY	33
7.1	Methods.....	34
7.1.1	Studies/Clinical Trials Used to Evaluate Safety	34
7.2	Adequacy of Safety Assessments	35
7.3	Major Safety Results	35
7.3.1	Deaths.....	35
7.3.2	Nonfatal Serious Adverse Events	35
7.4	Supportive Safety Results	35
7.4.5	Special Safety Studies/Clinical Trials	35
7.4.5.1	A Study of Person-to-Person Testosterone Transfer (Study M1IU09001).....	35
7.4.5.2	A Study of Washing Testosterone from Hands and Application Site (Study PRG-806).....	42
7.4.5.3	Skin Sensitization Study (DS102308)	44
7.4.5.4	Skin Irritation Study (DS310208).....	47
7.4.6	Immunogenicity	48
7.5	Other Safety Explorations.....	48
7.5.1	Dose Dependency for Adverse Events	48
7.5.2	Time Dependency for Adverse Events.....	48
7.5.3	Drug-Demographic Interactions	49
7.5.4	Drug-Disease Interactions.....	49
7.5.5	Drug-Drug Interactions.....	49
7.6	Additional Safety Evaluations	49
7.6.1	Human Carcinogenicity	49
7.6.2	Human Reproduction and Pregnancy Data.....	50
7.6.3	Pediatrics and Assessment of Effects on Growth	51
7.6.4	Overdose, Drug Abuse Potential, Withdrawal and Rebound.....	51
7.7	Additional Submissions / Safety Issues	51
8	POSTMARKET EXPERIENCE.....	51
9	APPENDICES.....	52
9.1	Literature Review/References	52
9.2	Labeling Recommendations	52
9.3	Advisory Committee Meeting.....	53

Table of Tables

Table 1. Currently Approved Medications for the Treatment of Male Hypogonadism	5
Table 2. Product Formulations	10
Table 3. Studies Supporting the Application.....	13
Table 4. Safety Studies Required.....	14
Table 5. Composition of Formulation 2, Batch T06P033	16
Table 6. Skin Assessment Grading Scale	20
Table 7. Skin Assessment Grading Scale	22
Table 8. Baseline Demographics for the Intent-to-Treat Population.....	31
Table 9. Summary of Statistical Comparisons of Testosterone Gel (b) (4) Formulation 2 (Lot #T06P033) and Androgel.....	33
Table 10. Studies Performed to Evaluate Formulation-Dependent Safety	34
Table 11. Discontinuations from Study M1IU09001	36
Table 12. Subject Demographics – Study M1IU09001.....	36
Table 13. AUC and C _{MAX} For Total Testosterone in Female Partners for 24 Hour Period Following Contact With a Male Partner Who Had Applied Testosterone Gel (b) (4)	37
Table 14. AUC and C _{MAX} For Total Testosterone in Female Partners for 24 Hour Period Following Contact With a Male Partner Who Had Applied Testosterone Gel (b) (4) as Percent of Baseline Value.....	37
Table 15. Mean Testosterone Levels Following Contact with a Male Partner Who Had Applied Testosterone Gel (b) (4)	37
Table 16. Maximum Increase in Baseline Corrected Serum Testosterone and AUC for each Subject Following contact with Male Partner Who Had Applied Testosterone Gel (b) (4)	39
Table 17. Maximal Testosterone Values seen in the 24-hr Period Following Contact...	40
Table 18. Demographics of the Washing-Study Analysis Population	42
Table 19. Amount of Testosterone Recovered After Hand and Application Site Washing (Mean µg ± SD)	43
Table 20. Testosterone Recovered After Hand and Application Site Washing (Percent of Applied Dose)	43
Table 21. Study DS102308 Subject Disposition	44
Table 22. Demographic Summary of Population	45
Table 23. Adverse Events Reported in Study DS102308.....	45
Table 24. Mean Cumulative Irritation Scores During Induction Phase	46
Table 25. Summary of Challenge Responses to Testosterone Gel (b) (4)	46
Table 26. Demographics of Study DS310208 Population	47
Table 27. Mean Cumulative Irritation Scores	48

Table of Figures

Figure 1. Mean Testosterone Levels Following Contact with a Male Who Had Applied Testosterone Gel (b) (4) - Observed Values.....	38
Figure 2. Mean Testosterone Levels Following Contact with a Male Who Had Applied Testosterone Gel (b) (4) - Baseline Corrected Values.....	38
Figure 3. Subject 18 Serum Testosterone Levels For 24 Hours Following Contact	41

1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

From a clinical perspective, Testosterone Gel for transdermal use should be approved for the indication of “hypogonadism” in adult males.

This recommendation is based on the demonstration of substantial evidence of bioequivalence to an approved testosterone gel, AndroGel, and on an acceptable safety profile demonstrated in safety studies carried out by the Sponsor of Testosterone Gel.

1.2 Risk Benefit Assessment

A comprehensive review of NDA 203,098 was carried out. This NDA submission has provided substantial evidence from an adequate study that the Sponsor’s testosterone gel is bioequivalent to the approved testosterone gel AndroGel. This demonstration of bioequivalence allows the reasonable conclusion that Testosterone Gel will have the effect claimed in labeling. This claim is that this gel is an effective treatment for men with hypogonadism.

Testosterone Gel has been shown to be generally safe for its intended use as recommended in the label by all tests reasonably applicable to assessment of safety. The pattern of general adverse events for this testosterone gel is reasonable and assumed to be similar to other drugs in the class. The most common adverse events (seen in >2% of subjects) for drugs in this class are: application site erythema and irritation, nasopharyngitis, increase in hematocrit, headache, diarrhea and vomiting.

The potential for transferring testosterone to another individual by direct contact was evaluated in a clinical study by the Sponsor. This evaluation showed that skin-to-skin contact resulted in significant transfer of testosterone to the female partner. The 24 hour AUC of testosterone in the partner following contact was approximately twice the baseline level. However, a clothing barrier was shown to be effective in preventing clinically significant transfer. The AUC of testosterone in the female partner following contact utilizing a clothing barrier was approximately 12% greater than the baseline level.

The ability to wash the product from the skin was also evaluated in a clinical study. This study showed that approximately 5% of the applied testosterone remained on the skin of the hands following washing the hands with soap and water. Following showering, approximately 20% of the applied testosterone remained at the application site.

In summary, the information that has been submitted by the Sponsor is adequate to allow the reasonable conclusion that Testosterone Gel is an effective and safe treatment for men with hypogonadism. The data also provide an adequate basis for labeling the product so that it can be used in a safe and effective manner.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

A Medication Guide should be required. This guide is necessary to communicate to patients the measures they should use to assure that the product is used safely. As with other transdermal testosterone products, transfer of testosterone to another individual is possible. Patients need to be aware of the measures to be taken to minimize the risk of this transfer.

1.4 Recommendations for Postmarket Requirements and Commitments

No postmarketing requirement and/or commitments are recommended.

2 Introduction and Regulatory Background

2.1 Product Information

Testosterone is an endogenous androgen that is responsible for normal growth and development of the male sex organs and for maintenance of secondary sex characteristics. Testosterone has effects that include the growth and maturation of the prostate, seminal vesicles, penis, and scrotum; the development of male hair distribution, such as facial, pubic, chest, and axillary hair; laryngeal enlargement; vocal cord thickening; alterations in body musculature; and fat distribution. Male hypogonadism results from insufficient production of testosterone and is characterized by low serum testosterone concentrations. Symptoms associated with male hypogonadism include decreased sexual desire with or without impotence, fatigue and loss of energy, mood depression, regression of secondary sexual characteristics, and osteoporosis.

The 2010 Endocrine Society guidelines suggest that the diagnosis of testosterone deficiency in adult men should be based on a comprehensive review of patient symptoms and signs, and measurement of serum testosterone levels by a reliable assay. The exact prevalence of androgen deficiency in men is not known. Although serum total and free testosterone concentrations decline in men with advancing age, the significance of age-related decline in testosterone concentration is incompletely understood.

Testosterone replacement therapy in men is chronic in nature and designed to improve clinical manifestations of low testosterone and also to place circulating levels of this important hormone into the normal physiological range for healthy men (~300 to ~1050 ng/dL). These replacement therapies are ideally based on short term titration regimens that result in an optimal dose of product for a particular patient.

Male hypogonadism has historically been treated with testosterone replacement therapy via oral or parenteral routes to elevate serum testosterone levels into the normal range. Currently available treatment options for hypogonadism include intramuscular injections, subdermal implants, buccal systems, oral formulations, and transdermal patches and gels. The most commonly used formulations are the gels which are applied with the hands to the shoulders and upper arms and/or abdomen.

The gel formulation which is the subject of this review contains (b) (4) testosterone dissolved in ethanol. The formulation also contains (b) (4) Carbomer 980, and (b) (4) Isostearic Acid. The product is packaged in two packaging configurations: 2.5g and 5g unit dose aluminum foil packets and bottles with non-aerosol metered-dose pumps. The product is applied by placing the desired dose of gel onto the palm of the hand and then rubbing the gel onto the skin of the shoulder and upper arm.

The ethanol assists in the transport of testosterone into the skin. On the skin, the ethanol quickly evaporates leaving a depot of testosterone which is further absorbed by the stratum corneum and dermis. From those sites it diffuses into the systemic circulation.

2.2 Tables of Currently Available Treatments for Proposed Indications

Table 1. Currently Approved Medications for the Treatment of Male Hypogonadism

Trade Name	Dose	Sponsor	Route of Administration	NDA Number	Date of Approval
Androderm	2.5mg & 5mg	Watson Labs	Transdermal Patch	20,489	September 29, 1995
Androgel 1%	1.25gm, 2.5gm & 5 gm	Unimed Pharma	Transdermal gel	21,015	February 28, 2000
Androgel 1.62%	40.5 mg starting dose	Abbott Products	Transdermal gel	22,309	April 29, 2011
Testim 1%	5gm	Auxilium Pharma	Transdermal gel	21,454	October 31, 2002
Axiron	60mg starting	Eli Lilly	Transdermal solution	22,504	November 23, 2010

Clinical Review
 Donald McNellis, MD
 NDA 203,098
 Testosterone ^{(b) (4)} Gel (Perrigo Israel Pharma Ltd.)

Trade Name	Dose*	Sponsor	Route of Administration	NDA Number	Date of Approval
	dose				
Fortesta	40mg starting dose	Endo Pharma	Transdermal gel	21,463	December 29, 2010
Testosterone Gel	50 mg starting dose	TEVA	Transdermal gel	202,763	February 14, 2012
Testopel	75mg	Slate Pharma	Pellet for implantation	ANDA 80,911	Prior to January 1, 1982
Striant	30mg	Columbia Labs	Extended Release tablet, buccal	21,543	June 19, 2003
Testosterone cypionate	200mg/ml	Paddock	Injection	ANDA 40,530	January 31, 2005
Depo-Testosterone	100 & 200mg/ml	Pharmacia & Upjohn	Injection	ANDA 85,635	Prior to January 1, 1982
Testosterone cypionate	100 & 200mg/ml	Sandoz	Injection	ANDA 40,615	August 10, 2006
Testosterone cypionate	200mg/ml	Synerx Pharma	Injection	ANDA 40,652	December 11, 2006
Testosterone cypionate	200mg/ml	Watson Labs	Injection	ANDA 86,030	Prior to January 1, 1982
Delatestryl	200mg/ml	Endo Pharma	Injection	9,165	Prior to January 1, 1982
Testosterone enanthate	200mg/ml	Paddock	Injection	ANDA 40,575	June 14, 2006
Testosterone enanthate	200mg/ml	Synerx Pharma	Injection	ANDA 40,647	October 5, 2009
Testosterone enanthate	200mg/ml	Watson Labs	Injection	ANDA 85,598	Prior to January 1, 1982

* Androgel 1% and Testim 1% doses are given as amount of gel, other products' doses are given as amount of testosterone.

2.3 Availability of Proposed Active Ingredient in the United States

Testosterone is currently available in the United States as a buccal tablet, a subcutaneous implant, a transdermal patch, a transdermal gel, a transdermal solution and a parenteral injection.

2.4 Important Safety Issues with Consideration to Related Drugs

Labeled risks of testosterone administration in hypogonadal men include erythrocytosis, induction or exacerbation of sleep apnea, breast tenderness or enlargement, liver toxicity, and acne. Two major areas of concern in older men with aging-associated decline in serum testosterone are the effects of long-term testosterone administration on the risks of prostate cancer and progression of atherosclerotic heart disease.

Transdermal testosterone preparations, which are applied to the skin, have been associated with secondary exposure of testosterone in women and children via direct skin to skin transference. The exposed women and children have experienced significant clinical sequela which prompted the FDA to mandate a Boxed Warning for all transdermal testosterone products.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

The Sponsor initially submitted an application to the Agency for Testosterone (b) (4) Gel in 2.5gm and 5 gm packets on June 15, 2007 (b) (4). On September 26, 2007, the Office of Generic Drugs (OGD) sent a Refusal to receive letter to the Sponsor stating that:

The inactive ingredient isosteric acid in your proposed formulation for Testosterone Gel (b) (4) has not been previously approved by the Agency in a transdermal product at the specified levels. Therefore, the proposed drug product cannot be received as an ANDA. Please provide examples of approved drug products administered by the same route of administration which contain these inactive ingredients in the same concentration range or provide information demonstrating that these inactive ingredients at these concentrations do not affect the safety of the proposed drug product.

The Sponsor resubmitted the ANDA, with the requested information, on November 19, 2007. On January 23, 2008, the Office of Generic Drugs (OGD) sent a Refusal to receive letter to the Sponsor stating that:

Your proposed drug product contains inactive ingredients that are significantly different than those contained in the RLD Androgel. The

Agency has concluded that additional information will be needed to demonstrate that your proposed product does not have the potential to cause greater skin irritation or sensitization than the RLD. Cumulative skin irritation and sensitization studies may provide sufficient information to address this issue.

The Sponsor performed the requested studies and on November 27, 2008 resubmitted (b) (4). At that time they also submitted (b) (4) for Testosterone (b) (4) Gel in a multi dose pump configuration. These applications were accepted for review by OGD on May 13, 2009 and May 20, 2009 respectively.

On August 28 and 29, 2009 the Sponsor received deficiency letters for both ANDA (b) (4). The deficiency was explained as:

CDER is concerned with the safety of transdermal testosterone gel products because of reports of significant adverse events resulting from unintentional transfer of testosterone from patients to young children and to female partners. We are unable to approve your abbreviated new drug application (ANDA). You have failed to provide data to show that your use of different inactive ingredients, including but not limited to the different penetration enhancers, from those found in the reference listed drug (RLD) do not affect the safety or effectiveness of your proposed drug product. See 21 CFR 314.94 (a) (9) (ii) and (a) (9) (v). We have determined that investigations such as clinical trials should be conducted to demonstrate that your inactive ingredients do not affect the safety and efficacy of your proposed drug product. Because these types of studies cannot be submitted in an ANDA, your ANDA cannot be approved. If you wish to pursue approval of your product, you are encouraged to contact the Division of Reproductive and Urologic Products in the Office of New Drugs.

The Sponsor then submitted IND 107,130 to the Division of Reproductive and Urologic Products (DRUP) and met with the Division on May 19, 2010 to discuss the design of the necessary transfer and washing studies and also to discuss their plans for an NDA submission. The Sponsor subsequently performed the requested studies and NDA 203098 was submitted to DRUP July 4, 2011.

The Sponsor initially submitted NDA 203,098 on July 4, 2011. On May 3, 2012 the Agency issued a Complete Response letter to the Sponsor which stated that they were unable to approve the application because of the following issues.

Your Bioequivalence (BE) study between the proposed product (testosterone gel) and the reference listed drug (RLD; AndroGel® 1%) cannot be adequately evaluated. As outlined in Form 483s (dated

March 1 and 30, 2012), there are unresolved clinical and bioanalytical site inspection deficiencies. Specifically, a major deficiency of missing dosing records for study period 3 was reported in FDA Form 483. As a result, data from study period 3 were excluded from statistical evaluation. The resultant small sample size makes it unfeasible to do any meaningful statistical analysis for the BE evaluation.

In addition, as reported in Form 483 from the bioanalytical site inspection, the measured concentrations of plasma testosterone are not adjusted for the endogenous testosterone in blank plasma used to prepare calibrators and quality control samples. To date, you have not adequately addressed these deficiencies.

The Sponsor has subsequently located the missing dosing records. In addition, after discussions with both the Division of Scientific Investigation and the Clinical Pharmacology reviewers, they have adjusted the blank plasma samples for endogenous testosterone using methodology that has been found to be acceptable by DSI and Clinical Pharmacology. The properly adjusted testosterone values were submitted with the Sponsor's Complete Response and are the basis for the bioequivalence study that is evaluated in this review.

2.6 Other Relevant Background Information

Table 2 presents the composition of the reference drug, Androgel, the original formulation of the Sponsor's product, and the planned commercial formulation of the Sponsor's product. All studies carried out by the Sponsor in support of this application were carried out using the original formulation of the product. The product was reformulated for several reasons.

The use of carbomer 940 results in (b) (4). Also, Androgel does not contain Carbomer 940 (although the initial label incorrectly indicated that it did). The Perrigo Testosterone Gel was reformulated to contain Carbomer 980, which is the Carbomer used in Androgel.

The ethanol content of the gel was also changed. The initial Androgel label incorrectly indicated that it contained 68.9% ethanol. The initial Perrigo Gel was formulated based on this information. The Androgel label was revised in December 2002 to show the correct ethanol content of 67%. The Perrigo reformulation incorporated 67% ethanol rather than the 68.9% in the initial formulation.

This reformulation was discussed with the Division at the May 19, 2010 meeting. The formulation differences were not believed to require any new studies. Perrigo was allowed to complete their studies with the initial formulation.

Table 2. Product Formulations

	Androgel	Perrigo Original Formulation	Perrigo Commercial Formulation
Component	mg/g gel		
Testosterone USP	10.00	10.00	10.00
Isopropyl myristate	(b) (4)		
Isosteric Acid	(b) (4)		
Alcohol (b) (4)	670.00	(b) (4)	670.00
Carbomer 940	(b) (4)		
Carbomer 980	(b) (4)		
(b) (4) NaOH	(b) (4)		
NaOH	(b) (4)		
Purified water	(b) (4)		

Source: NDA 203098 Module 3.2 P1 and US Patent 6,503,894, Table 5.

Reviewer's comment: *The only difference in formulation between the Sponsor's commercial formulation of Testosterone Gel and the Reference listed Drug, Androgel, is the substitution of Isosteric Acid in place of Isopropyl myristate (b) (4). The clinical performance of the Sponsor's product has been evaluated with a bioequivalence study as well as transfer, washing and skin irritation studies. These studies are evaluated in this review.*

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

The Sponsor has in place standard operating procedures that are consistent with ICH Good Clinical Practice. These include archiving of source data, internal audits, and documentation of qualifications of investigators.

As part of this review, an assessment of the datasets and Case Report Forms (CRF) of the Sponsor's studies was done and did not reveal miscoding or discrepancies between the data recorded on the CRFs and the datasets.

3.2 Compliance with Good Clinical Practices

The Sponsor has indicated that their studies were carried out according to the Declaration of Helsinki, the Code of Federal Regulations and the Notes for Guidance on

Good Clinical Practice (2000) (CPMP/ICH/135/95), the ICH GCP Guidelines and the EU Clinical Trials Directive (2001/20/EC).

3.3 Financial Disclosures

The Sponsor has certified that the compensation of all clinical investigators was independent of the study outcome. They have also certified that no investigator had a financial interest in the product or the Sponsor.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

A Chemistry review of the application has been conducted. The Chemistry reviewer has concluded that the sponsor has provided sufficient information on drug substance controls, manufacturing processes and process controls, and adequate specifications for assuring consistent product quality of the drug product. The sponsor has also provided sufficient stability information on the drug product to assure strength, purity and quality of the drug product during the expiration dating period.

The CMC reviewer has recommended approval in a review dated 1/8/2013.

4.2 Clinical Microbiology

A Microbiology review of the application was not conducted.

4.3 Preclinical Pharmacology/Toxicology

A Toxicology review of the application has been conducted. The applicant submitted no new nonclinical information, and is relying on published studies of testosterone and the FDA findings of safety and efficacy for AndroGel®, testosterone gel (b) (4) (NDA 21-015) for Approval. The overall toxicological profile of testosterone is well established. Nonclinical toxicities are not relevant for Approval due to the preponderance of clinical data for testosterone that supersedes any nonclinical findings. Literature references and a scientific rationale for the reliance on literature were submitted to support the nonclinical sections of the Labeling. While the formulation is different than other FDA approved testosterone gel products, the components are at or below the levels in other FDA-approved products.

The toxicology reviewer's opinion is that the nonclinical data support approval of Testosterone Gel for topical testosterone replacement in hypogonadal men.

4.4 Clinical Pharmacology

A clinical pharmacology review of the application has been conducted. The reviewer has concluded that the information supplied with the Sponsor's Complete Response now adequately supports the bioequivalence of testosterone gel and AndroGel 1%. The Clinical Pharmacology review team recommends that the product be approved.

4.4.1 Mechanism of Action

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

4.5 Office of Scientific Investigations

The Office of Scientific Investigations (OSI) performed inspections of the clinical and bioanalytical study sites during the first cycle of review of NDA 203098. Their inspections of the sites used for the Sponsor's bioequivalence study showed several significant deficiencies and these deficiencies resulted in the Complete Response that was issued May 3, 2012. The deficiencies were:

- 1. The proper dosing of subjects during Period 3 cannot be assured. Data from Period 3 should be excluded from statistical evaluation.*
- 2. The measured concentrations of plasma testosterone are not adjusted for the endogenous testosterone in blank plasma used to prepare calibrators and QCs.*

The result of recommendation 1 was that only 8 of 24 subjects included in the Sponsor's bioequivalence study had reliable data. This represented an inadequate cohort upon which to base a reasonable bioequivalence conclusion and was the primary reason for the Complete Response.

The Sponsor has subsequently located the records that are needed to confirm the proper dosing and these records have been found to be acceptable by the Office of Scientific Investigations.

A teleconference was held between the Sponsor, OSI, and the Clinical Pharmacology reviewers to discuss the second deficiency. At that conference a method of adjustment for the endogenous testosterone in blank plasma used to prepare calibrators and QCs was agreed to by the participants. The Sponsor has submitted the properly adjusted data with their Complete Response.

OSI has indicated that the Sponsor has responded adequately to each of the deficiencies outlined in the May 3, 2012 Complete Response letter and that the bioequivalence data included in the current application can be reasonably relied upon as a measure of the bioequivalence of the Sponsor's testosterone gel and the reference listed drug AndroGel 1%.

5 Sources of Clinical Data

Tables of Studies/Clinical Trials

This 505(b)(2) application is supported by five studies. Table 3 shows the studies that have been submitted.

Table 3. Studies Supporting the Application

Type of Study	Study Number	Study Objective	Study Design	Test Product	N	Type of Subjects
Bioequivalence	03-0415-001	Establish the bioequivalence of Testosterone ^{(b) (4)} Gel and AndroGel	Single-dose Three-way crossover study	AndroGel 1% and two formulations of Testosterone Gel	24	Hypogonadal Men
Skin Sensitization	DS102308	Evaluate the sensitization of the skin by Testosterone ^{(b) (4)} Gel	Randomized, controlled, within-subject comparison study	Testosterone Gel AndroGel 1%	226	Healthy volunteers
Skin Irritation	DS310208	Evaluate the irritation potential of Testosterone ^{(b) (4)} Gel to the skin	Cumulative Irritant Patch Test	Testosterone Gel AndroGel 1%	38	Healthy volunteers
Residual Testosterone after Washing	PRG-806	Evaluate the residual testosterone on the hands and the application site following	Open-label four period study	Testosterone Gel AndroGel 1%	36	Healthy male volunteers

Type of Study	Study Number	Study Objective	Study Design	Test Product	N	Type of Subjects
		washing				
Interpersonal Transfer of Testosterone	M1IU09001	Evaluate the transfer of testosterone from a treated male to an untreated female via skin contact	Single-dose, four-treatment, four-way open-label crossover study	Testosterone Gel Androgel	24 male/female pairs	Healthy volunteers

5.2 Review Strategy

The Sponsor has relied upon the FDA finding of safety and efficacy of Androgel in this 505(b)(2) application. The primary study demonstrating the bioequivalence of Testosterone Gel to Androgel is study 03-0415-001. This study will be reviewed to establish the bioequivalence of Testosterone Gel to Androgel. If bioequivalence is shown, Testosterone Gel will have shown adequate evidence of efficacy.

Once bioequivalence has been established, the prior finding of the safety of Androgel can also be relied on to establish the safety of Testosterone Gel. However, the inactive ingredients in Testosterone Gel are not identical to those of Androgel as shown in Table 2.

Because of the difference in inactive ingredients, it is inappropriate to rely on the finding of the safety of Androgel for several areas of safety. Therefore, the Sponsor was asked to perform studies to evaluate these safety features. The safety features that required evaluation, and the Sponsor's study number which evaluated that feature are shown in Table 4.

Table 4. Safety Studies Required

Safety Feature	Study Number
Skin sensitization	DS102308
Skin irritation	DS310208
Person-to-person testosterone transfer	M1IU09001
Ability to Wash Gel from hands	PRG-806
Ability to Wash Gel from application site	PRG-806

In summary, the review strategy for this application is to initially establish bioequivalence with the reference listed drug Androgel. Showing bioequivalence of Testosterone Gel to Androgel will allow the conclusion that Testosterone Gel is effective. Bioequivalence also will allow the conclusion that the drug is generally safe. However, skin safety, person-to-person transfer and washing characteristics are

potentially influenced by the different inactive ingredients in Testosterone Gel as compared to Androgel. These areas will be evaluated in the studies listed in Table 4.

5.3 Discussion of Individual Studies/Clinical Trials

5.3.1 Bioequivalence Trial – 03-0415-001

Trial 03-0415-001 was a single-dose, three-period, three-treatment, randomized crossover study to evaluate the pharmacokinetics of two Testosterone Gel formulations and the pharmacokinetics of the reference listed drug Androgel. It was carried out at a single site (b) (4) during September 2003. The samples obtained in this study were, after appropriate processing, shipped in a frozen state to the bioanalytic laboratory (b) (4) where analyses were performed in October 2003.

Study Design

This was an open label, randomized, single-dose, three-period, three-treatment crossover study in which hypogonadal men received three drug formulations in a crossover fashion. In each period, subjects received a single 10 gm topical dose of one of the drug products, applied to the shoulder/upper arm. The three drug products studied were (b) (4) Testosterone Gel (b) (4) Formulation 1, (b) (4) Testosterone Gel (b) (4) Formulation 2, and Androgel 1%.

A series of blood samples were taken prior to drug application and extended for 72 hours following drug application. The samples were taken at -12, 0, 1, 2, 3, 4, 6, 8, 10, 12, 14, 17, 20, 24, 30, 36, 48, and 72 hours. Immediately after sampling, plasma was harvested and then frozen at -20°C. Frozen samples were sent to the central analytic laboratory (b) (4), where they were assayed for total testosterone using a validated GC/MS method.

Subjects were randomized to receive the formulations in a random sequence. There was a one week washout period between each of the three drug applications. Subjects were monitored for adverse events.

Inclusion Criteria

Subjects were eligible for inclusion if they:

- Were hypogonadal males
- Had a Serum testosterone < 300 ng/dl
- Were 18 – 70 years of age
- Had a BMI > 15 and < 35
- Were reliable and capable of understanding test procedures
- Provided written informed consent

Exclusion Criteria

- Allergy to testosterone, soybeans, soy or soya lecithin
- Clinically significant abnormal findings on physical exam, medical history, or clinical laboratory results that would interfere with the conduct or interpretation of the study or jeopardize the subjects safety
- Skin conditions or excessive hair in the intended dosing area
- Carcinoma of the breast or known or suspected carcinoma of the prostate
- Serious psychological illness
- Significant history of drug or alcohol abuse
- A positive urine drug screen, a positive HIV, or hepatitis screen
- Use of oral or any topical exogenous testosterone during the two week period preceding study initiation, or any implantable testosterone during the six month period preceding study initiation
- Use of any medication which, in the opinion of the investigator, would interfere with the conduct or interpretation of the study or jeopardize the subjects safety
- Use of any concomitant medications during the course of the study
- Donation or loss of blood or participation in a clinical trial which involved withdrawal of 480 ml or more of blood during the six weeks prior to study initiation
- Donation of plasma during the two week period preceding study initiation
- Use of any investigational drug during the 30 day period preceding study initiation

Study Drugs

The three drugs tested were identified in the study report as:

- Testosterone Gel (b) (4), Formulation 1, Batch T06P030, manufacture date 7/29/2003
- Testosterone Gel (b) (4), Formulation 2, Batch T06P033, manufacture date 7/30/2003
- Androgel 1%, Unimed Pharmaceuticals, Lot number 20325, expiration date 12/04

The composition of Formulation 2, Batch T06P033 is shown in Table 5.

Table 5. Composition of Formulation 2, Batch T06P033

Ingredient	Amount % w/w
Testosterone	(b) (4)
Ethyl Alcohol	(b) (4)
Carbopol 940	(b) (4)
Isostearic Acid	(b) (4)
Sodium Hydroxide (b) (4)	(b) (4)
Purified Water	(b) (4)

Source: NDA 203098, Module 2.3, page 18

Reviewer's comment: *This formulation differs from the to-be-marketed formulation of Testosterone Gel (b) (4) which is shown in Table 2. There are two major differences between this initial formulation and the commercial formulation. The commercial formulation includes Carbomer 980 rather than Carbomer 940. The amount of alcohol has been reduced from 69% to 67%. These formulation differences were discussed in a pre-NDA meeting between the Sponsor and the Division. It was concluded that these formulation differences are small enough to be unlikely to affect the performance characteristics of the product. In this reviewer's opinion, this remains a reasonable conclusion.*

Study Endpoint

This was a study evaluating the bioavailability of two study drugs, Testosterone Gel (b) (4) Formulation 1 and Testosterone Gel (b) (4) Formulation 2, to the commercially available product Androgel. The endpoint of the study was a comparison of the pharmacokinetics of each study drug to Androgel over a 72 hour period following a single administration of each product.

A study drug would be found to be bioequivalent to Androgel if the 90% confidence intervals of the geometric mean test-to-reference AUC and C_{MAX} ratios were contained within the interval of 0.80 to 1.25.

Safety Endpoint

There were no specific safety endpoints. Adverse events that occurred following drug administration were collected and tabulated.

Study Results

The results of this study are discussed in section 6.1 Bioequivalence Study. Since Formulation 1 has not been included as part of this NDA submission, only the results for Formulation 2, which is the intended commercial product, are discussed.

5.3.2 Skin Sensitization Study - DS102308

This was a randomized, single center, controlled, within-subject comparison study of Perrigo Pharmaceuticals investigational product (testosterone gel (b) (4) the comparator control product (AndroGel [testosterone] 1%), the vehicle product, and controls under occlusive conditions, in healthy volunteers. All subjects had areas of skin designated for the Perrigo Pharmaceuticals investigational product (testosterone gel (b) (4) comparator control product (AndroGel [testosterone] 1%), the vehicle product, and the control patches (ie, sodium lauryl sulfate [SLS] 0.1% positive control and saline negative control) at randomly assigned, adjacent sites, for the purpose of determining sensitization potential.

Study Objective

The primary objective of this study was to determine the potential of testosterone gel (b) (4) to cause sensitization by repeated topical application to the healthy skin of humans under controlled conditions.

Study Drugs

- Investigational Product
 - Product: testosterone gel (b) (4)
 - Lot no. 006262
 - Manufacturer: Perrigo Israel Pharmaceuticals, Ltd.
- Comparator Control Product
 - Product: AndroGel (testosterone) 1%
 - Lot No: 31280
 - Manufacturer: Laboratoires Besins International, Montrouge, France
- Vehicle Product
 - Product: Testosterone gel, (b) (4) placebo
 - Lot No: 010962
 - Manufacturer: Perrigo Israel Pharmaceuticals, Ltd.
- Positive and Negative Controls
 - Commercially available SLS prepared as a 0.1% aqueous solution served as a positive control and commercially available saline served as a negative control.

Study Design

Induction

On Day 1, if the subject fulfilled all the inclusion and none of the exclusion criteria, he/she was allowed participation in the study and received a unique randomization number, which determined the application scheme of the study materials for that individual subject.

A set of 5 patches were prepared by the clinical staff according to the randomization scheme. Patches contained 0.2 g of investigational product, 0.2 g of the comparator control product, 0.2 g of vehicle, 0.2 mL of the positive control and 0.2 mL of the negative control. The clinical staff applied the prepared patches to the appropriate test sites on the subject's infrascapular area of the back. The choice of left or right side was made by the clinical staff based on a visual inspection of skin clarity and was recorded on the CRF to ensure consistent placement of the patches at subsequent visits. The distance between the patches was approximately $\frac{3}{4}$ inch. The numbering of the test sites remained the same throughout the study.

The induction phase consisted of a series of 9 applications of the study materials and subsequent evaluation of the application sites. Patches were applied on Mondays, Wednesdays and Fridays for 3 consecutive weeks. The subjects returned to the facility at 48- hour intervals to have the patches removed. Using a tissue, the evaluator removed any remaining excess study material to avoid transference of materials

between sites. The sites were evaluated within 15 minutes of patch removal using a 6-point integer scoring system, and identical patches were applied to the same sites. Patches applied on Friday remained in place for 72 hours until Monday.

Subjects who were absent once during the 3-week, 9-patch induction phase were instructed to keep the patches in place. They were scheduled to apply a make-up (MU) patch at the last induction visit. The MU patches were removed 48 hours later and the sites were evaluated. If subjects failed to return for removal/evaluation of the MU patch, a no ninth grading (N9G) was recorded.

Subjects who missed the 9th evaluation but had 9 patch applications were considered to have completed the induction phase.

In addition, at each of the study visits, concomitant medications, adverse events, and compliance was reviewed and recorded.

Rest Period

During the resting period of approximately 10 to 14 days, subjects did not receive any application of study materials.

Challenge

At challenge, subjects who completed the induction phase and the rest period, had patches identical to those that were used during the induction phase applied to naïve sites. Patches remained on the naïve sites for 48 hours to be evaluated within 30 minutes of patch removal and again at 24, 48, and 72 hours following patch removal (i.e., applied patch on Monday, removed patch on Wednesday, evaluated test sites on Wednesday, Thursday, Friday, and Saturday) using the procedures described above for the induction phase.

In addition, at each of the study visits, concomitant medications, adverse events, and compliance were reviewed and recorded.

To be considered a completed case, a subject had 9 applications of the study material and no fewer than 8 subsequent readings during induction and 1 application followed by all subsequent readings during challenge. Only completed cases were used to assess sensitization.

Rechallenge

A subject was rechallenged to any of the study materials if in the opinion of the Investigator, there was any sign suggestive of contact sensitization (erythema and/or papulation) which was observed at any of the evaluations following the removal of the challenge patch, ie, within 30 minutes of removal or at 24, 48, or 72 hours following patch removal.

Rechallenge patches were applied 2 weeks or more after the challenge phase. The study material was applied to naive sites on the back, in a manner similar to that used in the challenge phase. Rechallenge patches remained in place for 48 hours and patch sites were evaluated within 30 minutes of removal and again at 24, 48, and 72 hours after removal. As an example, patches were applied on Monday, removed on Wednesday, and test sites were evaluated on Wednesday, Thursday, Friday, and Saturday. In addition, at each of the study visits, concomitant medications, adverse events, and compliance were reviewed and recorded.

End of Study

At the end of the study, all patches were removed as described above, and the final evaluations of the test sites were made. In addition, concomitant medications and AEs were reviewed and recorded.

Local Tolerability Assessments

Assessment of the patch sites was done 9 times during the induction phase, 4 times during the challenge and, if applicable, 4 times during the rechallenge. The 6-point integer grading scale shown in Table 6 was used to express the response observed at the time of examination.

Table 6. Skin Assessment Grading Scale

Score	Definition
0	No visible reaction
1	Minimal erythema, no sign of edema
2	Definite erythema with no significant edema
3	Moderate erythema with no significant edema
4	Moderate erythema with edema and/or papular response
5	Severe erythema, edema, epidermal damage or papulovesicular response

Source: NDA 203098, Module 5.3.5.4.1, Study Report DS102308, Table 9-2, page 23.

Data Analysis

Individual irritancy scores through the induction period were displayed in a data listing for all subjects, products, and readings, along with the mean and total of the scores. Frequency counts of each assigned score at each reading for each product were presented. No data imputations were made for discontinued subjects or missed evaluations. However, when a patch was discontinued due to limiting irritation, the last observed score was carried forward through all subsequent readings.

The mean and total irritation scores during induction were tested pair wise for product differences using Fisher's protected least significant differences in the context of the 2-way analysis of variance (ANOVA), including main effects of subject and product, without interaction. Pairwise differences were tested only if the null hypothesis of a common mean score for all products was rejected at the 5% level.

Adverse Events

Adverse events were summarized as 1) an overall incidence of at least one event, 2) an incidence within body systems, and 3) an incidence by body system and preferred term. Each subject contributed only once (eg, the first occurrence) to each of the rates, regardless of the number of occurrences (events) the subject experiences.

Treatment-emergent AEs were summarized and tabulated by the system organ class and preferred term, by severity (mild, moderate, or severe), and by relationship to study product (unrelated, unlikely, possible, probable, or definite).

Treatment-emergent AE's were defined as any adverse event with an onset date on or after the first study product administration.. Any event with a missing onset date was included as a treatment-emergent AE.

Serious adverse events and deaths were listed by subject.

Study Results

The results of this study are discussed in section 7.5.4.3 Skin Sensitization Study (DS102308).

5.3.3 Skin Irritation Study – DS310208

Study DS310208 was a 21-Day, randomized, controlled study to evaluate the irritation potential of Testosterone Gel (b) (4) on healthy volunteers, using a cumulative irritant patch test design.

Study Objective

To determine the irritation potential of Perrigo Pharmaceuticals testosterone gel (b) (4) on normal skin.

Study Design

This was a randomized, single center, controlled, within-subject comparison study of Testosterone gel (b) (4) the comparator control product (AndroGel [testosterone] 1%), the vehicle product, and controls under occlusive conditions, in healthy volunteers. All subjects had areas of skin designated for Testosterone gel (b) (4) comparator control product (AndroGel [testosterone] 1%), the vehicle product, and the control patches (ie, sodium lauryl sulfate [SLS] 0.2% positive control and saline negative control) at randomly assigned, adjacent sites, for the purpose of determining irritation potential.

The investigational product, comparator product, the vehicle product, and the controls were applied occlusively to one side of the infrascapular area of the back. Evaluation of dermal reactions at the application sites were assessed clinically using an ordinal scale that rated the degree of erythema, edema, and other signs of cutaneous irritation.

A total of 21 patch applications were made over a period of 22 days.

Reviewer's comment: *The study design is acceptable.*

Study Drugs

- Investigational Product
 - Product: testosterone gel (b) (4)
 - Lot no. 006262
 - Manufacturer: Perrigo Israel Pharmaceuticals, Ltd.
- Comparator Control Product
 - Product: AndroGel (testosterone) 1%
 - Lot No: 31280
 - Manufacturer: Laboratoires Besins International, Montrouge, France
- Vehicle Product
 - Product: Testosterone gel, (b) (4) placebo
 - Lot No: 010962
 - Manufacturer: Perrigo Israel Pharmaceuticals, Ltd.
- Positive and Negative Controls
 - Commercially available SLS prepared as a 0.1% aqueous solution served as a positive control and commercially available saline served as a negative control.

Irritancy Assessments

Assessment of the patch sites was done 21 times during the study. The 6-point integer grading scale shown in Table 7 was used to express the response observed at the time of examination.

Table 7. Skin Assessment Grading Scale

Score	Definition
0	No visible reaction
1	Minimal erythema, no sign of edema
2	Definite erythema with no significant edema
3	Moderate erythema with no significant edema
4	Moderate erythema with edema and/or papular response
5	Severe erythema, edema, epidermal damage or papulovesicular response

Source: NDA 203098, Module 5.3.5.4.1, Study Report Table 9-2, page 20.

Data Analysis

The focus of the statistical analysis was the comparison of the cumulative irritation response of the controls as compared to the investigational product. The primary parameter for cumulative irritancy was the mean cumulative irritation score.

Inclusion Criteria

Subjects included in the study were those who:

- were males and females, 18 years of age or older and in good general health;
- were of any skin type or race, providing the skin pigmentation allowed discernment of any skin reactions;
- in the case of females, were not of childbearing potential, (ie, were surgically sterile or had experienced menopause);
- were free of any systemic or dermatologic disorder, which, in the opinion of the investigative personnel, would have interfered with the study results or increased the risk of adverse events;
- were able and willing to follow all study procedures, attend all scheduled visits, and successfully complete the study;
- completed a medical screening procedure; and
- read, understood and signed an informed consent containing HIPAA (Health Information Portability and Accountability Act) authorization.

Exclusion Criteria

Subjects excluded from the study were those who:

- had any visible skin disease at the application site which, in the opinion of the investigative personnel, would have interfered with the evaluation of the test sites;
- were not willing to refrain from using more than 8 baby (81 mg) aspirin per week and refrain from using any other aspirin products during the study (use of Tylenol was permitted);
- were using or had used systemic/topical corticosteroids within 3 weeks prior to the study, or will use during the study;
- were using or had used any systemic/topical antihistamines or anti-inflammatory drugs within 72 hours prior to the study, or will use during the study;
- were using medication which, in the opinion of the investigative personnel, would have interfered with the study results;
- had psoriasis and/or active atopic dermatitis/eczema;
- were females who were of childbearing potential;
- had a known sensitivity to topical testosterone or any components of AndroGel®;
- had damaged skin in or around the test sites, including sunburn, excessively deep tans, uneven skin tones, tattoos, scars, excessive hair, numerous freckles, or other disfigurements of the test site;
- had received treatment for any type of internal cancer within 5 years prior to study entry;
- had a history of, or were being treated for skin cancer;
- had a history of, or were being treated for prostate disorder;
- were participating in any concurrent clinical testing;
- had any known sensitivity to adhesives, and/or
- had received any investigational treatment(s) within 4 weeks prior to study entry.

Adverse Events

Information about all local and systemic adverse events, whether volunteered by the subject, discovered by investigator questioning, or detected through other means, were collected and recorded on the Adverse Event CRF and followed as appropriate.

An adverse event is defined as any untoward medical occurrence in a subject or clinical investigation in which the subject administered a pharmaceutical product, which did not necessarily have a causal relationship with this treatment. An AE can therefore, be any unfavorable and unintended sign, symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not considered related to the medicinal (investigational) product.

AEs were coded using the Medical Dictionary for Regulatory Activities (MedDRA).

Study Results

The results of this study are discussed in section 7.5.4.4 Skin Irritation Study (DS310208).

***Reviewer's comment:** The study design is acceptable.*

5.3.4 Residual Testosterone After Washing – Study PRG-806

This was a study to evaluate the residual amount of topically delivered Testosterone Gel ^{(b) (4)} present on normal skin of the hand, arm, and shoulder in healthy adult male subjects following washing procedures.

Study Objective

To quantify and compare the amount of residual testosterone remaining on the hands and arm/shoulder before and after the hand and application site washing that followed a single topical dose (10 g of gel for a total of 100 mg testosterone) of Testosterone Gel ^{(b) (4)}. This was also assessed for the comparator product for information only.

Study Design

This was an open-label, four-period, pivotal study, on healthy adult male subjects.

Subjects entered the clinic on study day 1 of each period and washed their hands and the arm/shoulder designated for drug application. Then, the hand and arm/shoulder designated for drug application were wiped with three ethanol dampened gauze (blank control sample). Subsequently, study staff applied a 10 gram dose (2 × 5-gram packets) of one of the testosterone gel formulations to the center area of the palm of one of the subject's hands. The subject then applied the dose to their opposite arm/shoulder.

Subjects followed their assigned hand residual removal procedure and had their hand wiped with three ethanol dampened gauze pads to obtain a residual hand sample for testosterone measurement. Finally, approximately 2 hours after the dose was applied, subjects followed their assigned arm/shoulder residual removal procedure and had their arm/shoulder wiped with three ethanol dampened gauze pads to obtain a residual application site sample for testosterone measurement. The gauze was retained for analytical quantification of recovered testosterone.

Subjects followed study exit procedures, showering to remove any residual dose of drug that remained on the skin (hands and application arm/shoulder).

The residual removal procedure for two (2) of the periods (one following the Perrigo formulation application, the other following the AndroGel application), was to wipe the dosed hand immediately following dosing and the arm/shoulder application site two (2) hours after dose application. The residual removal procedure in the remaining two (2) periods was to wash the hands and shower after dose application but before collection of the residual hand and residual arm/shoulder application site samples.

The residual hand gauze pads and residual application site gauze pads in each period were analyzed for testosterone.

Reviewer's comment: *The study design is acceptable.*

Study Drugs

- Investigational Product
 - Product: testosterone gel (b) (4)
 - Lot no. 028508
 - Manufacturer: Perrigo Israel Pharmaceuticals, Ltd.
 - Manufacture Date: December 22, 2009
- Comparator Control Product
 - Product: AndroGel (testosterone) 1%
 - Lot No: 31791
 - Manufacturer: Solvay Pharmaceuticals, Inc.
 - Manufacture Date: N/A
 - Expiration Date: November 2011

Drug Concentration Measurements

The residual hand gauze pads and residual application site gauze pads in each period were analyzed for testosterone. The quantification of testosterone present in the gauze was measured using extraction and liquid chromatography analytical methods developed for these samples, and according to the Analytical Laboratory's Standard Operating Procedures and FDA Guidelines as applicable.

Statistical and Analytical Plan

Data was tabulated and summarized. Data from subjects were included in summary tabulations if they completed at least 2 periods, which included both the washing and no washing periods for the Perrigo product. No statistical evaluations were planned.

Recovery assessments were determined as the total amount recovered from the gauze pads, from the hand and arm/shoulder.

Inclusion Criteria

Volunteers who met the following criteria were included as subjects in the study.

- Understood the study objectives, were willing to participate, and gave written informed consent for study participation.
- Volunteer's hands, upper arms, and shoulders were free from scars, cuts, excessively thick calluses, or skin diseases that could have affected absorption or interfered with evaluation of the test site.
- Male, non-smoking (minimum of 14 days), 18 to 65 years of age, inclusive, at the time of dosing.
- Body mass index (BMI) between 19 to 34 kg/m², inclusive.
- Judged by the Investigator on the basis of pre-study medical history to have no health conditions that would have impacted the safety of the subject or compliance during participation.
- Willing to shower using the same soap/cleansers between the Screening Visit and until completion of study related activities.
- Willing to follow study restrictions.

Exclusion Criteria

Volunteers or subjects who met any of the following criteria were excluded from the study:

- Reported participating in another investigational drug, medical device, or biologics study within 30 days prior to dosing.
- Reported a past or current medical condition that might have significantly affected percutaneous absorption to topical testosterone.
- Reported a history of sensitivity/allergy to the ingredients found in the test formulations or had a history of adverse reactions to topical or systemic corticosteroids.
- Reported a significant history of allergy to soaps, lotions, emollients, ointments, creams, cosmetics, adhesives, or latex.
- Reported a history of significant skin conditions or disorders, for example, psoriasis, atopic dermatitis, etc.
- Reported a history of significant dermatologic cancers, for example, melanoma or squamous cell carcinoma. Basal cell carcinomas that were superficial and did not involve the investigative site were acceptable.

- Reported a known or suspected case of prostate cancer.
- Displayed an obvious difference in skin color between hands, arm/shoulders or the presence of a skin condition, evidence of a recent sunburn, acne, scar tissue, tattoo, open wound, branding, or coloration that would have interfered with placement of test sites (hands, arms, shoulders), their assessments, and their reaction to drug or could have compromised the safety of the subject.
- Reported using a tobacco product within 14 days of study conduct.

Adverse Events

The staff recorded all adverse events observed, queried, or spontaneously volunteered by the subjects. An adverse event (AE) was defined as any untoward medical occurrence in a subject administered a pharmaceutical product (during the course of the study) and did not necessarily have a causal relationship with treatment.

Subjects were monitored throughout the study for any AEs. Subjects were instructed by the Investigator, or designee, to report the occurrence of any adverse event. All AEs were followed until resolution, as appropriate, or until a downward trend in the AE was observed. All AEs, whether elicited or observed by the Investigator, were recorded.

Study Results

The results of this study are discussed in section 7.4.5.2 A Study of Washing Testosterone from Hands and Application Site (Study PRG-806).

5.3.5 Testosterone Transfer – Study M1IU09001

Study Objective

This study assessed the relative transfer of testosterone from a male, who had been treated with a single topical dose of 10g of Testosterone Gel ^{(b) (4)} to a female partner. The transfer was evaluated both when the subject was wearing a T-shirt and without a T-shirt. The relative amounts of testosterone transfer from males to females with each treatment condition (with a T-shirt and without a T-shirt) for a comparator product was also assessed.

Study Design

This was an open-label, single-dose, randomized, four-period, four-treatment crossover study. The total duration of the study, screening to the end of the study, was approximately 12 weeks with at least a 7-day washout period between doses. Female subjects reported to the clinical site at least 48 hours prior to contact with the treated male subjects. The female subjects were required to stay for 26 hours after dosing of the male subjects (i.e. 24 hours after male and female contact). Male subjects reported to the clinical site at least 20 hours prior to dosing and were required to stay for at least 4 hours after dosing. Blood samples were collected from female subjects on the day prior to contact at 0, 2, 4, 6, 8, 10, 12, 16 and 24 hours. These sampling times were

relative to the time of male and female contact on Day 1 in such a way that the pre-contact blood sampling schedule on Day -1 was performed at the same clock times as the post-contact blood sampling schedule on Day 1.

The Testosterone Gel (b) (4) was applied to the male subject's arm/shoulder area. Skin contact occurred two hours after application of the gel. In two of the four study phases contact occurred directly between skin-to-skin. In the other two phases the subject's application site was covered with a T-shirt and contact was between the skin of the female's arm and the shirt overlying the subject's application site. Female subjects had one arm/shoulder designated as the "contact site" and were instructed to rub their upper arm and shoulder up and down the treated upper arm/shoulder of their male partner during a 15 minute contact period.

The details of the contact were as follows. Female subjects were instructed to gently rub (for approximately 15 seconds per stroke) their upper arms and shoulders up and down the treated upper arms and shoulders of their male partner during the contact period for a total of one minute. One minute periods of alternating active rubbing and resting of the female's arms on the male's shoulders occurred until the 15 minute time period was completed. Each couple was monitored and coached by one staff member throughout the contact period.

Following contact, blood samples were collected from female subjects immediately prior to contact (0 hour) and after contact at 2, 4, 6, 8, 10, 12, 16 and 24 hours. One single blood sample was collected to represent both the Day -1, 24 hour sample and the Day 1, 0 hour sample.

A total of 17 blood samples were collected from the female subjects per study period for a total of 68 samples or 408 mL total volume. There were no samples taken from the male subjects.

Reviewer's comment: *The study design is acceptable.*

Study Drugs

- Investigational Product
 - Product: testosterone gel (b) (4)
 - Lot no. 028508
 - Manufacturer: Perrigo Israel Pharmaceuticals, Ltd.
 - Manufacture Date: December 22, 2009
- Comparator Control Product
 - Product: AndroGel (testosterone) 1%
 - Lot No: 31791
 - Manufacturer: Solvay Pharmaceuticals, Inc.
 - Manufacture Date: N/A
 - Expiration Date: November 2011

Sample Handling and Testosterone Analysis

After local processing, the samples were shipped frozen (b) (4) for analysis.

Testosterone serum concentrations were measured using a validated bioanalytical method according to the bioanalytical laboratory's SOPs and FDA guidances. The validated detection range for total testosterone in females is approximately 0.05 to 50 ng/mL in human serum.

Statistical Analytical Plan

Pharmacokinetic and statistical analyses were performed for total testosterone serum concentration data from female subjects. Data were analyzed if the subjects completed at least 2 periods, which included Treatments A and B (Contact after Testosterone Gel (b) (4) with and without a shirt). Data from treatment groups C and D (Contact after Androgel with and without a shirt) were to be collected for information purposes only.

Data from subjects with missing concentration values (missed blood draws, lost samples, samples unable to be quantitated) were to be used if pharmacokinetic parameters could be estimated using the remaining data points. Otherwise, concentration data from these subjects were to be excluded from the final analysis.

Pharmacokinetic parameters were calculated based on both baseline adjusted and non-adjusted total testosterone serum concentrations using standard noncompartmental approaches. The following parameters were calculated:

- AUC_{0-t} The area under the serum concentration versus time curve, from time 0 to the last measurable concentration, as calculated by the linear trapezoidal method.
- C_{max} Maximum measured serum concentration over the time span specified.
- T_{max} Time of the maximum measured serum concentration. If the maximum value occurred at more than one time point, Tmax was to be defined as the first time point with this value.

Arithmetic means, standard deviations, and coefficients of variation were calculated for these parameters. Additionally, geometric means were calculated for AUC_{0-t} and C_{max}. Ratios of means were calculated using the LSM for ln-transformed AUC_{0-t} and C_{max}. The geometric mean values were reported. The ratios of primary interest are with-T-shirt to without T-shirt treatments for Testosterone Gel (b) (4). For information only, the ratios of the with-T-shirt to without-T-shirt treatments for Androgel were also presented.

Study Results

The results of this study are discussed in section 7.4.5.1 A Study of Person-to-Person Testosterone Transfer (Study M1IU09001).

6 Review of Bioequivalence

Summary

The efficacy of Testosterone Gel (b) (4) was not evaluated in a clinical study. Rather, the efficacy of the Gel will be established by a study showing that it is bioequivalent to the reference listed drug, Androgel 1%. Androgel has previously been shown to be an effective treatment for hypogonadal males. A study showing that Testosterone Gel (b) (4) provides equivalent blood levels of testosterone is a reasonable support for the conclusion that Testosterone Gel (b) (4) is also an effective treatment for this indication.

An analysis of the results of the bioequivalence study was done based upon the adjusted data submitted by the Sponsor in their Complete Response. This analysis is given in Section 6.1. Based on this analysis of the adjusted data, it is this reviewer's opinion that it is reasonable to conclude that the Sponsor's testosterone gel product is bioequivalent to the reference listed drug Androgel 1%.

6.1 Bioequivalence Study

As evidence of the bioequivalence of Testosterone Gel (b) (4) and Androgel, the Sponsor has submitted the results of Study 03-0415-001. The study design is discussed in section 5.3.1 Bioequivalence Trial – 03-0415-001. The results of the study will be reviewed in this section.

6.1.1 GCP and GLP Certification

The director of quality assurance, Elizabeth Himsl, C.M.A., C.C.R.C., has certified that the study was conducted in compliance with 21CFR and Good Clinical Practice Guidelines. The director of study analytics, Dr. Alwin Baumeister, has certified that the analysis of study samples was conducted in compliance with the Principles of Good Laboratory Practice.

6.1.2 Demographics

The demographics of the study subjects is presented in Table 8.

Table 8. Baseline Demographics for the Intent-to-Treat Population

Parameter	Value
Number	24
Age (years)	
Range	31 - 69
Mean	55.8
Median	59.5
Height (cm)	
Range	165.1 – 190.5
Mean	176.0
Median	176.5
Weight (kg)	
Range	65.0 – 116.4
Mean	91.3
Median	92.0
BMI (kg/m ²)	
Range	21.8 – 35.5
Mean	29.4
Median	29.2

Source: NDA 203098, Module 2.3.1.2.1, Study Report, Table 2

Reviewer’s Comment: *The population studied is reasonably representative of the intended treatment population. The demographics are acceptable.*

6.1.3 Subject Disposition

All 24 subjects enrolled in the intent to treat population completed the study. All subjects provided 18 scheduled blood samples during each of the three study periods; there were no missing samples.

Reviewer’s comment: *The Office of Scientific Investigations, based upon their inspection of the clinical site, initially concluded that there were incomplete dosing records for 16 subjects. The Sponsor has subsequently located the missing records and OSI now concludes that the data may be relied upon.*

Forty-one samples were reanalyzed. Twelve of forty-one samples were reanalyzed to confirm the initial analysis. Fourteen were reanalyzed because of a poor initial chromatography or because of a destroyed initial sample. Fifteen were reanalyzed due

to values that were greater than the upper limit of quantification during the first measurement.

6.1.4 Pharmacokinetic Procedures

All the available data from the 24 subjects who completed the study were used in the pharmacokinetic analyses. All pharmacokinetic calculations were performed using SAS (PC version 6.12). Any sample concentration reported less than the assay limit of quantitation was set to zero. Pharmacokinetic analyses were performed on the testosterone results after correction for endogenous levels.

The reported concentrations for each subject in each period were corrected by subtracting the average testosterone concentration in the -12 hour and 0 hour samples. Any corrected value that was less than zero was set to zero for use in the analyses. The 0 hour samples were likewise set to zero concentration.

Pharmacokinetic parameters, AUC and T_{max} , were calculated using the actual rather than the scheduled times of sample collection. Peak concentration, C_{max} , was the observed maximum value during the collection period of 0 to 72 hours. The time to peak concentration, T_{max} , was the time at which C_{max} , was first observed. Area under the curve, AUC_{0-t} , to the last measured concentration was calculated by the linear trapezoidal method.

6.1.5 Statistical Analyses

Statistical Analyses were performed using the General Linear Models (GLM) procedure of the SAS statistical program (PC version 6.12). The pharmacokinetic parameter estimates, as well as the concentrations at each scheduled sample time, were evaluated by analysis of variance. Hypothesis testing for treatment effects in the analysis was conducted at $\alpha= 0.05$.

6.1.6 Results

Statistical analyses were performed on the pharmacokinetic results in order to compare two (b) (4) Testosterone Gel formulations to Androgel, when each was administered as a single 10 gm topical dose to 24 hypogonadal males.

Table 9 summarizes the results of the statistical analyses of the pharmacokinetic parameters for baseline corrected results for Testosterone Gel (b) (4) Formulation 2 and Androgel.

Table 9. Summary of Statistical Comparisons of Testosterone Gel (b) (4) Formulation 2 (Lot #T06P033) and AndroGel

Parameter	Least-Squares Mean		Ratio	90% Confidence Interval	
	Formulation 2	AndroGel		Lower	Upper
AUC _{0-t} (ng-hr/ml)	101	97.1	1.042	0.892	1.191
C _{max} (ng/ml)	5.46	5.19	1.053	0.855	1.252
T _{max} (hour)	18.6	19.2	0.970	-	-
Ln-Transformed					
AUC _{0-t} (ng-hr/ml)	84.3	88.0	0.958	0.832	1.103
C _{max} (ng/ml)	4.65	4.82	0.965	0.805	1.157

Source: NDA 203098, Module 5.3.1.2.1, Study Report 03-0415-001, Statistical Report, Table 1.2

6.1.7 Bioequivalence Conclusions

Based upon the revised data submitted with this supplement, it is this reviewer's opinion that this study has provided reliable evidence of the bioequivalence of the Sponsor's product and the reference listed drug, AndroGel.

7 Review of Safety

Safety Summary

The safety of Testosterone Gel (b) (4) was not evaluated in a clinical study. Rather, the safety of the Gel will be established by a study showing that it is bioequivalent to the reference listed drug, AndroGel. AndroGel has previously been shown to be safe and effective as a treatment for hypogonadal males. A study showing that Testosterone Gel (b) (4) provides equivalent blood levels of testosterone is a reasonable support for the conclusion that Testosterone Gel (b) (4) is safe as a treatment for this indication.

Because the Sponsors formulation of Testosterone Gel differs somewhat from the formulation of AndroGel, the Sponsor was asked to perform clinical studies evaluating areas of safety that could possibly be affected by the formulation difference. These studies were an evaluation of the potential for irritation and sensitization of the skin, an evaluation of the potential to transfer testosterone from the skin of a patient to another individual by direct skin to skin contact, and an evaluation of the ability to wash the Gel from the hands and application site after the drug is applied.

Reviewer’s Comment: Based on the results of the studies of the formulation-dependent areas of product safety submitted with this application, the conclusion of this reviewer is that Testosterone Gel has been shown to be reasonably safe with respect to person-to-person transfer, the ability to wash the product from the skin, and with respect to skin irritation and sensitization. Further conclusions regarding the safety of the product are not warranted given the lack of established bioequivalence to a reference listed drug.

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

The studies used to evaluate the formulation dependent areas of safety are listed in Table 10.

Table 10. Studies Performed to Evaluate Formulation-Dependent Safety

Type of Study	Study Number	Study Objective	Study Design	Test Product	N	Type of Subjects
Skin Sensitization	DS102308	Evaluate the sensitization of the skin by Testosterone ^{(b) (4)} Gel	Randomized, controlled, within-subject comparison study	Testosterone ^{(b) (4)} Gel Androgel 1%	226	Healthy volunteers
Skin Irritation	DS310208	Evaluate the irritation potential of Testosterone ^{(b) (4)} Gel to the skin	Cumulative Irritant Patch Test	Testosterone ^{(b) (4)} Gel Androgel 1%	38	Healthy volunteers
Residual Testosterone after Washing	PRG-806	Evaluate the residual testosterone on the hands and the application site following washing	Open-label four period study	Testosterone ^{(b) (4)} Gel Androgel 1%	36	Healthy male volunteers
Interpersonal Transfer of Testosterone	M11U09001	Evaluate the transfer of testosterone from a treated male to an untreated female via skin contact	Single-dose, four-treatment, four-way open-label crossover study	Testosterone ^{(b) (4)} Gel Androgel	24 male/female pairs	Healthy volunteers

The designs of these studies were presented in section 5.3 Discussion of Individual Studies/Clinical Trials, and the results are presented in section 7.4.5 Special Safety Studies/Clinical Trials.

7.2 Adequacy of Safety Assessments

If the product had been found to be bioequivalent to the listed drug Androgel, the Agencies prior finding of safety for the reference drug, and the formulation-dependent safety studies that were submitted would constitute an adequate evaluation of the safety of this drug product in the opinion of this reviewer. Given the lack of proof of bioequivalence that has previously been discussed and the resulting inability to rely upon the safety history of Androgel, this reviewer is not able to reasonably conclude that the Sponsor has established the safety of the product.

7.3 Major Safety Results

7.3.1 Deaths

There were no subject deaths during the studies of bioequivalence or formulation-dependent safety.

7.3.2 Nonfatal Serious Adverse Events

There were no serious adverse events that were related to the drug product during the studies of bioequivalence or formulation-dependent safety.

7.4 Supportive Safety Results

7.4.5 Special Safety Studies/Clinical Trials

Four safety studies were conducted for this product. See Table 10. The design of each study is presented in section 5.3 Discussion of Individual Studies/Clinical Trials. The results of each study is discussed in this section.

7.4.5.1 A Study of Person-to-Person Testosterone Transfer (Study M1IU09001)

The design of this study is presented in section 5.3.5 Testosterone Transfer – Study M1IU09001.

Disposition of Subjects

Twenty four male/female couples were enrolled in the study. Twenty of the couples completed the study in accordance with the study protocol. The reasons for failure of four couples to complete the study is shown in Table 11.

Table 11. Discontinuations from Study M1IU09001

Subject No.	Reason for Withdrawal	Gender	Age	Race
03	Female partner tested positive for Benzodiazopine on Day 1 Period 1.	Female	63	W
		Male	51	W
08	Male partner tested positive for THC on Day 1 Period 1.	Female	56	W
		Male	26	W
14	Female partner tested positive for cotinine at Period 4 admission.	Female	48	W
		Male	38	W
16	Non compliance of female partner on Day 1 Period 1.	Female	57	W
		Male	58	W

Source: NDA 203098, Module 5.3.5.4.1, Table 10.1-1, page 30

Reviewer’s Comment: *The withdrawals from the study are reasonable and unrelated to adverse events.*

Subject Demographics

Table 12 shows the demographics for the female subjects completing the study.

Table 12. Subject Demographics – Study M1IU09001

		Female Completers (N=20)
Age (years)	Mean ± SD	53.9 ± 4.8
	Range	44 – 62
Race	Black	2 (10%)
	White	18 (90%)
BMI	Mean ± SD	28.1 ± 2.1
	Range	24.7 – 31.0

Source: NDA 203098, Module 5.3.5.4.1, Table 11.2-1, Page 34

Results

Table 13 shows the mean AUC and C_{MAX} for total testosterone in the female partners following contact with a male partner who had applied Testosterone Gel (b) (4)

Table 13. AUC and C_{MAX} For Total Testosterone in Female Partners for 24 Hour Period Following Contact With a Male Partner Who Had Applied Testosterone Gel

Parameter	Observed Values		Baseline corrected Values	
	Without Shirt	With Shirt	Without Shirt	With Shirt
AUC _{0-t} (ng-hr/ml)	6.108	2.992	3.289	0.322
C _{MAX} (ng/ml)	0.411	0.159	0.260	0.047

Source: NDA 203098, Module 5.3.5.4.1, Table 11.4.2-1, page 35 and Table 11.4.2-2, page 36.

Table 14 shows the observed values as a percentage of the baseline values.

Table 14. AUC and C_{MAX} For Total Testosterone in Female Partners for 24 Hour Period Following Contact With a Male Partner Who Had Applied Testosterone Gel as Percent of Baseline Value

Parameter	Observed Values as % of Baseline Value	
	Without Shirt	With Shirt
AUC _{0-t} (ng-hr/ml)	209%	112%
C _{MAX} (ng/ml)	272%	142%

Source: Medical Officer Calculation based on values shown in Table 13.

Table 15 shows the mean serum testosterone levels for the female partners during the 24 hours following contact with the male partner. Both actual observed values and baseline corrected values are presented.

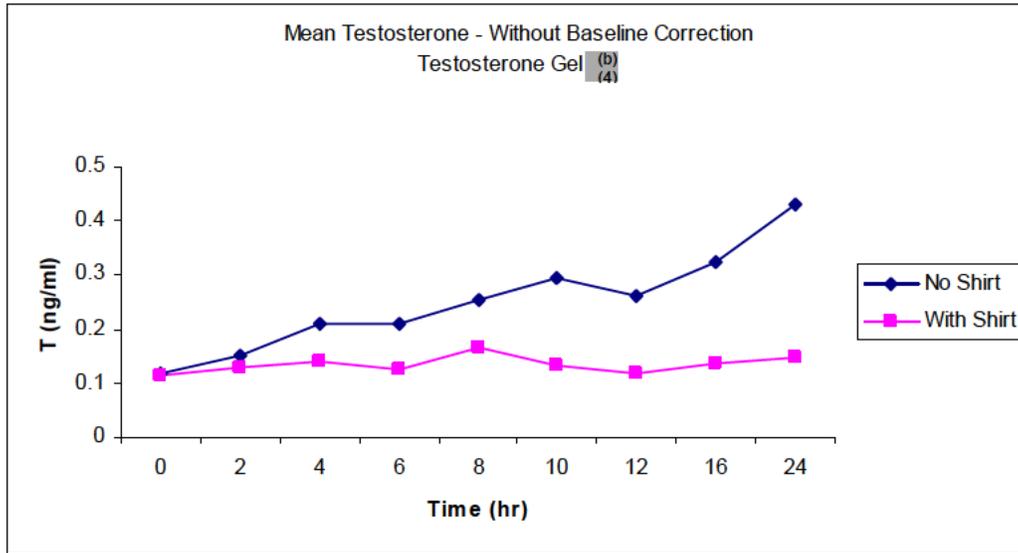
Table 15. Mean Testosterone Levels Following Contact with a Male Partner Who Had Applied Testosterone Gel

Time after contact (hr)	Observed Values (ng/ml)		Baseline corrected Values (ng/ml)	
	Without Shirt	With Shirt	Without Shirt	With Shirt
0	0.118	0.115	0.003	0.002
2	0.151	0.128	0.035	0.010
4	0.208	0.140	0.094	0.023
6	0.209	0.126	0.090	0.009
8	0.253	0.164	0.130	0.043
10	0.294	0.132	0.185	0.026
12	0.261	0.117	0.146	0.011
16	0.324	0.136	0.192	0.011
24	0.431	0.149	0.313	0.034

Source: Reviewer analysis of NDA 203098, Module 5.3.5.4.25.2.1, Datasets Final Export V3 Unadjusted, Final Export V2 Baseline Adjusted B vs A.

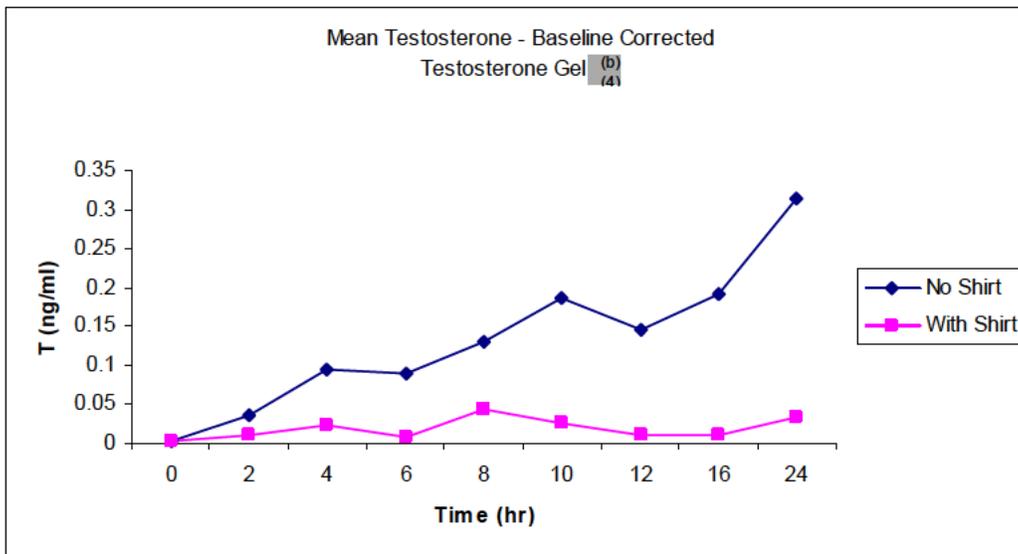
This information is displayed graphically in Figure 1 and Figure 2.

Figure 1. Mean Testosterone Levels Following Contact with a Male Who Had Applied Testosterone Gel (b) (4) - Observed Values



Source: Reviewer analysis of NDA 203098, Module 5.3.5.4.25.2.1, Datasets Final Export V3 Unadjusted, Final Export V2 Baseline Adjusted B vs A.

Figure 2. Mean Testosterone Levels Following Contact with a Male Who Had Applied Testosterone Gel (b) (4) - Baseline Corrected Values



Source: Reviewer analysis of NDA 203098, Module 5.3.5.4.25.2.1, Datasets Final Export V3 Unadjusted, Final Export V2 Baseline Adjusted B vs A.

Reviewer’s comment: *In this reviewer’s opinion, there is a clinically meaningful reduction in transfer when a clothing barrier is present. However, transfer is not eliminated by the barrier.*

The maximum baseline corrected increase in serum testosterone and AUC_{0-t} in female partners following contact with a male partner who had applied Testosterone Gel (b) (4) is shown for each subject in Table 16.

Table 16. Maximum Increase in Baseline Corrected Serum Testosterone and AUC for each Subject Following contact with Male Partner Who Had Applied Testosterone Gel (b) (4)

Subject	Maximum Increase (ng/ml)	Maximum Increase (ng/dl)	Time of Maximum Increase (Hours)	AUC (ng-hr/ml)
1	0.0195	1.95	4	0.104
2	0.0258	2.58	4	0.248
4	0.0842	8.42	24	0.951
5	0.0557	5.57	6	0.789
6	0.0300	3.00	4	0.284
7	0.0681	6.81	12	0.410
9	0.0587	5.87	10	0.591
10	0.1019	10.19	10	1.425
11	0.0236	2.36	10	0.336
12	0.0587	5.87	2	0.344
13	0.0293	2.93	24	-0.079
15	0.0317	3.17	24	0.126
17	0.0765	7.65	24	0.594
18	0.7382	73.82	8	1.842
19	0.0266	2.66	10	0.228
20	0.0180	1.80	24	-0.030
21	0.0528	5.28	24	0.015
22	0.0403	4.03	4	0.475
23	0.0462	4.62	24	0.410
24	0.0413	4.13	4	0.067

Source: NDA 203098, Module 5.3.5.4.25.2.1, Dataset Final Export V2 Baseline Adjusted B vs A.

Table 17 shows the actual observed maximum values over the 24 hour period following contact.

Table 17. Maximal Testosterone Values seen in the 24-hr Period Following Contact

Subject	Maximal Total Testosterone (ng/dl)	
	With Shirt	Without Shirt
1	8.38	19.56
2	9.40	25.54
4	18.66	35.7
5	18.98	46.12
6	17.16	86.59
7	9.33	22.09
9	21.63	43.12
10	18.31	111.5
11	9.42	21.38
12	11.74	150.7
13	19.61	24.53
15	8.74	30.36
17	31.52	38.96
18	92.18	92.9
19	10.57	14.98
20	11.42	30.38
21	22.44	37.53
22	22.01	47.64
23	12.67	37.02
24	15.36	101.7
Mean	15.65*	51.0
Range	8.4 - 31.5*	15.0 - 150.7

Excluding subject 18 – see discussion.

Source: Reviewers analysis, NDA 203098, Module 5.3.5.4.25.2.1, Datasets Final Export V3 Unadjusted

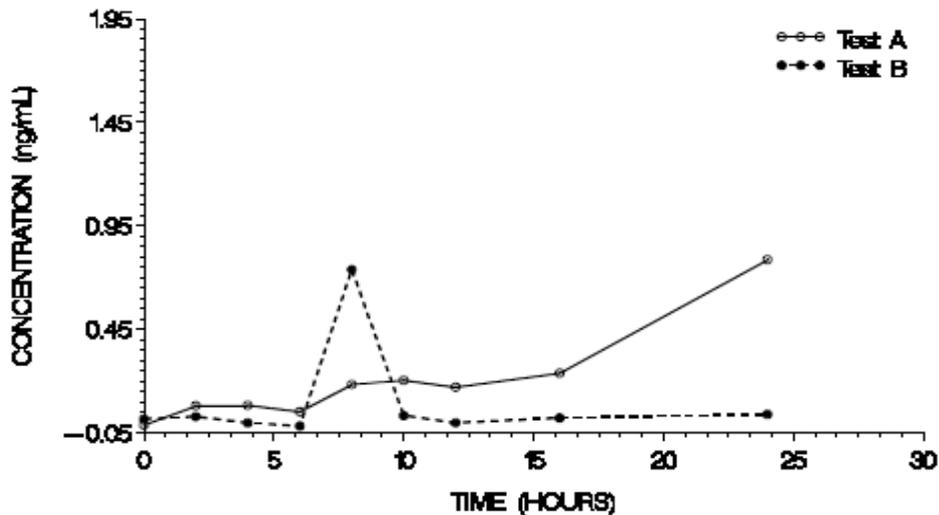
Reviewer's Discussion

The objective of this study was to evaluate the ability of a clothing barrier to prevent testosterone transfer from a treated patient to another individual with whom they have direct contact. The study shows that, with a clothing barrier, the mean maximal increase from baseline testosterone level at any time during the 24 hours following contact is 0.043 ng/ml (4.3 ng/dl). This compares to a mean maximal increase from baseline of 0.313 ng/ml (31.3 ng/dl) when contact occurs without the clothing barrier.

In evaluating the individual subjects maximal baseline corrected increase, subject number 18 appears to be an outlier with an increase of 73.8 ng/dl. Figure 3 shows this subject's 24 hour testosterone levels. This indicates that the 8 hour value, which was used to determine the maximal baseline corrected increase, is inconsistent with the 6 hour and 10 hour values. I believe that it is reasonable to conclude that this is an invalid

result and that this subject's data should be withheld from an analysis of the maximal increases following contact.

Figure 3. Subject 18 Serum Testosterone Levels For 24 Hours Following Contact



Test A = without a shirt, Test B = with a shirt
Source: NDA 203098, Module 5.3.5.4.25.2.1, Dataset Final Export V2 Baseline Adjusted B vs A.

If the remaining 19 subjects are analyzed, the mean maximum change is 4.68 ng/dl and the median maximal change is 4.13 ng/dl. Eleven of the 19 subjects had maximal increases less than 5 ng/dl and only one subject had a maximal increase greater than 10 mg/dl.

The maximal actual values, again without subject 18, is 15.65 with a range of 8.3 – 31.5. Normal testosterone levels in healthy women may range up to 70 ng/dl.

Conclusions

Direct skin-to-skin contact between a man treated with Testosterone Gel (b) (4) and a female partner does transfer testosterone to the female partner. Maximum serum testosterone levels following this contact ranged as high as 150ng/dl.

It is reasonable to conclude that a clothing barrier prevents clinically significant transfer of testosterone from a male treated with Testosterone Gel (b) (4) to an untreated female with whom he has direct contact. The maximum value seen in the female partner after contact with a man wearing a shirt was 31ng/dl. Serum testosterone levels in these women remain within the range of normal and the mean increase from baseline is less than 5 ng/dl.

The testosterone Gel (b) (4) label should contain information about the potential for transfer and also about the ability of a clothing barrier to prevent transfer.

7.4.5.2 A Study of Washing Testosterone from Hands and Application Site (Study PRG-806)

This was a study to evaluate the ability to wash the Testosterone Gel product from the hands and from the application site. The design of this study is presented in section 5.3.4 Residual Testosterone After Washing – Study PRG-806.

Study Subjects

Thirty-six healthy non-smoking male subjects were enrolled in the study. Thirty-three subjects completed the entire study and are included in the analysis population. Two subjects withdrew because of scheduling conflicts that prevented further participation and one subject withdrew because of a viral illness. The entire thirty-six subjects are included in the safety population.

Subject Demographics

Table 18 shows the characteristics of the analysis population.

Table 18. Demographics of the Washing-Study Analysis Population

Parameter	Value
Age	30.0 (19 – 63)
Weight (lbs)	186.4 (137.5 – 260.0)
Height (in)	70.3 (65 – 76.1)
BMI	26.5 (21.1 – 33.6)
Race	
Native American	1 (3.0%)
Asian	3 (9.1%)
African American	1 (3.0%)
White	28 (84.8%)

Source: NDA 203098, Module 5.3.5.4.1, Table 11.2-2

Results

This study quantified the amount of drug remaining on the hands and arm/shoulder after a hand and application site wash and compared this amount to the amount present before washing.

Data are the mean \pm SD micrograms of testosterone. Application sites were sampled in three pre-define areas totally 150 cm² and the results are normalized to the 400 cm² total application area. Dose was 100 mg of testosterone applied as 10 grams of

Testosterone (b) (4) Gel formulation. Table 19 shows the recovered testosterone, both from the hands and the application site. The percentage recovery is shown in Table 20.

Table 19. Amount of Testosterone Recovered After Hand and Application Site Washing (Mean $\mu\text{g} \pm \text{SD}$)

Site	Recovery Without Wash	Recovery Following Wash
Hand	8478 \pm 3552	399 \pm 199
Application Site	28326 \pm 7627	5802 \pm 2770

Source: NDA 203098, Module 5.3.5.4.1, Table 11.4.7-1

Table 20. Testosterone Recovered After Hand and Application Site Washing (Percent of Applied Dose)

Site	Recovery Without Wash	Recovery Following Wash	Reduction in Recovery following Wash
Hand	8.48 \pm 3.55	0.4 \pm 0.2	95.3 %
Application Site	28.33 \pm 7.63	5.8 \pm 2.8	79.5 %

Source: NDA 203098, Module 5.3.5.4.1, Table 11.4.7-2

Discussion

This study has demonstrated that the wash-off from the hands (approximately 95%) differs from the wash-off from the shoulder/upper arm application site (approximately 80%). This appears to be a reasonable result. A larger portion of the product is washed from the hands shortly after it has been applied than can be removed from the application site two hours after application. Two factors potentially contribute to this difference.

First, the two hour time difference between the hand washing and the site washing would allow a greater portion of the applied dose to penetrate the epithelium where soap and water washing would be less likely to remove it, but where it could still be recovered by the ethanol-impregnated sponges used in the recovery process. This could explain the smaller fraction remaining on the hands as compared to the application site.

Secondly, the washing effort used to remove the product from the hands is quite localized to the site of interest (the hands) whereas the washing effort during the shower is directed at the entire body rather than merely at the site of interest (the shoulder/upper arm). Therefore the amount of effort used in washing the actual site of interest is likely to be greater with the hand washing as compared to the site washing.

The Sponsor included a comparator arm in the study that evaluated the wash-off of the reference listed drug AndroGel 1% from both the hands and the application site. This showed that the wash-off of the RLD was similar to the wash-off of the Testosterone Gel

(b) (4) both from the hands (Androgel 95.3%, Testosterone Gel (b) (4) 95.3%) and from the application site (Androgel 75.9%, Testosterone Gel (b) (4) 79.5%).

Conclusion

This study has demonstrated that the product can be acceptably washed from the hands and from the application site. It provides the information necessary to properly label the product.

7.5.4.3 Skin Sensitization Study (DS102308)

This was a study to evaluate the sensitizing potential of Testosterone Gel (b) (4) on normal skin. The study design is discussed in section 5.3.2 Skin Sensitization Study - DS102308.

Study Subjects

Two hundred twenty-six subjects were enrolled in the study and two hundred and three completed it. Table 21 shows the disposition of the patients.

Table 21. Study DS102308 Subject Disposition

	Number
Subjects enrolled	226
Reason for Discontinuation	
Adverse event	9
Non-compliance	1
Withdrawn consent	7
Lost to follow-up	1
Excluded medication	1
Total Subjects Discontinued	23
Subjects Completing Study	203

Source: NDA 203098, Module 5.3.5.4.1, Table 10-1, page 31.

The demographics of the study population is shown in Table 22.

Table 22. Demographic Summary of Population

N = 226	
Age	
Mean ± SD	49 ± 13
Range	18 – 75
Gender	
Male	107 (47.3%)
Female	119 (52.7%)
Race	
White	184 (81.4%)
Black	38 (16.8%)
Asian	4 (1.8%)

Source: NDA 203098, Module 5.3.5.4.1, Table 10-2, page 32

Adverse Events

There were a total of 21 adverse events reported in 15 subjects. This included one serious adverse event. Ten subjects discontinued medication because of an adverse event. Table 23 shows a list of the adverse events reported.

Table 23. Adverse Events Reported in Study DS102308

Event	Number	Drug Related
Headache	12	Possible
Phlebitis	1	Unrelated
Diarrhea	1	Possible
Flea Bites	1	Unlikely
Chest Pain	1	Unlikely
Priapism	1	Possible
Dyspnea	1	Possible
Insomnia	1	Possible
Discolored penis	1	Possible
Breast tenderness	1	Probable

Source: NDA 203098, Module 5.3.5.4.1, Appendix 16.2.8

The SAE was an episode of phlebitis of the right calf. The patient was hospitalized for the initiation of anti-coagulation. The problem was resolved.

Reviewer's Comment: *The adverse events seen do not suggest events due to this product that differ from those seen with other testosterone products.*

Results – Dermal Sensitization

Two hundred three subjects (203) completed the challenge phase of the study and were included in the sensitization analysis. A summary of the repeated insult patch test responses during the induction phase is provided in Table 24.

Table 24. Mean Cumulative Irritation Scores During Induction Phase

Product Tested	Mean Irritation Score	P value vs				
		Testosterone Gel (b) (4)	Androgel	Vehicle	Positive Control	Saline
Testosterone Gel (b) (4)	0.169	-	0.345	0.070	<0.001	0.005
Androgel	0.141	-	-	0.385	<0.001	0.066
Vehicle	0.117	-	-	-	<0.001	0.333
Positive Control	0.586	-	-	-	-	<0.001
Saline	0.089	-	-	-	-	-

Source: NDA 203098, Module 5.3.5.4.1, Table 12-1, page 33

The responses to challenge following the induction phase is shown in Table 25.

Table 25. Summary of Challenge Responses to Testosterone Gel (b) (4)

Response Score	Time following Challenge Patch Removal			
	0.5 hr	24 hr	48 hr	72 hr
0	196	187	194	197
1	5	12	5	5
2	2	3	3	1
3	0	1	1	0

Source: NDA 203098, Module 5.3.5.4.1, Table 11-1, page 32

In the challenge phase of the study, 1 subject (Subject 154) who exhibited minimal to definite erythema (scores of 1 and 2) during induction to both the investigational product and the AndroGel®, exhibited moderate erythema with no significant edema (score of 3) to both products 24 and 48 hour after challenge patch removal. Subject No. 172 who exhibited definite to moderate erythema with no significant edema (scores of 2 and 3) during induction at the vehicle site exhibited moderate erythema with no edema (score of 3) at 24 and 48 hours after challenge patch removal. Both subjects had the reactions decrease to definite erythema (score of 2) by the 72-hour challenge evaluation. With the exception of these 2 subjects, there was no more than minimal erythema observed (score of 1) at the 72-hour challenge evaluation for the testosterone gel (b) (4) AndroGel®, Vehicle and 0.1% SLS aqueous solution. There were no reactions observed at the 72-hour challenge evaluation for the saline.

There were no reactions to either the investigational product or the comparator product at challenge indicative of a possible sensitization response, nor any that required rechallenge.

Reviewer's Comment: Study DS102308 provides evidence that there is no significant sensitization of the skin by Testosterone Gel (b) (4). It also provides support for the conclusions of Study DS310208 that Testosterone Gel (b) (4) does not have a significant likelihood of irritating the skin.

7.5.4.4 Skin Irritation Study (DS310208)

This was a study to evaluate the irritation potential of Testosterone Gel (b) (4) on normal skin. The study design is discussed in section 5.3.3 Skin Irritation Study – DS310208.

Study Subjects

Thirty-eight subjects were enrolled into the study and thirty-three completed it. Four subjects withdrew the consent for the study. One subject withdrew from the study because of an adverse event, a knee injury, which was unrelated to the investigational product. Table 26 shows the demographics of the enrolled population.

Table 26. Demographics of Study DS310208 Population

	N = 38
Age	
Mean	43.5
Range	19 – 68
Gender	
Male	19
Female	19
Race	
Caucasian	35
Black	3

Source: NDA 203098, Module 5.3.5.4.1, Table 10-2, page 27

Adverse Events

Two subjects reported adverse events. One subject withdrew from the study after a knee injury which required surgical correction. A second subject reported a head cold. Neither event was judged to be related to the investigational product. There were no deaths or serious adverse events reported.

Results

Table 27 shows the mean cumulative irritation scores for Testosterone Gel (b) (4) and for the Androgel, vehicle, positive control and saline comparators.

Table 27. Mean Cumulative Irritation Scores

Product Tested	Mean Irritation Score	P value vs				
		Testosterone Gel (b) (4)	Androgel	Vehicle	Positive Control	Saline
Testosterone Gel (b) (4)	0.016	-	0.266	0.580	<0.001	0.747
Androgel	0.090	-	-	0.575	<0.001	0.429
Vehicle	0.053	-	-	-	<0.001	0.818
Positive Control	2.824	-	-	-	-	<0.001
Saline	0.037	-	-	-	-	-

Source: NDA 203098, Module 5.3.5.4.1, Table 11-1, page 28

Study Conclusions

The Testosterone Gel (b) (4), AndroGel, Vehicle, and Saline showed no evidence of significant irritation. Testosterone gel (b) (4) had a mean cumulative irritation scores of 0.016, AndroGel had a score of 0.090, the Vehicle had a score of 0.053 and the Saline had a score of 0.037. There was no statistically significant difference between the testosterone gel (b) (4), AndroGel, Vehicle and Saline. All products were statistically significantly less irritating than the SLS 0.2% positive control ($P < .001$), which had a mean cumulative irritation score of 2.824.

7.4.6 Immunogenicity

Testosterone is a substance that has a long history of human use with no immunogenicity issues. No studies of immunogenicity were done to support this application.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

No evaluation of adverse events relative to dose was done.

7.5.2 Time Dependency for Adverse Events

No evaluation of time dependency of adverse events was done.

7.5.3 Drug-Demographic Interactions

No evaluation of Drug-Demographic Interactions was done.

7.5.4 Drug-Disease Interactions

No drug-disease interaction studies or analyses were performed.

7.5.5 Drug-Drug Interactions

No drug-drug interaction studies were performed.

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

There are several lines of evidence that suggest the potential for a relation between testosterone and prostate cancer development.

Firstly, the clinical incidence of prostate cancer varies significantly across the world, with the highest incidence occurring in African-Americans (79 per 100 000) and the lowest in Japanese males (4 per 100 000)¹. Ross et al.² have demonstrated that at the time of puberty African American males have 10 to 15% higher levels of circulating testosterone than their Caucasian counterparts, but equal levels compared with Japanese men, who because of a genetic deficiency of 5 α -reductase actually have lower DHT levels in the prostate. In addition, differences in the function of 5 α -reductase genes affecting the AR and androgen metabolism contribute to an increased risk of prostate cancer in African-American men.³

Secondly, prostate cancer can be induced in rats to whom large amounts of testosterone have been administered.⁴ Thirdly, men castrated prior to puberty do not develop prostate cancer.⁵ A reduced risk of this cancer has been also been associated

1 Oesterling J, Fuks Z, Lee CT. Cancer of the Prostate. in : Devita V, Hellman S, Rosenberg S, editors. Cancer: principles and practices in Oncology. 5th ed. Lippincott-Raven 1997.

2 Ross R, Bernstein L, Lobo R. 5-alpha-reductase activity and risk of prostate cancer among Japanese and US white and black males. Lancet 1992; 339: 887-9

3 Devgan SA, Henderson BE, Yu MC, et al. Genetic variation of 3 beta-hydroxysteroid dehydrogenase type II in three racial/ethnic groups: implications for prostate cancer risk. Prostate 1997; 33 (1): 9-12

4 Nobel R. The development of prostatic adenocarcinoma in Nb rats, following prolonged sex hormone administration. Cancer Res 1977; 37: 1929-33

5 Huggins C, Hodges C. Studies on prostatic cancer 1: the effect of castration, of estrogen and of androgen injection on serum phosphatases in metastatic carcinoma of the prostate. Cancer Res 1941; 1: 293-7

with hyperoestrogenic states (e.g. cirrhosis cases)⁶, and estrogen therapy has a palliative role in advanced prostate cancer because it competes with testosterone in the hypothalamus and suppresses gonadotropin production. Finally, prostate cancer may be successfully treated by surgical or medical androgen ablation.

Despite these suggestions of a relationship between testosterone and the development of prostate cancer, there is no evidence that suggests that elevated levels of testosterone or testosterone treatment of hypogonadal men is associated with an increase in prostate cancer.^{7,8} A recent meta-analysis⁹ examined 51 placebo controlled trials of testosterone therapy. The conclusion was that, although the quality of the evidence was low to medium, “testosterone therapy had no significant effects on all-cause mortality, (or) prostatic ... outcomes...”

There have, however, been numerous reports of the effect of testosterone therapy resulting in an occult prostate carcinoma becoming clinically manifest^{10,11,12}. The possibility of “unmasking” an occult tumor with testosterone therapy is something that prescribers should be made aware of.

Reviewer’s comment: *The best evidence at this time is that, despite the known effects of testosterone on established prostate cancer, there is no evidence to suggest that there is a relationship between testosterone therapy and the development of prostate cancer.*

7.6.2 Human Reproduction and Pregnancy Data

Testosterone Gel ^{(b) (4)} is not intended for use by, and should not be used by pregnant or lactating women. Safety information is not available for use in pregnancy and lactation. The amount of applied testosterone that would appear in human milk is unknown. It is known that exposure of a fetus to androgens may result in varying degrees of virilization.

6 Glantz C. Cirrhosis and carcinoma of the prostate gland. J Urol 1964; 91: 291-3

7 Eaton NE, Reeves GK, Appleby PN et al. Endogenous sex hormones and prostate cancer: a quantitative review of prospective studies. Brit J of Cancer 1999; 80(7): 930-934.

8 Hsing AW, Comstock GW. Serological Precursors of Cancer: Serum Hormones and Risk of Subsequent Prostate Cancer. Cancer Epidemiology 1993; 2: 27-32.

9 Fernandez-Balsells M, Murad MH, Lane M et al. Adverse Effects of Testosterone Therapy in Adult Men: A Systematic Review and Meta-Analysis. J Clin Endo Metab. 2010; 96(6): 2560-2575.

10 Loughlin KR, and Richie JP: Prostate cancer after exogenous testosterone treatment for impotence. J Urol 157: 1845, 1997.

11 Morgenthaler A, Bruning CO III, and DeWolf WC: Incidence of occult prostate cancer in men with low total or free serum testosterone. JAMA 276: 1904–1906, 1996.

12 Curran MJ, and Bihrlle W. Dramatic rise in prostate-specific antigen after androgen replacement in a hypogonadal man with occult adenocarcinoma of the prostate. Urology 53: 423–424, 1999.

7.6.3 Pediatrics and Assessment of Effects on Growth

The safety and efficacy of Testosterone Gel (b) (4) in males <18 years old has not been established. Use in prepubertal males would have the potential to result in premature closure of the epiphyses. Testosterone Gel (b) (4) is not indicated for use in this population.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

There was no experience with overdosage in the development program for Testosterone Gel (b) (4). A non-clinical report¹³ of the effect of testosterone overdose in hamsters showed that, at high doses, testosterone causes central autonomic depression. There is testosterone overdose reported in the label of a testosterone gel, (AndroGel) – “There is one report of acute overdosage with use of an approved injectable testosterone product: this subject had serum testosterone levels of up to 11,400 ng/dL with a cerebrovascular accident.” This reviewer is unaware of any further details of this case. Treatment of overdosage would consist of discontinuation of testosterone treatment together with appropriate symptomatic and supportive care.

Androgenic steroids are drugs of abuse. They are taken in large quantities by athletes and others to increase performance, with negative health consequences. As a result, in 1991 testosterone and related androgenic steroids were declared controlled substances.

No information on testosterone withdrawal or rebound is available.

7.7 Additional Submissions / Safety Issues

There were no additional submissions or safety issues beyond those discussed earlier in this review.

8 Postmarket Experience

There is no postmarketing experience with this new product.

¹³ Peters KD, Wood RI. Androgen dependence in hamsters: overdose, tolerance, and potential opioidergic mechanisms. *Neuroscience* 130(4): 971-981. 2005

9 Appendices

9.1 Literature Review/References

None.

9.2 Labeling Recommendations

- The boxed warning that has been adopted by other topical testosterone products should be included in the testosterone gel label. This warning should discuss the potential for interpersonal transfer of testosterone and the consequences of that transfer.
- Dosing recommendations should be the same as those for the reference drug, Androgel.
- The label should indicate that testosterone gel is contraindicated in men with breast or prostate carcinoma. It should also include a contraindication for women who are, or may become, pregnant.
- The label should include warnings concerning the effects of testosterone on BPH, fertility, edema, gynecomastia and sleep apnea. Warnings concerning interpersonal transfer should be included. Methods of minimizing the risk of transfer such as hand and site washing, and covering the application site with clothing should be discussed.
- The potential for significant rise in red cell mass should be emphasized. In accordance with recent Endocrine Society Guidelines¹⁴, the label should discuss that appropriate monitoring would include a baseline measure of red cell mass such as hematocrit, and that the effect of the product on this should be assessed with a repeat measurement several months after the start of treatment.
- Because of the potential for an occult tumor becoming clinically apparent, discussed in section 7.6.1 Human Carcinogenicity, the label should advise evaluation for prostate carcinoma in appropriate individuals at baseline and 3-6 months after the start of therapy. This recommendation would be in accordance with the Endocrine Society's 2010 Guidelines regarding testosterone therapy.
- In accordance with current Division policy, the label should not include reference to secondary endpoints such as increased libido, less erectile dysfunction, etc.

¹⁴ Testosterone Therapy in Adult Men with Androgen Deficiency Syndromes: An Endocrine Society Clinical Practice Guideline. 2010.

Clinical Review
Donald McNellis, MD
NDA 203,098
Testosterone ^{(b) (4)} Gel (Perrigo Israel Pharma Ltd.)

9.3 Advisory Committee Meeting

No advisory committee meeting was held to discuss this product.

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

/s/

DONALD R MCNELLIS
01/30/2013

SURESH KAUL
01/30/2013

Acting Deputy Division Director Summary Review

Date	May 3, 2012
From	Audrey Gassman, MD
NDA #	203098
Applicant name	Perrigo Israel Pharmaceuticals, Ltd.
Date of submission receipt	July 5, 2011
PDUFA goal date	May 5, 2012
Proprietary name/established name	None/testosterone
Dosage form/strengths/presentations	Gel/ 25 mg and 50 mg testosterone in packets and 12.5 mg testosterone per actuation in a metered dose pump applied once daily
Proposed indication	Testosterone replacement therapy for adult men with either primary or secondary hypogonadism
Action	Complete Response

Material reviewed/consulted	Names of discipline reviewers
CDTL Review	Suresh Kaul, MD, MPH
Medical Officer Review	Donald McNellis, MD
Statistical Review	Kate Dwyer, PhD Mahboob Sobhan, PhD
Pharmacology/toxicology Review	Jeffrey Bray, PhD Lynnda Reid, PhD
Clinical Pharmacology Review	Li Li, PharmD, MS Myong-Jin Kim, PharmD
CMC Review	Rajiv Agarwal, PhD Moo Jhong Rhee, PhD
ONDQA Biopharmaceutics	Tapash Ghosh, PhD Angelica Dorantes, PhD
Controlled Substance Staff	James Tolliver, PhD Silvia Calderon, PhD Michael Klein, PhD
DRISK	Cynthia LaCivita, PharmD Claudia Manzo, Pharm D
OPDP	Jessica Cleck Derenick, PhD Jina Kwak, PharmD
OSI	Gopa Biswas, PhD Sam Haidar, PhD, RPh William Taylor, PhD, DABT

OND=Office of New Drugs

CDTL=Cross-Discipline Team Leader

ONDQA = Chemistry, Manufacturing and Controls - Office of New Drug Quality Assessment

DMEPA=Division of Medication Error Prevention and Analysis

DSI=Division of Scientific Investigations

DRISK=Division of Risk Management

OMPP = Office of Medical Policy Programs

OPDP=Office of Prescription Drug Promotion

OSI=Office of Scientific Investigations

- 1. Introduction**
- 2. Background**
- 3. CMC**
- 4. Nonclinical Pharmacology/Toxicology**
- 5. Clinical Pharmacology**
- 6. Clinical Microbiology**
- 7. Efficacy/Statistics**
- 8. Safety**
- 9. Advisory Committee Meeting**
- 10. Pediatrics**
- 11. Other Relevant Regulatory Issues**
- 12. Labeling**
- 13. Decision/Action/Risk Benefit Assessment**

1. Introduction

The Applicant, Perrigo Israel Pharmaceuticals Ltd., submitted an NDA (203-098) proposing a new testosterone transdermal product containing testosterone in a hydroalcoholic gel base for topical application. The indication for this new testosterone gel formulation is testosterone replacement therapy in males for conditions associated with a deficiency or absence of endogenous testosterone including both primary hypogonadism and hypogonadotropic hypogonadism. The goal of this testosterone therapy is to replace testosterone at serum levels within the normal physiologic range.

Multiple testosterone formulations have been previously approved for testosterone replacement therapy including patches, transdermal gels, a transdermal solution, a buccal tablet and parenteral injections. The Applicant's testosterone product will be supplied in 25 mg (2.5 gram of gel) and 50 mg (5 grams of gel) in aluminum foil packets and also in bottles with non-aerosol metered dose pumps (each pump delivers 12.5 mg of testosterone [1.25 grams of gel] per actuation). The recommended starting dose of testosterone gel is 5 g once daily (preferably in the morning) to clean, dry, intact skin of the shoulders and/or upper arms.

The skin transfer of topically applied testosterone gel products from patients to others (particularly children) has been recognized as a significant safety concern. This transfer issue was discussed at a Pediatric Advisory Committee meeting held on June 23, 2009. Currently, all topically applied testosterone products have been required to have a Boxed Warning, a Medication Guide, and a Risk Evaluation and Mitigation Strategy [REMS] to address this safety concern related to transfer. As this testosterone product is a topically applied testosterone, a Boxed Warning, a REMS, and a Medication Guide would be required as part of Approval to address the safety issue of interpersonal transfer.

The main objective of this NDA was to demonstrate bioequivalence of the proposed product to a reference listed drug (AndroGel 1%, hereafter referred to as AndroGel), and to demonstrate acceptable safety in the special safety studies (washing and transfer)

required by FDA. Demonstration of bioequivalence between the testosterone gel product and AndroGel was the basis of a clinical bridge necessary to establish the determination that the new testosterone gel formulation will be safe and effective in clinical use.

2. Background

The Applicant initially submitted an application to the Agency for testosterone gel in 2.5gm and 5 gm packets on June 15, 2007, [REDACTED] (b) (4). On September 26, 2007, the Office of Generic Drugs (OGD) sent a Refusal to Receive letter to the Applicant because an inactive ingredient (isosteric acid) had not been previously approved by the Agency at the specified level and therefore, could not be filed as an ANDA. The Applicant was asked to resubmit and provide examples of other topically applied products that contained the same concentration range of the inactive ingredient or, alternatively, provide information demonstrating that the inactive ingredients at the concentrations specified would not affect the safety of the proposed product.

The Applicant resubmitted a revised ANDA with the requested information, on November 19, 2007. On January 23, 2008, the Office of Generic Drugs (OGD) sent a Refusal to Receive letter to the Applicant stating that:

“Your proposed drug product contains inactive ingredients that are significantly different than those contained in the RLD Androgel. The Agency has concluded that additional information will be needed to demonstrate that your proposed product does not have the potential to cause greater skin irritation or sensitization than the RLD. Cumulative skin irritation and sensitization studies may provide sufficient information to address this issue.”

The Applicant performed the requested bioequivalence and skin irritation and sensitization studies and resubmitted [REDACTED] (b) (4). At that time they also submitted [REDACTED] (b) (4) for the new testosterone gel formulation in a multi dose pump configuration. These two applications were accepted for review by OGD on May 13, 2009, and May 20, 2009, respectively.

On August 28 and 29, 2009, the Applicant received deficiency letters requesting additional clinical safety studies to support regulatory approval of both [REDACTED] (b) (4). The deficiency for these ANDAs was explained as:

“CDER is concerned with the safety of transdermal testosterone gel products because of reports of significant adverse events resulting from unintentional transfer of testosterone from patients to young children and to female partners. We are unable to approve your abbreviated new drug application (ANDA). You have failed to provide data to show that your use of different inactive ingredients, [REDACTED] (b) (4), from those found in the reference listed drug (RLD) do not affect the safety or effectiveness of your proposed drug

product. See 21 CFR 314.94 (a) (9) (ii) and (a) (9) (v). We have determined that investigations such as clinical trials should be conducted to demonstrate that your inactive ingredients do not affect the safety and efficacy of your proposed drug product. Because these types of studies cannot be submitted in an ANDA, your ANDA cannot be approved. If you wish to pursue approval of your product, you are encouraged to contact the Division of Reproductive and Urologic Products in the Office of New Drugs.”

The Applicant subsequently opened IND 107,130 and also met with the Division of Reproductive and Urologic Products (DRUP) on May 19, 2010, to discuss the design of the necessary safety studies and plans for an NDA submission.

NDA 203-098 was submitted to DRUP July 4, 2011, with six clinical studies to confirm the safety and efficacy of the new testosterone gel formulation. The bioequivalence study (03-0415-001) was reviewed as the pivotal efficacy study comparing bioavailability of the proposed testosterone product to an RLD product (AndroGel 1%). The other five studies were considered supportive safety studies and included the following clinical studies: Skin sensitization (DS102308), Skin irritation (DS310208), Person-to-person testosterone transfer (M11U09001), Ability to Wash Gel from Hands (PRG-806) and Ability to Wash Gel from Application Site (PRG-806).

3. CMC

The proposed testosterone gel formulation is a clear colorless hydroalcoholic gel with the drug substance solubilized mostly in ethanol and other inactive ingredients to provide a stable gel dose form of the drug product. (b) (4) (carbomer) provide a convenient dispensing of the gel and sodium hydroxide is used (b) (4) of the formulation. All excipients, with the exception of isosteric acid, are USP/NF.

The product is packaged in two packaging configurations: 2.5g and 5g unit dose aluminum foil packets and bottles with non-aerosol metered-dose pumps (1.25 g gel per actuation).

- Packets: (b) (4)
(b) (4)
In the (b) (4) non-aerosol metered-dose pump, the drug product is filled in (b) (4). The inner layer of the pouch, which comes in contact with the drug product, is identical to the inner layer of the unit dose Aluminum foil packets. The packaging is suitable to package the hydroalcoholic drug product.
- Metered-dose pump: The pump can dispense 75 g of gel or 60 metered 1.25 g doses (net quantity of the gel is 88 gm). Before using the pump for the first time, the patient is advised to prime the pump by fully depressing the pump three times and discarding the gel. (b) (4)
(b) (4)

The CMC review team concluded in their review, dated March 6, 2012, that, “The applicant of the NDA has not provided sufficient information to assure the identity, strength, purity, and quality of the drug product. The Office of Compliance has made an overall “Acceptable” recommendation for the facilities involved in this application. Labels are satisfactorily finalized, but final labeling is pending. Therefore, from the ONDQA perspective, this NDA is not recommended for approval per 21 CFR 314.125(b)(1) and (6) in its present form until the issues delineated in the List of Deficiencies (p. 68) are satisfactorily resolved.”

In an addendum to the March, 2012, CMC review, the CMC review team stated on April 11, 2012, that, “This NDA is not recommended for approval from the ONDQA perspective in its present form per 21 CFR 314.125(b)(6) until the labeling issues are satisfactorily resolved.”

No postmarketing commitments or requirements were recommended by ONDQA.

In their review dated March 22, 2012, the Biopharmaceutics review team concluded that “From the Biopharmaceutics perspective NDA 203-098 for Testosterone Gel ^{(b) (4)} is recommended for approval.”

Comments:

- 1. I concur with the recommendations of the CMC and ONDQA Biopharmaceutics review teams that the outstanding issue from the CMC perspective would be labeling.*
- 2. The strength of the product was original expressed as testosterone gel ^{(b) (4)} however, to be consistent with recently marketed testosterone products, ONDQA, The Division of Medication Errors Prevention and Analysis (DMEPA) and the clinical review team agreed that the strength should be expressed in terms of the mg of testosterone - 25 mg and 50 mg testosterone per packet and 12.5 mg testosterone per actuation. Labeling and carton/container changes were implemented to reflect these recommendations. This will be implemented in labeling when the Applicant provides their Complete Response submission.*

3. Nonclinical Pharmacology/Toxicology

The pharmacology/toxicology review team stated that the applicant submitted no nonclinical information and relied on published studies of testosterone and FDA findings of efficacy and safety for AndroGel (testosterone gel 1%)/NDA 21-015 for Approval. The pharmacology/toxicology team concluded in their review dated January 30, 2012, that “Nonclinical data support Approval of testosterone gel ^{(b) (4)} for testosterone replacement in hypogonadal men.”

In addition, the pharmacology/toxicology review team also evaluated the label from a nonclinical perspective and concluded, “Class labeling is appropriate. No significant nonclinical labeling issues were identified nor are significant changes required.” (See review dated January 30, 2012).

Comment: I concur with the recommendations of the pharmacology/toxicology review team. There are no outstanding pharmacology/toxicology issues.

4. Clinical Pharmacology

The clinical pharmacology review team evaluated the clinical pharmacology data including the pharmacokinetic data provided from the pivotal bioequivalence trial (Study 03-0415-0010). The clinical pharmacology team concluded in their clinical pharmacology review dated May 1, 2012, that, “The Office of Clinical Pharmacology/ Division of Clinical Pharmacology 3 (OCP/DCP3) finds NDA 203098 not acceptable. The pivotal BE study results cannot be used to support the approval of proposed product (T gel (b) (4)) based on the findings of the Office of Scientific Investigations (OSI) following an audit of the study.”

The Clinical Pharmacology reviewer also stated that, “A study demonstrating the safety and efficacy of the proposed product needs to be conducted. This can be done by conducting a pivotal BE study using an approved T product as a RLD or a new clinical trial to assess the efficacy and safety of the proposed product. This should be submitted as a part of the NDA resubmission.”

Comment: I concur with the recommendations of the clinical pharmacology review team that the submitted pivotal bioequivalence study cannot be used to support approval

5. Clinical Microbiology

A Microbiology review was not conducted for this application.

6. Efficacy/Statistics

The principal study to support the efficacy of the Applicant’s proposed testosterone gel product that was submitted to the NDA is Study 03-0415-001. Because the Applicant demonstrated comparable exposure of their product to the approved comparator (AndroGel), efficacy for the Applicant’s testosterone product could be bridged to the efficacy data for AndroGel. The other submitted supportive studies (irritation/sensitization, hand/application site washing and interpersonal transfer) were considered safety-related and are briefly outlined in section 8 of this review.

Bioequivalence study 03-0415-001:

The pivotal study reviewed to determine efficacy of this testosterone gel was bioequivalence study 03-0415-001. The objective of Study 03-0415-001 was to compare the pharmacokinetics of (b) (4) testosterone gel (b) (4) formulation 1 (hereafter referred to as testosterone gel formulation 1) and (b) (4) testosterone gel (b) (4) formulation 2 (hereafter referred to as testosterone gel formulation 2) to the pharmacokinetics of AndroGel after a single dose in fasted, hypogonadal men with baseline testosterone levels less than 300 mg/dL. Study 03-0415-001 was a randomized,

single-dose, three-period, three-treatment crossover bioequivalence study. A total of 24 hypogonadal male subjects were enrolled and dosed in the study; all subjects completed the study. The trial was performed at a single site (b) (4) with samples from this study analyzed at a bioanalytic laboratory (b) (4).

In each period, subjects received a single 10 gm topical dose of one of the drug products, applied to the shoulder/upper arm. The three drug products studied were testosterone gel formulation 1, testosterone gel formulation 2, and AndroGel 1%. There was a one week washout period between each of the three drug applications. Blood samples were collected prior to drug application, immediately before drug application, and post-dose in each treatment period. The efficacy evaluation included the following pharmacokinetic parameters: AUC_{0-t} , $AUC_{0-\infty}$, C_{max} , T_{max} , K_{el} and $T_{1/2}$ for baseline uncorrected and baseline corrected testosterone. Bioequivalence would be determined based on the 90% confidence intervals on the geometric mean test-to-reference AUC_{0-t} and C_{max} ratios contained within the bioequivalence interval 0.80-1.25 using baseline corrected values. Adverse events, vital sign measurements, physical examination and laboratory evaluations were also collected and analyzed as safety parameters.

Efficacy assessment (Study 03-0415-001):

Two testosterone gel formulations were evaluated (testosterone gel formulation 1 and testosterone gel formulation 2). A testosterone formulation would be found to be bioequivalent to AndroGel if the 90% confidence intervals of the geometric mean test-to-reference AUC_{0-t} and C_{max} ratios were contained within the interval of 0.80 to 1.25. Statistical analyses were performed on the pharmacokinetic results in order to compare the two testosterone gel formulations to AndroGel, when each was administered as a single 10 gm topical dose to 24 hypogonadal males. Pharmacokinetic analyses were performed on the testosterone results after correcting for endogenous levels.

The Office of Scientific Investigation (OSI) conducted an investigation of the records of the clinical study from a record-archiving facility (b) (4) and also of the analytic portion which was conducted (b) (4). Form FDA 483 containing inspectional observations were issued at the end of both inspections. In a report issued on April 4, 2012, the OSI memo stated the following, "Following evaluation of the inspectional observations for clinical and analytical portions of study 03-0415-001, DBGC (the Division of Bioequivalence and GLP Compliance) recommends that:

1. The proper dosing of subjects during Period 3 cannot be assured. Data from Period 3 should be excluded from statistical evaluation.
2. The measured concentrations of plasma testosterone are not adjusted for the endogenous testosterone in blank plasma used to prepare calibrators and QCs.

On April 20, 2012, OSI provided a memo regarding the responses to the Form 483 observations that were issued for the clinical portions of the bioequivalence study. The OSI memo stated that, "...DBGC's recommendations remain same as provided earlier:

1. The proper dosing of subjects during Period 3 cannot be assured. Data from Period 3 should be excluded from statistical evaluation.
2. The measured concentrations of plasma testosterone are not adjusted for the endogenous testosterone in blank plasma used to prepare calibrators and QCs.”

In his review dated May 2, 2012, the Medical Officer concluded that, “An analysis of the results of the bioequivalence study, based upon the data submitted by the Sponsor, is given in Section 6.1. However, based upon an inspection of the clinical and analytic sites by the Office of Scientific Investigations, Division of Bioequivalence, it has been determined that the data for 16 of the 24 subjects included in the study is not reliable. See Section 4.5. It is this reviewer’s opinion that a reasonable conclusion of bioequivalence is not possible based upon the remaining eight subjects.”

In his review dated May 2, 2012, the CDTL review concluded that, “Based on the recommendation from OSI on clinical portion, we excluded the data from study period 3. As a result, the number of study subjects eligible for BE analysis changed from 24 to 8. The small sample size (N=8) of the BE study makes it unfeasible to do any meaningful statistical analysis from a BE perspective (see Clin Pharm review). Therefore, the sponsor should be asked to respond and correct the deficiencies as identified in Form 483’s or repeat the Bioequivalence study and resubmit the data for review.”

Statistical review:

On April 26, 2012, the statistical review team stated in their brief review memo that, “... no statistical review was necessary.”

In an addendum to the April, 2012, statistical review (also dated April 26, 2012), the statistical team stated that, “At the request of DRUP and DCP3, DBGC conducted inspections of the clinical and analytical portions of the bioequivalence study (BE): Study 03-0415-001 “A Randomized, Single-Dose, Three-Way Crossover Relative Bioavailability Study of Testosterone Gel Formulations in Hypogonadal Men”. A Form 483 was issued because there were no records for time or dosing of subjects for study period 3. DBGC recommend that data from study period 3 should be excluded from statistical evaluation. This results in sample size for the BE analysis changed from 24 to 8. Therefore, from a statistical perspective, bioequivalence of Testosterone gel (b) (4) to the reference listed drug AndroGel® cannot be established due to inadequate sample size.”

Comment: I concur with the conclusion of the Clinical Pharmacology review team, Medical Officer, CDTL and Division of Biometrics that there is an inadequate sample size from the clinical trial to determine bioequivalence. Therefore, there are insufficient data to base an approval for the proposed testosterone gel product.

In a final addendum dated May 2, 2012, the Division of Bioequivalence and GLP Compliance in the Office of Scientific Investigation stated the following:

“Following evaluation of the responses to Form FDA 483 observations for the analytical portion of study 03-0415-001, this DBGC reviewer’s recommendations remain the same as provided earlier:

1. The proper dosing of subjects [REDACTED] ^{(b) (4)} during Period 3 cannot be assured. Data from Period 3 should be excluded from statistical evaluation.
2. The measured concentrations of plasma testosterone in study samples have not yet been adjusted for endogenous testosterone levels from blank plasma samples used to prepare calibrators and QCs. The concentrations of calibration standards and QCs were adjusted with an extrapolated value (0.128 ng/mL) for endogenous testosterone derived from calibration lines in 25 analytical runs. This reviewer recommends adding the same 0.128 ng/mL concentration to study sample measurements.”

Comment: I concur with the conclusions of the Office of Scientific Investigation that there are outstanding deficiencies related to the Bioequivalence study that have not been adequately addressed. After exclusion of data from the Period in question, I agree with the Clinical Pharmacology and Clinical review teams that insufficient subjects remain to form an adequate clinical bridge to allow approval of this testosterone product.

Efficacy summary:

The main objective of the Applicant’s NDA submission was to demonstrate bioequivalence of their proposed testosterone gel product to the reference listed drug (RLD) AndroGel 1%. However, because of outstanding deficiencies in responses to Form 483s issued related to the pivotal clinical bioequivalence study, it is not possible to establish the necessary clinical bridge from this product to an approved testosterone gel product. Therefore, efficacy for this testosterone gel product cannot be established based on the clinical trial data submitted.

7. Safety

The safety data for this application are derived from one pivotal bioequivalence study (03-0415-001) and five supportive clinical studies that included: Skin sensitization (DS102308), Skin irritation (DS310208), Person-to-person testosterone transfer (M1IU09001), Ability to Wash Gel from Hands (PRG-806) and Ability to Wash Gel from Application Site (PRG-806).

Deaths, Serious Adverse Events and Discontinuations due to Adverse Events:

No deaths occurred in the 6 studies conducted for this NDA. No serious adverse events related to use of the testosterone drug product were reported in any of the studies conducted for this NDA.

Comment: The clinical reviewer and cross-discipline team leader concurred with the assessments of the SAEs and withdrawal as not related to the proposed product. I concur with their assessments.

Bioequivalence study – Study 03-0415-001

No deaths or SAEs related to the drug product reported during the clinical bioequivalence study.

Comment: However, as previously stated, because of concerns related to inspectional issues, further detailed clinical review of the adverse events in the bioequivalence study was not performed.

Skin Sensitization Study – Study DS102308

Study DS102308 was a randomized, single center, controlled, within-subject comparison study of the proposed testosterone gel to a comparator control product (AndroGel), the vehicle product, and controls under occlusive conditions, in a total of 226 healthy volunteers. The primary objective was to determine the potential of testosterone gel ^{(b) (4)} to cause sensitization by repeated topical application to the healthy skin of humans under controlled conditions. All subjects had areas of skin designated for the proposed testosterone product, the comparator control product (AndroGel), the vehicle product, and the control patches (i.e., sodium lauryl sulfate [SLS] 0.1% positive control and saline negative control) at randomly assigned, adjacent sites, for the purpose of determining sensitization potential.

To determine sensitization, a set of 5 patches were prepared by the clinical staff according to the randomization scheme. Patches contained 0.2 g of investigational product, 0.2 g of the comparator control product, 0.2 g of vehicle, 0.2 mL of the positive control and 0.2 mL of the negative control. The clinical staff applied the prepared patches to the appropriate test sites on the subject's infrascapular area of the back. Subjects were treated in three phases: an induction phase, a rest phase and a challenge phase as described below:

- The induction phase consisted of 9 applications of study materials and subsequent evaluation of the application sites for three weeks.
- A resting phase of 10-14 days occurred after the induction phase. During this period, no application of study medication occurred.
- The challenge phase consisted of subjects receiving identical patches on naïve sites for a total of 48 hours, These challenge sites were evaluated within 30 minutes of removal and again at 24, 48, and 72 hours following each patch removal.
- Subjects were rechallenged, if in the opinion of the investigator, there was any sign of contact sensitization.

Assessment of the patch sites was done 9 times during the induction phase, 4 times during the challenge and, if applicable, 4 times during the rechallenge. The 6-point integer grading scale (shown in the table below) was used to express the response observed at the time of examination.

Table 3: Skin Assessment Grading Scale

Score	Definition
0	No visible reaction
1	Minimal erythema, no sign of edema
2	Definite erythema with no significant edema
3	Moderate erythema with no significant edema
4	Moderate erythema with edema and/or papular response
5	Severe erythema, edema, epidermal damage or papulovesicular response

Source: Adapted from Table 6 of the Medical Officer's review dated May 2, 2012.

Two hundred three subjects (203) completed the challenge phase of the study and were included in the sensitization analysis. A summary of the repeated insult patch test responses during the induction phase is provided in the table below:

Table 4: Summary of Challenge Responses to Testosterone Gel (b) (4)

Response Score	Time following Challenge Patch Removal			
	0.5 hr	24 hr	48 hr	72 hr
0	196	187	194	197
1	5	12	5	5
2	2	3	3	1
3	0	1	1	0

Source: Adapted from Table 26 of the Medical Officer's review dated May 2, 2012

No reactions were reported for either the investigational product or the comparator product at challenge interpreted by the Applicant as a possible sensitization response, nor any that required rechallenge.

The Medical Officer evaluated the data from this study in his May 2, 2012, review and concluded that, "Study DS102308 provides evidence that there is no significant sensitization of the skin by Testosterone Gel (b) (4). It also provides support for the conclusions of Study DS310208 that Testosterone Gel (b) (4) does not have a significant likelihood of irritating the skin."

Comment: I concur with the Medical Officer's conclusions regarding skin sensitization.

Skin Irritation Study – Study DS310208

Study DS310208 was a randomized, single center, controlled, within subject comparison study of the proposed testosterone gel compared to a control product (AndroGel) that enrolled 38 healthy subjects. The primary objective of this study was to determine the irritation potential of the proposed testosterone gel on normal skin. All subjects had areas of skin designated for testosterone gel, comparator control product (AndroGel), the vehicle product, and the control patches (i.e., sodium lauryl sulfate [SLS] 0.2% positive control and saline negative control) at randomly assigned, adjacent sites, for the purpose of determining irritation potential. The investigational product, comparator product, the vehicle product, and the controls were applied occlusively to one side of the infrascapular area of the back. Evaluation of dermal reactions at the application sites were assessed

clinically using an ordinal scale that rated the degree of erythema, edema, and other signs of cutaneous irritation. A total of 21 patch applications were made over a period of 22 days.

Assessment of the patch sites was done 21 times during the study. The 6-point integer grading scale shown in the table below was used to express the response observed at the time of examination.

Table 5: Skin Assessment Grading Scale

Score	Definition
0	No visible reaction
1	Minimal erythema, no sign of edema
2	Definite erythema with no significant edema
3	Moderate erythema with no significant edema
4	Moderate erythema with edema and/or papular response
5	Severe erythema, edema, epidermal damage or papulovesicular response

Source: Adapted from Table 6 of the Medical Officer's review dated May 2, 2012.

The mean cumulative irritation scores from Study DS210208 are outlined below

Table 6: Mean Cumulative Irritation Scores

Product Tested	Mean Irritation Score	Testosterone Gel ^{(b) (4)}	AndroGel	Vehicle	Positive Control	Saline
Testosterone Gel	0.016	-	0.266	0.580	<0.001	0.747
AndroGel	0.090	-	-	0.575	<0.001	0.429
Vehicle	0.053	-	-	-	<0.001	0.818
Positive Control	2.824	-	-	-	-	<0.001
Saline	0.037	-	-	-	-	-

Source: Adapted from Table 28 of the Medical Officer's review dated May 2, 2012.

Based on the above cumulative irritation scores, the Applicant concluded that there was no evidence of significant irritation.

The Medical Officer reviewed the data from this study and concluded in his May 2, 2012, review that, "The Testosterone Gel ^{(b) (4)}, AndroGel, Vehicle, and Saline showed no evidence of significant irritation.

Comment: I concur with the Medical Officer's conclusions regarding skin irritation.

Residual Testosterone After Washing Study – Study PRG-806:

Study PRG-806 was an open-label, four-period study in 36 healthy adult male subjects. This study was designed to quantify and compare the amount of residual drug remaining on the hands and application site after a washing procedure that followed a single topical

dose of the proposed testosterone gel product (10 gm) and after a single topical dose of an approved comparator product (AndroGel). A total of 36 healthy male subjects applied a dose of each product to their hands and the arm/shoulder designated for drug application after appropriate preparation. Subsequently, study staff applied one of the testosterone gel formulations to the center area of the palm of one of the subject's hands. The subject then applied the dose to their opposite arm/shoulder.

Subjects followed their assigned hand residual removal procedure and had their hand wiped with three ethanol dampened gauze pads to obtain a residual hand sample for testosterone measurement. Finally, approximately 2 hours after the dose was applied, subjects followed their assigned arm/shoulder residual removal procedure and had their arm/shoulder wiped with three ethanol dampened gauze pads to obtain a residual application site sample for testosterone measurement. The gauze was retained for analytical quantification of recovered testosterone.

The residual hand gauze pads and residual application site gauze pads in each period were analyzed for testosterone. The results of washing of the hand and application site are outlined in the table below:

Table 7: Amount of Testosterone Recovered After Hand and Application Site Washing (Mean $\mu\text{g} \pm \text{SD}$)

Site	Recovery Without Wash	Recovery Following Wash
Hand	8478 \pm 3552	399 \pm 199
Application Site	28326 \pm 7627	5802 \pm 2770

Source: Adapted from Table 20 of the Medical Officer's review dated May 2, 2012

The clinical and clinical pharmacology review teams reviewed the results of the hand and application site washing study.

- The Clinical Pharmacology reviewer concluded (in a review dated May 1, 2012) that, "The results from T gel ^{(b) (4)} showed that hand washing removed 95.3% of recoverable T and showering procedure (2 hours after dose application) removed 79.5% of recoverable T from the arm/shoulder dosing area, indicating that washing hands with soap and water and a shower can sufficiently remove T gel ^{(b) (4)} from the hands and application sites."
- The Medical Officer concurred with the Clinical Pharmacology reviewer and stated in his review dated May 2, 2012, that, "This study has demonstrated that the product can be acceptably washed from the hands and from the application site. It provides the information necessary to properly label the product."

Comment: I concur with the clinical pharmacology and clinical review teams that there are sufficient data from hand and application site washing study to allow labeling of the proposed testosterone product.

Transfer Study – Study M1U09001:

Study M1U09001 was an open-label, single-dose, randomized, 4-period, 4- treatment crossover study that assessed the relative transfer of testosterone from a male, who had been treated with a single topical dose of the proposed testosterone gel, to a female partner. A total of 24 healthy male/female couples were enrolled in this study. Transfer was evaluated both when the male subject was wearing a T-shirt and without a T-shirt. The relative amounts of testosterone transfer from males to females with each treatment condition (with a T-shirt and without a T-shirt) for a comparator product was also assessed.

The key comparison in this study was systemic exposure to testosterone in women who had physical contact with men using the Applicant's testosterone gel with and without a T-shirt. Comparisons were also made for AndroGel with and without a T-shirt, as well as between Applicant's testosterone gel and AndroGel. The results of the transfer study for the Applicant's product are outlined in the table below:

Table 8: Maximal Testosterone Values seen in the 24-hr Period Following Contact

Subject	Maximal Total Testosterone (ng/dl)	
	With Shirt	Without Shirt
1	8.38	19.56
2	9.40	25.54
4	18.66	35.7
5	18.98	46.12
6	17.16	86.59
7	9.33	22.09
9	21.63	43.12
10	18.31	111.5
11	9.42	21.38
12	11.74	150.7
13	19.61	24.53
15	8.74	30.36
17	31.52	38.96
18	92.18	92.9
19	10.57	14.98
20	11.42	30.38
21	22.44	37.53
22	22.01	47.64
23	12.67	37.02
24	15.36	101.7
Mean	15.65*	51.0
Range	8.4 - 31.5*	15.0 - 150.7

*Excluding subject 18 who was determined to have an invalid result by the clinical review team

**Source: Adapted from Table 18 of the Medical Officer's review dated May 2, 2012.

Data from Study M1U09001 indicated that use of a clothing barrier resulted in a mean maximal increase from baseline testosterone level at any time during the 24 hours following contact of 0.043 ng/ml (4.3 ng/dl). This level compares to a mean maximal increase from baseline of 0.313 ng/ml (31.3 ng/dl) when contact occurs without the clothing barrier.

The Clinical Pharmacology review team stated in their review dated May 1, 2012 that, “The results of the study indicated that covering the application site with clothing barrier such as a t-shirt may significantly reduce the T transfer to others.” The Medical Officer also commented in his review dated May 2, 2012, that, “It is reasonable to conclude that a clothing barrier prevents clinically significant transfer of testosterone from a male treated with Testosterone Gel (b) (4) to an untreated female with whom he has direct contact.”

The CDTL reviewer concurred with the Clinical Pharmacology and Medical Officer and summarized his conclusions in his review dated May 2, 2012 that, “...Therefore, the results of the study indicated that covering the application site with clothing barrier such as a t-shirt may prevent the T transfer to others. Similar trend was observed for the RLD.”

Comment: I concur with the assessments of the clinical pharmacology, Medical Officer and CDTL reviewers that no new safety signals related to transfer to others were identified for this product and that clothing over the application site appears to mitigate the risk of transfer.

Safety summary:

The safety data from the special studies for this testosterone product, although limited, support that there is no evidence to suggest that the safety profile of this product would be substantially different from other topically applied testosterone gel products currently marketed. The known safety profile of these topically applied testosterone products can be adequately labeled. Finally, the concerns of interpersonal testosterone transfer in a gel formulation would be addressed through a Medication Guide-only Risk Evaluation and Mitigation Strategy (REMS). The REMS for this product would be similar to those for other topically applied testosterone products.

Comment: I concur with the recommendations of the primary medical officer reviewer and cross-discipline team leader that no new safety signals or trends, such as transfer to others, were identified based on the safety data submitted in to this NDA. However, because of inspectional concerns related to the pivotal bioequivalence study, no final determination of safety can be made with the available information.

8. Advisory Committee Meeting

Testosterone gel products have been approved for the US market since 2000 and other formulations of testosterone have been used for many years prior to that time. The safety issues associated with testosterone therapy are well known and can be adequately labeled.

No Advisory Committee was convened for this application as the deficiencies related to the conduct of the bioequivalence study.

9. Pediatrics

The Pediatric Research Equity Act (PREA) does not apply to this application as this NDA does not seek a new active ingredient, new indication, new dosage form, new dosing regimen, or new route of administration.

10. Other Relevant Regulatory Issues

Controlled Substance Staff:

The Controlled Substance Staff made labeling recommendations for sections 9.1, 9.2, and 9.3 of labeling in a review date April 9, 2012. These recommendations will be implemented when the Applicant resubmits this NDA submission.

Division of Risk Management (DRISK):

DRISK reviewed the Risk Evaluation and Mitigation Strategy (REMS) document and made recommendations in their review dated March 2, 2012. The recommendations will be implemented when the Applicant provides a Complete Response to the NDA submission.

Office of Prescription Drug Promotion (OPDP):

On April 23, 2012, OPDP was notified that final labeling negotiations would not be initiated during the current review cycle and a Complete Response letter would be issued. The OPDP review team stated that, "Therefore, OPDP will provide comments regarding labeling for this application during a subsequent review cycle. OPDP kindly requests that DRUP submit a new consult request during the subsequent review cycle."

Office of Scientific Investigations (OSI):

OSI audited the clinical and analytical portions of the pivotal bioequivalence study 03-0415-001. For additional details on the findings of these investigations, see section 6 above.

Division of Medication Error Prevention and Analysis (DMEPA):

The DMEPA review team was not required as labeling negotiations were precluded by identification of deficiencies in the pivotal bioequivalence study (See section 6 above).

Financial Disclosure:

The clinical review team did not identify any issues related to financial disclosures for these studies (See Medical Officer review dated May 2, 2012).

Study Endpoints and Labeling Development Team (SEALD):

The SEALD review was not required as labeling negotiations were precluded by identification of deficiencies in the pivotal bioequivalence study (See section 6 above).

11. Labeling

Labeling negotiations were precluded by identification of the serious deficiencies at the clinical and bioanalytic sites for the pivotal bioequivalence study (Study 03-0415-001) outlined above in section 6 above.

12. Decision/Action/Risk Benefit Assessment

Decision:

I agree with the cross-discipline team leader, primary medical officer, and the clinical pharmacology, CMC, and statistical reviewers that this testosterone gel product should receive a Complete Response action.

Risk Benefit Assessment:

The pharmacokinetic data from the pivotal phase 1 bioequivalence study (Study 03-0415-001) were designed to be “bridging data” to support the approval of this proposed testosterone gel product from an efficacy standpoint. Based on the conclusions of the OSI inspection, the CDTL, medical officer, and the clinical pharmacology and statistical reviewers believe that because of the outstanding inspectional issues, the submitted data were insufficient to determine efficacy and I agree.

It is also reasonable to conclude from the special safety studies, including the transfer study, submitted that no new safety signals or trends were identified. However, at this time, the submitted data do not adequately inform a risk/benefit evaluation for the Applicant’s testosterone gel.

Post-Marketing Requirement/Commitment and Risk Evaluation and Mitigation Strategies (REMS):

- A REMS to include a Medication Guide and assessment plan will be required when this product is approved. This is consistent with all currently marketed testosterone gels to mitigate the potential for drug transfer, primarily to children and women. The final REMS document from the Applicant was submitted on February 3, 2012.

- No postmarketing requirements or commitments were recommended by any of the review teams during this review cycle.

Comments on REMS requirement for this proposed testosterone gel product:

- *I concur with the decision that this testosterone gel product should have a class REMS containing a Medication Guide because of the known risk of secondary exposure with use of topical testosterone products. The Applicant will need to resubmit the Medication Guide-only REMS at the time of response to the Division's Complete Response action letter.*

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

/s/

AUDREY L GASSMAN
05/03/2012

Cross-Discipline Team Leader Review

Date	May 2, 2012
From	Suresh Kaul, MD, MPH
Subject	Cross-Discipline Team Leader Review
NDA#	203,098
Applicant	Perrigo Israel Pharma Ltd.
Date of Submission	July 4, 2011
PDUFA Goal Date	May 5, 2012
Proprietary Name / Established (USAN) names	Testosterone ^{(b) (4)} Gel
Dosage forms / Strength	Gel for Transdermal use
Proposed Indication(s)	Treatment of Male Hypogonadism
Recommended:	<i>Complete Response(CR)</i>

1. Introduction

The active moiety in the proposed product is testosterone. Testosterone therapy is available in the United States as several formulations, including: topical gels and solutions, transdermal patch, buccal patch, intramuscular injections and implanted pellets.

Testosterone is an endogenous androgen that is responsible for normal growth and development of the male sex organs and for maintenance of secondary sex characteristics. Testosterone has effects that include the growth and maturation of the prostate, seminal vesicles, penis, and scrotum; the development of male hair distribution, such as facial, pubic, chest, and axillary hair; laryngeal enlargement; vocal cord thickening; alterations in body musculature; and fat distribution.

Male hypogonadism results from insufficient secretion of testosterone and is characterized by low serum testosterone. Signs and symptoms reported to be associated with male hypogonadism include: erectile dysfunction, decreased sexual desire, fatigue, mood depression, regression of secondary sexual characteristics and osteoporosis.

Testosterone replacement therapy in men is chronic in nature and designed to improve clinical manifestations of low testosterone and also to place circulating levels of this important hormone into the normal physiological range for healthy men (~300 to ~1050ng/dL). These replacement therapies are ideally based on short term titration regimens that result in an optimal dose of product for a particular patient.

Male hypogonadism has historically been treated with testosterone replacement therapy via oral or parenteral routes to elevate serum testosterone levels into the normal range. Currently available treatment options for hypogonadism include intramuscular injections, subdermal implants, buccal systems, oral formulations, and transdermal patches and gels. The most commonly used formulations are the gels which are applied with the hands to the shoulders and upper arms and/or abdomen.

Product Information

Formulation

The sponsor’s gel formulation contains (b) (4) testosterone dissolved in ethanol. The formulation also contains (b) (4), Carbomer 980, and (b) (4), Isostearic Acid. All studies in support of this application were carried out using the original formulation of the product (with carbomer 940). (b) (4). The Perrigo Testosterone Gel (b) (4) was reformulated to contain Carbomer 980, which is the Carbomer used in Androgel. (b) (4). The Perrigo reformulation incorporated 67% ethanol (u) (4) in the initial formulation. Ethanol assists in the transport of testosterone into the skin. On skin, the ethanol quickly evaporates leaving a depot of testosterone which is further absorbed by the stratum corneum and dermis. From those sites it diffuses into the systemic circulation.

Product Formulations

	Androgel	Perrigo Original Formulation	Perrigo Commercial Formulation
Component	mg/g gel		
Testosterone USP	10.00	10.00	10.00
Isopropyl myristate	(b) (4)		
Isosteric Acid			
Alcohol (b) (4)			
Carbomer 940			
Carbomer 980			
(b) (4) NaOH			
NaOH			
Purified water			

Source: NDA 203098 Module 3.2 P1 and US Patent 6,503,894, Table 5.

This reformulation was discussed with the Division at the May 19, 2010 meeting. The formulation differences were not believed to require any new studies. Perrigo was allowed to complete their studies with the initial formulation.

CDTL Comment

There are two major differences between the initial formulation and the commercial formulation. The commercial formulation includes Carbomer 980 rather than Carbomer 940 and the amount of alcohol has been reduced from 69% to 67%. These formulation differences were discussed and agreed upon during the pre-NDA meeting between the Sponsor and the Division. It was concluded that these formulation differences are small enough and unlikely to affect the performance characteristics of the product. In my clinical opinion, it is a reasonable conclusion.

Currently approved medications for the treatment of Male Hypogonadism

Andoderm 2.5mg & 5mg, Androgel 1%, Androgel 1.62%, Testim 1%, Axiron, Fortesta, Testosterone Gel, Testopel, Striant and Testosterone injections.

2. Regulatory Background

The Sponsor initially submitted an application to the Agency for Testosterone (b) (4) Gel in 2.5gm and 5gm packets on June 15, 2007 (b) (4). On September 26, 2007, the Office of Generic Drugs (OGD) sent a Refusal to Receive letter to the Sponsor stating that:

The inactive ingredient isosteric acid in your proposed formulation for Testosterone Gel (b) (4) has not been previously approved by the Agency in a transdermal product at the specified levels. Therefore, the proposed drug product cannot be received as an ANDA. Please provide examples of approved drug products administered by the same route of administration which contain these inactive ingredients in the same concentration range or provide information demonstrating that these inactive ingredients at these concentrations do not affect the safety of the proposed drug product.

The Sponsor resubmitted the ANDA, with the requested information, on November 19, 2007. On January 23, 2008, the Office of Generic Drugs (OGD) sent a Refusal to Receive letter to the Sponsor stating that:

Your proposed drug product contains inactive ingredients that are significantly different than those contained in the RLD Androgel. The Agency has concluded that additional information will be needed to demonstrate that your proposed product does not have the potential to cause greater skin irritation or sensitization than the RLD. Cumulative skin irritation and sensitization studies may provide sufficient information to address this issue.

The Sponsor performed the requested studies and on November 27, 2008 and resubmitted (b) (4). At that time they also submitted (b) (4) for Testosterone (b) (4) Gel in a multi dose pump configuration. These applications were accepted for review by OGD on May 13, 2009 and May 20, 2009 respectively.

On August 28 and 29, 2009 the Sponsor received deficiency letters for both [REDACTED] (b) (4) [REDACTED]. The deficiency was explained as follows:

CDER is concerned with the safety of transdermal testosterone gel products because of reports of significant adverse events resulting from unintentional transfer of testosterone from patients to young children and to female partners. Therefore, we are unable to approve your abbreviated new drug application (ANDA). You have failed to provide data to show that your use of different inactive ingredients, including but not limited to the different penetration enhancers, from those found in the reference listed drug (RLD) do not affect the safety or effectiveness of your proposed drug product. See 21 CFR 314.94 (a) (9) (ii) and (a) (9) (v). We have determined that investigations such as clinical trials should be conducted to demonstrate that your inactive ingredients do not affect the safety and efficacy of your proposed drug product. Because these types of studies cannot be submitted in an ANDA, your ANDA cannot be approved. If you wish to pursue approval of your product, you are encouraged to contact the Division of Reproductive and Urologic Products in the Office of New Drugs.

The Sponsor then submitted IND 107,130 to the Division of Reproductive and Urologic Products and met with the Division on May 19, 2010 to discuss the design of the necessary transfer and washing studies and also to discuss their plans for an NDA submission. The Sponsor subsequently performed the requested studies and NDA 203098 was submitted to DRUP on July 4, 2011.

PRIMARY MEDICAL REVIEWER'S RECOMMENDATION FOR APPROVABILITY

The primary reviewer, Donald McNellis, MD, stated in his final review, dated April 26, 2011:

“Recommendation on Regulatory Action: From a clinical perspective, this reviewer recommends that Perrigo's, [REDACTED] (b) (4) testosterone transdermal gel receive a Complete Response (CR) for the indication of:

- *“Primary hypogonadism (congenital or acquired)” or*
- *“Hypogonadotropic or secondary hypogonadism (congenital or acquired)”.*

The Clinical Review Team and other disciplines through their reviews believe that the results from sensitization study, hand washing study, and transfer study included in this 505(b)(2) NDA submission are acceptable. The results of these studies demonstrate that Perrigo's [REDACTED] (b) (4) testosterone gel product is safe for the replacement of testosterone in hypogonadal men.

However, for efficacy, the bioequivalence study site inspection revealed failure to produce record of correct dosing for period 3 of crossover study resulting in an exclusion of the data from that period. As a result, the number of study subjects eligible for BE analysis changed from 24 to 8. The small sample size (N=8) of the BE study thus makes it unfeasible to do any meaningful statistical analysis for BE evaluation.

As for all topical testosterone gel products, a Black Box Warning and a Medication Guide addressing the potential for secondary exposure via skin transfer of testosterone to children have been included in labeling and are acceptable.”

CDTL Comment

Inspections of both clinical and analytical sites were conducted by the Division of Bioequivalence and GLP Compliance (DBGC)/OSI. Form 483 was issued to both sites for their deficiencies. These deficiencies were further discussed with the sponsor via a Teleconference after obtaining an authorization [REDACTED] (b) (4). One of the main deficiencies for the BE study site as identified by DBGC is as follows:

“Investigational drug disposition records are not adequate with respect to dates. Specifically, the drug administration records for Period 3 do not indicate the date and time at which the drug was administered”.

[REDACTED] (b) (4) Response to the above deficiency

The Firm stated that the current processes and protocols assure complete record retention.

Perrigo Response to the above deficiency

Perrigo stated that the dosing data were transcribed electronically into the CFR's. Perrigo also referred to “Protocol Deviations” in their response, which lists deviations for blood sampling times but none for dosing.

DBGC notes that the CRFs only indicate the scheduled dosing times, but not the actual blood sampling times, for all three periods. Documents to show dosing date and time during period 3, comparable to the records available for periods 1 and 2, have not been located. DBGC finds the transcribed CRFs insufficient to document dosing each subject with a specific product at a specific time during period 3.

DBGC Conclusions:

Following evaluation of the responses to Form FDA 483 observations for the clinical portions of study 03-0415-001, DBGC's recommendation remain same as provided earlier:

The proper dosing of subjects during Period 3 cannot be assured. Data from Period 3 should be excluded from statistical evaluation.

The measured concentrations of plasma testosterone have not yet been adjusted for endogenous testosterone in blank plasma used to prepare calibrators and QCs.

CDTL Recommendation

Therefore, in view of the above recommendation from the Division of Bioequivalence and GLP Compliance (DBGC), it is my opinion that a Complete Response (CR) action may be given to the sponsor at this time. The sponsor should be asked to respond and correct all the deficiencies as identified in Form 483's or alternatively repeat the Bioequivalence study and resubmit the data for review.

3. CMC/Device

The CMC review team, Rajiv Agarwal, Ph.D and Moo-Jhong Rhee, Ph.D made the following recommendation:

1. On March 22 and March 26th, 2012, the applicant provided adequate information on the final “drug product specification” including the new agreed upon acceptance criterion for IVRT. The stability data was also provided to justify the newly proposed 18 months of expiration dating period. Based on the provided information, 18 months of the expiration dating period can be granted.

All the CMC comments for the label have been incorporated, however the agency’s agreed upon label has not yet been sent to the applicant due to the issuance of Form 483’s for their BE study clinical and analytical site inspections and inability on the sponsor’s part to correct the deficiencies during this review cycle. Therefore, the CMC recommendation is “Not Approvable” until an agreed upon label is finalized with the sponsor.

CDTL Comment

I concur with CMC team’s recommendation.

4. Nonclinical Pharmacology/Toxicology

The Toxicology review team, Jeffrey D. Bray, Ph.D and Lynnda L.Reid, PH.D, made the following comments and recommendation:

“The applicant submitted no new nonclinical information, and is relying on published studies of testosterone and the FDA findings of safety and efficacy for AndroGel®, testosterone gel 1% (NDA 21-015) for Approval. The overall toxicological profile of testosterone is well established. Nonclinical toxicities are not relevant for Approval due to the preponderance of clinical data for testosterone that supersedes any nonclinical findings. Literature references and a scientific rationale for the reliance on literature were submitted to support the nonclinical sections of the Labeling. While the formulation is different than other FDA-approved testosterone gel products, the components are at or below the levels in other FDA-approved products.”

Recommendations

Approvability

Nonclinical data support **Approval** of testosterone gel ^{(b) (4)} for testosterone replacement in hypogonadal men.

Additional Non Clinical Recommendations

None.

Labeling

Class labeling is appropriate. No significant nonclinical labeling issues were identified nor are significant changes required.

CDTL Comment

I concur with the Pharm-Tox review team.

5. Clinical Pharmacology/Biopharmaceutics

A final review from the Clinical Pharmacology review team of Li Li, Ph.D and MJ Kim, Pharm. D was received on May 1, 2012.

Clinical Pharmacology review team made the following recommendation:

“The Office of Clinical Pharmacology (OCP)/Division of Clinical Pharmacology 3 (OCP/DCP-3) finds NDA 203098 not acceptable. The pivotal BE study results cannot be used to support the approval of proposed product (T gel) based on the findings of the Office of Scientific Investigations (OSI).”

“A study demonstrating the safety and efficacy of the proposed product needs to be conducted. This can be done by conducting a pivotal BE study using an approved T product as a RLD or a new clinical trial to assess the efficacy and safety of the proposed product. This should be submitted as a part of the NDA resubmission.”

Phase IV Requirement:

None

“Summary of Important Clinical Pharmacology Findings”, Clinical Pharmacology made the following key comments:

An inspection of clinical and bioanalytical sites of the pivotal BE study (Study 03-0415-0010) was conducted by Office of Scientific Investigations (OSI). Two major deficiencies were reported after inspection. 1) Clinical site: drug administration records for Period 3 did not indicate the date and time at which the drug was administered. Therefore, proper dosing of subjects during Period 3 cannot be assured. 2) Bioanalytical site: the measured concentrations of plasma T are not adjusted for the endogenous T in blank plasma used to prepare calibrators and quality control (QC) samples. Details of these OSI inspection findings can be found in Dr. Gopa Biswas’s OSI consult review and addendum dated April 2, 2012 and April 20, 2012, respectively, in DARRTS.

Based on the recommendation from OSI on clinical portion, we excluded the data from study period 3. As a result, the number of study subjects eligible for BE analysis changed from 24 to 8. The small sample size (N=8) of the BE study makes it unfeasible to do any meaningful statistical analysis for BE evaluation.

The Clinical-Pharmacology review team had the following review comments:

BE Study:

It should be noted that given the high intra-subject variability (30%, rough estimation) and small subjects numbers (N=24), statistic power of the BE Analysis is only about 57%.

Nonetheless, as the 90% CI for the geometric mean ratio (GMR) was contained within the BE limit of 80% to 125%, Formulation T06P033 is considered BE to the RLD. However, the site inspections conducted by OSI revealed missing drug administration record for period 3 of BE three way crossover study. As such, per OSI inspector Dr. Gopa Biswas proper dosing of subjects during Period 3 cannot be assured. Therefore, data from Period 3 should be excluded from statistical evaluation.

Transfer Study

The results from T Gel ^{(b) (4)} showed that unprotected female partners had a 136% and 250% increase from baseline for mean T AUC_{0-24hr} and C_{max}, respectively, after direct skin contact. In contrast, when a shirt covered the application site, female subjects had a 16% and 48% increase in AUC₀₋₂₄ and C_{max}, respectively, compared to baseline values, and the T concentrations remain within the normal range for female of 0- 90 ng/dL. Therefore, the results of the study indicated that covering the application site with clothing barrier such as a t-shirt may prevent the T transfer to others. Similar trend was observed for the RLD.

Hand-Washing Study

The study showed that hand washing removed 95.3% of recoverable T and showering procedure (2 hours after dose application) removed 79.5% of recoverable T from the arm/shoulder dosing area, indicating that washing hands with soap and water and a shower can sufficiently remove T Gel ^{(b) (4)} from the hands and application sites. Similar trend was observed for the RLD.

Drug-Drug Interactions

No new DDI studies were conducted with T Gel ^{(b) (4)}. The Sponsor is proposing to use the publically available information for the RLD for their product.

Specific Populations

- Pediatric use: No pediatric studies were conducted. An exemption for the pediatric study was granted.
- Geriatric use: No geriatric studies were conducted
- Renal or hepatic impairment: No studies were conducted in patients with renal or hepatic impairments
- Contraindicated for pregnant or breast feeding women
- Warnings and Precaution for children and women for secondary exposure

Bioanalytical Method Validation

Study samples were analyzed for total T concentration by validated bioanalytical methods.

- BE study: Gas Chromatography/Mass Spectrometry (GC/MS)
- Inter-personal transfer study: Liquid Chromatography with Tandem Mass Spectrometry (LC-MS/MS)
- Hand and application sites washing study: High performance liquid chromatography with ultraviolet detector (HPLC-UV).

CDTL Comment

I concur with the Clinical Pharmacology review team's comments and the recommendation.

6. Clinical Microbiology

Microbiology consult was not requested for this NDA. ONDQA offered neither objections nor concerns regarding the microbiological attributes of the proposed product.

7. Clinical/Statistical- Efficacy

The Sponsor has relied upon the FDA finding of safety and efficacy of Androgel in this 505(b)(2) application. The efficacy of Testosterone Gel (b) (4) was not evaluated in a clinical study. Rather, the efficacy of the Gel will be established by a study showing that it is bioequivalent to the reference listed drug, Androgel. Androgel has previously been shown to be an effective treatment for hypogonadal males. A study showing that Testosterone Gel (b) (4) provides equivalent blood levels of testosterone is a reasonable support for the conclusion that Testosterone Gel (b) (4) is also an effective treatment for this indication.

The primary study demonstrating the bioequivalence of Testosterone Gel to Androgel was **study 03-0415-001**.

Bioequivalence Trial – 03-0415-001

This was a single-dose, three-period, three-treatment, randomized crossover study to evaluate the pharmacokinetics of two Testosterone Gel formulations and the pharmacokinetics of the reference listed drug (AndroGel). It was carried out at a single site (b) (4) during September 2003. The samples obtained in this study were, after appropriate processing, shipped in a frozen state to the bioanalytic laboratory (b) (4) where analyses was performed in October 2003.

Study Design

This was an open label, randomized, single-dose, three-period, three-treatment crossover study in which hypogonadal men received three drug formulations in a crossover fashion. In each period, subjects received a single 10gm topical dose of one of the drug products, applied to the shoulder/upper arm. The three drug products studied were (b) (4) Testosterone Gel (b) (4) Formulation 1, (b) (4) Testosterone Gel (b) (4) Formulation 2, and AndroGel 1%.

A series of blood samples were obtained prior to drug application and extended for 72 hours following drug application. The samples were taken at -12, 0, 1, 2, 3, 4, 6, 8, 10, 12, 14, 17, 20, 24, 30, 36, 48, and 72 hours. Immediately after sampling, plasma was harvested and then frozen at -20°C. Frozen samples were sent to the central analytic laboratory in (b) (4) where they were assayed for total testosterone using a validated GC/MS method.

Subjects were randomized to receive the formulations in a random sequence. There was one week washout period between each of the three drug applications. Subjects were monitored for adverse events.

Study Drugs

The three drugs tested were identified in the study report as:

- Testosterone Gel (b) (4) Formulation 1, Batch T06P030, manufacture date 7/29/2003
- Testosterone Gel (b) (4) Formulation 2, Batch T06P033, manufacture date 7/30/2003
- Androgel 1%, Unimed Pharmaceuticals, Lot number 20325, expiration date 12/04

Study Endpoint

This was a study evaluating the bioavailability of two study drugs, Testosterone Gel (b) (4) Formulation 1 and Testosterone Gel (b) (4) Formulation 2, to the commercially available product AndroGel. The endpoint of the study was a comparison of the pharmacokinetics of each study drug to AndroGel over a 72 hour period following a single administration of each product.

Subject Disposition

All 24 subjects enrolled in the intent to treat population completed the study. All subjects provided 18 scheduled blood samples during each of the three study periods; there were no missing samples.

A total of forty-one samples were analyzed. Twelve of forty-one samples were reanalyzed to confirm the initial analysis. Fourteen were reanalyzed because of a poor initial chromatography or because of a destroyed initial sample. Fifteen were reanalyzed due to values that were greater than the upper limit of quantification during the first measurement.

Results

Statistical analyses were performed on the pharmacokinetic results in order to compare two (b) (4) Testosterone Gel formulations to AndroGel, when each was administered as a single 10 gm topical dose to 24 hypogonadal males.

Table 3 summarizes the results of the statistical analyses of the pharmacokinetic parameters for baseline corrected results for Testosterone Gel (b) (4) Formulation 1 and Androgel.

Table 3. Summary of Statistical Comparisons of Testosterone Gel ^{(b) (4)} Formulation 1 (Lot #T06P030) and AndroGel

Parameter	Least-Squares Mean		Ratio	90% Confidence Interval	
	Formulation 1	Androgel		Lower	Upper
AUC _{0-t} (ng-hr/ml)	101	96.9	1.044	0.895	1.194
C _{max} (ng/ml)	5.72	5.18	1.104	0.905	1.303
T _{max} (hour)	20.2	19.2	1.050	-	-
Ln-Transformed					
AUC _{0-t} (ng-hr/ml)	89.3	87.9	1.015	0.882	1.169
C _{max} (ng/ml)	5.11	4.82	1.061	0.885	1.273

Source: NDA 203098, Module 5.3.1.2.1, Study Report 03-0415-001, Statistical Report, Table 1.1

Table 4 summarizes the results of the statistical analyses of the pharmacokinetic parameters for baseline corrected results for Testosterone Gel ^{(b) (4)} Formulation 2 and AndroGel.

Table 4. Summary of Statistical Comparisons of Testosterone Gel ^{(b) (4)} Formulation 2 (Lot #T06P033) and AndroGel

Parameter	Least-Squares Mean		Ratio	90% Confidence Interval	
	Formulation 2	Androgel		Lower	Upper
AUC _{0-t} (ng-hr/ml)	101	96.9	1.044	0.894	1.193
C _{max} (ng/ml)	5.46	5.18	1.054	0.855	1.253
T _{max} (hour)	18.6	19.2	0.970	-	-
Ln-Transformed					
AUC _{0-t} (ng-hr/ml)	84.3	87.9	0.959	0.833	1.104
C _{max} (ng/ml)	4.65	4.82	0.965	0.805	1.158

Source: NDA 203098, Module 5.3.1.2.1, Study Report 03-0415-001, Statistical Report, Table 1.2

CDTL Comment: As discussed previously, the reformulated product is closer in composition to the reference drug Androgel than was Lot #T06P033. In my opinion, it is reasonable to conclude that the reformulated product is also bioequivalent to the reference drug.

Additional CDTL Comment

Although, Sponsor's formulation of Testosterone ^{(b) (4)} was determined to be bioequivalent to the reference drug Androgel, the inspection of the clinical site ^{(b) (4)} (conducted by Office of Scientific Investigations, OSI) failed to produce the records for Period 3 of the BE trial.

Therefore, the proper dosing of subjects during Period 3 cannot be assured according to OSI inspector Dr. Biswas. She further recommended that the data from Period 3 of the cross-over trial should be excluded from pharmacokinetic and statistical evaluation. I concur with the OSI recommendation as there are no subjects who would have completed PK profiles in three complete periods with all three drug products (two formulations and the reference drug, Androgel).

CDTL Recommendation

Therefore, in view of the above recommendation from the Division of Bioequivalence and GLP Compliance (DBGC), it is the opinion of this CDTL that a Complete Response (CR) action be given to the sponsor at this time. Sponsor should be asked to respond to the deficiencies as indicated in Form 483's or alternatively repeat the Bioequivalence study and resubmit the data for review.

Statistical Analyses

Statistical Analyses were performed using the General Linear Models (GLM) procedure of the SAS statistical program (PC version 6.12). The pharmacokinetic parameter estimates, as well as the concentrations at each scheduled sample time, were evaluated by analysis of variance. Hypothesis testing for treatment effects in the analysis was conducted at $\alpha= 0.05$.

The Statistical Reviewer Kate Dwyer, Ph.D and Mahboob Sobhan, Ph.D made the following comment and recommendation on April 25, 2012 and April 26, 2012:

“This 505(b) (2) submission is cross-referencing FDA’s previous findings of the safety and efficacy data on testosterone gel (b) (4) indicated for hypogonadal men. There was no new clinical efficacy data submitted in support of this submission. Therefore, no statistical review was necessary.”

Dr. Dwyer further added on April 26, 2012, “a Form 483 was issued after the inspection of the BE study site because there were no records obtained for time and dosing of subjects in study period 3. Also, DBGC recommended that data from study period 3 should be excluded from statistical evaluation. This results in sample size for the BE analysis to change from 24 to 8. As such, from a statistical perspective, bioequivalence of testosterone gel to the reference listed drug Androgel cannot be established due to inadequate sample size.”

CDTL Comment

I concur with the statistical review team.

8. Safety

Sponsors formulation of Testosterone Gel differs (b) (4) from the formulation of AndroGel, therefore, the Sponsor was asked to perform clinical studies evaluating areas of safety that could possibly be affected by the formulation difference. These studies were an evaluation of the potential to transfer testosterone from the skin of a patient to another individual by direct skin to skin contact, and an evaluation of the ability to wash the Gel from

the hands and application site after the drug is applied and an evaluation of the potential for irritation and sensitization of the skin.

Testosterone Transfer – Study M1IU09001

Study Objective

This study assessed the relative transfer of testosterone from a male, who had been treated with a single topical dose of 10g of Testosterone Gel (b) (4) to a female partner. The transfer was evaluated both when the subject was wearing a T-shirt and without a T-shirt. The relative amounts of testosterone transfer from males to females with each treatment condition (with a T-shirt and without a T-shirt) for a comparator product was also assessed.

Study Design

This was an open-label, single-dose, randomized, four-period, four-treatment crossover study. The total duration of the study, screening to the end of the study, was approximately 12 weeks with at least a 7-day washout period between doses. Female subjects reported to the clinical site at least 48 hours prior to contact with the treated male subjects. The female subjects were required to stay for 26 hours after dosing of the male subjects (i.e. 24 hours after male and female contact). Male subjects reported to the clinical site at least 20 hours prior to dosing and were required to stay for at least 4 hours after dosing. Blood samples were collected from female subjects on the day prior to contact at 0, 2, 4, 6, 8, 10, 12, 16 and 24 hours. These sampling times were relative to the time of male and female contact on Day 1 in such a way that the pre-contact blood sampling schedule on Day -1 was performed at the same clock times as the post-contact blood sampling schedule on Day 1.

The testosterone gel product was applied to the male subject's arm/shoulder area. Skin contact occurred two hours after application of the gel. In two of the four study phases contact occurred directly between skin-to-skin. In the other two phases the subject's application site was covered with a T-shirt and contact was between the skin of the female's arm and the shirt overlying the subject's application site. Female subjects had one arm/shoulder designated as the "contact site" and were instructed to rub their upper arm and shoulder up and down the treated upper arm/shoulder of their male partner during a 15 minute contact period.

Following contact, blood samples were collected from female subjects immediately prior to contact (0 hour) and after contact at 2, 4, 6, 8, 10, 12, 16 and 24 hours. One single blood sample was collected to represent both the Day -1, 24 hour sample and the Day 1, 0 hour sample. A total of 17 blood samples were collected from the female subjects per study period for a total of 68 samples or 408 mL total volume. There were no samples taken from the male subjects.

Serum testosterone concentrations were measured using a validated bioanalytical method according to the bioanalytical laboratory's SOPs and FDA guidance's. The validated detection range for total testosterone in females is approximately 0.05 to 50 ng/mL in human serum.

Study Results

Table 5 shows the mean AUC and C_{MAX} for total testosterone in the female partners following contact with a male partner who had applied the proposed testosterone gel.

Table 5. AUC and C_{MAX} For Total Testosterone in Female Partners for 24 Hour Period Following Contact With a Male Partner Who Had Applied the proposed testosterone gel

(b) (4)

Parameter	Observed Values		Baseline corrected Values	
	Without Shirt	With Shirt	Without Shirt	With Shirt
AUC _{0-t} (ng-hr/ml)	6.108	2.992	3.289	0.322
C _{MAX} (ng/ml)	0.411	0.159	0.260	0.047

Source: NDA 203098, Module 5.3.5.4.1, Table 11.4.2-1, page 35 and Table 11.4.2-2, page 36.

Table 6. shows the observed values as a percentage of the baseline values.

Table 6. AUC and C_{MAX} For Total Testosterone in Female Partners for 24 Hour Period Following Contact With a Male Partner Who Had Applied the proposed testosterone gel as Percent of Baseline Value

Parameter	Observed Values as % of Baseline Value	
	Without Shirt	With Shirt
AUC _{0-t} (ng-hr/ml)	209%	112%
C _{MAX} (ng/ml)	272%	142%

Source: Medical Officer Calculation based on values shown in Table 13.

Table 7 shows the mean serum testosterone levels for the female partners during the 24 hours following contact with the male partner. Both actual observed values and baseline corrected values are presented.

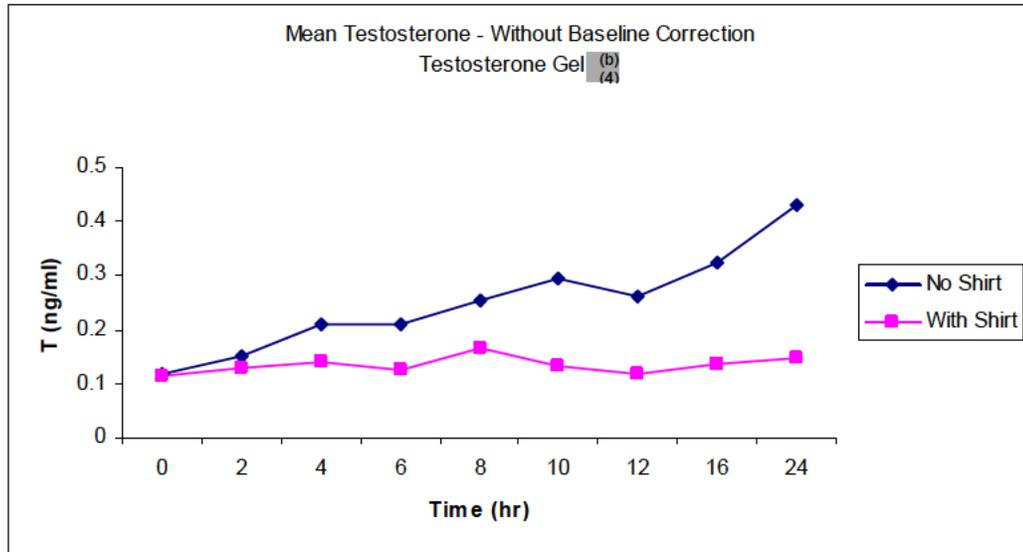
Table 7. Mean Testosterone Levels Following Contact with a Male Partner Who Had Applied the proposed testosterone gel

Time after contact (hr)	Observed Values (ng/ml)		Baseline corrected Values (ng/ml)	
	Without Shirt	With Shirt	Without Shirt	With Shirt
0	0.118	0.115	0.003	0.002
2	0.151	0.128	0.035	0.010
4	0.208	0.140	0.094	0.023
6	0.209	0.126	0.090	0.009
8	0.253	0.164	0.130	0.043
10	0.294	0.132	0.185	0.026
12	0.261	0.117	0.146	0.011
16	0.324	0.136	0.192	0.011
24	0.431	0.149	0.313	0.034

Source: Reviewer analysis of NDA 203098, Module 5.3.5.4.25.2.1, Datasets Final Export V3 Unadjusted, Final Export V2 Baseline Adjusted B vs A.

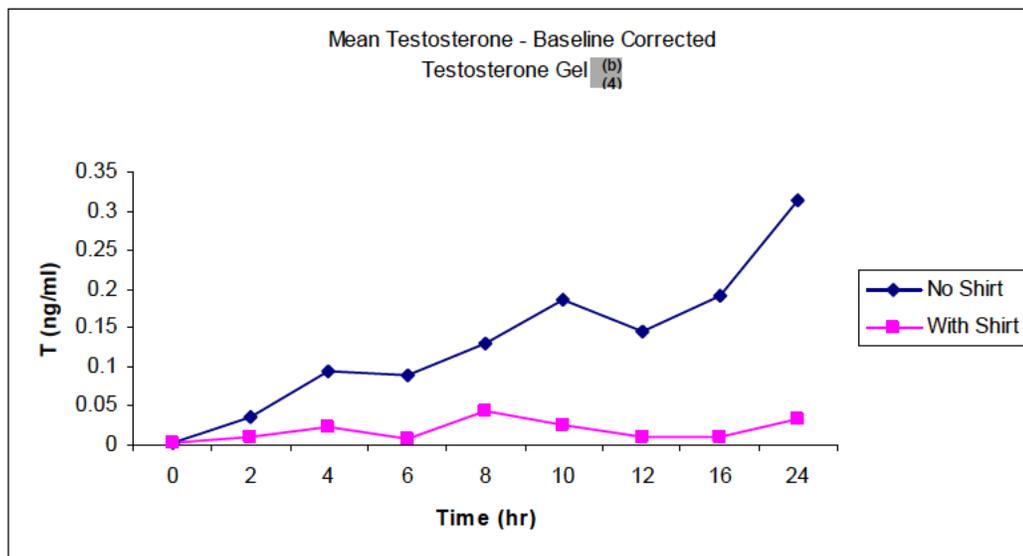
This information is displayed graphically in Figure 1 and Figure 2.

Figure 1. Mean Testosterone Levels Following Contact with a Male Who Had Applied Testosterone Gel (b) (4) - Observed Values



Source: Reviewer analysis of NDA 203098, Module 5.3.5.4.25.2.1, Datasets Final Export V3 Unadjusted, Final Export V2 Baseline Adjusted B vs A.

Figure 2. Mean Testosterone Levels Following Contact with a Male Who Had Applied Testosterone Gel (b) (4) - Baseline Corrected Values



Source: Reviewer analysis of NDA 203098, Module 5.3.5.4.25.2.1, Datasets Final Export V3 Unadjusted, Final Export V2 Baseline Adjusted B vs A.

CDTL Comment: The objective of this study was to evaluate the ability of a clothing barrier to prevent testosterone transfer from a testosterone treated patient to another individual with

whom he has direct contact. The study shows that, with a clothing barrier, the mean maximal increase from baseline testosterone level at any time during the 24 hours following contact is 0.043 ng/ml (4.3 ng/dl). This compares to a mean maximal increase from baseline of 0.313 ng/ml (31.3 ng/dl) when contact occurs without the clothing barrier.

In summary, there is a clinically meaningful reduction in the transfer of testosterone from person to person, when a clothing barrier is present. However, transfer is not eliminated completely by the barrier as has been reported with many other testosterone gel products.

Residual Testosterone after Washing – Study PRG-806

This was a study to evaluate the residual amount of topically delivered Testosterone Gel ^{(b) (4)} present on normal skin of the hand, arm, and shoulder in healthy adult male subjects following washing procedures.

Study Objective

To quantify and compare the amount of residual testosterone remaining on the hands and arm/shoulder before and after the hand and application site washing that followed a single topical dose (10 g of gel for a total of 100 mg testosterone) of Testosterone Gel ^{(b) (4)}. This was also assessed for the comparator product for information only.

Study Design

This was an open-label, four-period, pivotal study, in healthy adult male subjects.

Subjects entered the clinic on study day 1 of each period and washed their hands and the arm/shoulder designated for drug application. Then, the hand and arm/shoulder designated for drug application were wiped with three ethanol dampened gauze (blank control sample). Subsequently, study staff applied a 10 gram dose (2 × 5-gram packets) of one of the testosterone gel formulations to the center area of the palm of one of the subject's hands. The subject then applied the dose to their opposite arm/shoulder.

Subjects followed their assigned hand residual removal procedure and had their hand wiped with three ethanol dampened gauze pads to obtain a residual hand sample for testosterone measurement. Approximately 2 hours after the dose was applied, subjects followed their assigned arm/shoulder residual removal procedure and had their arm/shoulder wiped with three ethanol dampened gauze pads to obtain a residual application site sample for testosterone measurement. The gauze was retained for analytical quantification of recovered testosterone.

Subjects followed study exit procedures, showering to remove any residual dose of drug that remained on the skin (hands and application arm/shoulder).

The residual removal procedure for two (2) of the periods (one following the Perrigo formulation application, the other following the AndroGel application), was to wipe the dosed hand immediately following dosing and the arm/shoulder application site two (2) hours after dose application. The residual removal procedure in the remaining two (2) periods was to wash

the hands and shower after dose application but before collection of the residual hand and residual arm/shoulder application site samples.

The residual hand gauze pads and residual application site gauze pads in each period were analyzed for testosterone.

CDTL Comment: The study design was acceptable.

Drug Concentration Measurements

The residual hand gauze pads and residual application site gauze pads in each period were analyzed for testosterone. The quantification of testosterone present in the gauze was measured using extraction and liquid chromatography analytical methods developed for these samples, and according to the Analytical Laboratory’s Standard Operating Procedures and FDA Guidelines as applicable.

Study Results

This study quantified the amount of drug remaining on the hands and arm/shoulder after a hand and application site wash and compared this amount to the amount present before washing.

Application sites were sampled in three pre-defined application areas. Dose was 100 mg of testosterone applied as 10 grams of Testosterone Gel formulation. Table 8 shows the recovered testosterone, both from the hands and the application site. The percentage recovery is shown in Table 9.

Table 8. Amount of Testosterone Recovered After Hand and Application Site Washing (Mean µg ± SD)

Site	Recovery Without Wash	Recovery Following Wash
Hand	8478 ± 3552	399 ± 199
Application Site	28326 ± 7627	5802 ± 2770

Source: NDA 203098, Module 5.3.5.4.1, Table 11.4.7-1

Table 9. Testosterone Recovered After Hand and Application Site Washing (Percent of Applied Dose)

Site	Recovery Without Wash	Recovery Following Wash	Reduction in Recovery following Wash
Hand	8.48 ± 3.55	0.4 ± 0.2	95.3 %
Application Site	28.33 ± 7.63	5.8 ± 2.8	79.5 %

Source: NDA 203098, Module 5.3.5.4.1, Table 11.4.7-2

CDTL Comment

This study demonstrated that the wash-off from the hands (approximately 95%) differs from the wash-off from the shoulder/upper arm application site (approximately 80%). A larger

portion of the product is washed from the hands shortly after it has been applied and then the rest can be removed from the application site two hours after application. Two factors potentially contribute to this difference.

First, the two hour time difference between the hand washing and the site washing allows a greater portion of the applied dose to penetrate the epithelium where soap and water washing would be less likely to remove it, but some of it could still be recovered by ethanol-impregnated sponges used in the recovery process. This explains about the smaller fraction remaining on the hands as compared to the application site.

Secondly, the washing effort used to remove the product from the hands is quite localized to the site of interest (the hands) whereas the washing effort during the shower is directed at the entire body rather than merely at the site of interest (the shoulder/upper arm). Therefore the amount of effort used in washing the actual site of interest is likely to be greater with the hand washing as compared to the site washing.

The Sponsor included a comparator arm in the study that evaluated the wash-off of the reference listed drug AndroGel 1% from both the hands and the application site. Results from AndroGel treatment showed that the wash-off of the RLD was similar to the wash-off of the Testosterone Gel, both from the hands (AndroGel 95.3%, Testosterone Gel (b) (4) 95.3%) and from the application site (AndroGel 75.9%, Testosterone Gel (b) (4) 79.5%).

Conclusion

In my opinion, this study has demonstrated that the proposed testosterone drug product can be acceptably washed from the hands and from the application site. It provides the information necessary to properly label the product.

Skin Sensitization Study (DS102308)

This was a study to evaluate the sensitizing potential of Testosterone Gel on normal skin.

The primary objective of this study was to determine the potential of testosterone gel to cause sensitization by repeated topical application to the healthy skin of humans under controlled conditions.

Study Subjects

Two hundred twenty-six subjects were enrolled in the study and two hundred and three completed it.

Study Design

A set of 5 patches were prepared by the clinical staff according to the randomization scheme. Patches contained 0.2 g of investigational product, 0.2 g of the comparator control product, 0.2 g of vehicle, 0.2 mL of the positive control and 0.2 mL of the negative control. The clinical staff applied the prepared patches to the appropriate test sites on the subject's infrascapular area of the back. The choice of left or right side was made by the clinical staff based on a visual inspection of skin clarity and was recorded on the CRF to ensure consistent placement

of the patches at subsequent visits. The distance between the patches was approximately ¾ inch. The numbering of the test sites remained the same throughout the study. To be considered a completed case, a subject had 9 applications of the study material and no fewer than 8 subsequent readings during induction and 1 application followed by all subsequent readings during challenge. Only completed cases were used to assess Sensitization.

A subject was rechallenged to any of the study materials if in the opinion of the Investigator, there was any sign suggestive of contact sensitization (erythema and/or papulation) which was observed at any of the evaluations following the removal of the challenge patch, ie, within 30 minutes of removal or at 24, 48, or 72 hours following patch removal.

Local Tolerability Assessments

Assessment of the patch sites was done 9 times during the induction phase, 4 times during the challenge and, if applicable, 4 times during the rechallenge. The 6-point integer grading scale was used to express the response observed at the time of examination.

Results – Dermal Sensitization

Two hundred three subjects (203) completed the challenge phase of the study and were included in the sensitization analysis. A summary of the repeated insult patch test responses during the induction phase is provided in Table 10.

Table 10. Mean Cumulative Irritation Scores During Induction Phase

Product Tested	Mean Irritation Score	P value vs				
		Testosterone Gel ^{(b) (4)}	Androgel	Vehicle	Positive Control	Saline
Testosterone Gel ^{(b) (4)}	0.169	-	0.345	0.070	<0.001	0.005
Androgel	0.141	-	-	0.385	<0.001	0.066
Vehicle	0.117	-	-	-	<0.001	0.333
Positive Control	0.586	-	-	-	-	<0.001
Saline	0.089	-	-	-	-	-

Source: NDA 203098, Module 5.3.5.4.1,

The responses to challenge following the induction phase are shown in Table 11.

Table 11. Summary of Challenge Responses to Testosterone Gel ^{(b) (4)}

Response Score	Time following Challenge Patch Removal			
	0.5 hr	24 hr	48 hr	72 hr
0	196	187	194	197
1	5	12	5	5

2	2	3	3	1
3	0	1	1	0

Source: NDA 203098, Module 5.3.5.4.1, Table 11-1, page 32

CDTL Comment

There was one subject, who exhibited minimal to definite erythema (scores of 1 and 2) during induction to both the investigational product and the AndroGel®, and exhibited moderate erythema with no significant edema (score of 3) to both products 24 and 48 hour after challenge patch removal. There was another subject, who exhibited definite to moderate erythema with no significant edema (scores of 2 and 3) during induction at the vehicle site and exhibited moderate erythema with no edema (score of 3) at 24 and 48 hours after challenge patch removal. Both subjects had reactions that decreased to definite erythema (score of 2) by the 72-hour challenge evaluation. With the exception of these 2 subjects, there was no more than minimal erythema observed (score of 1) at the 72-hour challenge evaluation for the testosterone gel, AndroGel®, Vehicle and 0.1% SLS aqueous solution. No reactions were observed at the 72-hour challenge evaluation for the saline.

In summary, from a clinical perspective, there were no reactions to either the investigational product or the comparator product at challenge indicative of a possible sensitization response, nor any that required rechallenge.

Therefore, study DS102308 provides evidence that there is no significant sensitization of the skin by the proposed testosterone Gel. It also provides support for the conclusion that the proposed testosterone gel does not have a significant likelihood of irritating the skin with chronic use.

Skin Irritation Study (DS310208)

This was a 21 Day, randomized, controlled study to evaluate the irritation potential of Testosterone Gel on normal skin of healthy volunteers using cumulative irritant patch test design.

Study Subjects

Thirty-eight subjects were enrolled into the study and thirty-three completed it. Four subjects withdrew the consent for the study. One subject withdrew from the study because of an adverse event, a knee injury, which was unrelated to the investigational product.

The investigational product, comparator product, the vehicle product, and the controls were applied occlusively to one side of the infrascapular area of the back. Evaluation of dermal reactions at the application sites were assessed clinically using an ordinal scale that rated the degree of erythema, edema, and other signs of cutaneous irritation.

Study Design

This was a randomized, single center, controlled, within-subject comparison study of Testosterone gel, the comparator control product (AndroGel [testosterone gel] 1%), the vehicle product, and controls under occlusive conditions, in healthy volunteers. All subjects had areas

of skin designated for Testosterone gel, comparator control product (AndroGel [testosterone] 1%), the vehicle product, and the control patches (ie, sodium lauryl sulfate [SLS] 0.2% positive control and saline negative control) at randomly assigned, adjacent sites, for the purpose of determining irritation potential.

The investigational product, comparator product, the vehicle product, and the controls were applied to one side of the infrascapular area of the back. Evaluation of dermal reactions at the application sites were assessed clinically using an ordinal scale that rated the degree of erythema, edema, and other signs of cutaneous irritation.

Irritancy Assessments

Assessment of the patch sites was done 21 times during the study. The 6-point integer grading scale used to express the response observed at the time of examination.

Results

Table 12 shows the mean cumulative irritation scores for the proposed testosterone gel (b) (4) and for the AndroGel, vehicle, positive control and saline comparators.

Table 12. Mean Cumulative Irritation Scores

Product Tested	Mean Irritation Score	P value vs				
		Testosterone Gel (b) (4)	Androgel	Vehicle	Positive Control	Saline
Testosterone Gel (b) (4)	0.016	-	0.266	0.580	<0.001	0.747
Androgel	0.090	-	-	0.575	<0.001	0.429
Vehicle	0.053	-	-	-	<0.001	0.818
Positive Control	2.824	-	-	-	-	<0.001
Saline	0.037	-	-	-	-	-

Source: NDA 203098, Module 5.3.5.4.1,

CDTL Comment

The proposed testosterone gel, AndroGel, Vehicle, and Saline showed no evidence of significant irritation. Testosterone gel subjects had a mean cumulative irritation scores of 0.016, AndroGel subjects had a mean score of 0.090, Vehicle treated subjects had a mean score of 0.053 and the Saline treated subjects had a score of 0.037. No statistically significant difference was reported between the testosterone gel, AndroGel, Vehicle and Saline treated groups. All products were statistically significantly less irritating than the SLS 0.2% positive control group (P<.001), which had a mean cumulative irritation score of 2.824.

Adverse Events

There were a total of 21 adverse events reported in 15 subjects. Ten subjects discontinued medication because of an adverse event. Table 13 shows a list of the adverse events reported.

Table 13. Adverse Events Reported in Study DS102308

Event	Number	Drug Related
Headache	12	Possible
Phlebitis	1	Unrelated
Diarrhea	1	Possible
Flea Bites	1	Unlikely
Chest Pain	1	Unlikely
Priapism	1	Possible
Dyspnea	1	Possible
Insomnia	1	Possible
Discolored penis	1	Possible
Breast tenderness	1	Probable

There was one serious adverse event reported in this study. The SAE was an episode of phlebitis of the right calf. The patient was hospitalized for the initiation of anti-coagulation. The SAE was reported as resolved.

CDTL Comment: The adverse events reported above do not suggest any events from this product different from those reported with other approved testosterone gel products.

Overall Assessment of Safety Findings

Based on the results of the interpersonal transferability study, the hand washing study, and skin sensitization study, Perrigo's testosterone gel demonstrated acceptable safety.

9. Advisory Committee Meeting

No advisory committee meeting was held to discuss this product. Safety concerns associated with topical testosterone therapy are well known, and no additional outside expertise was necessary to make an approvability determination for this product.

10. Pediatrics

The Applicant stated that a request for waiver of pediatric studies is not applicable, as this NDA does not seek a new active ingredient, new indication, new dosage form, new dosing regimen, or new route of administration. This is consistent with guidance that the Division has received previously from PeRC for other testosterone gel products.

11. Other Relevant Regulatory Issues

The Division of Clinical Pharmacology had requested both clinical site inspection (b) (4) and the analytical site inspection (b) (4).

Clinical and Analytical site Inspections

1. Clinical site (b) (4)

Inspection date (b) (4)

Results: Form 483 was issued for having no records for time or dosing of subject for study period 3 (Observation 3). There were other deficiencies listed in the Form 483 that were considered as minor by the DSI inspector, Dr. Biswas, but still needed to be corrected.

Bioequivalence and GLP compliance Branch Comments from the Site Inspection:

Investigational drug disposition records are not adequate with respect to dates. Specifically, the drug administration records for Period 3 do not indicate the date and time at which the drug was administered. Therefore, execution of drug administration for period 3 is missing.

Dr. Gopa Biswas from OSI had the following comments:

Due to the lack of documentation of date, time, and the product administered to each subject, the administration of study drug products during Period 3 cannot be assured. Therefore, OSI is of the opinion that data from Period 3 are not reliable, and the data should be excluded from consideration. This will lead to incomplete subject blocks in the study design, with no subjects that received all three drugs. The clinical reviewer should further evaluate the impact of exclusion of data.

(b) (4) responded to Form 483 with the following comment specific to Observation 3: Although, this study was not conducted under current (b) (4) processes, the following processes in place within our operations are designed to prevent such occurrence for studies we conduct.

- (b) (4) clinical operations use a Clinical Trial Management System (CTMS) and/or paper to record clinical raw data.
- In accordance with our current SOP, the CTMS and/or paper documents are adequately prepared to ensure that all required information related to the administration of investigational drugs/co-medications can be adequately recorded. The CTMS automatically records the actual time of any clinical tasks once it is complete in the system.

CDTL Comment

Although, (b) (4) has responded to Form 483 in a timely manner, it does not address the specific deficiencies as identified by the inspector from OSI. This was conveyed to the sponsor via a Teleconference on April 1, 2012 during a discussion related to inspection site deficiencies.

2. Analytical site (b) (4)

Inspection date: (b) (4)

Inspection Site: (b) (4)

Inspection Results: (b) (4) did not have any of the electronic chromatographic data or the audit trails for Testosterone Gel study (NDA 203098). Therefore, there is no way of determining that they are the true representation of the original data as acquired from the first analysis or original analysis. Additionally, the measured concentrations of plasma testosterone are not adjusted for the endogenous testosterone in blank plasma used to prepare calibrators and QC's.

Dr. Biswas's Conclusion of Inspection findings:

Following evaluation of the inspectional observations for clinical and analytical portions of study 03-0415-001, DBGC recommends that:

1. The proper dosing of subjects during Period 3 cannot be assured. Data from Period 3 should be excluded from statistical evaluation.
2. The measured concentrations of plasma testosterone in the study samples have not been adjusted for the endogenous testosterone in blank plasma used to prepare calibrators and QCs.

Dr. Biswas, the OSI inspector made the following recommendation after receiving the response for Form 483 from (b) (4) site:

The concentration of calibration standards and Qc's were adgusted with an extrapolated value (0.128ng/mL) for endogenous testosterone derived from calibration lines in 25 analytical runs. Therefore, OSI recommends adding the same 0.128ng/mL concentration to the study sample measurements.

CDTL Comment

Therefore, in view of the above recommendation from the Division of Bioequivalence and GLP Compliance (DBGC), it is the opinion of this CDTL that a Complete Response (CR) action may be granted to the sponsor at this time. Sponsor should be asked to respond and correct the deficiencies as identified in Form 483's or repeat the Bioequivalence study and resubmit the data for review.

Controlled Substances Staff (CSS)

In their final review of the NDA, CSS confirmed that Testosterone gel is in Schedule III of the Controlled Substances Act (not the Anabolic Steroids Control Act). CSS also provided specific recommendations for revisions to Section 9 of the proposed label (Drug Abuse and Dependence). The revisions include information that anabolic steroids, such as testosterone, are abused. CSS stated that while drug dependence has not be documented in individuals using therapeutic doses for approved indications, dependence has been observed in some individuals using high doses of anabolic steroids.

The CSS recommendations were implemented.

12. Labeling

Although, this is a 505(b)2 application, approvability determination required that the proposed testosterone gel product be bioequivalent to the reference related drug (RLD) Androgel 1%, the clinical reviewer Dr. Donald McNellis recommended updating the clinical section of the label with the BE study data and safety section with the Transfer, Hand and Application site washing data and Skin Sensitization and Irritation data respectively. These and other recommended changes were incorporated into a substantially completed label. However, final labeling could not be completed because of outstanding OSI findings (See section 11)

13. Recommendations/Risk Benefit Assessment

Recommendation

From a clinical perspective, Testosterone Gel for transdermal use should receive a Complete Response (CR) action for the indication of “hypogonadism” in adult males.

This recommendation is based on failure of the applicant to produce proper dosing records for Period 3 of bioequivalence (BE) study identified by the Division of Bioequivalence and GLP Compliance (DBGC)/OSI.

The recommendation by OSI was based on an inspection of clinical and bioanalytical sites of the pivotal BE study (Study 03-0415-0010) was conducted by Office of Scientific Investigations (OSI). Two major deficiencies were reported after inspection. 1) Clinical site: drug administration records for Period 3 did not indicate the date and time at which the drug was administered. Therefore, proper dosing of subjects during Period 3 cannot be assured and as such, data from Period 3 should be excluded from statistical evaluation. 2) Bioanalytical site: the measured concentrations of plasma T are not adjusted for the endogenous T in blank plasma used to prepare calibrators and quality control (QC) samples. Details of these OSI inspection findings can be found in Dr. Gopa Biswas’s OSI consult review and addendum dated April 2, 2012 and April 20, 2012, respectively, in DARRTS.

*Based on the recommendation from OSI on clinical portion, we excluded the data from study period 3. As a result, the number of study subjects eligible for BE analysis changed from 24 to 8. The small sample size (N=8) of the BE study makes it **unfeasible** to do any meaningful statistical analysis from a BE perspective (see Clin Pharm review) . Therefore, the sponsor should be asked to respond and correct the deficiencies as identified in Form 483’s or repeat the Bioequivalence study and resubmit the data for review.*

Risk Benefit Assessment

It is not possible to perform a risk-benefit assessment for this product because of issues identified by OSI. Failure to produce proper dosing records of subjects for Period 3 of bioequivalence (BE) study (b) (4) as identified by the Division of Bioequivalence and GLP Compliance (DBGC)/OSI during the most recent inspection

Despite the concerns related to the bioequivalence study, the proposed testosterone gel product was shown in the safety studies (Transfer, Washing of Hands and Application site and Skin sensitization) to be reasonably safe for its intended use from a clinical perspective. The pattern of general adverse events for this testosterone gel product was reasonable and trends are likely to be similar to other drugs in the class. The most common adverse events (seen in >2% of subjects) for drugs in this class are: application site erythema and irritation, nasopharyngitis, increase in hematocrit, headache, diarrhea and vomiting, which is similar in profile to other approved testosterone products.

The potential for transferring testosterone to another individual by direct contact was evaluated in a clinical study by the Sponsor. This evaluation showed that skin-to-skin contact resulted in transfer of testosterone to the female partner. The 24 hour AUC of testosterone in the partner following contact was approximately twice the baseline level. However, a clothing barrier was shown to be effective in preventing clinically significant transfer. The AUC of testosterone in the female partner following contact through a clothing barrier was approximately 12% greater than the baseline level, which is acceptable from a clinical perspective.

The ability to wash the product from the skin was also evaluated in a clinical study. This study showed that approximately 5% of the applied testosterone remained on the skin of the hands following washing the hands with soap and water. Following showering, approximately 20% of the applied testosterone remained at the application site. This finding is similar to that for other testosterone products, and is therefore acceptable.

In summary, I conclude that the information submitted by the Sponsor was adequate to allow the reasonable conclusion that the proposed testosterone gel would be safe for treatment of men with primary or secondary hypogonadism. However, the risk-benefit profile cannot be assessed until the sponsor responds to the deficiencies as identified in Form 483's by the OSI inspector or performs a repeat bioequivalence study (BE). Therefore, I recommend that this application receive a complete response action.

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/s/

SURESH KAUL
05/02/2012

AUDREY L GASSMAN
05/02/2012

CLINICAL REVIEW

Application Type NDA, 505(b)(2)
Application Number(s) 203,098
Priority or Standard Standard

Submit Date(s) July 4, 2011
Received Date(s) July 5, 2011
PDUFA Goal Date May 5, 2012
Division / Office Division of Reproductive and
Urologic Products

Reviewer Name(s) Donald McNellis, MD
Review Completion Date April 26, 2012

Established Name Testosterone Gel
(Proposed) Trade Name None
Therapeutic Class Testosterone replacement
Applicant Perrigo Israel Pharma Ltd.

Formulation(s) Gel for transdermal use
Dosing Regimen Once daily
Indication(s) Male hypogonadism
Intended Population(s) Males ≥ 18 years of age with
hypogonadism

Template Version: March 6, 2009

Table of Contents

1	RECOMMENDATIONS/RISK BENEFIT ASSESSMENT	3
1.1	Recommendation on Regulatory Action	3
1.2	Risk Benefit Assessment.....	3
1.3	Recommendations for Postmarket Risk Evaluation and Mitigation Strategies ...	4
1.4	Recommendations for Postmarket Requirements and Commitments	4
2	INTRODUCTION AND REGULATORY BACKGROUND	4
2.1	Product Information	4
2.2	Tables of Currently Available Treatments for Proposed Indications	5
2.3	Availability of Proposed Active Ingredient in the United States	6
2.4	Important Safety Issues With Consideration to Related Drugs.....	7
2.5	Summary of Presubmission Regulatory Activity Related to Submission	7
2.6	Other Relevant Background Information	8
3.1	Submission Quality and Integrity	9
3.2	Compliance with Good Clinical Practices	10
3.3	Financial Disclosures.....	10
4	SIGNIFICANT EFFICACY/SAFETY ISSUES RELATED TO OTHER REVIEW DISCIPLINES	10
4.1	Chemistry Manufacturing and Controls	10
4.2	Clinical Microbiology.....	10
4.3	Preclinical Pharmacology/Toxicology	11
4.4	Clinical Pharmacology.....	11
4.4.1	Mechanism of Action	11
4.5	Office of Scientific Investigations	11
5	SOURCES OF CLINICAL DATA.....	12
5.1	Tables of Studies/Clinical Trials	12
5.2	Review Strategy	13
5.3	Discussion of Individual Studies/Clinical Trials.....	14
5.3.1	Bioequivalence Trial – 03-0415-001.....	14
5.3.2	Skin Sensitization Study - DS102308.....	16
5.3.3	Skin Irritation Study – DS310208	20
5.3.4	Residual Testosterone After Washing – Study PRG-806	23
5.3.5	Testosterone Transfer – Study M1IU09001	26
6	REVIEW OF BIOEQUIVALENCE.....	29
6.1	Bioequivalence Study.....	29
6.1.1	GCP and GLP Certification	29
6.1.2	Demographics.....	29
6.1.3	Subject Disposition.....	30
6.1.4	Pharmacokinetic Procedures	31

6.1.5	Statistical Analyses	31
6.1.6	Results	31
6.1.7	Bioequivalence Conclusions	32
7	REVIEW OF SAFETY	33
7.1	Methods.....	33
7.1.1	Studies/Clinical Trials Used to Evaluate Safety	33
7.2	Adequacy of Safety Assessments	34
7.3	Major Safety Results	35
7.3.1	Deaths.....	35
7.3.2	Nonfatal Serious Adverse Events	35
7.4	Supportive Safety Results	35
7.4.5	Special Safety Studies/Clinical Trials	35
7.4.5.1	A Study of Person-to-Person Testosterone Transfer (Study M1IU09001).....	35
7.4.5.2	A Study of Washing Testosterone from Hands and Application Site (Study PRG-806).....	42
7.4.5.3	Skin Sensitization Study (DS102308)	44
7.4.5.4	Skin Irritation Study (DS310208).....	47
7.4.6	Immunogenicity	48
7.5	Other Safety Explorations.....	48
7.5.1	Dose Dependency for Adverse Events	48
7.5.2	Time Dependency for Adverse Events.....	48
7.5.3	Drug-Demographic Interactions	49
7.5.4	Drug-Disease Interactions.....	49
7.5.5	Drug-Drug Interactions.....	49
7.6	Additional Safety Evaluations	49
7.6.1	Human Carcinogenicity	49
7.6.2	Human Reproduction and Pregnancy Data.....	50
7.6.3	Pediatrics and Assessment of Effects on Growth	51
7.6.4	Overdose, Drug Abuse Potential, Withdrawal and Rebound.....	51
7.7	Additional Submissions / Safety Issues	51
8	POSTMARKET EXPERIENCE.....	51
9	APPENDICES.....	52
9.1	Literature Review/References	52
9.2	Labeling Recommendations	52
9.3	Advisory Committee Meeting.....	52
9.4	Office of Scientific Investigations Report of Bioequivalence Site Inspections	52
9.5	Office of Scientific Investigations Addendum Report of Bioequivalence Site Inspections	67

Table of Tables

Table 1. Currently Approved Medications for the Treatment of Male Hypogonadism	5
Table 2. Product Formulations	9
Table 3. Studies Supporting the Application.....	12
Table 4. Safety Studies Required.....	13
Table 5. Composition of Formulation 2, Batch T06P033	15
Table 6. Skin Assessment Grading Scale	19
Table 7. Skin Assessment Grading Scale	21
Table 8. Baseline Demographics for the Intent-to-Treat Population.....	30
Table 9. Summary of Statistical Comparisons of Testosterone Gel (b) (4) Formulation 1 (Lot #T06P030) and Androgel.....	32
Table 10. Summary of Statistical Comparisons of Testosterone Gel (b) (4) Formulation 2 (Lot #T06P033) and Androgel.....	32
Table 11. Studies Performed to Evaluate Formulation-Dependent Safety	34
Table 12. Discontinuations from Study M11U09001	36
Table 13. Subject Demographics – Study M11U09001	36
Table 14. AUC and C _{MAX} For Total Testosterone in Female Partners for 24 Hour Period Following Contact With a Male Partner Who Had Applied Testosterone Gel (b) (4)	37
Table 15. AUC and C _{MAX} For Total Testosterone in Female Partners for 24 Hour Period Following Contact With a Male Partner Who Had Applied Testosterone Gel (b) (4) as Percent of Baseline Value.....	37
Table 16. Mean Testosterone Levels Following Contact with a Male Partner Who Had Applied Testosterone Gel (b) (4)	37
Table 17. Maximum Increase in Baseline Corrected Serum Testosterone and AUC for each Subject Following contact with Male Partner Who Had Applied Testosterone Gel (b) (4)	39
Table 18. Maximal Testosterone Values seen in the 24-hr Period Following Contact...	39
Table 19. Demographics of the Washing-Study Analysis Population.....	42
Table 20. Amount of Testosterone Recovered After Hand and Application Site Washing (Mean µg ± SD)	43
Table 21. Testosterone Recovered After Hand and Application Site Washing (Percent of Applied Dose)	43
Table 22. Study DS102308 Subject Disposition.....	44
Table 23. Demographic Summary of Population.....	45
Table 24. Adverse Events Reported in Study DS102308.....	45
Table 25. Mean Cumulative Irritation Scores During Induction Phase	46
Table 26. Summary of Challenge Responses to Testosterone Gel (b) (4)	46
Table 27. Demographics of Study DS310208 Population	47
Table 28. Mean Cumulative Irritation Scores	48

Table of Figures

Figure 1. Mean Testosterone Levels Following Contact with a Male Who Had Applied Testosterone Gel (b) (4) - Observed Values.....	38
Figure 2. Mean Testosterone Levels Following Contact with a Male Who Had Applied Testosterone Gel (b) (4) - Baseline Corrected Values.....	38
Figure 3. Subject 18 Serum Testosterone Levels For 24 Hours Following Contact	41

1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

From a clinical perspective, Testosterone Gel for transdermal use should receive a Complete Response action for the indication of “hypogonadism” in adult males.

This recommendation is based on failure of the applicant to produce proper dosing records for Period 3 of their pivotal bioequivalence study as identified by the Division of Bioequivalence and GLP Compliance of the Office of Scientific Investigations. The failure to produce these records results in an inability to rely upon data from this Period of the study. Therefore, reliable data for establishing bioequivalence is only available for eight subjects. In this reviewer’s opinion, it is unfeasible to do a meaningful statistical analysis of bioequivalence based on this cohort of subjects.

1.2 Risk Benefit Assessment

A comprehensive review of NDA 203,098 was carried out. Because of the inability of the Sponsor to provide complete records of dosing for their bioequivalence study, upon which the Sponsor was relying for a demonstration of efficacy, this NDA submission has not provided substantial evidence that the Sponsor’s testosterone gel is bioequivalent to an approved testosterone gel. This lack of demonstration of bioequivalence prevents the reasonable conclusion that Testosterone Gel will have the effect the Sponsor wishes to claim in labeling. This claim is that this gel is an effective treatment for men with hypogonadism.

The potential for transferring testosterone to another individual by direct contact was evaluated in a clinical study by the Sponsor. This evaluation showed that skin-to-skin contact resulted in significant transfer of testosterone to the female partner. The 24 hour AUC of testosterone in the partner following contact was approximately twice the baseline level. However, a clothing barrier was shown to be effective in preventing clinically significant transfer. The AUC of testosterone in the female partner following contact utilizing a clothing barrier was approximately 12% greater than the baseline level.

The ability to wash the product from the skin was also evaluated in a clinical study. This study showed that approximately 5% of the applied testosterone remained on the skin of the hands following washing the hands with soap and water. Following showering, approximately 20% of the applied testosterone remained at the application site.

In summary, the information that has been submitted by the Sponsor is inadequate to allow the reasonable conclusion that Testosterone Gel is bioequivalent to an approved testosterone gel. Therefore, a Complete Response action is recommended. The sponsor should be asked to correct the deficiencies as identified in Form 483's or repeat the bioequivalence study and resubmit the data for review.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

It is premature to consider postmarket requirements at this time.

1.4 Recommendations for Postmarket Requirements and Commitments

No postmarketing requirement and/or commitments are recommended.

2 Introduction and Regulatory Background

2.1 Product Information

Testosterone is an endogenous androgen that is responsible for normal growth and development of the male sex organs and for maintenance of secondary sex characteristics. Testosterone has effects that include the growth and maturation of the prostate, seminal vesicles, penis, and scrotum; the development of male hair distribution, such as facial, pubic, chest, and axillary hair; laryngeal enlargement; vocal cord thickening; alterations in body musculature; and fat distribution. Male hypogonadism results from insufficient production of testosterone and is characterized by low serum testosterone concentrations. Symptoms associated with male hypogonadism include decreased sexual desire with or without impotence, fatigue and loss of energy, mood depression, regression of secondary sexual characteristics, and osteoporosis.

The 2010 Endocrine Society guidelines suggest that the diagnosis of testosterone deficiency in adult men should be based on a comprehensive review of patient symptoms and signs, and measurement of serum testosterone levels by a reliable assay. The exact prevalence of androgen deficiency in men is not known. Although serum total and free testosterone concentrations decline in men with advancing age, the significance of age-related decline in testosterone concentration is incompletely understood.

Testosterone replacement therapy in men is chronic in nature and designed to improve clinical manifestations of low testosterone and also to place circulating levels of this important hormone into the normal physiological range for healthy men (~300 to ~1050

ng/dL). These replacement therapies are ideally based on short term titration regimens that result in an optimal dose of product for a particular patient.

Male hypogonadism has historically been treated with testosterone replacement therapy via oral or parenteral routes to elevate serum testosterone levels into the normal range. Currently available treatment options for hypogonadism include intramuscular injections, subdermal implants, buccal systems, oral formulations, and transdermal patches and gels. The most commonly used formulations are the gels which are applied with the hands to the shoulders and upper arms and/or abdomen.

The gel formulation which is the subject of this review contains (b) (4) testosterone dissolved in ethanol. The formulation also contains (b) (4) Carbomer 980, and (b) (4) Isostearic Acid. The product is packaged in two packaging configurations: 2.5g and 5g unit dose aluminum foil packets and bottles with non-aerosol metered-dose pumps. The product is applied by placing the desired dose of gel onto the palm of the hand and then rubbing the gel onto the skin of the shoulder and upper arm.

The ethanol assists in the transport of testosterone into the skin. On the skin, the ethanol quickly evaporates leaving a depot of testosterone which is further absorbed by the stratum corneum and dermis. From those sites it diffuses into the systemic circulation.

2.2 Tables of Currently Available Treatments for Proposed Indications

Table 1. Currently Approved Medications for the Treatment of Male Hypogonadism

Trade Name	Dose	Sponsor	Route of Administration	NDA Number	Date of Approval
Androderm	2.5mg & 5mg	Watson Labs	Transdermal Patch	20,489	September 29, 1995
AndroGel 1%	1.25gm, 2.5gm & 5 gm	Unimed Pharma	Transdermal gel	21,015	February 28, 2000
AndroGel 1.62%	40.5 mg starting dose	Abbott Products	Transdermal gel	22,309	April 29, 2011
Testim 1%	5gm	Auxilium Pharma	Transdermal gel	21,454	October 31, 2002
Axiron	60mg starting dose	Eli Lilly	Transdermal solution	22,504	November 23, 2010
Fortesta	40mg starting	Endo Pharma	Transdermal gel	21,463	December 29, 2010

Trade Name	Dose*	Sponsor	Route of Administration	NDA Number	Date of Approval
	dose				
Testosterone Gel	50 mg starting dose	TEVA	Transdermal gel	202,763	February 14, 2012
Testopel	75mg	Slate Pharma	Pellet for implantation	ANDA 80,911	Prior to January 1, 1982
Striant	30mg	Columbia Labs	Extended Release tablet, buccal	21,543	June 19, 2003
Testosterone cypionate	200mg/ml	Paddock	Injection	ANDA 40,530	January 31, 2005
Depo-Testosterone	100 & 200mg/ml	Pharmacia & Upjohn	Injection	ANDA 85,635	Prior to January 1, 1982
Testosterone cypionate	100 & 200mg/ml	Sandoz	Injection	ANDA 40,615	August 10, 2006
Testosterone cypionate	200mg/ml	Synerx Pharma	Injection	ANDA 40,652	December 11, 2006
Testosterone cypionate	200mg/ml	Watson Labs	Injection	ANDA 86,030	Prior to January 1, 1982
Delatestryl	200mg/ml	Endo Pharma	Injection	9,165	Prior to January 1, 1982
Testosterone enanthate	200mg/ml	Paddock	Injection	ANDA 40,575	June 14, 2006
Testosterone enanthate	200mg/ml	Synerx Pharma	Injection	ANDA 40,647	October 5, 2009
Testosterone enanthate	200mg/ml	Watson Labs	Injection	ANDA 85,598	Prior to January 1, 1982

* Androgel 1% and Testim 1% doses are given as amount of gel, other products' doses are given as amount of testosterone.

2.3 Availability of Proposed Active Ingredient in the United States

Testosterone is currently available in the United States as a buccal tablet, a subcutaneous implant, a transdermal patch, a transdermal gel, a transdermal solution and a parenteral injection.

2.4 Important Safety Issues With Consideration to Related Drugs

Labeled risks of testosterone administration in hypogonadal men include erythrocytosis, induction or exacerbation of sleep apnea, breast tenderness or enlargement, liver toxicity, and acne. Two major areas of concern in older men with aging-associated decline in serum testosterone are the effects of long-term testosterone administration on the risks of prostate cancer and progression of atherosclerotic heart disease.

Transdermal testosterone preparations, which are applied to the skin, have been associated with secondary exposure of testosterone in women and children via direct skin to skin transference. The exposed women and children have experienced significant clinical sequela which prompted the FDA to mandate a Boxed Warning for all transdermal testosterone products.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

The Sponsor initially submitted an application to the Agency for Testosterone (b) (4) Gel in 2.5gm and 5 gm packets on June 15, 2007 (b) (4). On September 26, 2007, the Office of Generic Drugs (OGD) sent a Refusal to Receive letter to the Sponsor stating that:

The inactive ingredient isosteric acid in your proposed formulation for Testosterone Gel (b) (4) has not been previously approved by the Agency in a transdermal product at the specified levels. Therefore, the proposed drug product cannot be received as an ANDA. Please provide examples of approved drug products administered by the same route of administration which contain these inactive ingredients in the same concentration range or provide information demonstrating that these inactive ingredients at these concentrations do not affect the safety of the proposed drug product.

The Sponsor resubmitted the ANDA, with the requested information, on November 19, 2007. On January 23, 2008, the Office of Generic Drugs (OGD) sent a Refusal to Receive letter to the Sponsor stating that:

Your proposed drug product contains inactive ingredients that are significantly different than those contained in the RLD Androgel. The Agency has concluded that additional information will be needed to demonstrate that your proposed product does not have the potential to cause greater skin irritation or sensitization than the RLD. Cumulative skin irritation and sensitization studies may provide sufficient information to address this issue.

The Sponsor performed the requested studies and on November 27, 2008 resubmitted (b) (4). At that time they also submitted (b) (4) for Testosterone (b) (4) Gel in a multi dose pump configuration. These applications were accepted for review by OGD on May 13, 2009 and May 20, 2009 respectively.

On August 28 and 29, 2009 the Sponsor received deficiency letters (b) (4). The deficiency was explained as:

CDER is concerned with the safety of transdermal testosterone gel products because of reports of significant adverse events resulting from unintentional transfer of testosterone from patients to young children and to female partners. We are unable to approve your abbreviated new drug application (ANDA). You have failed to provide data to show that your use of different inactive ingredients, including but not limited to the different (b) (4) from those found in the reference listed drug (RLD) do not affect the safety or effectiveness of your proposed drug product. See 21 CFR 314.94 (a) (9) (ii) and (a) (9) (v). We have determined that investigations such as clinical trials should be conducted to demonstrate that your inactive ingredients do not affect the safety and efficacy of your proposed drug product. Because these types of studies cannot be submitted in an ANDA, your ANDA cannot be approved. If you wish to pursue approval of your product, you are encouraged to contact the Division of Reproductive and Urologic Products in the Office of New Drugs.

The Sponsor then submitted IND 107,130 to the Division of Reproductive and Urologic Products and met with the Division on May 19, 2010 to discuss the design of the necessary transfer and washing studies and also to discuss their plans for an NDA submission. The Sponsor subsequently performed the requested studies and NDA 203098 was submitted to DRUP July 4, 2011.

2.6 Other Relevant Background Information

Table 2 presents the composition of the reference drug, Androgel, the original formulation of the Sponsor's product, and the planned commercial formulation of the Sponsor's product. All studies carried out by the Sponsor in support of this application were carried out using the original formulation of the product. The product was reformulated for several reasons.

The use of carbomer 940 results in (b) (4). Also, Androgel does not contain Carbomer 940 (although the initial label incorrectly indicated that it did). The Perrigo Testosterone Gel was reformulated to contain Carbomer 980, which is the Carbomer used in Androgel.

The ethanol content of the gel was also changed. The initial Androgel label incorrectly indicated that it contained 68.9% ethanol. The initial Perrigo Gel was formulated based on this information. The Androgel label was revised in December 2002 to show the correct ethanol content of 67%. The Perrigo reformulation incorporated 67% ethanol rather than the 68.9% in the initial formulation.

This reformulation was discussed with the Division at the May 19, 2010 meeting. The formulation differences were not believed to require any new studies. Perrigo was allowed to complete their studies with the initial formulation.

Table 2. Product Formulations

	Androgel	Perrigo Original Formulation	Perrigo Commercial Formulation
Component	mg/g gel		
Testosterone USP	10.00	10.00	10.00
Isopropyl myristate	(b) (4)		
Isosteric Acid			
Alcohol (b) (4)			
Carbomer 940			
Carbomer 980			
(b) (4) NaOH			
NaOH			
Purified water			

Source: NDA 203098 Module 3.2 P1 and US Patent 6,503,894, Table 5.

Reviewer's comment: *The only difference in formulation between the Sponsor's commercial formulation of Testosterone Gel and the Reference listed Drug, Androgel, is the substitution of Isosteric Acid in place of Isopropyl myristate (b) (4). The clinical performance of the Sponsor's product has been evaluated with a bioequivalence study as well as transfer, washing and skin irritation studies. These studies are evaluated in this review.*

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

The Sponsor has in place standard operating procedures that are consistent with ICH Good Clinical Practice. These include archiving of source data, internal audits, and documentation of qualifications of investigators.

As part of this review, an assessment of the datasets and Case Report Forms (CRF) of the Sponsor's studies was done and did not reveal miscoding or discrepancies between the data recorded on the CRFs and the datasets.

3.2 Compliance with Good Clinical Practices

The Sponsor has indicated that their studies were carried out according to the Declaration of Helsinki, the Code of Federal Regulations and the Notes for Guidance on Good Clinical Practice (2000) (CPMP/ICH/135/95), the ICH GCP Guidelines and the EU Clinical Trials Directive (2001/20/EC).

3.3 Financial Disclosures

The Sponsor has certified that the compensation of all clinical investigators was independent of the study outcome. They have also certified that no investigator had a financial interest in the product or the Sponsor.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

A Chemistry review of the application has been conducted. The Chemistry reviewer has concluded that the sponsor has provided sufficient information on drug substance controls, manufacturing processes and process controls, and adequate specifications for assuring consistent product quality of the drug product. The sponsor has also provided sufficient stability information on the drug product to assure strength, purity and quality of the drug product during the expiration dating period.

The reviewer has withheld a recommendation for approval pending the negotiation of an acceptable label. A label has not been negotiated at this time due to the deficiencies identified in Form 483's for clinical and analytical sites of BE study.

4.2 Clinical Microbiology

A Microbiology review of the application was not conducted.

4.3 Preclinical Pharmacology/Toxicology

A Toxicology review of the application has been conducted. The applicant submitted no new nonclinical information, and is relying on published studies of testosterone and the FDA findings of safety and efficacy for AndroGel®, testosterone gel 1% (NDA 21-015) for Approval. The overall toxicological profile of testosterone is well established. Nonclinical toxicities are not relevant for Approval due to the preponderance of clinical data for testosterone that supersedes any nonclinical findings. Literature references and a scientific rationale for the reliance on literature were submitted to support the nonclinical sections of the Labeling. While the formulation is different than other FDA approved testosterone gel products, the components are at or below the levels in other FDA-approved products.

The toxicology reviewer's opinion is that the nonclinical data support approval of Testosterone Gel for topical testosterone replacement in hypogonadal men.

4.4 Clinical Pharmacology

A clinical pharmacology review of the application has been conducted. The reviewer has concluded that the information supplied does not adequately support the approvability of the product because of the lack of complete dosing records for Period 3 of their pivotal bioequivalence study. This results in a cohort of study subjects having reliable data that is too small to support a meaningful analysis of bioequivalence.

4.4.1 Mechanism of Action

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

4.5 Office of Scientific Investigations

A consult to the Office of Scientific Investigations (OSI) was made for clinical and bioanalytical study sites inspections. Their inspections of the clinical and analytic sites used for the Sponsor's bioequivalence study have shown several significant

deficiencies. The full reports of the OSI Bioequivalence Inspections are included in Appendices 9.4 and 9.5. The conclusions of the inspectors are:

Following evaluation of the inspectional observations for clinical and analytical portions of study 03-0415-001, DBGC recommends that:

1. *The proper dosing of subjects during Period 3 cannot be assured. Data from Period 3 should be excluded from statistical evaluation.*
2. *The measured concentrations of plasma testosterone are not adjusted for the endogenous testosterone in blank plasma used to prepare calibrators and QCs.*

The result of recommendation 1 is that only 8 of 24 subjects included in the Sponsor's bioequivalence study have reliable data. It is the opinion of this reviewer that this represents too small a cohort upon which to base a reasonable bioequivalence conclusion.

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

This 505(b)(2) application is supported by five studies. Table 3 shows the studies that have been submitted.

Table 3. Studies Supporting the Application

Type of Study	Study Number	Study Objective	Study Design	Test Product	N	Type of Subjects
Bioequivalence	03-0415-001	Establish the bioequivalence of Testosterone ^{(b) (4)} Gel and Androgel	Single-dose Three-way crossover study	Androgel 1% and two formulations of Testosterone Gel	24	Hypogonadal Men
Skin Sensitization	DS102308	Evaluate the sensitization of the skin by Testosterone ^{(b) (4)} Gel	Randomized, controlled, within-subject comparison study	Testosterone Gel Androgel 1%	226	Healthy volunteers
Skin Irritation	DS310208	Evaluate the irritation potential of Testosterone ^{(b) (4)} Gel to the skin	Cumulative Irritant Patch Test	Testosterone Gel Androgel 1%	38	Healthy volunteers
Residual	PRG-806	Evaluate the	Open-label	Testosterone	36	Healthy male

Type of Study	Study Number	Study Objective	Study Design	Test Product	N	Type of Subjects
Testosterone after Washing		residual testosterone on the hands and the application site following washing	four period study	Gel AndroGel 1%		volunteers
Interpersonal Transfer of Testosterone	M1IU09001	Evaluate the transfer of testosterone from a treated male to an untreated female via skin contact	Single-dose, four-treatment, four-way open-label crossover study	Testosterone Gel AndroGel	24 male/female pairs	Healthy volunteers

5.2 Review Strategy

The Sponsor has relied upon the FDA finding of safety and efficacy of AndroGel in this 505(b)(2) application. The primary study demonstrating the bioequivalence of Testosterone Gel to AndroGel is study 03-0415-001. This study will be reviewed to establish the bioequivalence of Testosterone Gel to AndroGel. If bioequivalence is shown, Testosterone Gel will have shown adequate evidence of efficacy.

Once bioequivalence has been established, the prior finding of the safety of AndroGel can also be relied on to establish the safety of Testosterone Gel. However, the inactive ingredients in Testosterone Gel are not identical to those of AndroGel as shown in Table 2.

Because of the difference in inactive ingredients, it is inappropriate to rely on the finding of the safety of AndroGel for several areas of safety. Therefore, the Sponsor was asked to perform studies to evaluate these safety features. The safety features that required evaluation, and the Sponsor's study number which evaluated that feature are shown in Table 4.

Table 4. Safety Studies Required

Safety Feature	Study Number
Skin sensitization	DS102308
Skin irritation	DS310208
Person-to-person testosterone transfer	M1IU09001
Ability to Wash Gel from hands	PRG-806
Ability to Wash Gel from application site	PRG-806

In summary, the review strategy for this application is to initially establish bioequivalence with the reference listed drug Androgel. Showing bioequivalence of Testosterone Gel to Androgel will allow the conclusion that Testosterone Gel is effective. Bioequivalence also will allow the conclusion that the drug is generally safe. However, skin safety, person-to-person transfer and washing characteristics are potentially influenced by the different inactive ingredients in Testosterone Gel as compared to Androgel. These areas will be evaluated in the studies listed in Table 4.

5.3 Discussion of Individual Studies/Clinical Trials

5.3.1 Bioequivalence Trial – 03-0415-001

Trial 03-0415-001 was a single-dose, three-period, three-treatment, randomized crossover study to evaluate the pharmacokinetics of two Testosterone Gel formulations and the pharmacokinetics of the reference listed drug Androgel. It was carried out at a single site (b) (4) during September 2003. The samples obtained in this study were, after appropriate processing, shipped in a frozen state to the bioanalytic laboratory (b) (4) where analyses were performed in October 2003.

Study Design

This was an open label, randomized, single-dose, three-period, three-treatment crossover study in which hypogonadal men received three drug formulations in a crossover fashion. In each period, subjects received a single 10 gm topical dose of one of the drug products, applied to the shoulder/upper arm. The three drug products studied were (b) (4) Testosterone Gel (b) (4) Formulation 1, (b) (4) Testosterone Gel (b) (4) Formulation 2, and Androgel 1%.

A series of blood samples were taken prior to drug application and extended for 72 hours following drug application. The samples were taken at -12, 0, 1, 2, 3, 4, 6, 8, 10, 12, 14, 17, 20, 24, 30, 36, 48, and 72 hours. Immediately after sampling, plasma was harvested and then frozen at -20°C. Frozen samples were sent to the central analytic laboratory in (b) (4) where they were assayed for total testosterone using a validated GC/MS method.

Subjects were randomized to receive the formulations in a random sequence. There was a one week washout period between each of the three drug applications. Subjects were monitored for adverse events.

Inclusion Criteria

Subjects were eligible for inclusion if they:

- Were hypogonadal males
- Had a Serum testosterone < 300 ng/dl
- Were 18 – 70 years of age

- Had a BMI > 15 and < 35
- Were reliable and capable of understanding test procedures
- Provided written informed consent

Exclusion Criteria

- Allergy to testosterone, soybeans, soy or soya lecithin
- Clinically significant abnormal findings on physical exam, medical history, or clinical laboratory results that would interfere with the conduct or interpretation of the study or jeopardize the subjects safety
- Skin conditions or excessive hair in the intended dosing area
- Carcinoma of the breast or known or suspected carcinoma of the prostate
- Serious psychological illness
- Significant history of drug or alcohol abuse
- A positive urine drug screen, a positive HIV, or hepatitis screen
- Use of oral or any topical exogenous testosterone during the two week period preceding study initiation, or any implantable testosterone during the six month period preceding study initiation
- Use of any medication which, in the opinion of the investigator, would interfere with the conduct or interpretation of the study or jeopardize the subjects safety
- Use of any concomitant medications during the course of the study
- Donation or loss of blood or participation in a clinical trial which involved withdrawal of 480 ml or more of blood during the six weeks prior to study initiation
- Donation of plasma during the two week period preceding study initiation
- Use of any investigational drug during the 30 day period preceding study initiation

Study Drugs

The three drugs tested were identified in the study report as:

- Testosterone Gel (b) (4), Formulation 1, Batch T06P030, manufacture date 7/29/2003
- Testosterone Gel (b) (4) Formulation 2, Batch T06P033, manufacture date 7/30/2003
- Androgel 1%, Unimed Pharmaceuticals, Lot number 20325, expiration date 12/04

The composition of Formulation 2, Batch T06P033 is shown in Table 5.

Table 5. Composition of Formulation 2, Batch T06P033

Ingredient	Amount % w/w
Testosterone	(b) (4)
Ethyl Alcohol	(b) (4)
Carbopol 940	(b) (4)

Ingredient	Amount % w/w
Isostearic Acid	(b) (4)
Sodium Hydroxide (b) (4)	(b) (4)
Purified Water	(b) (4)

Source: NDA 203098, Module 2.3, page 18

Reviewer's comment: *This formulation differs from the to-be-marketed formulation of Testosterone Gel (b) (4) which is shown in Table 2. There are two major differences between this initial formulation and the commercial formulation. The commercial formulation includes Carbomer 980 rather than Carbomer 940. The amount of alcohol has been reduced from 69% to 67%. These formulation differences were discussed in a pre-NDA meeting between the Sponsor and the Division., It was concluded that these formulation differences are small enough to be unlikely to affect the performance characteristics of the product. In this reviewer's opinion, this remains a reasonable conclusion.*

Study Endpoint

This was a study evaluating the bioavailability of two study drugs, Testosterone Gel (b) (4) Formulation 1 and Testosterone Gel (b) (4) Formulation 2, to the commercially available product AndroGel. The endpoint of the study was a comparison of the pharmacokinetics of each study drug to AndroGel over a 72 hour period following a single administration of each product.

A study drug would be found to be bioequivalent to AndroGel if the 90% confidence intervals of the geometric mean test-to-reference AUC and C_{MAX} ratios were contained within the interval of 0.80 to 1.25.

Safety Endpoint

There were no specific safety endpoints. Adverse events that occurred following drug administration were collected and tabulated.

Study Results

The results of this study are discussed in section 6.1 Bioequivalence Study. Section 4.5 Office of Scientific Investigations discusses the deficiencies found by an inspection of the clinical and analytic sites by the Office of Scientific Investigations.

5.3.2 Skin Sensitization Study - DS102308

This was a randomized, single center, controlled, within-subject comparison study of Perrigo Pharmaceuticals investigational product (testosterone gel (b) (4)), the comparator control product (AndroGel [testosterone] 1%), the vehicle product, and controls under occlusive conditions, in healthy volunteers. All subjects had areas of skin designated for the Perrigo Pharmaceuticals investigational product (testosterone gel (b) (4)), comparator

control product (AndroGel [testosterone] 1%), the vehicle product, and the control patches (ie, sodium lauryl sulfate [SLS] 0.1% positive control and saline negative control) at randomly assigned, adjacent sites, for the purpose of determining sensitization potential.

Study Objective

The primary objective of this study was to determine the potential of testosterone gel (b) (4) to cause sensitization by repeated topical application to the healthy skin of humans under controlled conditions.

Study Drugs

- Investigational Product
 - Product: testosterone gel (b) (4)
 - Lot no. 006262
 - Manufacturer: Perrigo Israel Pharmaceuticals, Ltd.
- Comparator Control Product
 - Product: AndroGel (testosterone) 1%
 - Lot No: 31280
 - Manufacturer: Laboratoires Besins International, Montrouge, France
- Vehicle Product
 - Product: Testosterone gel, (b) (4) placebo
 - Lot No: 010962
 - Manufacturer: Perrigo Israel Pharmaceuticals, Ltd.
- Positive and Negative Controls
 - Commercially available SLS prepared as a 0.1% aqueous solution served as a positive control and commercially available saline served as a negative control.

Study Design

Induction

On Day 1, if the subject fulfilled all the inclusion and none of the exclusion criteria, he/she was allowed participation in the study and received a unique randomization number, which determined the application scheme of the study materials for that individual subject.

A set of 5 patches were prepared by the clinical staff according to the randomization scheme. Patches contained 0.2 g of investigational product, 0.2 g of the comparator control product, 0.2 g of vehicle, 0.2 mL of the positive control and 0.2 mL of the negative control. The clinical staff applied the prepared patches to the appropriate test sites on the subject's infrascapular area of the back. The choice of left or right side was made by the clinical staff based on a visual inspection of skin clarity and was recorded on the CRF to ensure consistent placement of the patches at subsequent visits. The distance between the patches was approximately $\frac{3}{4}$ inch. The numbering of the test sites remained the same throughout the study.

The induction phase consisted of a series of 9 applications of the study materials and subsequent evaluation of the application sites. Patches were applied on Mondays, Wednesdays and Fridays for 3 consecutive weeks. The subjects returned to the facility at 48- hour intervals to have the patches removed. Using a tissue, the evaluator removed any remaining excess study material to avoid transference of materials between sites. The sites were evaluated within 15 minutes of patch removal using a 6-point integer scoring system, and identical patches were applied to the same sites. Patches applied on Friday remained in place for 72 hours until Monday.

Subjects who were absent once during the 3-week, 9-patch induction phase were instructed to keep the patches in place. They were scheduled to apply a make-up (MU) patch at the last induction visit. The MU patches were removed 48 hours later and the sites were evaluated. If subjects failed to return for removal/evaluation of the MU patch, a no ninth grading (N9G) was recorded.

Subjects who missed the 9th evaluation but had 9 patch applications were considered to have completed the induction phase.

In addition, at each of the study visits, concomitant medications, adverse events, and compliance was reviewed and recorded.

Rest Period

During the resting period of approximately 10 to 14 days, subjects did not receive any application of study materials.

Challenge

At challenge, subjects who completed the induction phase and the rest period, had patches identical to those that were used during the induction phase applied to naïve sites. Patches remained on the naïve sites for 48 hours to be evaluated within 30 minutes of patch removal and again at 24, 48, and 72 hours following patch removal (i.e., applied patch on Monday, removed patch on Wednesday, evaluated test sites on Wednesday, Thursday, Friday, and Saturday) using the procedures described above for the induction phase.

In addition, at each of the study visits, concomitant medications, adverse events, and compliance were reviewed and recorded.

To be considered a completed case, a subject had 9 applications of the study material and no fewer than 8 subsequent readings during induction and 1 application followed by all subsequent readings during challenge. Only completed cases were used to assess sensitization.

Rechallenge

A subject was rechallenged to any of the study materials if in the opinion of the Investigator, there was any sign suggestive of contact sensitization (erythema and/or papulation) which was observed at any of the evaluations following the removal of the challenge patch, ie, within 30 minutes of removal or at 24, 48, or 72 hours following patch removal.

Rechallenge patches were applied 2 weeks or more after the challenge phase. The study material was applied to naive sites on the back, in a manner similar to that used in the challenge phase. Rechallenge patches remained in place for 48 hours and patch sites were evaluated within 30 minutes of removal and again at 24, 48, and 72 hours after removal. As an example, patches were applied on Monday, removed on Wednesday, and test sites were evaluated on Wednesday, Thursday, Friday, and Saturday. In addition, at each of the study visits, concomitant medications, adverse events, and compliance were reviewed and recorded.

End of Study

At the end of the study, all patches were removed as described above, and the final evaluations of the test sites were made. In addition, concomitant medications and AEs were reviewed and recorded.

Local Tolerability Assessments

Assessment of the patch sites was done 9 times during the induction phase, 4 times during the challenge and, if applicable, 4 times during the rechallenge. The 6-point integer grading scale shown in Table 6 was used to express the response observed at the time of examination.

Table 6. Skin Assessment Grading Scale

Score	Definition
0	No visible reaction
1	Minimal erythema, no sign of edema
2	Definite erythema with no significant edema
3	Moderate erythema with no significant edema
4	Moderate erythema with edema and/or papular response
5	Severe erythema, edema, epidermal damage or papulovesicular response

Source: NDA 203098, Module 5.3.5.4.1, Study Report DS102308, Table 9-2, page 23.

Data Analysis

Individual irritancy scores through the induction period were displayed in a data listing for all subjects, products, and readings, along with the mean and total of the scores. Frequency counts of each assigned score at each reading for each product were presented. No data imputations were made for discontinued subjects or missed evaluations. However, when a patch was discontinued due to limiting irritation, the last observed score was carried forward through all subsequent readings.

The mean and total irritation scores during induction were tested pair wise for product differences using Fisher's protected least significant differences in the context of the 2-way analysis of variance (ANOVA), including main effects of subject and product, without interaction. Pairwise differences were tested only if the null hypothesis of a common mean score for all products was rejected at the 5% level.

Adverse Events

Adverse events were summarized as 1) an overall incidence of at least one event, 2) an incidence within body systems, and 3) an incidence by body system and preferred term. Each subject contributed only once (eg, the first occurrence) to each of the rates, regardless of the number of occurrences (events) the subject experiences.

Treatment-emergent AEs were summarized and tabulated by the system organ class and preferred term, by severity (mild, moderate, or severe), and by relationship to study product (unrelated, unlikely, possible, probable, or definite).

Treatment-emergent AE's were defined as any adverse event with an onset date on or after the first study product administration.. Any event with a missing onset date was included as a treatment-emergent AE.

Serious adverse events and deaths were listed by subject.

Study Results

The results of this study are discussed in section 7.5.4.3 Skin Sensitization Study (DS102308).

5.3.3 Skin Irritation Study – DS310208

Study DS310208 was a 21-Day, randomized, controlled study to evaluate the irritation potential of Testosterone Gel (b) (4) on healthy volunteers, using a cumulative irritant patch test design.

Study Objective

To determine the irritation potential of Perrigo Pharmaceuticals testosterone gel (b) (4) on normal skin.

Study Design

This was a randomized, single center, controlled, within-subject comparison study of Testosterone gel (b) (4), the comparator control product (AndroGel [testosterone] 1%), the vehicle product, and controls under occlusive conditions, in healthy volunteers. All subjects had areas of skin designated for Testosterone gel (b) (4), comparator control product (AndroGel [testosterone] 1%), the vehicle product, and the control patches (ie, sodium lauryl sulfate [SLS] 0.2% positive control and saline negative control) at randomly assigned, adjacent sites, for the purpose of determining irritation potential.

The investigational product, comparator product, the vehicle product, and the controls were applied occlusively to one side of the infrascapular area of the back. Evaluation of dermal reactions at the application sites were assessed clinically using an ordinal scale that rated the degree of erythema, edema, and other signs of cutaneous irritation.

A total of 21 patch applications were made over a period of 22 days.

Reviewer's comment: *The study design is acceptable.*

Study Drugs

- Investigational Product
 - Product: testosterone gel (b) (4)
 - Lot no. 006262
 - Manufacturer: Perrigo Israel Pharmaceuticals, Ltd.
- Comparator Control Product
 - Product: AndroGel (testosterone) 1%
 - Lot No: 31280
 - Manufacturer: Laboratoires Besins International, Montrouge, France
- Vehicle Product
 - Product: Testosterone gel, (b) (4) placebo
 - Lot No: 010962
 - Manufacturer: Perrigo Israel Pharmaceuticals, Ltd.
- Positive and Negative Controls
 - Commercially available SLS prepared as a 0.1% aqueous solution served as a positive control and commercially available saline served as a negative control.

Irritancy Assessments

Assessment of the patch sites was done 21 times during the study. The 6-point integer grading scale shown in Table 7 was used to express the response observed at the time of examination.

Table 7. Skin Assessment Grading Scale

Score	Definition
0	No visible reaction
1	Minimal erythema, no sign of edema
2	Definite erythema with no significant edema
3	Moderate erythema with no significant edema
4	Moderate erythema with edema and/or papular response
5	Severe erythema, edema, epidermal damage or papulovesicular response

Source: NDA 203098, Module 5.3.5.4.1, Study Report Table 9-2, page 20.

Data Analysis

The focus of the statistical analysis was the comparison of the cumulative irritation response of the controls as compared to the investigational product. The primary parameter for cumulative irritancy was the mean cumulative irritation score.

Inclusion Criteria

Subjects included in the study were those who:

- were males and females, 18 years of age or older and in good general health;
- were of any skin type or race, providing the skin pigmentation allowed discernment of any skin reactions;
- in the case of females, were not of childbearing potential, (ie, were surgically sterile or had experienced menopause);
- were free of any systemic or dermatologic disorder, which, in the opinion of the investigative personnel, would have interfered with the study results or increased the risk of adverse events;
- were able and willing to follow all study procedures, attend all scheduled visits, and successfully complete the study;
- completed a medical screening procedure; and
- read, understood and signed an informed consent containing HIPAA (Health Information Portability and Accountability Act) authorization.

Exclusion Criteria

Subjects excluded from the study were those who:

- had any visible skin disease at the application site which, in the opinion of the investigative personnel, would have interfered with the evaluation of the test sites;
- were not willing to refrain from using more than 8 baby (81 mg) aspirin per week and refrain from using any other aspirin products during the study (use of Tylenol was permitted);
- were using or had used systemic/topical corticosteroids within 3 weeks prior to the study, or will use during the study;
- were using or had used any systemic/topical antihistamines or anti-inflammatory drugs within 72 hours prior to the study, or will use during the study;
- were using medication which, in the opinion of the investigative personnel, would have interfered with the study results;
- had psoriasis and/or active atopic dermatitis/eczema;
- were females who were of childbearing potential;
- had a known sensitivity to topical testosterone or any components of AndroGel®;
- had damaged skin in or around the test sites, including sunburn, excessively deep tans, uneven skin tones, tattoos, scars, excessive hair, numerous freckles, or other disfigurements of the test site;
- had received treatment for any type of internal cancer within 5 years prior to study entry;

- had a history of, or were being treated for skin cancer;
- had a history of, or were being treated for prostate disorder;
- were participating in any concurrent clinical testing;
- had any known sensitivity to adhesives, and/or
- had received any investigational treatment(s) within 4 weeks prior to study entry.

Adverse Events

Information about all local and systemic adverse events, whether volunteered by the subject, discovered by investigator questioning, or detected through other means, were collected and recorded on the Adverse Event CRF and followed as appropriate.

An adverse event is defined as any untoward medical occurrence in a subject or clinical investigation in which the subject administered a pharmaceutical product, which did not necessarily have a causal relationship with this treatment. An AE can therefore, be any unfavorable and unintended sign, symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not considered related to the medicinal (investigational) product.

AEs were coded using the Medical Dictionary for Regulatory Activities (MedDRA).

Study Results

The results of this study are discussed in section 7.5.4.4 Skin Irritation Study (DS310208).

Reviewer's comment: *The study design is acceptable.*

5.3.4 Residual Testosterone After Washing – Study PRG-806

This was a study to evaluate the residual amount of topically delivered Testosterone Gel (b) (4) present on normal skin of the hand, arm, and shoulder in healthy adult male subjects following washing procedures.

Study Objective

To quantify and compare the amount of residual testosterone remaining on the hands and arm/shoulder before and after the hand and application site washing that followed a single topical dose (10 g of gel for a total of 100 mg testosterone) of Testosterone Gel (b) (4). This was also assessed for the comparator product for information only.

Study Design

This was an open-label, four-period, pivotal study, on healthy adult male subjects.

Subjects entered the clinic on study day 1 of each period and washed their hands and the arm/shoulder designated for drug application. Then, the hand and arm/shoulder

designated for drug application were wiped with three ethanol dampened gauze (blank control sample). Subsequently, study staff applied a 10 gram dose (2 × 5-gram packets) of one of the testosterone gel formulations to the center area of the palm of one of the subject's hands. The subject then applied the dose to their opposite arm/shoulder.

Subjects followed their assigned hand residual removal procedure and had their hand wiped with three ethanol dampened gauze pads to obtain a residual hand sample for testosterone measurement. Finally, approximately 2 hours after the dose was applied, subjects followed their assigned arm/shoulder residual removal procedure and had their arm/shoulder wiped with three ethanol dampened gauze pads to obtain a residual application site sample for testosterone measurement. The gauze was retained for analytical quantification of recovered testosterone.

Subjects followed study exit procedures, showering to remove any residual dose of drug that remained on the skin (hands and application arm/shoulder).

The residual removal procedure for two (2) of the periods (one following the Perrigo formulation application, the other following the AndroGel application), was to wipe the dosed hand immediately following dosing and the arm/shoulder application site two (2) hours after dose application. The residual removal procedure in the remaining two (2) periods was to wash the hands and shower after dose application but before collection of the residual hand and residual arm/shoulder application site samples.

The residual hand gauze pads and residual application site gauze pads in each period were analyzed for testosterone.

Reviewer's comment: *The study design is acceptable.*

Study Drugs

- Investigational Product
 - Product: testosterone gel (b) (4)
 - Lot no. 028508
 - Manufacturer: Perrigo Israel Pharmaceuticals, Ltd.
 - Manufacture Date: December 22, 2009
- Comparator Control Product
 - Product: AndroGel (testosterone) 1%
 - Lot No: 31791
 - Manufacturer: Solvay Pharmaceuticals, Inc.
 - Manufacture Date: N/A
 - Expiration Date: November 2011

Drug Concentration Measurements

The residual hand gauze pads and residual application site gauze pads in each period were analyzed for testosterone. The quantification of testosterone present in the gauze was measured using extraction and liquid chromatography analytical methods developed for these samples, and according to the Analytical Laboratory's Standard Operating Procedures and FDA Guidelines as applicable.

Statistical and Analytical Plan

Data was tabulated and summarized. Data from subjects were included in summary tabulations if they completed at least 2 periods, which included both the washing and no washing periods for the Perrigo product. No statistical evaluations were planned.

Recovery assessments were determined as the total amount recovered from the gauze pads, from the hand and arm/shoulder.

Inclusion Criteria

Volunteers who met the following criteria were included as subjects in the study.

- Understood the study objectives, were willing to participate, and gave written informed consent for study participation.
- Volunteer's hands, upper arms, and shoulders were free from scars, cuts, excessively thick calluses, or skin diseases that could have affected absorption or interfered with evaluation of the test site.
- Male, non-smoking (minimum of 14 days), 18 to 65 years of age, inclusive, at the time of dosing.
- Body mass index (BMI) between 19 to 34 kg/m², inclusive.
- Judged by the Investigator on the basis of pre-study medical history to have no health conditions that would have impacted the safety of the subject or compliance during participation.
- Willing to shower using the same soap/cleansers between the Screening Visit and until completion of study related activities.
- Willing to follow study restrictions.

Exclusion Criteria

Volunteers or subjects who met any of the following criteria were excluded from the study:

- Reported participating in another investigational drug, medical device, or biologics study within 30 days prior to dosing.
- Reported a past or current medical condition that might have significantly affected percutaneous absorption to topical testosterone.
- Reported a history of sensitivity/allergy to the ingredients found in the test formulations or had a history of adverse reactions to topical or systemic corticosteroids.
- Reported a significant history of allergy to soaps, lotions, emollients, ointments, creams, cosmetics, adhesives, or latex.

- Reported a history of significant skin conditions or disorders, for example, psoriasis, atopic dermatitis, etc.
- Reported a history of significant dermatologic cancers, for example, melanoma or squamous cell carcinoma. Basal cell carcinomas that were superficial and did not involve the investigative site were acceptable.
- Reported a known or suspected case of prostate cancer.
- Displayed an obvious difference in skin color between hands, arm/shoulders or the presence of a skin condition, evidence of a recent sunburn, acne, scar tissue, tattoo, open wound, branding, or coloration that would have interfered with placement of test sites (hands, arms, shoulders), their assessments, and their reaction to drug or could have compromised the safety of the subject.
- Reported using a tobacco product within 14 days of study conduct.

Adverse Events

The staff recorded all adverse events observed, queried, or spontaneously volunteered by the subjects. An adverse event (AE) was defined as any untoward medical occurrence in a subject administered a pharmaceutical product (during the course of the study) and did not necessarily have a causal relationship with treatment.

Subjects were monitored throughout the study for any AEs. Subjects were instructed by the Investigator, or designee, to report the occurrence of any adverse event. All AEs were followed until resolution, as appropriate, or until a downward trend in the AE was observed. All AEs, whether elicited or observed by the Investigator, were recorded.

Study Results

The results of this study are discussed in section 7.4.5.2 A Study of Washing Testosterone from Hands and Application Site (Study PRG-806).

5.3.5 Testosterone Transfer – Study M1IU09001

Study Objective

This study assessed the relative transfer of testosterone from a male, who had been treated with a single topical dose of 10g of Testosterone Gel ^{(b) (4)}, to a female partner. The transfer was evaluated both when the subject was wearing a T-shirt and without a T-shirt. The relative amounts of testosterone transfer from males to females with each treatment condition (with a T-shirt and without a T-shirt) for a comparator product was also assessed.

Study Design

This was an open-label, single-dose, randomized, four-period, four-treatment crossover study. The total duration of the study, screening to the end of the study, was approximately 12 weeks with at least a 7-day washout period between doses. Female subjects reported to the clinical site at least 48 hours prior to contact with the treated

male subjects. The female subjects were required to stay for 26 hours after dosing of the male subjects (i.e. 24 hours after male and female contact). Male subjects reported to the clinical site at least 20 hours prior to dosing and were required to stay for at least 4 hours after dosing. Blood samples were collected from female subjects on the day prior to contact at 0, 2, 4, 6, 8, 10, 12, 16 and 24 hours. These sampling times were relative to the time of male and female contact on Day 1 in such a way that the pre-contact blood sampling schedule on Day -1 was performed at the same clock times as the post-contact blood sampling schedule on Day 1.

The Testosterone Ge (b) (4) was applied to the male subject's arm/shoulder area. Skin contact occurred two hours after application of the gel. In two of the four study phases contact occurred directly between skin-to-skin. In the other two phases the subject's application site was covered with a T-shirt and contact was between the skin of the female's arm and the shirt overlying the subject's application site. Female subjects had one arm/shoulder designated as the "contact site" and were instructed to rub their upper arm and shoulder up and down the treated upper arm/shoulder of their male partner during a 15 minute contact period.

The details of the contact were as follows. Female subjects were instructed to gently rub (for approximately 15 seconds per stroke) their upper arms and shoulders up and down the treated upper arms and shoulders of their male partner during the contact period for a total of one minute. One minute periods of alternating active rubbing and resting of the female's arms on the male's shoulders occurred until the 15 minute time period was completed. Each couple was monitored and coached by one staff member throughout the contact period.

Following contact, blood samples were collected from female subjects immediately prior to contact (0 hour) and after contact at 2, 4, 6, 8, 10, 12, 16 and 24 hours. One single blood sample was collected to represent both the Day -1, 24 hour sample and the Day 1, 0 hour sample.

A total of 17 blood samples were collected from the female subjects per study period for a total of 68 samples or 408 mL total volume. There were no samples taken from the male subjects.

Reviewer's comment: *The study design is acceptable.*

Study Drugs

- Investigational Product
 - Product: testosterone gel (b) (4)
 - Lot no. 028508
 - Manufacturer: Perrigo Israel Pharmaceuticals, Ltd.
 - Manufacture Date: December 22, 2009
- Comparator Control Product

- Product: AndroGel (testosterone) 1%
- Lot No: 31791
- Manufacturer: Solvay Pharmaceuticals, Inc.
- Manufacture Date: N/A
- Expiration Date: November 2011

Sample Handling and Testosterone Analysis

After local processing, the samples were shipped frozen (b) (4) for analysis.

Testosterone serum concentrations were measured using a validated bioanalytical method according to the bioanalytical laboratory's SOPs and FDA guidances. The validated detection range for total testosterone in females is approximately 0.05 to 50 ng/mL in human serum.

Statistical Analytical Plan

Pharmacokinetic and statistical analyses were performed for total testosterone serum concentration data from female subjects. Data were analyzed if the subjects completed at least 2 periods, which included Treatments A and B (Contact after Testosterone Gel (b) (4) with and without a shirt). Data from treatment groups C and D (Contact after Androgel with and without a shirt) were to be collected for information purposes only.

Data from subjects with missing concentration values (missed blood draws, lost samples, samples unable to be quantitated) were to be used if pharmacokinetic parameters could be estimated using the remaining data points. Otherwise, concentration data from these subjects were to be excluded from the final analysis.

Pharmacokinetic parameters were calculated based on both baseline adjusted and non-adjusted total testosterone serum concentrations using standard noncompartmental approaches. The following parameters were calculated:

- AUC_{0-t} The area under the serum concentration versus time curve, from time 0 to the last measurable concentration, as calculated by the linear trapezoidal method.
- C_{max} Maximum measured serum concentration over the time span specified.
- T_{max} Time of the maximum measured serum concentration. If the maximum value occurred at more than one time point, T_{max} was to be defined as the first time point with this value.

Arithmetic means, standard deviations, and coefficients of variation were calculated for these parameters. Additionally, geometric means were calculated for AUC_{0-t} and C_{max}. Ratios of means were calculated using the LSM for ln-transformed AUC_{0-t} and C_{max}. The geometric mean values were reported. The ratios of primary interest are with T-shirt to

without T-shirt treatments for Testosterone Gel (b) (4). For information only, the ratios of the with-T-shirt to without-T-shirt treatments for Androgel were also presented.

Study Results

The results of this study are discussed in section 7.4.5.1 A Study of Person-to-Person Testosterone Transfer (Study M11U09001).

6 Review of Bioequivalence

Summary

The efficacy of Testosterone Ge (b) (4) was not evaluated in a clinical study. Rather, the efficacy of the Gel will be established by a study showing that it is bioequivalent to the reference listed drug, Androgel. Androgel has previously been shown to be an effective treatment for hypogonadal males. A study showing that Testosterone Gel (b) (4) provides equivalent blood levels of testosterone is a reasonable support for the conclusion that Testosterone Gel (b) (4) is also an effective treatment for this indication.

An analysis of the results of the bioequivalence study, based upon the data submitted by the Sponsor, is given in Section 6.1. However, based upon an inspection of the clinical and analytic sites by the Office of Scientific Investigations, Division of Bioequivalence, it has been determined that the data for 16 of the 24 subjects included in the study is not reliable. See Section 4.5. It is this reviewer's opinion that a reasonable conclusion of bioequivalence is not possible based upon the remaining eight subjects.

6.1 Bioequivalence Study

As evidence of the bioequivalence of Testosterone Gel (b) (4) and Androgel, the Sponsor has submitted the results of Study 03-0415-001. The study design is discussed in section 5.3.1 Bioequivalence Trial – 03-0415-001. The results of the study will be reviewed in this section.

6.1.1 GCP and GLP Certification

The director of quality assurance, Elizabeth Himsl, C.M.A., C.C.R.C., has certified that the study was conducted in compliance with 21CFR and Good Clinical Practice Guidelines. The director of study analytics, Dr. Alwin Baumeister, has certified that the analysis of study samples was conducted in compliance with the Principles of Good Laboratory Practice.

6.1.2 Demographics

The demographics of the study subjects is presented in Table 8.

Table 8. Baseline Demographics for the Intent-to-Treat Population

Parameter	Value
Number	24
Age (years)	
Range	31 - 69
Mean	55.8
Median	59.5
Height (cm)	
Range	165.1 – 190.5
Mean	176.0
Median	176.5
Weight (kg)	
Range	65.0 – 116.4
Mean	91.3
Median	92.0
BMI (kg/m ²)	
Range	21.8 – 35.5
Mean	29.4
Median	29.2

Source: NDA 203098, Module 2.3.1.2.1, Study Report, Table 2

Reviewer’s Comment: *The population studied is reasonably representative of the intended treatment population. The demographics are acceptable.*

6.1.3 Subject Disposition

All 24 subjects enrolled in the intent to treat population completed the study. All subjects provided 18 scheduled blood samples during each of the three study periods; there were no missing samples.

Reviewer’s comment: *The Office of Scientific Investigations, based upon their inspection of the clinical site, have concluded that all data collected in the third study period is unreliable and should be excluded from the analysis. When this data is excluded only eight subjects have reliable study data for both the test product and the reference listed drug, AndroGel. It is this reviewer’s opinion that data from eight subjects is insufficient to serve as the basis for a reasonable bioequivalence conclusion.*

Forty-one samples were reanalyzed. Twelve of forty-one samples were reanalyzed to confirm the initial analysis. Fourteen were reanalyzed because of a poor initial

chromatography or because of a destroyed initial sample. Fifteen were reanalyzed due to values that were greater than the upper limit of quantification during the first measurement.

6.1.4 Pharmacokinetic Procedures

All the available data from the 24 subjects who completed the study were used in the pharmacokinetic analyses. All pharmacokinetic calculations were performed using SAS (PC version 6.12). Any sample concentration reported less than the assay limit of quantitation was set to zero. Pharmacokinetic analyses were performed on the testosterone results after correction for endogenous levels.

The reported concentrations for each subject in each period were corrected by subtracting the average testosterone concentration in the -12 hour and 0 hour samples. Any corrected value that was less than zero was set to zero for use in the analyses. The 0 hour samples were likewise set to zero concentration.

Pharmacokinetic parameters, AUC and T_{max} , were calculated using the actual rather than the scheduled times of sample collection. Peak concentration, C_{max} , was the observed maximum value during the collection period of 0 to 72 hours. The time to peak concentration, T_{max} , was the time at which C_{max} , was first observed. Area under the curve, AUC_{0-t} , to the last measured concentration was calculated by the linear trapezoidal method.

6.1.5 Statistical Analyses

Statistical Analyses were performed using the General Linear Models (GLM) procedure of the SAS statistical program (PC version 6.12). The pharmacokinetic parameter estimates, as well as the concentrations at each scheduled sample time, were evaluated by analysis of variance. Hypothesis testing for treatment effects in the analysis was conducted at $\alpha = 0.05$.

6.1.6 Results

Statistical analyses were performed on the pharmacokinetic results in order to compare two (b) (4) Testosterone Gel formulations to Androgel, when each was administered as a single 10 gm topical dose to 24 hypogonadal males.

Table 9 summarizes the results of the statistical analyses of the pharmacokinetic parameters for baseline corrected results for Testosterone Gel (b) (4) Formulation 1 and Androgel.

Table 9. Summary of Statistical Comparisons of Testosterone Gel ^{(b) (4)} Formulation 1 (Lot #T06P030) and Androgel

Parameter	Least-Squares Mean		Ratio	90% Confidence Interval	
	Formulation 1	Androgel		Lower	Upper
AUC _{0-t} (ng-hr/ml)	101	96.9	1.044	0.895	1.194
C _{max} (ng/ml)	5.72	5.18	1.104	0.905	1.303
T _{max} (hour)	20.2	19.2	1.050	-	-
Ln-Transformed					
AUC _{0-t} (ng-hr/ml)	89.3	87.9	1.015	0.882	1.169
C _{max} (ng/ml)	5.11	4.82	1.061	0.885	1.273

Source: NDA 203098, Module 5.3.1.2.1, Study Report 03-0415-001, Statistical Report, Table 1.1

Table 10 summarizes the results of the statistical analyses of the pharmacokinetic parameters for baseline corrected results for Testosterone Gel ^{(b) (4)} Formulation 2 and Androgel.

Table 10. Summary of Statistical Comparisons of Testosterone Gel ^{(b) (4)} Formulation 2 (Lot #T06P033) and Androgel

Parameter	Least-Squares Mean		Ratio	90% Confidence Interval	
	Formulation 2	Androgel		Lower	Upper
AUC _{0-t} (ng-hr/ml)	101	96.9	1.044	0.894	1.193
C _{max} (ng/ml)	5.46	5.18	1.054	0.855	1.253
T _{max} (hour)	18.6	19.2	0.970	-	-
Ln-Transformed					
AUC _{0-t} (ng-hr/ml)	84.3	87.9	0.959	0.833	1.104
C _{max} (ng/ml)	4.65	4.82	0.965	0.805	1.158

Source: NDA 203098, Module 5.3.1.2.1, Study Report 03-0415-001, Statistical Report, Table 1.2

6.1.7 Bioequivalence Conclusions

The analysis presented in section 6.1.6 was based upon the full cohort of 24 subjects. Based upon the OSI inspection of the clinical study site it has been determined that the

data for 16 of the subjects is not reliable. Therefore, this analysis can not be relied upon to demonstrate bioequivalence. An analysis using the remaining eight subjects would not be a reasonable basis for establishing bioequivalence.

Therefore, this reviewer's opinion is that this study has not provided reliable evidence of the bioequivalence of the Sponsor's product and the reference listed drug, Androgel.

7 Review of Safety

Safety Summary

The safety of Testosterone Gel (b) (4) was not evaluated in a clinical study. Rather, the safety of the Gel will be established by a study showing that it is bioequivalent to the reference listed drug, Androgel. Androgel has previously been shown to be safe and effective as a treatment for hypogonadal males. A study showing that Testosterone Gel (b) (4) provides equivalent blood levels of testosterone is a reasonable support for the conclusion that Testosterone Gel (b) (4) is safe as a treatment for this indication.

Because the Sponsors formulation of Testosterone Gel differs somewhat from the formulation of Androgel, the Sponsor was asked to perform clinical studies evaluating areas of safety that could possibly be affected by the formulation difference. These studies were an evaluation of the potential for irritation and sensitization of the skin, an evaluation of the potential to transfer testosterone from the skin of a patient to another individual by direct skin to skin contact, and an evaluation of the ability to wash the Gel from the hands and application site after the drug is applied.

Reviewer's Comment: *Based on the results of the studies of the formulation-dependent areas of product safety submitted with this application, the conclusion of this reviewer is that Testosterone Gel has been shown to be reasonably safe with respect to person-to-person transfer, the ability to wash the product from the skin, and with respect to skin irritation and sensitization. Further conclusions regarding the safety of the product are not warranted given the lack of established bioequivalence to a reference listed drug.*

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

The studies used to evaluate the formulation dependent areas of safety are listed in Table 11.

Table 11. Studies Performed to Evaluate Formulation-Dependent Safety

Type of Study	Study Number	Study Objective	Study Design	Test Product	N	Type of Subjects
Skin Sensitization	DS102308	Evaluate the sensitization of the skin by Testosterone ^{(b) (4)} Gel	Randomized, controlled, within-subject comparison study	Testosterone ^{(b) (4)} Gel Androgel 1%	226	Healthy volunteers
Skin Irritation	DS310208	Evaluate the irritation potential of Testosterone ^{(b) (4)} Gel to the skin	Cumulative Irritant Patch Test	Testosterone ^{(b) (4)} Gel Androgel 1%	38	Healthy volunteers
Residual Testosterone after Washing	PRG-806	Evaluate the residual testosterone on the hands and the application site following washing	Open-label four period study	Testosterone ^{(b) (4)} Gel Androgel 1%	36	Healthy male volunteers
Interpersonal Transfer of Testosterone	M11U09001	Evaluate the transfer of testosterone from a treated male to an untreated female via skin contact	Single-dose, four-treatment, four-way open-label crossover study	Testosterone ^{(b) (4)} Gel Androgel	24 male/female pairs	Healthy volunteers

The designs of these studies were presented in section 5.3 Discussion of Individual Studies/Clinical Trials, and the results are presented in section 7.4.5 Special Safety Studies/Clinical Trials.

7.2 Adequacy of Safety Assessments

If the product had been found to be bioequivalent to the listed drug Androgel, the Agencies prior finding of safety for the reference drug, and the formulation-dependent safety studies that were submitted would constitute an adequate evaluation of the safety of this drug product in the opinion of this reviewer. Given the lack of proof of bioequivalence that has previously been discussed and the resulting inability to rely upon the safety history of Androgel, this reviewer is not able to reasonably conclude that the Sponsor has established the safety of the product.

7.3 Major Safety Results

7.3.1 Deaths

There were no subject deaths during the studies of bioequivalence or formulation-dependent safety.

7.3.2 Nonfatal Serious Adverse Events

There were no serious adverse events that were related to the drug product during the studies of bioequivalence or formulation-dependent safety.

7.4 Supportive Safety Results

7.4.5 Special Safety Studies/Clinical Trials

Four safety studies were conducted for this product. See Table 11. The design of each study is presented in section 5.3 Discussion of Individual Studies/Clinical Trials. The results of each study is discussed in this section.

7.4.5.1 A Study of Person-to-Person Testosterone Transfer (Study M1IU09001)

The design of this study is presented in section 5.3.5 Testosterone Transfer – Study M1IU09001.

Disposition of Subjects

Twenty four male/female couples were enrolled in the study. Twenty of the couples completed the study in accordance with the study protocol. The reasons for failure of four couples to complete the study is shown in Table 12.

Table 12. Discontinuations from Study M1IU09001

Subject No.	Reason for Withdrawal	Gender	Age	Race
03	Female partner tested positive for Benzodiazopine on Day 1 Period 1.	Female	63	W
		Male	51	W
08	Male partner tested positive for THC on Day 1 Period 1.	Female	56	W
		Male	26	W
14	Female partner tested positive for cotinine at Period 4 admission.	Female	48	W
		Male	38	W
16	Non compliance of female partner on Day 1 Period 1.	Female	57	W
		Male	58	W

Source: NDA 203098, Module 5.3.5.4.1, Table 10.1-1, page 30

Reviewer's Comment: *The withdrawals from the study are reasonable and unrelated to adverse events.*

Subject Demographics

Table 13 shows the demographics for the female subjects completing the study.

Table 13. Subject Demographics – Study M1IU09001

		Female Completers (N=20)
Age (years)	Mean ± SD	53.9 ± 4.8
	Range	44 – 62
Race	Black	2 (10%)
	White	18 (90%)
BMI	Mean ± SD	28.1 ± 2.1
	Range	24.7 – 31.0

Source: NDA 203098, Module 5.3.5.4.1, Table 11.2-1, Page 34

Results

Table 14 shows the mean AUC and C_{MAX} for total testosterone in the female partners following contact with a male partner who had applied Testosterone Gel ^{(b) (4)}.

Table 14. AUC and C_{MAX} For Total Testosterone in Female Partners for 24 Hour Period Following Contact With a Male Partner Who Had Applied Testosterone Gel

Parameter	Observed Values		Baseline corrected Values	
	Without Shirt	With Shirt	Without Shirt	With Shirt
AUC _{0-t} (ng-hr/ml)	6.108	2.992	3.289	0.322
C _{MAX} (ng/ml)	0.411	0.159	0.260	0.047

Source: NDA 203098, Module 5.3.5.4.1, Table 11.4.2-1, page 35 and Table 11.4.2-2, page 36.

Table 15 shows the observed values as a percentage of the baseline values.

Table 15. AUC and C_{MAX} For Total Testosterone in Female Partners for 24 Hour Period Following Contact With a Male Partner Who Had Applied Testosterone Gel as Percent of Baseline Value

Parameter	Observed Values as % of Baseline Value	
	Without Shirt	With Shirt
AUC _{0-t} (ng-hr/ml)	209%	112%
C _{MAX} (ng/ml)	272%	142%

Source: Medical Officer Calculation based on values shown in Table 13.

Table 16 shows the mean serum testosterone levels for the female partners during the 24 hours following contact with the male partner. Both actual observed values and baseline corrected values are presented.

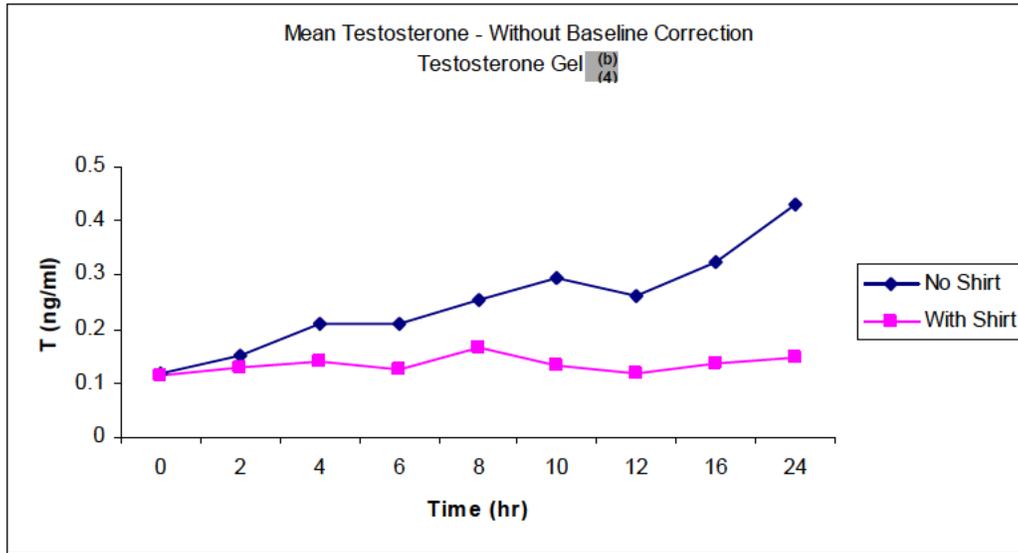
Table 16. Mean Testosterone Levels Following Contact with a Male Partner Who Had Applied Testosterone Gel

Time after contact (hr)	Observed Values (ng/ml)		Baseline corrected Values (ng/ml)	
	Without Shirt	With Shirt	Without Shirt	With Shirt
0	0.118	0.115	0.003	0.002
2	0.151	0.128	0.035	0.010
4	0.208	0.140	0.094	0.023
6	0.209	0.126	0.090	0.009
8	0.253	0.164	0.130	0.043
10	0.294	0.132	0.185	0.026
12	0.261	0.117	0.146	0.011
16	0.324	0.136	0.192	0.011
24	0.431	0.149	0.313	0.034

Source: Reviewer analysis of NDA 203098, Module 5.3.5.4.25.2.1, Datasets Final Export V3 Unadjusted, Final Export V2 Baseline Adjusted B vs A.

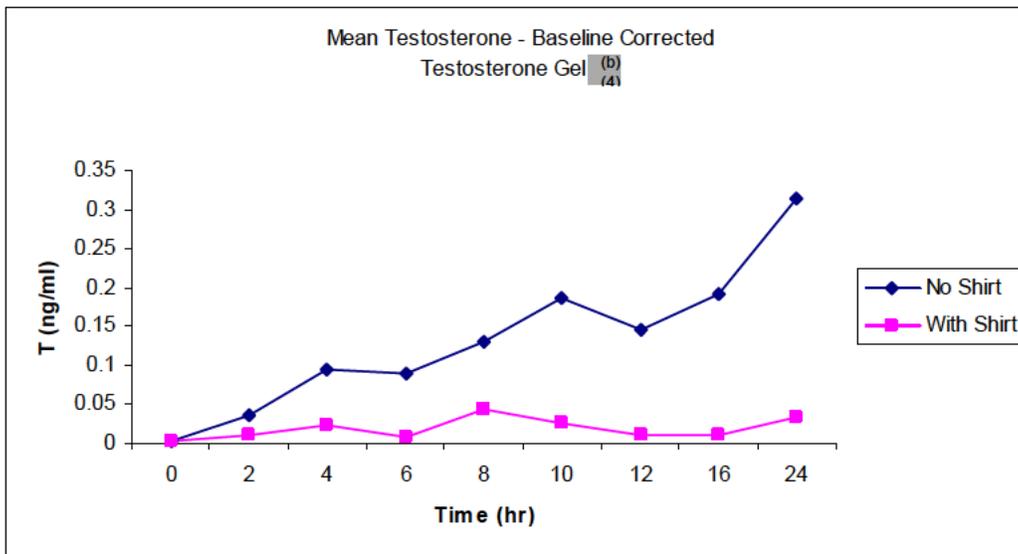
This information is displayed graphically in Figure 1 and Figure 2.

Figure 1. Mean Testosterone Levels Following Contact with a Male Who Had Applied Testosterone Gel (b) (4) - Observed Values



Source: Reviewer analysis of NDA 203098, Module 5.3.5.4.25.2.1, Datasets Final Export V3 Unadjusted, Final Export V2 Baseline Adjusted B vs A.

Figure 2. Mean Testosterone Levels Following Contact with a Male Who Had Applied Testosterone Gel (b) (4) - Baseline Corrected Values



Source: Reviewer analysis of NDA 203098, Module 5.3.5.4.25.2.1, Datasets Final Export V3 Unadjusted, Final Export V2 Baseline Adjusted B vs A.

Reviewer's comment: *In this reviewer's opinion, there is a clinically meaningful reduction in transfer when a clothing barrier is present. However, transfer is not eliminated by the barrier.*

The maximum baseline corrected increase in serum testosterone and AUC_{0-t} in female partners following contact with a male partner who had applied Testosterone Gel (b) (4) is shown for each subject in Table 17.

Table 17. Maximum Increase in Baseline Corrected Serum Testosterone and AUC for each Subject Following contact with Male Partner Who Had Applied Testosterone Gel (b) (4)

Subject	Maximum Increase (ng/ml)	Maximum Increase (ng/dl)	Time of Maximum Increase (Hours)	AUC (ng-hr/ml)
1	0.0195	1.95	4	0.104
2	0.0258	2.58	4	0.248
4	0.0842	8.42	24	0.951
5	0.0557	5.57	6	0.789
6	0.0300	3.00	4	0.284
7	0.0681	6.81	12	0.410
9	0.0587	5.87	10	0.591
10	0.1019	10.19	10	1.425
11	0.0236	2.36	10	0.336
12	0.0587	5.87	2	0.344
13	0.0293	2.93	24	-0.079
15	0.0317	3.17	24	0.126
17	0.0765	7.65	24	0.594
18	0.7382	73.82	8	1.842
19	0.0266	2.66	10	0.228
20	0.0180	1.80	24	-0.030
21	0.0528	5.28	24	0.015
22	0.0403	4.03	4	0.475
23	0.0462	4.62	24	0.410
24	0.0413	4.13	4	0.067

Source: NDA 203098, Module 5.3.5.4.25.2.1, Dataset Final Export V2 Baseline Adjusted B vs A.

Table 18 shows the actual observed maximum values over the 24 hour period following contact.

Table 18. Maximal Testosterone Values seen in the 24-hr Period Following Contact

Subject	Maximal Total Testosterone (ng/dl)	
	With Shirt	Without Shirt
1	8.38	19.56

Subject	Maximal Total Testosterone (ng/dl)	
	With Shirt	Without Shirt
2	9.40	25.54
4	18.66	35.7
5	18.98	46.12
6	17.16	86.59
7	9.33	22.09
9	21.63	43.12
10	18.31	111.5
11	9.42	21.38
12	11.74	150.7
13	19.61	24.53
15	8.74	30.36
17	31.52	38.96
18	92.18	92.9
19	10.57	14.98
20	11.42	30.38
21	22.44	37.53
22	22.01	47.64
23	12.67	37.02
24	15.36	101.7
Mean	15.65*	51.0
Range	8.4 - 31.5*	15.0 - 150.7

Excluding subject 18 – see discussion.

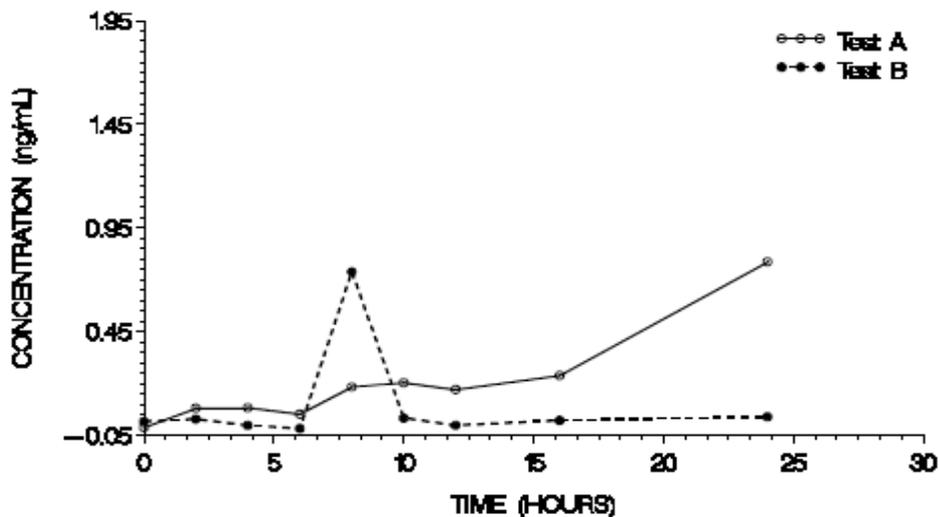
Source: Reviewers analysis, NDA 203098, Module 5.3.5.4.25.2.1, Datasets Final Export V3 Unadjusted

Reviewer's Discussion

The objective of this study was to evaluate the ability of a clothing barrier to prevent testosterone transfer from a treated patient to another individual with whom they have direct contact. The study shows that, with a clothing barrier, the mean maximal increase from baseline testosterone level at any time during the 24 hours following contact is 0.043 ng/ml (4.3 ng/dl). This compares to a mean maximal increase from baseline of 0.313 ng/ml (31.3 ng/dl) when contact occurs without the clothing barrier.

In evaluating the individual subjects maximal baseline corrected increase, subject number 18 appears to be an outlier with an increase of 73.8 ng/dl. Figure 3 shows this subject's 24 hour testosterone levels. This indicates that the 8 hour value, which was used to determine the maximal baseline corrected increase, is inconsistent with the 6 hour and 10 hour values. I believe that it is reasonable to conclude that this is an invalid result and that this subject's data should be withheld from an analysis of the maximal increases following contact.

Figure 3. Subject 18 Serum Testosterone Levels For 24 Hours Following Contact



Test A = without a shirt, Test B = with a shirt
Source: NDA 203098, Module 5.3.5.4.25.2.1, Dataset Final Export V2 Baseline Adjusted B vs A.

If the remaining 19 subjects are analyzed, the mean maximum change is 4.68 ng/dl and the median maximal change is 4.13 ng/dl. Eleven of the 19 subjects had maximal increases less than 5 ng/dl and only one subject had a maximal increase greater than 10 mg/dl.

The maximal actual values, again without subject 18, is 15.65 with a range of 8.3 – 31.5. Normal testosterone levels in healthy women may range up to 70 ng/dl.

Conclusions

Direct skin-to-skin contact between a man treated with Testosterone Gel (b) (4) and a female partner does transfer testosterone to the female partner. Maximum serum testosterone levels following this contact ranged as high as 150ng/dl.

It is reasonable to conclude that a clothing barrier prevents clinically significant transfer of testosterone from a male treated with Testosterone Gel (b) (4) to an untreated female with whom he has direct contact. The maximum value seen in the female partner after contact with a man wearing a shirt was 31ng/dl. Serum testosterone levels in these women remain within the range of normal and the mean increase from baseline is less than 5 ng/dl.

The testosterone Gel (b) (4) label should contain information about the potential for transfer and also about the ability of a clothing barrier to prevent transfer.

7.4.5.2 A Study of Washing Testosterone from Hands and Application Site (Study PRG-806)

This was a study to evaluate the ability to wash the Testosterone Gel product from the hands and from the application site. The design of this study is presented in section 5.3.4 Residual Testosterone After Washing – Study PRG-806.

Study Subjects

Thirty-six healthy non-smoking male subjects were enrolled in the study. Thirty-three subjects completed the entire study and are included in the analysis population. Two subjects withdrew because of scheduling conflicts that prevented further participation and one subject withdrew because of a viral illness. The entire thirty-six subjects are included in the safety population.

Subject Demographics

Table 19 shows the characteristics of the analysis population.

Table 19. Demographics of the Washing-Study Analysis Population

Parameter	Value
Age	30.0 (19 – 63)
Weight (lbs)	186.4 (137.5 – 260.0)
Height (in)	70.3 (65 – 76.1)
BMI	26.5 (21.1 – 33.6)
Race	
Native American	1 (3.0%)
Asian	3 (9.1%)
African American	1 (3.0%)
White	28 (84.8%)

Source: NDA 203098, Module 5.3.5.4.1, Table 11.2-2

Results

This study quantified the amount of drug remaining on the hands and arm/shoulder after a hand and application site wash and compared this amount to the amount present before washing.

Data are the mean \pm SD micrograms of testosterone. Application sites were sampled in three pre-define areas totally 150 cm² and the results are normalized to the 400 cm² total application area. Dose was 100 mg of testosterone applied as 10 grams of Testosterone ^{(b) (4)} Gel formulation. Table 20 shows the recovered testosterone, both from the hands and the application site. The percentage recovery is shown in Table 21.

Table 20. Amount of Testosterone Recovered After Hand and Application Site Washing (Mean µg ± SD)

Site	Recovery Without Wash	Recovery Following Wash
Hand	8478 ± 3552	399 ± 199
Application Site	28326 ± 7627	5802 ± 2770

Source: NDA 203098, Module 5.3.5.4.1, Table 11.4.7-1

Table 21. Testosterone Recovered After Hand and Application Site Washing (Percent of Applied Dose)

Site	Recovery Without Wash	Recovery Following Wash	Reduction in Recovery following Wash
Hand	8.48 ± 3.55	0.4 ± 0.2	95.3 %
Application Site	28.33 ± 7.63	5.8 ± 2.8	79.5 %

Source: NDA 203098, Module 5.3.5.4.1, Table 11.4.7-2

Discussion

This study has demonstrated that the wash-off from the hands (approximately 95%) differs from the wash-off from the shoulder/upper arm application site (approximately 80%). This appears to be a reasonable result. A larger portion of the product is washed from the hands shortly after it has been applied than can be removed from the application site two hours after application. Two factors potentially contribute to this difference.

First, the two hour time difference between the hand washing and the site washing would allow a greater portion of the applied dose to penetrate the epithelium where soap and water washing would be less likely to remove it, but where it could still be recovered by the ethanol-impregnated sponges used in the recovery process. This could explain the smaller fraction remaining on the hands as compared to the application site.

Secondly, the washing effort used to remove the product from the hands is quite localized to the site of interest (the hands) whereas the washing effort during the shower is directed at the entire body rather than merely at the site of interest (the shoulder/upper arm). Therefore the amount of effort used in washing the actual site of interest is likely to be greater with the hand washing as compared to the site washing.

The Sponsor included a comparator arm in the study that evaluated the wash-off of the reference listed drug Androgel 1% from both the hands and the application site. This showed that the wash-off of the RLD was similar to the wash-off of the Testosterone Gel (b) (4) both from the hands (Androgel 95.3%, Testosterone Gel (b) (4) 95.3%) and from the application site (Androgel 75.9%, Testosterone Ge (b) (4) 79.5%).

Conclusion

This study has demonstrated that the product can be acceptably washed from the hands and from the application site. It provides the information necessary to properly label the product.

7.5.4.3 Skin Sensitization Study (DS102308)

This was a study to evaluate the sensitizing potential of Testosterone Gel (b) (4) on normal skin. The study design is discussed in section 5.3.2 Skin Sensitization Study - DS102308.

Study Subjects

Two hundred twenty-six subjects were enrolled in the study and two hundred and three completed it. Table 22 shows the disposition of the patients.

Table 22. Study DS102308 Subject Disposition

	Number
Subjects enrolled	226
Reason for Discontinuation	
Adverse event	9
Non-compliance	1
Withdrawn consent	7
Lost to follow-up	1
Excluded medication	1
Total Subjects Discontinued	23
Subjects Completing Study	203

Source: NDA 203098, Module 5.3.5.4.1, Table 10-1, page 31.

The demographics of the study population is shown in Table 23.

Table 23. Demographic Summary of Population

N = 226	
Age	
Mean ± SD	49 ± 13
Range	18 – 75
Gender	
Male	107 (47.3%)
Female	119 (52.7%)
Race	
White	184 (81.4%)
Black	38 (16.8%)
Asian	4 (1.8%)

Source: NDA 203098, Module 5.3.5.4.1, Table 10-2, page 32

Adverse Events

There were a total of 21 adverse events reported in 15 subjects. This included one serious adverse event. Ten subjects discontinued medication because of an adverse event. Table 24 shows a list of the adverse events reported.

Table 24. Adverse Events Reported in Study DS102308

Event	Number	Drug Related
Headache	12	Possible
Phlebitis	1	Unrelated
Diarrhea	1	Possible
Flea Bites	1	Unlikely
Chest Pain	1	Unlikely
Priapism	1	Possible
Dyspnea	1	Possible
Insomnia	1	Possible
Discolored penis	1	Possible
Breast tenderness	1	Probable

Source: NDA 203098, Module 5.3.5.4.1, Appendix 16.2.8

The SAE was an episode of phlebitis of the right calf. The patient was hospitalized for the initiation of anti-coagulation. The problem was resolved.

Reviewer's Comment: *The adverse events seen do not suggest events due to this product that differ from those seen with other testosterone products.*

Results – Dermal Sensitization

Two hundred three subjects (203) completed the challenge phase of the study and were included in the sensitization analysis. A summary of the repeated insult patch test responses during the induction phase is provided in Table 25.

Table 25. Mean Cumulative Irritation Scores During Induction Phase

Product Tested	Mean Irritation Score	P value vs				
		Testosterone Gel (b) (4)	Androgel	Vehicle	Positive Control	Saline
Testosterone Gel (b) (4)	0.169	-	0.345	0.070	<0.001	0.005
Androgel	0.141	-	-	0.385	<0.001	0.066
Vehicle	0.117	-	-	-	<0.001	0.333
Positive Control	0.586	-	-	-	-	<0.001
Saline	0.089	-	-	-	-	-

Source: NDA 203098, Module 5.3.5.4.1, Table 12-1, page 33

The responses to challenge following the induction phase is shown in Table 26.

Table 26. Summary of Challenge Responses to Testosterone Gel (b) (4)

Response Score	Time following Challenge Patch Removal			
	0.5 hr	24 hr	48 hr	72 hr
0	196	187	194	197
1	5	12	5	5
2	2	3	3	1
3	0	1	1	0

Source: NDA 203098, Module 5.3.5.4.1, Table 11-1, page 32

In the challenge phase of the study, 1 subject (Subject 154) who exhibited minimal to definite erythema (scores of 1 and 2) during induction to both the investigational product and the AndroGel®, exhibited moderate erythema with no significant edema (score of 3) to both products 24 and 48 hour after challenge patch removal. Subject No. 172 who exhibited definite to moderate erythema with no significant edema (scores of 2 and 3) during induction at the vehicle site exhibited moderate erythema with no edema (score of 3) at 24 and 48 hours after challenge patch removal. Both subjects had the reactions decrease to definite erythema (score of 2) by the 72-hour challenge evaluation. With the exception of these 2 subjects, there was no more than minimal erythema observed (score of 1) at the 72-hour challenge evaluation for the testosterone gel (b) (4), AndroGel®, Vehicle and 0.1% SLS aqueous solution. There were no reactions observed at the 72-hour challenge evaluation for the saline.

There were no reactions to either the investigational product or the comparator product at challenge indicative of a possible sensitization response, nor any that required rechallenge.

Reviewer's Comment: Study DS102308 provides evidence that there is no significant sensitization of the skin by Testosterone Gel (b) (4). It also provides support for the conclusions of Study DS310208 that Testosterone Gel (b) (4) does not have a significant likelihood of irritating the skin.

7.5.4.4 Skin Irritation Study (DS310208)

This was a study to evaluate the irritation potential of Testosterone Gel (b) (4) on normal skin. The study design is discussed in section 5.3.3 Skin Irritation Study – DS310208.

Study Subjects

Thirty-eight subjects were enrolled into the study and thirty-three completed it. Four subjects withdrew the consent for the study. One subject withdrew from the study because of an adverse event, a knee injury, which was unrelated to the investigational product. Table 27 shows the demographics of the enrolled population.

Table 27. Demographics of Study DS310208 Population

	N = 38
Age	
Mean	43.5
Range	19 – 68
Gender	
Male	19
Female	19
Race	
Caucasian	35
Black	3

Source: NDA 203098, Module 5.3.5.4.1, Table 10-2, page 27

Adverse Events

Two subjects reported adverse events. One subject withdrew from the study after a knee injury which required surgical correction. A second subject reported a head cold. Neither event was judged to be related to the investigational product. There were no deaths or serious adverse events reported.

Results

Table 28 shows the mean cumulative irritation scores for Testosterone Gel (b) (4) and for the Androgel, vehicle, positive control and saline comparators.

Table 28. Mean Cumulative Irritation Scores

Product Tested	Mean Irritation Score	P value vs				
		Testosterone Gel (b) (4)	Androgel	Vehicle	Positive Control	Saline
Testosterone Gel (b) (4)	0.016	-	0.266	0.580	<0.001	0.747
Androgel	0.090	-	-	0.575	<0.001	0.429
Vehicle	0.053	-	-	-	<0.001	0.818
Positive Control	2.824	-	-	-	-	<0.001
Saline	0.037	-	-	-	-	-

Source: NDA 203098, Module 5.3.5.4.1, Table 11-1, page 28

Study Conclusions

The Testosterone Gel (b) (4), AndroGel, Vehicle, and Saline showed no evidence of significant irritation. Testosterone gel (b) (4) had a mean cumulative irritation scores of 0.016, AndroGel had a score of 0.090, the Vehicle had a score of 0.053 and the Saline had a score of 0.037. There was no statistically significant difference between the testosterone gel (b) (4), AndroGel, Vehicle and Saline. All products were statistically significantly less irritating than the SLS 0.2% positive control ($P < .001$), which had a mean cumulative irritation score of 2.824.

7.4.6 Immunogenicity

Testosterone is a substance that has a long history of human use with no immunogenicity issues. No studies of immunogenicity were done to support this application.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

No evaluation of adverse events relative to dose was done.

7.5.2 Time Dependency for Adverse Events

No evaluation of time dependency of adverse events was done.

7.5.3 Drug-Demographic Interactions

No evaluation of Drug-Demographic Interactions was done.

7.5.4 Drug-Disease Interactions

No drug-disease interaction studies or analyses were performed.

7.5.5 Drug-Drug Interactions

No drug-drug interaction studies were performed.

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

There are several lines of evidence that suggest the potential for a relation between testosterone and prostate cancer development.

Firstly, the clinical incidence of prostate cancer varies significantly across the world, with the highest incidence occurring in African-Americans (79 per 100 000) and the lowest in Japanese males (4 per 100 000)¹. Ross et al.² have demonstrated that at the time of puberty African American males have 10 to 15% higher levels of circulating testosterone than their Caucasian counterparts, but equal levels compared with Japanese men, who because of a genetic deficiency of 5 α -reductase actually have lower DHT levels in the prostate. In addition, differences in the function of 5 α -reductase genes affecting the AR and androgen metabolism contribute to an increased risk of prostate cancer in African-American men.³

Secondly, prostate cancer can be induced in rats to whom large amounts of testosterone have been administered.⁴ Thirdly, men castrated prior to puberty do not develop prostate cancer.⁵ A reduced risk of this cancer has been also been associated

1 Oesterling J, Fuks Z, Lee CT. Cancer of the Prostate. in : Devita V, Hellman S, Rosenberg S, editors. Cancer: principles and practices in Oncology. 5th ed. Lippincott-Raven 1997.

2 Ross R, Bernstein L, Lobo R. 5-alpha-reductase activity and risk of prostate cancer among Japanese and US white and black males. Lancet 1992; 339: 887-9

3 Devgan SA, Henderson BE, Yu MC, et al. Genetic variation of 3 beta-hydroxysteroid dehydrogenase type II in three racial/ethnic groups: implications for prostate cancer risk. Prostate 1997; 33 (1): 9-12

4 Nobel R. The development of prostatic adenocarcinoma in Nb rats, following prolonged sex hormone administration. Cancer Res 1977; 37: 1929-33

5 Huggins C, Hodges C. Studies on prostatic cancer 1: the effect of castration, of estrogen and of androgen injection on serum phosphatases in metastatic carcinoma of the prostate. Cancer Res 1941; 1: 293-7

with hyperoestrogenic states (e.g. cirrhosis cases)⁶, and estrogen therapy has a palliative role in advanced prostate cancer because it competes with testosterone in the hypothalamus and suppresses gonadotropin production. Finally, prostate cancer may be successfully treated by surgical or medical androgen ablation.

Despite these suggestions of a relationship between testosterone and the development of prostate cancer, there is no evidence that suggests that elevated levels of testosterone or testosterone treatment of hypogonadal men is associated with an increase in prostate cancer.^{7,8} A recent meta-analysis⁹ examined 51 placebo controlled trials of testosterone therapy. The conclusion was that, although the quality of the evidence was low to medium, “testosterone therapy had no significant effects on all-cause mortality, (or) prostatic ... outcomes...”

There have, however, been numerous reports of the effect of testosterone therapy resulting in an occult prostate carcinoma becoming clinically manifest^{10,11,12}. The possibility of “unmasking” an occult tumor with testosterone therapy is something that prescribers should be made aware of.

Reviewer’s comment: *The best evidence at this time is that, despite the known effects of testosterone on established prostate cancer, there is no evidence to suggest that there is a relationship between testosterone therapy and the development of prostate cancer.*

7.6.2 Human Reproduction and Pregnancy Data

Testosterone Gel ^{(b) (4)} is not intended for use by, and should not be used by pregnant or lactating women. Safety information is not available for use in pregnancy and lactation. The amount of applied testosterone that would appear in human milk is unknown. It is known that exposure of a fetus to androgens may result in varying degrees of virilization.

6 Glantz C. Cirrhosis and carcinoma of the prostate gland. J Urol 1964; 91: 291-3

7 Eaton NE, Reeves GK, Appleby PN et al. Endogenous sex hormones and prostate cancer: a quantitative review of prospective studies. Brit J of Cancer 1999; 80(7): 930-934.

8 Hsing AW, Comstock GW. Serological Precursors of Cancer: Serum Hormones and Risk of Subsequent Prostate Cancer. Cancer Epidemiology 1993; 2: 27-32.

9 Fernandez-Balsells M, Murad MH, Lane M et al. Adverse Effects of Testosterone Therapy in Adult Men: A Systematic Review and Meta-Analysis. J Clin Endo Metab. 2010; 96(6): 2560-2575.

10 Loughlin KR, and Richie JP: Prostate cancer after exogenous testosterone treatment for impotence. J Urol 157: 1845, 1997.

11 Morgenthaler A, Bruning CO III, and DeWolf WC: Incidence of occult prostate cancer in men with low total or free serum testosterone. JAMA 276: 1904–1906, 1996.

12 Curran MJ, and Bihrlle W. Dramatic rise in prostate-specific antigen after androgen replacement in a hypogonadal man with occult adenocarcinoma of the prostate. Urology 53: 423–424, 1999.

7.6.3 Pediatrics and Assessment of Effects on Growth

The safety and efficacy of Testosterone Gel (b) (4) in males <18 years old has not been established. Use in prepubertal males would have the potential to result in premature closure of the epiphyses. Testosterone Gel (b) (4) is not indicated for use in this population.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

There was no experience with overdosage in the development program for Testosterone Gel (b) (4). A non-clinical report¹³ of the effect of testosterone overdose in hamsters showed that, at high doses, testosterone causes central autonomic depression. There is testosterone overdose reported in the label of a testosterone gel, (AndroGel) – “There is one report of acute overdosage with use of an approved injectable testosterone product: this subject had serum testosterone levels of up to 11,400 ng/dL with a cerebrovascular accident.” This reviewer is unaware of any further details of this case. Treatment of overdosage would consist of discontinuation of testosterone treatment together with appropriate symptomatic and supportive care.

Androgenic steroids are drugs of abuse. They are taken in large quantities by athletes and others to increase performance, with negative health consequences. As a result, in 1991 testosterone and related androgenic steroids were declared controlled substances.

No information on testosterone withdrawal or rebound is available.

7.7 Additional Submissions / Safety Issues

There were no additional submissions or safety issues beyond those discussed earlier in this review.

8 Postmarket Experience

There is no postmarketing experience with this new product.

¹³ Peters KD, Wood RI. Androgen dependence in hamsters: overdose, tolerance, and potential opioidergic mechanisms. *Neuroscience* 130(4): 971-981. 2005

9 Appendices

9.1 Literature Review/References

None.

9.2 Labeling Recommendations

It is premature to discuss labeling recommendations at this time,

9.3 Advisory Committee Meeting

No advisory committee meeting was held to discuss this product.

9.4 Office of Scientific Investigations Report of Bioequivalence Site Inspections

The report from the Office of Scientific Investigations, Division of Bioequivalence concerning the inspections of the clinical and analytical sites involved in the Sponsor's bioequivalence study 03-0415-001 is attached.

Clinical Review
Donald McNellis, MD
NDA 203,098
Testosterone ^{(b) (4)} Gel (Perrigo Israel Pharma Ltd.)

MEMORANDUM

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

DATE: April 2, 2012

TO: Audrey L. Gassman, M.D.
Deputy Director, Division of Reproductive and
Urologic
Products

Dennis Bashaw, Pharm.D.
Director, Division of Clinical Pharmacology 3
(DCP3)
Office of Clinical Pharmacology

FROM: Gopa Biswas, Ph.D.
Bioequivalence Branch
Division of Bioequivalence and GLP Compliance
Office of Scientific Investigations

THROUGH: Sam H. Haidar, Ph.D., RPh
Chief, Bioequivalence Investigations Branch,
Division of Bioequivalence and GLP Compliance
Office of Scientific Investigations

William H. Taylor,
Ph.D., DABT Director
(Acting)
Division of Bioequivalence and GLP Compliance
Office of Scientific Investigations

SUBJECT: Review of EIRs Covering NDA 203-098,
Testosterone Gel
^{(b) (4)}, sponsored by Perrigo Israel
Pharmaceuticals

At the request of DRUP and DCP3, DBGC conducted inspections of the clinical and analytical portions of the following bioequivalence study:

Study Number: 03-0415-001

Study Title: "A Randomized, Single-Dose, Three-Way Crossover Relative Bioavailability Study of Testosterone Gel Formulations in Hypogonadal Men"

The clinical portion of the study was conducted at (b) (4). However this facility closed in 2006 after being acquired (b) (4). Records of the clinical study were transferred to a record-archiving facility (b) (4), where they were audited from February 27-March 1, 2012. The bioequivalence reserve samples were stored (b) (4).

The reserve samples were collected at this site during (b) (4), with the written assurance executed by a (b) (4) representative. The inspection for the analytical portion was conducted (b) (4).

Form

FDA-483 containing inspectional observations was issued at the end of both inspections (**Attachments 1 and 2**).

A written response to inspectional observations has not been received (b) (4) as of this writing. This review is being expedited in order to meet the Review Division's deadline requirement and will be amended upon receipt of a response.

Our evaluation of the observations follows:

Clinical Site : (b) (4)

1. An investigation was not conducted in accordance with the investigational plan. Specifically, A. Subject 12 experienced an adverse event of hypertension that was not reported to the sponsor.

The firm should have reported the adverse event to the sponsor as required by the study protocol. However, this observation is not likely to have any impact on bioequivalence outcomes.

B. Period 1 pre-dose erythema and edema scores were not recorded for any of the 24 subjects.

Because the subjects were not yet dosed at this time, this observation was not likely to have impact on subjects' safety or on study outcomes.

C. 48-hour erythema and edema scores were not recorded for subjects 01 (Period 1), 12 (Period 3), and 19 (Period 3).

This observation is not likely to have impact on study outcomes.

D. Four blood samples were taken outside of the protocol specified window.

- 1. Subject 02's Period 2/hour 4 blood draw was 10 minutes late & Period 3/hour 3 blood draw was 4 minutes late.**

2. Subject 06's Period 1/hour 1 blood draw was 3 minutes late.
3. Subject 19's Period 2/hour 72 blood draw was 286 minutes late.

These sampling deviations were reported in the clinical study report. These sampling time deviations are unlikely to affect pharmacokinetic analyses.

- E. Subject 02 did not receive a hepatitis C test at screening.
- F. Subject 05 did not receive a CBC test at screening.
- G. Subject 20 took medication during the 10 hour post dose restriction period. The subject was dosed at 0816 on 09/06/03, 09/13/03, and 09/20/03. The 10 hour restriction period expired at 1816.
 1. On 09/06/03 he took Humalog at 0832 and 1805.
 2. On 09/13/03 he took Altace, aspirin, and Coreg at 1810 and Humalog at 1805.
 3. On 09/20/03 he took Humalog at 0855, 1229 & 1802.

These deviations were reported to the study sponsors and included in the final study report. This observation is not likely to have an impact on study outcomes.

2. The general requirements for informed consent were not met in that the information given was not in language understandable to the subject or the subject's representative. Specifically, Subject 22 was originally consented into the study on 08/18/03 using a Spanish language consent form. He was re-consented with an English version of the updated ICF on 09/05/03.

It is not known if the subject's safety or welfare was compromised due to incomplete documentation of informed consent. However, no adverse events were reported for Subject 22 during the study. This observation is not likely to have an impact on study outcomes.

3. Investigational drug disposition records are not adequate with respect to dates. Specifically, the drug administration records for Period 3 do not indicate the date and time at which the drug was administered.

Due to the lack of documentation of date, time, and the product administered to each subject, the administration of study drug products during Period 3 cannot be assured. Therefore, OSI is of the opinion that data from Period 3 are not reliable, and that the data should be excluded from consideration. However, this will lead to incomplete subject blocks in the study design, with no subjects that received all three drugs. The clinical reviewer should further evaluate the impact of exclusion of data. Although (b) (4) has not responded to this observation, it is unlikely that Period 3 dosing records can be found at this time.

Analytical site: (b) (4)

1. **Failure to adjust calibrator and QC samples concentrations for endogenous testosterone in blank plasma matrix used for preparing them.**

(b) (4) used plasma obtained from female donors to use as blank matrix for preparation of calibrators and QCs. However, the firm did not determine a baseline level of testosterone in blank matrix and adjust the concentrations of standards and QCs used during method validation and study. As a result the accuracy of testosterone determination can not be assured.

2. **Failure to document the following aspects of method validation and study conduct:**
 - a) **For freeze-thaw stability demonstration at (b) (4), movements of QC samples during freeze-thaw cycles were not documented in sample processing sheet or freezer log book.**
 - b) **A freezer log for (b) (4) freezer was not maintained to record sample movement from and to the freezer during validation and study sample analysis.**

Although records for demonstration of stability during validation are incomplete, during the study conduct QC samples were stored with study samples. Because there were no rejected runs due to failure of calibration curve or QCs, the incomplete pre-study validation of stability is not likely to have significant impact on study outcomes.

- c) **Failure to document anticoagulant used for all the plasma lots used as blanks or for preparing calibrators and, QC samples, during method validation and study sample analysis.**

- d) Documents were not available to ensure that all plasma lots used during method validation and study were stripped with charcoal in order to eliminate endogenous testosterone.

The incomplete records for blank plasma used during method validation and the study did not ensure the use of appropriate blank matrix for preparation of calibrators and QCs. Moreover, it could not be verified that plasma lots used for preparing calibrators and QCs were stripped with charcoal to remove endogenous testosterone. As a result, the absolute concentrations of measured testosterone cannot be assured.

3. Failure to reject analytical runs with blank samples showing 20% or more of LLOQC response. Blank samples in the majority of analytical runs showed 20% to 30% of LLOQC response but all the runs were accepted based on SOP BAS-RMT-02.

The SOP BAS-RMT-02 only required r^2 for the fitted calibration line to be more than 0.98, irrespective of blank samples or QC results. The inaccuracies due to testosterone in blank samples are unlikely to have impact on bioequivalence assessments.

Firm has revised their SOP and the current version includes Agency recommended criteria.

- 4a) Failure to demonstrate selectivity in charcoal stripped plasma.
4b) Failure to reject selectivity experiment in non-stripped plasma although the (b) (4) activity samples failed acceptance criteria (b) (4).

The firm should demonstrate selectivity in charcoal stripped plasma. The firm's selectivity experiments in non-stripped plasma failed due to QCs having more than (b) (4) of nominal concentration.

Conclusions:

Following evaluation of the inspectional observations for clinical and analytical portions of study 03-0415-001, DBGC recommends that:

1. The proper dosing of subjects during Period 3 cannot be assured. Data from Period 3 should be excluded from statistical evaluation.
2. The measured concentrations of plasma testosterone are not adjusted for the endogenous testosterone in blank plasma used to prepare calibrators and QCs.

Gopa Biswas, Ph.D.

Bioequivalence Branch, DBGC, OSI

Final Classifications:

VAI-

VAI:

(b) (4)

cc: OSI/Ball/Moreno
OSI/DBGC/Taylor/Dejernett
OSI/DBGC/BB/Haidar/Skelly/Biswas
OTS/OCP/DCPIII/Bashaw/Kim/Li
OND/ODE3/DRUP/Kaul/Roule/Gassman
SE-FO/FLA-DO/FIB/Torres/Sinninger
HFR-CE1520/Keefer
HFR-SE2585/Gunn
HFR-PA2530/Sawyer
Draft: GB 4/2/2012
Edit: MFS 4/3/12
DSI: 6306; O:\BE\eircover\203098per.tes.doc
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/s/

GOPA BISWAS
04/03/2012

SAM H HAIDAR
04/03/2012

WILLIAM H TAYLOR
04/04/2012

9.5 Office of Scientific Investigations Addendum Report of Bioequivalence Site Inspections

The Office of Scientific Investigations report following the Sponsor's responses to the deficiencies noted in the initial inspection report is attached.

MEMORANDUM

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

DATE: April 18, 2012

TO: Audrey L. Gassman, M.D.
Deputy Director, Division of Reproductive and Urologic
Products

Dennis Bashaw, Pharm.D.
Director, Division of Clinical Pharmacology 3 (DCP3)
Office of Clinical Pharmacology

FROM: Gopa Biswas, Ph.D.
Bioequivalence Branch
Division of Bioequivalence and GLP Compliance
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THROUGH: Sam H. Haidar, Ph.D., RPh
Chief, Bioequivalence Investigations Branch,
Division of Bioequivalence and GLP Compliance
Office of Scientific Investigations

William H. Taylor, Ph.D., DABT
Director (Acting)
Division of Bioequivalence and GLP Compliance
Office of Scientific Investigations

SUBJECT: Addendum to Review of EIRs Covering NDA 203-098,
Testosterone Gel (b)
(4), sponsored by Perrigo Israel
Pharmaceuticals

At the request of DRUP and DCP3, DBGC conducted inspections of the clinical and analytical portions of the following bioequivalence study:

Study Number: 03-0415-001

Study Title: "A Randomized, Single-Dose, Three-Way Crossover Relative Bioavailability Study of Testosterone Gel Formulations in Hypogonadal Men"

DBGC's evaluation of inspectional findings at the clinical and analytical sites for this study was provided to DRUP and DCP3 in a memorandum dated April 4, 2012. DBGC received a response to inspectional findings for the clinical portion of the study on

April 10, 2012 from (b) (4) (**Attachment 1**). An additional response to address observation #3 from the sponsor Perrigo was received on April 13, 2012 following a teleconference with DRUP, DCP3, and OSI on April 11, 2012 (**Attachment 2**). When a response from analytical site (b) (4) is received an additional amended review will be provided after DBGC evaluation of the response. This addendum provides our evaluation of the responses for clinical portion only:

Clinical Site: (b) (4)

1. An investigation was not conducted in accordance with the investigational plan. Specifically,
 - A. Subject 12 experienced an adverse event of hypertension that was not reported to the sponsor.
 - B. Period 1 pre-dose erythema and edema scores were not recorded for any of the 24 subjects.
 - C. 48-hour erythema and edema scores were not recorded for subjects 01 (Period 1), 12 (Period 3), and 19 (Period 3).
 - D. Four blood samples were taken outside of the protocol specified window.
 1. Subject 02's Period 2/hour 4 blood draw was 10 minutes late & Period 3/hour 3 blood draw was 4 minutes late.
 2. Subject 06's Period 1/hour 1 blood draw was 3 minutes late.
 3. Subject 19's Period 2/hour 72 blood draw was 286 minutes late.
 - E. Subject 02 did not receive a hepatitis C test at screening.
 - F. Subject 05 did not receive a CBC test at screening.
 - G. Subject 20 took medication during the 10 hour post dose restriction period. The subject was dosed at 0816 on 09/06/03, 09/13/03, and 09/20/03. The 10 hour restriction period expired at 1816.
 1. On 09/06/03 he took Humalog at 0832 and 1805.
 2. On 09/13/03 he took Altace, aspirin, and Coreg at 1810 and Humalog at 1805.
 3. On 09/20/03 he took Humalog at 0855, 1229 & 1802.

(b) (4) Response:

The firm stated that current (b) (4) processes at other sites prevent similar events.

OSI is of the opinion that the observations are not likely to have impacted subject safety or study outcomes.

- 2. The general requirements for informed consent were not met in that the information given was not in language understandable to the subject or the subject's representative. Specifically, Subject 22 was originally consented into the study on 08/18/03 using a Spanish language consent form. He was re-consented with an English version of the updated ICF on 09/05/03.**

(b) (4) Response:

The firm stated that current (b) (4) processes protocols are designed to prevent such incidents.

OSI is of the opinion that the screening tests before 9/5/2003 are not likely to have impacted subject safety even without effective informed consent. Notably the English ICF was executed on 9/5/2003 before the first period dosing on 9/6/2003.

- 3. Investigational drug disposition records are not adequate with respect to dates. Specifically, the drug administration records for Period 3 do not indicate the date and time at which the drug was administered.**

(b) (4) Response:

The firm stated that current processes and protocols assure complete record retention.

Perrigo Response:

Perrigo stated that the dosing data were transcribed electronically into the CRFs. Perrigo also referred to "Attachment 5: Protocol Deviations" in their response, which lists deviations for blood sampling times but none for dosing.

DBCg notes that the CRFs only indicate the scheduled dosing times, with scheduled and actual blood sampling times, for all three periods. However, documents to show dosing date and time during period 3, comparable to the records available for periods 1 and 2, have not been located. The inspection (b) (4)

documented (**Attachment 3**, EIR and dosing logs, pp. 13, 15, 17) that the dosing records are available only for periods 1 and 2. DBGC finds the transcribed CRFs insufficient to document dosing each subject with a specific product at a specific time during period 3.

Conclusions:

Following evaluation of the responses to Form FDA 483 observations for the clinical portions of study 03-0415-001, DBGC's recommendations remain same as provided earlier:

1. The proper dosing of subjects during Period 3 cannot be assured. Data from Period 3 should be excluded from statistical evaluation.
2. The measured concentrations of plasma testosterone have not yet been adjusted for endogenous testosterone in blank plasma used to prepare calibrators and QCs.

Gopa Biswas, Ph.D.

Bioequivalence Branch, DBGC, OSI

Final Classifications:

VAI-

VAI:

(b) (4)

cc: OSI/Ball/Moreno
OSI/DBGC/Taylor/Dejernett
OSI/DBGC/BB/Haidar/Skelly/Biswas
OTS/OCF/DCPIII/Bashaw/Kim/Li
OND/ODE3/DRUP/Kaul/Roule/Gassman
SE-FO/FLA-DO/FIB/Torres/Sinninger
HFR-CE1520/Keefer
HFR-SE2585/Gunn
HFR-PA2530/Sawyer
Draft: GB 4/18/2012
Edit: MFS 4/19/12
DSI: 6306; O:\BE\eircover\203098per.tes.addendum.doc
FACTS: 1378734

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/s/

DONALD R MCNELLIS
05/02/2012

SURESH KAUL
05/02/2012

AUDREY L GASSMAN
05/02/2012

NDA 203,098
Testosterone Gel (b) (4)

Medical Officer's Filing Review Memorandum

Application Letter Date: July 4, 2011
45-Day Filing Review Date: September 3, 2011
PDUFA Goal Date: May 5, 2012
Sponsor: Perrigo Israel Pharmaceuticals Ltd.
Product and Dose: Testosterone Gel (b) (4)
Indication: Hypogonadism in males

1. Executive Summary Objective: This review is conducted to fulfill a regulatory requirement of reviewing **NDA 203098** (testosterone Gel (b) (4)) to determine its suitability for filing under 21 CFR 314.50. This document will also serve as the basis for communicating to the sponsor the review issues identified during the initial filing period.

Recommendation: Following a preliminary review of results from the pivotal bioequivalence study, as well as from the skin irritation, the hand/site washing and the transfer studies, it is the impression of the clinical reviewer that the application is sufficiently complete to permit a substantive clinical review and should be filed.

2. NDA Filing Review

Testosterone is an endogenous androgen that is responsible for normal growth and development of the male sex organs and for maintenance of secondary sex characteristics. Male hypogonadism results from insufficient production of testosterone and is characterized by low serum testosterone concentrations. Symptoms associated with male hypogonadism include decreased sexual desire with or without impotence, fatigue and loss of energy, mood depression, regression of secondary sexual characteristics, and osteoporosis. The Endocrine Society guidelines suggest that the diagnosis of testosterone deficiency in adult men should be based on a comprehensive review of patient symptoms and signs, and measurement of serum testosterone levels by a reliable assay.

Testosterone replacement therapy in men is chronic in nature and designed to improve clinical manifestations of low testosterone and also to place circulating levels of this important hormone into the normal physiological range for healthy men (~300 to ~1050 ng/dL). Male hypogonadism has historically been treated with testosterone replacement therapy via oral or parenteral routes to elevate serum testosterone levels into the normal range.

Currently available treatment options for hypogonadism include intramuscular injections, sub dermal implants, buccal systems, oral formulations, and transdermal patches and gels. The most commonly used formulations are the gels, which are applied with the hands to the shoulders and upper arms and/or abdomen.

This is a 505(b)(2) application and the reference listed drug is Androgel. The Sponsor's gel formulation differs from Androgel in that it contains isostearic acid, (b) (4) rather than isopropyl myristate. The Sponsor's application includes three dosage forms – 2.5 gm and 5 gm foil packages and a multidose pump. This corresponds to the three dosage forms of Androgel.

Criteria for Filing: This review is based on the three criteria proposed in the FDA Guidance “New Drug Evaluation Guidance Document: Refusal to File” (July 12, 1993), which represents FDA's interpretation of 21 CFR 314.50. These criteria are:

- Omission of a section of the NDA required under 21 CFR 314.50, or presentation of a section in an incomplete manner
- Failure to include evidence of effectiveness compatible with the statute and regulations
- Omission of critical data, information or analyses needed to evaluate effectiveness and safety or failure to provide adequate directions for use.

Question 1: Does this NDA omit a section required under CFR 314.50 or was a particular section presented in such a manner to render it incomplete for clinical review?

Answer: No

This application is a 505(b)(2) submission. The Sponsor will rely on the Agency's finding of the efficacy and safety of Androgel. They have submitted a study evaluating the bioavailability of their Testosterone (b) (4) gel as compared to the bioavailability of Androgel. In addition, as requested by the Agency, they have evaluated the skin tolerability of their product, the ability to wash it from the skin, and the potential for transfer to other individuals.

This NDA contains the critical sections in sufficient detail to permit a substantive Clinical review. As requested by the Division, the Sponsor has submitted the report of a bioequivalence study evaluating their product in relation to Androgel. They have also submitted safety data that is consistent with ICH requirements, labeling, and Safety/Efficacy summaries. This data includes a skin sensitization study, a skin irritation study, studies of hand and application site washing effectiveness, and a study of the transfer of testosterone from a treated individual to another by direct contact.

Question 2: Does the NDA clearly fail to include evidence of effectiveness compatible with the statute and regulations, for example:

- **Lack of any adequate and well-controlled studies, including use of obviously inappropriate or clinically irrelevant study endpoints**
- **Presentation or what appears to be only a single adequate and well-controlled trial without adequate explanation**
- **Use of study design clearly inappropriate**

Answer: No

The Sponsor is relying on the Agency's finding of the effectiveness of Androgel. In support of the appropriateness of that reliance, the Sponsor has conducted a bioequivalence study evaluating the pharmacokinetics of their product as compared to Androgel.

Trial Design

The Sponsor's trial was a single-dose, three-period, three-treatment, three-sequence, randomized, crossover study. The three treatments consisted of two test formulations of Testosterone Gel ^{(b) (4)} and the reference drug, Androgel.

Twenty-four subjects were randomized. In each period, each subject received a 10-gram application of either one of the test formulations or the reference formulation applied to the shoulders and upper arms. A series of blood samples were collected pre-dose and for 72 hours following the application. These samples were used for determination of plasma testosterone concentration. A one-week washout period separated each of the three treatment periods.

Primary Objective

The primary objective of the study was to compare the pharmacokinetics of each of the two test formulation to the pharmacokinetics of Androgel.

Results

The results for each test formulation are shown in the following Tables.

Table 1. Test Formulation 1 (Lot T06P030) Compared to AndroGel

Parameter	Least-Squares Means ¹		Ratio ²	CV% ³	90% Confidence Interval ⁴	
	Formulation-1	Reference			Lower	Upper
AUC 0-t (ng-hr/ml)	101	96.9	1.044	-	0.895	1.194
Cmax (ng/ml)	5.72	5.18	1.104	-	0.905	1.303
Tmax (hour)	20.2	19.2	1.050	-	-	-
Ln-Transformed:						
AUC 0-t (ng-hr/ml)	89.3	87.9	1.015	29.6	0.882	1.169
Cmax (ng/ml)	5.11	4.82	1.061	38.9	0.885	1.273

Table 2. Test Formulation 2 (Lot T06P033) Compared to AndroGel

Parameter	Least-Squares Means ¹		Ratio ²	CV% ³	90% Confidence Interval ⁴	
	Formulation-2	Reference			Lower	Upper
AUC 0-t (ng-hr/ml)	101	96.9	1.044	-	0.894	1.193
Cmax (ng/ml)	5.46	5.18	1.054	-	0.855	1.253
Tmax (hour)	18.6	19.2	0.970	-	-	-
Ln-Transformed:						
AUC 0-t (ng-hr/ml)	84.3	87.9	0.959	29.6	0.833	1.104
Cmax (ng/ml)	4.65	4.82	0.965	38.9	0.805	1.158

1. Least-squares geometric means for ln-transformed data.
2. Ratio calculated as Test least-squares mean divided by the Reference least-squares mean. None of the comparisons was detected as statistically significant by ANOVA ($\alpha=0.05$).
3. Estimated intra-subject coefficient of variation, $CV\%=100*\text{SQRT}(e^{\text{MSE}}-1)$, where MSE is the mean square error term from the ANOVA.
4. Confidence interval on the ratio.

Comment: These data show that test formulation 1 fails to show bioequivalence to AndroGel since the upper range of the 90% confidence interval for the ratio of Cmax falls

outside of the acceptable range of 80 – 125%. Test formulation 2, however, is shown to be bioequivalent to Androgel with confidence intervals for the ratios of both Cmax and AUC falling entirely within the acceptable range. Test formulation 2 is the formulation on which the remainder of the application is based and is the intended commercial formulation.

Question 3: Does the NDA omit critical data, information or analyses needed to evaluate effectiveness and safety or provide adequate directions for use, for example:

- **Total patient exposure at relevant doses that is clearly inadequate to evaluate safety**
- **Clearly inadequate evaluation for safety and/or effectiveness of the population intended to use the drug, including pertinent subsets, such as gender, age and racial subsets**
- **Absence of comprehensive analysis of safety data**
- **Absence of an analysis of data supporting the proposed dose and dose interval**

Answer: No

In addition to the bioequivalence study that is the primary mode of evaluating the efficacy of the product, the Sponsor has provided reports of four studies that were designed to evaluate potential safety issues associated with testosterone gel products. These are: 1) a skin sensitization study, 2) a skin irritation study, 3) a study evaluating the ability to wash the gel from the skin, and 4) a study evaluating transfer of testosterone from a patient via interpersonal contact.

Study DS102308 - A Randomized, Controlled Study to Evaluate the Sensitizing Potential of Testosterone Gel (b) (4) on Healthy Volunteers, Using a Repeat Insult Patch Test Design

Two hundred and three subjects were enrolled in this study. The substances evaluated were the Testosterone Gel (b) (4), Androgel 1%, gel vehicle, and two control substances. Sodium lauryl sulfate 0.1% was used as a positive control and saline was used as a negative control. During the induction phase of the study, each subject had 0.2 ml of each of the five substances applied to 2x2 cm patch of skin on the back three times weekly for three weeks and was covered by a patch. Following a rest period of approximately 10 to 14 days, a single challenge application was performed. Local tolerability was assessed visually using an ordinal scoring system at the time of removal of each patch.

The results of the challenge application were that one subject exhibited moderate erythema with no significant edema (score of 3) to both the testosterone gel (b) (4) and the AndroGel at the 24- and 48-hour evaluations. One subject exhibited moderate erythema with no edema (score of 3) at 24 and 48 hours after challenge patch removal at the vehicle site. Both subjects had the reactions decrease to definite erythema (score of 2) by the 72-hour challenge evaluation. With the exception of these 2 subjects, there was no more than minimal erythema observed at the 72-hour challenge evaluation for the testosterone gel (b) (4), AndroGel, Vehicle and 0.1% SLS aqueous solution. There were no reactions observed at the 72-hour challenge evaluation for the saline.

Comment: This study appears to indicate that Testosterone (b) (4) gel has a skin sensitization potential similar to the reference product AndroGel.

As part of this study, skin irritation was evaluated at each application during the induction phase. Two hundred twenty-six (226) subjects were included in the cumulative irritancy analysis. The mean cumulative irritation score for testosterone gel (b) (4) was 0.169. The means scores for the AndroGel, Vehicle, SLS 0.1% control, and Saline were 0.141, 0.117, 0.586, and 0.089, respectively. There was no statistically significant difference between testosterone gel (b) (4) and the AndroGel ($P=0.345$), or between the testosterone gel (b) (4) and the Vehicle ($P=0.070$). There was a statistically significant difference between the testosterone gel 1% and the Saline ($P=0.005$), and the testosterone gel (b) (4) compared to the 0.1% SLS control ($P<0.001$).

Comment: Testosterone gel (b) (4) does not appear to be a significant skin irritant based on these results. Skin irritation was also evaluated in the following study.

Study DS310208 - A 21-Day, Randomized, Controlled Study to Evaluate the Irritation Potential of Testosterone Gel (b) (4) on Healthy Volunteers, Using a Cumulative Irritant Patch Test Design

Thirty-three subjects completed this study, which evaluated the skin irritation of the same five substances as study DS102308. Each of the five substances was applied topically to the skin once daily over three consecutive weeks (21 applications). 0.2 grams of each product was applied to a 2 cm x 2 cm area of skin. Cumulative irritancy was quantified for each subject/product by the mean and total cumulative irritancy score.

The testosterone gel (b) (4), AndroGel, vehicle, and saline showed no evidence of significant irritation. Testosterone gel had a mean cumulative irritation score of 0.016, AndroGel had a score of 0.090, the vehicle had a score of 0.053 and the saline had a score of 0.037. There was no statistically significant difference between the testosterone gel (b) (4), AndroGel, vehicle, and saline. All products were statistically significantly less irritating than the SLS 0.2% positive control ($P<0.001$), which had a mean cumulative irritation score of 2.824.

Comment: Similar to the irritation results of study DS102308, this study appears to show that testosterone gel (b) (4) has an acceptable skin irritation potential.

Study PRG-806 - A Pivotal Study to Evaluate the Residual Amount of Topically Delivered Testosterone Gel (b) (4) Present on Normal Skin of the Hand, Arm, and Shoulder in Healthy Adult Male Subjects following Washing Procedures

This was an open-label, four-period, pivotal study, on healthy adult male subjects. The purpose of this study was to quantify and compare the amount of testosterone on the hands and arm/shoulder of a patient who has applied testosterone gel before and after a hand wash and before and after an application site wash. The Sponsor included AndroGel arms for information purposes.

The Division provided input to the Sponsor in designing the study. The Sponsor appears to have incorporated the Division's comments into the design.

Subjects entered the clinic on study day 1 of each period and washed their hands and the arm/shoulder designated for drug application. Then, the hand and arm/shoulder designated for drug application were wiped with three ethanol dampened gauze (blank control sample). Subsequently, (b) (4) staff applied a 10 gram dose (2×5 -gram packets) of one of the testosterone

gel formulations to the center area of the palm of one hand. The subject then applied the dose to their opposite arm/shoulder.

Subjects followed their assigned hand residual removal procedure (wash or no wash) and then had their hand wiped with three ethanol dampened gauze pads. Finally, approximately 2 hours after the dose was applied, subjects followed their assigned arm/shoulder residual removal procedure (shower or no shower) and then had their arm/shoulder wiped with three ethanol dampened gauze pads. The gauze pads were then analyzed for quantification of recovered testosterone.

The following table summarizes the amount of testosterone recovered, as micrograms, for the hand and for the arm/shoulder.

	AndroGel® 1%		Testosterone Gel, (b) (4) (Perrigo)	
	Treatment B (No Wash)	Treatment D (Wash)	Treatment A (No Wash)	Treatment C (Wash)
Hand	8322.9 ± 3060.4	394.6 ± 197.0	8478.2 ± 3552.3	398.8 ± 198.7
Application Site	27754.1 ± 7285.3	6692.8 ± 4675.2	28326.0 ± 7627.2	5801.9 ± 2769.6

The following table summarizes the amount recovered, as percent of nominally applied dose, for the hand and for the application site.

	AndroGel® 1%		Testosterone Gel, (b) (4) (Perrigo)	
	Treatment B (No Wash)	Treatment D (Wash)	Treatment A (No Wash)	Treatment C (Wash)
Hand	8.32 ± 3.06	0.39 ± 0.20	8.48 ± 3.55	0.40 ± 0.20
Application Site	27.75 ± 7.29	6.69 ± 4.68	28.33 ± 7.63	5.80 ± 2.77

Comment: These data indicate that the gel is much more efficiently removed from the hands, where the post washing recovery is approximately 5% of the unwashed recovery, than from the application site, where the post showering recovery is approximately 20% of the unshowered recovery. However, the ability to wash the Testosterone (b) (4) gel from the skin appears to be no worse than the ability to wash Androgel from the skin.

Study M11U09001 - A Study To Determine The Transfer Of Testosterone From A Male To His Female Partner For Perrigo Pharmaceuticals (b) (4) Testosterone Gel

This study assessed the transfer of testosterone from male to female partners when the male, who had been treated with testosterone gel, was and was not wearing a T-shirt. The relative amounts of testosterone transfer from males to females with each treatment condition (with a T-shirt and without a T-shirt) for a comparator product, Androgel, was also assessed.

This was an open-label, single-dose, randomized, four-period, four-treatment crossover study. The four treatments were transfer following Testosterone gel (b) (4) without a t-shirt, transfer following Testosterone gel (b) (4) with a t-shirt, transfer following Androgel without a t-shirt, and transfer following Androgel with a t-shirt. The Cmax and AUC of testosterone in the female partners for the 24 hours following contact, as compared to the Cmax and AUC for the 24 hours prior to contact was the endpoint.

Twenty male/female partners completed the study.

The following table summarizes the pharmacokinetic results for the females that had been exposed to males that had been treated with Testosterone Gel (b) (4)

Baseline Adjusted Data for Females exposed to males treated with Testosterone Gel (b) (4)			
Parameter	Contact with Shirt	Contact without Shirt	% Ratio
AUC_{0-t} (ng-hr/ml)	0.3216	3.2889	9.78
C_{max} (ng/ml)	0.0472	0.2605	18.12

For comparison purposes, the following table summarizes the results for females that had been exposed to males that had been treated with Androgel.

Baseline Adjusted Data for Females exposed to males treated with Androgel			
Parameter	Contact with Shirt	Contact without Shirt	% Ratio
AUC_{0-t} (ng-hr/ml)	0.2722	3.8806	7.01
C_{max} (ng/ml)	0.0355	0.3007	11.82

Comment: A t-shirt blocks a lower percentage of the transfer for Testosterone Gel (b) (4) as compared to Androgel. A full review of the study will be needed to assess the significance of this.

3. Reviewer's Conclusions

A preliminary review of the Sponsor's submission indicates that they appear to have submitted adequate evidence of bioequivalence to the reference drug, Androgel. In addition, the Sponsor has submitted data to allow a substantive review of the safety of testosterone (b) (4) gel to be conducted. This safety information includes data from hand washing, site washing and interpersonal transfer studies that appear to have been designed and conducted according to the advice provided by the Division.

4. Recommended Regulatory Action

From a clinical perspective, the application is suitable for filing.

Donald McNellis
 Medical Officer
 Division of Reproductive and Urological Products

	Content Parameter	Yes	No	NA	Comment
EFFICACY					
14.	Do there appear to be the requisite number of adequate and well-controlled studies in the application? Pivotal Study #1 Indication: Pivotal Study #2 Indication:	X			BE Study, Skin sensitization & irritation studies, Washing & Transfer Studies
15.	Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?	X			
16.	Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints.	X			
17.	Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission?			X	US Data
SAFETY					
18.	Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division?	X			
19.	Has the applicant submitted adequate information to assess the arrhythmogenic potential of the product (e.g., QT interval studies, if needed)?			X	
20.	Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product?	X			
21.	For chronically administered drugs, have an adequate number of patients (based on ICH guidelines for exposure ¹) been exposed at the dose (or dose range) believed to be efficacious?			X	Product approval will hinge on bioequivalence to Androgel, for which there is an extensive safety history
22.	For drugs not chronically administered (intermittent or short course), have the requisite number of patients been			X	

¹ For chronically administered drugs, the ICH guidelines recommend 1500 patients overall, 300-600 patients for six months, and 100 patients for one year. These exposures MUST occur at the dose or dose range believed to be efficacious.

	Content Parameter	Yes	No	NA	Comment
	exposed as requested by the Division?				
23.	Has the applicant submitted the coding dictionary ² used for mapping investigator verbatim terms to preferred terms?		X		
24.	Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs?	X			
25.	Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)?			X	No deaths or SAEs were encountered in the Sponsor's studies
OTHER STUDIES					
26.	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?	X			Transfer and washing studies
27.	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (e.g., label comprehension, self selection and/or actual use)?			X	
PEDIATRIC USE					
28.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?	X			
ABUSE LIABILITY					
29.	If relevant, has the applicant submitted information to assess the abuse liability of the product?			X	
FOREIGN STUDIES					
30.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?			X	
DATASETS					
31.	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?	X			
32.	Has the applicant submitted datasets in the format agreed to previously by the Division?			X	
33.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?	X			
34.	Are all datasets to support the critical safety analyses available and complete?	X			
35.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?	X			
CASE REPORT FORMS					
36.	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?			X	
37.	Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?			X	

² The "coding dictionary" consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

	Content Parameter	Yes	No	NA	Comment
FINANCIAL DISCLOSURE					
38.	Has the applicant submitted the required Financial Disclosure information?	X			
GOOD CLINICAL PRACTICE					
39.	Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?	X			

IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE? _Yes_____

If the Application is not fileable from the clinical perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

 Reviewing Medical Officer

 Date

 Clinical Team Leader

 Date

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

/s/

DONALD R MCNELLIS
09/01/2011

SURESH KAUL
09/14/2011