

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**202763Orig1s000**

**CLINICAL PHARMACOLOGY AND  
BIOPHARMACEUTICS REVIEW(S)**



## **1 Executive Summary**

The Sponsor submitted a 505(b)(2) application for Testosterone (T) Gel 1% with a pivotal bioequivalence (BE) study on January 14, 2011. Sponsor used AndroGel® (1%, w/w) (NDA 021015, approved on February 20, 2000) now marketed by Abbott Laboratories as the reference listed drug (RLD). T Gel 1% is non-sterile, transdermally applied T solution for treatment of male hypogonadism associated with deficiency or absence of endogenous T. T Gel 1% is proposed to be marketed as either 2.5 g packets or 5 g packets. T Gel 1% is to be administered transdermally once daily (preferably in the morning) to clean, dry, intact skin of shoulders, upper arms and/or abdomen.

The recommended starting dose for T Gel 1% is 5 g once daily. Serum T concentrations should be measured periodically for dose adjustments. Dose adjustment is recommended if the serum total T concentration is outside of the pre-specified T normal range of 298-1,043 ng/dL. If the serum T concentration is below the normal range, the daily T Gel 1% dose may be increased from 5 g to 7.5 g and from 7.5 g to 10 g for adult males. If the serum T concentration exceeds the normal range, the daily T Gel, 1% dose should be decreased. If the serum T concentration consistently exceeds the normal range at a daily dose of 5 g, T Gel 1% therapy should be discontinued.

The Sponsor submitted 4 Clinical Pharmacology and Clinical studies including a single-dose, BE study (Study 70343), a hand washing study (Study CRI-00018704), an evaluation of interpersonal transferability (Study M1FX10001), and a skin irritation and sensitization study (Study 10936025).

Out of the 4 studies submitted, 3 studies containing relevant Clinical Pharmacology information acquired during the T Gel 1% product development were reviewed. The skin irritation and sensitization study was not reviewed as it was reviewed by the Clinical reviewer. A formal consult to the Office of Scientific Investigations (OSI) was made for clinical and bioanalytical study site inspections and there are no unresolved issues related to the approvability of T Gel 1%.

The Sponsor demonstrated comparable bioavailability of T between T Gel 1% and the RLD, AndroGel® 1% in Study 70343. In addition, there were no additional safety signals found in the clinical safety studies submitted.

### **1.1 Recommendation**

The Office of Clinical Pharmacology (OCP)/Division of Clinical Pharmacology 3 (DCP-3) has reviewed NDA 202763 submitted on January 14, 2011, April 21, 2011, May 18, 2011, June 10, 2011, July 29, 2011, September 14, 2011, November 3, 2011, and December 5, 2011. The overall Clinical Pharmacology information submitted to support this NDA is acceptable provided that a satisfactory agreement is reached regarding the labeling language and the Sponsor agrees on the post-marketing requirement (PMR) recommended below.

### **1.2 Post-marketing Requirements or Commitments**

There was no application site washing study conducted in this application. This reviewer believes that a study evaluating the effect of washing on removing residual T from the application site is necessary in addition to the hand-washing study submitted. The application site washing study is needed to support labeling indicating that washing the application site will limit the potential for interpersonal transfer of T. In this study, post-dose control samples before washing

should be collected (e.g., use one side as the control and the opposite side as the test) and the recovered T before and after washing and the recovery percentage should be reported, respectively.

Therefore, this reviewer recommends that the Sponsor should conduct an application site washing study as a PMR for the condition of approval of this application with the following timelines:

- Final Protocol Submission: 3 months from the approval date
- Study/Trial Completion: 6 months from the approval date
- Final Report Submission: 12 months from the approval date

The possibility of this PMR was conveyed to the Sponsor in the Division's Filing Communication Letter dated March 28, 2011 available in DARRTS and the following comment has been conveyed to the Sponsor on January 11, 2012 via email through the Division's regulatory project manager, Jeannie Roule:

*The Division believes that a study evaluating the effect of washing on removing residual testosterone from the application site is necessary in addition to the hand-washing study submitted. The application site washing study is needed to support labeling indicating that washing the application site will limit the potential for interpersonal transfer. In this study, post-dose control samples before washing should be collected (e.g., use one side as the control and the opposite side as the test) and the recovered testosterone before and after washing should be reported, respectively.*

The Sponsor responded back via email agreeing to the PMR on January 12, 2012. A memorandum to file regarding this communication dated January 13, 2012 is available in DARRTS.

### 1.3 Summary of Important Clinical Pharmacology Findings

#### BE Assessment:

A multi-center, randomized, single-dose, two way-crossover, pivotal BE study (Study 70343) was conducted in 93 hypogonadal males to compare the Sponsor's T Gel 1% product and the RLD (i.e., AndroGel<sup>®</sup> 1%) under fasting condition. The T baseline measurements occurred at 12 hr, 6 hr, and immediately before drug administration. A single topical dose of either T Gel 1% or the AndroGel<sup>®</sup> 1% was administered as 2 x 5 g packets (5 g applied on each shoulder/upper arm) on the designated area predefined with an individual template (outlining a 500 cm<sup>2</sup> area). The treatment periods were separated by a 7 day washout period between treatment periods.

**Table 1:** Baseline Corrected BE Analysis Results (Study 70343; N=72)

	AUC <sub>0-t</sub>	C <sub>max</sub>
Ratio <sup>1</sup>	105.3%	116.2%
90% Geometric C.I. <sup>2</sup>	96.0% to 115.5%	106.6% to 126.7%
Intra-Subject CV	33.5%	30.8%

<sup>1</sup> Calculated using least-squares means according to the formula:  $e^{(T\text{ Gel } 1\%,(A) - \text{AndroGel } 1\%(B))} \times 100$

<sup>2</sup> 90% Geometric Confidence Interval using ln-transformed data

This reviewer concludes that BE between T Gel 1% and AndroGel<sup>®</sup> 1% has been established regarding AUC following a single 100 mg dose (2 x 5 g packets) of T to the upper arms/shoulders (5 g gel applied to each side) of hypogonadal males. However, the upper 90% CI of C<sub>max</sub> was slightly higher (by 1.7%) compared to the BE acceptance range (i.e., 80.00-125.00%) but it is still

acceptable given that there is no concern regarding the lack of efficacy as it is slightly exceeded the upper limit of the 90% CI of the BE acceptance criteria and there were no additional safety signals detected in the clinical safety studies submitted in this NDA. Details of the BE analysis can be found in Sections 2.2.6 and 4.1.1 of this review.

#### **Distribution, Metabolism, and Excretion**

Specific studies describing the distribution, metabolism, and excretion of T were not conducted using T Gel 1%. The Sponsor is proposing to use the publically available information of the RLD (i.e., AndroGel® 1%) for their product.

#### **Transfer Potential Assessment**

A single-dose, four-period, four-treatment, crossover study to assess the interpersonal transfer potential of T was conducted in 96 healthy subjects (48 male and female couples). A single 10 g topical dose (i.e., 2 x 5 g packets) of either T Gel 1% or AndroGel® 1% was applied to the upper arm/shoulder of one side of male subjects either wearing or not wearing a 100% cotton long-sleeved T-shirt. The T baseline of females was characterized by conducting a 24 hr PK measurement. Two hours after dosing to the male subjects, female subjects were instructed to gently rub their arms and shoulders up and down the upper arms and shoulders of their male partners for 15 minutes. For those periods that males were to wear the T-shirts, subjects waited at least 5 minutes for either T Gel 1% or AndroGel® 1% to dry before putting clothes over the application area. Then, the T-shirt was worn throughout the study. There was a 7 day washout period between treatment periods.

Study results show approximately 11% and 16% increase in T AUC(0-24) and  $C_{max}$ , respectively, compared to baseline of females when males were wearing a T-shirt following a 10 g T Gel 1% application to the upper arm/shoulder of one side. It should be noted that the interpersonal transfer potential of topical T applied on the abdomen was not assessed and therefore, the same conclusion cannot be extrapolated to when T Gel 1% is applied to the abdomen. This should be clearly reflected on the product label. The overall percent difference of the PK parameters for females was much lower when males were wearing a T-shirt during the transfer procedure than without a T-shirt, indicating that there is less exposure to T when a T-shirt is covering the application site.

#### **Hand Washing Study**

A single-dose, open label, two-period, crossover study in 48 healthy adult men was conducted to evaluate the residual amount of topically delivered T Gel following hand washing procedure. Ten grams (2 x 5 g packets) of either the T Gel 1% or AndroGel® 1% was applied to the subject's palm of their dominate hand by the clinical staff. Then subjects applied the dose to their opposing arm and shoulder with monitoring by the clinical staff each time. Approximately 5 minutes after dose application, subjects washed their hands following the pre-determined hand washing instructions. There was a 14 day washout period between treatment periods.

The Sponsor did not report the percentage of T removed by the hand washing procedure as the measurement of residual T on the subjects' hands (after applying the drug product to the application site) prior to hand-washing was not carried out. However, considering that the mean residual amount of T was very small compared to the theoretical dose of 100 mg T (i.e., 2.85%) and that it is comparable to the residual amount following hand washing after application of AndroGel® 1%, this reviewer concludes that T from T Gel 1% is sufficiently removed from the hands following a hand washing procedure.

#### **Application Site Washing Study**

No application site washing study was conducted.

**Drug-Drug Interactions (DDI):**

No new DDI studies were conducted with T Gel 1%. The Sponsor is proposing to use the publically available information of the RLD (i.e., AndroGel® 1%) for their product.

**Use in Specific Populations:**

Use in pregnant or breast feeding women

This product is contraindicated for pregnant or breast feeding women

Pediatric Use

No pediatric studies were conducted with T Gel 1%. Pediatric Research Equity Act (PREA) (21 U.S.C. 355c) does not apply to this application because none of the following apply:

- New active ingredient(s) (includes new combination);
- New indication(s);
- New dosage form;
- New dosing regimen; or
- New route of administration

The proposed product label has Warnings and Precaution information for children and women for secondary exposure.

Renal or Hepatic Impairment

No studies were conducted with T Gel 1% in patients with renal or hepatic impairments.

**Drug Product Formulation:**

T Gel 1% is a colorless hydroalcoholic gel containing 1% T for topical administration to clean, dry, intact skin surface of shoulders and upper arms and/or abdomen. The active ingredient, route of administration, dosage form, and strength for the proposed drug product are the same as those of AndroGel® 1%. [REDACTED]

[REDACTED] T Gel 1% is proposed to be marketed as either 2.5 g packets or 5 g packets.

Studies 70343, CRI-00018704, M1FX10001, and 10936025 were all conducted with the to-be-marketed (TBM) formulation (i.e., T Gel, 1%).

**Bioanalytical Methods:**

Serum samples were analyzed for total T using validated bioanalytical methods. A validated high performance liquid chromatography method using an ultraviolet detector (HPLC-UV) was used in Study CRI-00018704. In Studies 70343 and M1FX10001, a validated liquid chromatography-tandem mass spectrometry (LC-MS/MS) method was used.

An OSI inspection of clinical and bioanalytical sites of the pivotal BE study (Study 70343) has been conducted. In summary, inappropriate conduct of data integration was found during the Agency's OSI inspection and all chromatograms of the BE study were reintegrated as a result. In addition, data from 6 subjects and the repeat analysis of 22 samples were found to be invalid and were additionally excluded from the BE reanalysis. Details of these OSI inspection findings can be found in Dr. Sripal Mada's OSI consult review and addendum dated July 1, 2011 and July 30, 2011, respectively, available in DARRTS that are also attached to Section 4.2 of this review.

Acceptance criteria and method performance for T concentration measurements were in compliance with the Agency's *Bioanalytical Method Validation Guidance* and the bioanalytical methods were found to be acceptable.

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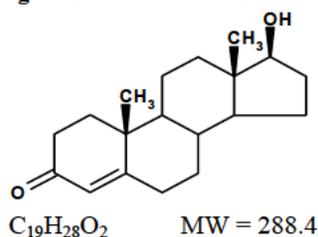
## 2 Question Based Review

### 2.1 General Attributes

#### 2.1.1 What is the T Gel 1% and its active pharmacological ingredient?

T Gel 1% is a colorless hydroalcoholic gel containing 1% T for topical administration to clean, dry, intact skin surface of shoulders and upper arms and/or abdomen. The active pharmacologic ingredient in T Gel 1% is T. T USP is a white to slightly creamy white crystalline powder chemically described as 17-beta hydroxyandrost-4-en-3-one. The structural formula is:

Figure 1: Structural Formula of T



Inactive ingredients in T gel are carbomer homopolymer type C, dehydrated alcohol 67%, isopropyl palmitate, purified water, and sodium hydroxide. These ingredients are not pharmacologically active.

#### 2.1.2 What is the regulatory history of the product?

Reference is made to Sponsor's original ANDA (b) (4) for T Gel 1% submitted to the Office of Generic Drugs (OGD) on December 29, 2008 and the OGD's Refuse to Receive Letter dated April 7, 2009. The basis for the letter was that Sponsor's formulation contained different ingredients than those contained in the RLD. (b) (4)

During the filing review, it was noted that there was no application site washing study conducted. The following comment was conveyed to the Sponsor in the Division's Filing Communication Letter dated March 28, 2011 available in DARRTS: "We note that there was no application site washing study conducted. We believe that a study evaluating the effect of washing on removing residual testosterone from the application site is necessary in addition to the hand-washing study. We believe that the application site washing study, conducted at 2 hours after application of the product, is needed to support labeling language indicating that washing the application site will limit the potential for interpersonal transfer. You may propose to conduct this study under the terms of a post-marketing requirement."

Initially, T Gel 1% was proposed to be marketed in the following dosage forms: 2.5 g packets, 5 g packets, (b) (4)

On September 14, 2011, the Sponsor submitted their response to the Division's August 2, 2011 and August 22, 2011 information requests (IR) (i.e., to reintegrate all chromatograms in Study 70343 and conduct BE reanalysis excluding data from the 6 subjects under question). This amendment contains a new clinical and statistical report for the pivotal BE Study 70343, entitled "Randomized, open-label, 2-way crossover, bioequivalence study of testosterone 1% topical gel formulation and Androgel (reference) following a 100 mg dose in hypogonadal volunteers." As the receipt date is within 3 months of the user fee goal date, it was considered as a major amendment and therefore, the Division has extended the goal date by 3 months to provide time for a full review of the submission. The extended user fee goal date is February 14, 2012.

## 2.2 General Clinical Pharmacology

### 2.2.1 What Clinical Pharmacology and Clinical efficacy/safety related information was submitted to support this NDA?

This NDA contains the following:

- Draft product label in PLR format (PLR conversion)
- Information on the composition of drug products used in the clinical studies
- Full clinical trial reports of the 4 Clinical Pharmacology and Clinical studies
- Bioanalytical study reports and method validation reports
- Request of waiver for pediatric studies

The submitted studies are summarized in the Table 2 below:

**Table 2: Summary of Clinical Pharmacology and Clinical Studies submitted in NDA 202763**

Type of Study	Study Identifier	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
Bioequivalence	70343	Determine the bioequivalence between a new (generic) drug product and a marketed reference product under fasting conditions	Multiple-centre, Bioequivalence, Open-label Randomized, 2-way crossover study.	Testosterone 1% Topical Gel	93 (90 Completed)	Hypogonadal Adult Male Subject	Single-Dose	Completed
Irritation and Sensitization	10936025	Compare cumulative skin irritation and sensitization potential between two new (generic) products and two marketed reference products.	Multiple Site, Multiple-Application, Double-Blind, Randomized, Two Phase Irritation and Sensitization Study	Testosterone 1% Topical Gel	265 (233 included in PPPI and 222 included in PPPS)	Healthy Adult Male Subjects	Multiple-Dose	Completed
Hand-Washing	CRI-00018704	Quantify and compare the amount of residual drug remaining on the hands between a new (generic) product and a marketed reference product.	Open-label, Two Period, Crossover, pivotal study on healthy adult male subjects	10 g of Testosterone 1% Topical Gel in each study period, topical	48 (46 Completed)	Healthy Adult Male Subjects	Single-Dose	Completed
BA Transfer	M1FX10001	Quantify and compare the relative bioavailability between a new (generic) product and a marketed reference product in female subjects following direct transfer from healthy male subjects	Open-label, Randomized, Four Period, Four Treatment Crossover Study.	Testosterone 1% Topical Gel	A vs. C 48 male and female couples (47 couples completed)	Healthy Adult Male and Female Subjects	Single-Dose	Completed
				Testosterone 1% Topical Gel	B vs. D 48 male and female couples (43 couples completed)			

### **2.2.2 What is the mechanism of action?**

Endogenous androgens, including T and dihydrotestosterone (DHT), are responsible for the normal growth and development of the male sex organs and for maintenance of secondary sex characteristics. These effects include the growth and maturation of prostate, seminal vesicles, penis, and scrotum; the development of male hair distribution, such as facial, pubic, chest, and axillary hair; laryngeal enlargement, vocal chord thickening, alterations in body musculature and fat distribution. 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.

Male hypogonadism has two main etiologies. Primary hypogonadism is caused by defects of the gonads, such as Klinefelter's Syndrome or Leydig cell aplasia, whereas secondary hypogonadism is the failure of the hypothalamus (or pituitary) to produce sufficient gonadotropins (i.e., FSH, LH).

T Gel 1% was developed with an aim to ensure that the desired serum T concentrations (i.e., 298-1,043 ng/dL) are achieved in hypogonadal men following treatment with T Gel 1%.

### **2.2.3 What are the administration instructions?**

T Gel 1% should be applied to clean, dry, intact skin of the shoulders and upper arms and/or abdomen (area of application should be limited to the area that will be covered by the patient's short sleeve t-shirt). T Gel 1% should not be applied to the genitals.

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

After applying the gel, the application site should be allowed to dry for a few minutes prior to dressing. User should avoid fire, flames or smoking until the gel has dried since alcohol based products, including T Gel 1% are flammable. Hands should be washed with soap and water after T Gel 1% has been applied

It should be noted that in the Phase 3 clinical trial (Study UMD-96-017) conducted with Androgel<sup>®</sup> 1% in the original NDA 021015 (approved on February 20, 2000), 2 different Androgel<sup>®</sup> 1% dose strengths were evaluated (i.e., 5 g and 10 g Androgel<sup>®</sup> 1% that contained 50 mg and 100 mg T, respectively). Patients randomized to 5 g Androgel<sup>®</sup> 1% received 2 bottles, 1 containing Androgel<sup>®</sup> 1% and the other containing vehicle alone. Patients randomized to 10 g Androgel<sup>®</sup> 1% received 2 bottles, each containing Androgel<sup>®</sup> 1%. Study medication was applied daily to the right and left upper arms/shoulders and to the right and left sides of the abdomen on an alternative basis. For example, on the first day of application, patients applied 2 actuations from 1 bottle, 1 each to the left and right upper arm/shoulder and 2 actuations from the second bottle, 1 each to the left and right abdomen. On the following treatment day, the application procedures were reversed. Alternating application sites continued on a daily basis throughout the study. Application sites were allowed to dry for 3-5 minutes prior to covering with clothing, and

patients were instructed to wash their hands thoroughly with soap and water following application of the gel.

Table 3 summarizes the product strengths, doses, applications sites, and how the topical T products are supplied as of January 10, 2012.

**Table 3: Topical T Products as of January 10, 2012**

NDA	Product	Strength	Dose	How Supplied	Application Site
NDA 202763 TEVA	Testosterone Gel 1%	25 mg, 50 mg testosterone per packet	50 mg to 100 mg testosterone daily	25 mg packet in 2.5 g of gel 50 mg packet in 5 g of gel	shoulders, upper arms, abdomen
(b) (4)					
NDA 021015 RLD	Androgel (Testosterone) Gel	1%	5 g to 10 g daily	75 g Multi-dose Pump (1.25 g per actuation) 2.5 g, 5 g packet	shoulders, upper arms, abdomen
NDA 022309	Androgel 1.62%, (Testosterone) Gel	20.25 mg Testosterone per actuation	20.25 mg to 81 mg or 1 to 4 pumps) daily	Metered-dose pump (20.25 mg testosterone per actuation)	shoulders, upper arms
		20.25 mg, 40.5 mg of testosterone	20.25 mg to 81 mg testosterone	20.25 mg in 1.25 g of gel 40.5 mg in 2.5 g of gel	
NDA 021454	Testim (Testosterone Gel)	1% (50 mg)	5 g gel containing 50 mg testosterone	50 mg testosterone in 5 g gel tube	shoulders, upper arms
NDA 021463	Fortesta (Testosterone) Gel	10 mg testosterone per actuation	10 mg to 70 mg testosterone (1 to 7 pump actuations)	Metered-dose pump (10 mg testosterone per actuation)	front and inner thighs
NDA 022504	Axiron (Testosterone) solution	30 mg Testosterone per actuation	30 mg to 120 mg testosterone (1 to 4 pump actuations)	Metered-dose pump (30 mg testosterone per actuation)	axilla

\* Shaded boxes indicate NDAs under review as of January 10, 2012

#### 2.2.4 What are the dosing regimen and dose adjustment scheme?

The recommended starting dose of T Gel 1% is 5 g once daily (preferably in the morning). To ensure proper dosing, serum T levels should be measured periodically and replaced (e.g., in the Phase 3 clinical study with AndroGel® 1%, T concentration was measured using a single blood sample on Day 60 and dose adjusted on Day 91) to serum T concentrations in the normal range (i.e., 298-1,043 ng/dL). If the serum T concentration is below the normal range, the daily T Gel 1% dose may be increased from 5 g to 7.5 g and from 7.5 g to 10 g for adult males as instructed by the physician. If the serum T concentration exceeds the normal range, the daily T Gel 1% dose may be decreased. If the serum T concentration consistently exceeds the normal range at a daily dose of 5 g, T Gel 1% therapy should be discontinued.

It should be noted that there are no detail information of the dose adjustment scheme in the current AndroGel® 1% product label regarding when (i.e., on which day) and based on what (e.g., based on a single blood draw [e.g., C<sub>2hr</sub>] or average of several T concentration measurements [e.g., C<sub>ave</sub>]) the dose adjustment should take place. Therefore, no information regarding detail dose adjustment scheme will be available on the T Gel 1% product label. Please refer to Section 3 of this review for more information on this topic.

### 2.2.5 What are the single dose PK parameters of Total T?

The baseline corrected single dose PK parameters of total T obtained from a multi-center, randomized, single-dose, two way-crossover, pivotal BE study (Study 70343) are summarized in Table 4.

**Table 4:** Mean, SD, and % CV of Baseline Corrected T PK Parameters Following a Single Dose of either T Gel 1% or AndroGel 1% (Study 70343; N=72)

Parameters	Test (T Gel 1% (A))			Reference (AndroGel 1% (B))		
	Mean	SD	CV (%)	Mean	SD	CV (%)
AUC <sub>0-t</sub> (pg·h/mL)	65898.89	34034.54	51.65	61144.45	27227.53	44.53
C <sub>max</sub> (pg/mL)	3826.24	2478.19	64.77	3216.90	1567.72	48.73
T <sub>max</sub> (h)	19.6	10.7	54.74	19.2	10.5	54.89
T <sub>max</sub> * (h)	20.0	4.0	-	20.0	6.0	-

\* Medians and interquartile ranges are presented

### 2.2.6 Was BE between T Gel 1% and the RLD established adequately?

A multi-center, randomized, single-dose, two way-crossover, pivotal BE study (Study 70343) was conducted in 93 hypogonadal males to compare the Sponsor's T Gel 1% product and the RLD (i.e., AndroGel® 1%) under fasting condition. The T baseline measurements occurred at 12 and 6 hr pre-dose and immediately before application. Mean baseline T concentrations were calculated for each subject by averaging the 3 pre-dose values for each period. A single topical dose of either the T Gel 1% or AndroGel® 1% was administered as 2 x 5 g packets (1 packet applied on each shoulder/upper arm) on the designated area predefined with an individual template (outlining a 500 cm<sup>2</sup> area). Blood samples for PK characterization were collected up to 60 hours post-dose. The treatment periods were separated by a 7 day washout period.

In this study, two 5 g packets of T Gel 1% (each containing 50 mg of T; total dose of 100 mg T) were applied (one packet applied on each shoulder and upper arm) with a spatula to each hypogonadal subject after a supervised overnight fast of at least 10 hours. Following dosing, subjects fasted for a period of at least 4 hours.

Prior to gel application, the shoulders and upper arms of each subject were washed with warm water and mild soap and were rinsed with clean, warm water, and allowed to dry for approximately 1 hour before gel was applied.

In each period, using gloved hands and a spatula applicator, the pre-weighted topical gel was applied directly on the application site by the study staff (5 g per shoulder/arm for a total of 10 g) on the designated area predefined with an individual template (outlining a 500 cm<sup>2</sup> area; each subject was designed his own template) to insure consistent size of the application area between and within subjects. The application site was allowed to dry until after the 30 minutes local irritation evaluation. Subjects were instructed not to touch the application site for at least 4 hours after gel application. After the gel had dried, subjects covered the application site with clothing (e.g., a shirt - type [long or short] not specified) (within ~30 minutes) to avoid transfer to another person. Washing the treated area was prohibited from 2 hours before until 48 hours after gel application, unless required by study procedures. After the 48 hour blood sample collection, subjects had the dosing area washed by clinical staff member to remove any residual, unabsorbed study drug, and were given the option to shower and wear a clean shirt.

It should be noted that while the approved application sites of AndroGel<sup>®</sup> 1% (NDA 021015; approved on February 28, 2000) are shoulder/upper arms and/or abdomen, the application sites in this BE study were shoulder/upper arms but did not include abdomen. However, it should be noted that results from a clinical study conducted with AndroGel<sup>®</sup> 1% (Study UMD-98-012) did not show any statistically significant differences in PK parameters of T following 1-site (i.e., left upper arm/shoulder) or 4-sites (i.e., left upper arm/shoulder, right upper arm/shoulder, left abdomen, and right abdomen). Reference is made to Dr. Dhruva J. Chatterjee's Clinical Pharmacology review dated February 25, 2000 available at [http://www.accessdata.fda.gov/drugsatfda\\_docs/nda/2000/21-015\\_AndroGel\\_BioPharmr.pdf](http://www.accessdata.fda.gov/drugsatfda_docs/nda/2000/21-015_AndroGel_BioPharmr.pdf).

Among the 90 subjects who completed the study, the following subjects in Table 5 were also excluded from the BE analysis by the Sponsor:

**Table 5:** Subjects who Completed the Study but were Excluded from the Original BE Analysis (N=13)

<b>Subject Number</b>	<b>Reason for exclusion from statistical analysis</b>
24	This subject samples stability exceeded validation data.
03, 15, 25, 27, 35, 37, 40, 70, 84, 87, 88, and 89	These subjects had a mean baseline T serum concentration in at least one period that was higher than 350 ng/dL.

In the study protocol it is stated that “if the baseline T serum concentration mean for any study period is higher than 350 ng/dL all of the study data from that subject will be excluded from the PK analysis.”

As there was inappropriate conduct of data integration found by the Agency's OSI inspection, all chromatograms of this study was reintegrated and as a result, the baseline T concentrations were changed. Subject 70 was not included in the original BE analysis as its T baseline concentration was 352.9 mg/dL in Period 1. However, the T baseline following reintegration of chromatograms for Subject 70 fell below 350 mg/dL and therefore was included in the BE reanalysis.

Out of the 78 subjects included in the Sponsor's reanalysis, data from Subjects 60, 61, 62, 92, 93, and 94 and the repeat analysis of 22 samples were found to be invalid as the bioanalyst responsible these samples made an error during sample handling and further investigation of this

bioanalyst's training records revealed that this bioanalyst was not trained properly to conduct sample handling appropriately. Therefore, these 6 subjects were additionally excluded from the BE reanalysis. Details of these OSI inspection findings can be found in Dr. Sripal Mada's OSI consult reviews in Section 4.2 of this review.

In addition, it should be noted that the baseline value for Subject 88 was 351.3 ng/dL but as the -6 hr baseline sample of Period 2 was excluded as being one of the 22 reanalysis samples invalidated, the baseline for Subject 88 became 337.0 ng/dL and was included in the final BE reanalysis. In a similar manner, the baseline value for Subject 96 was 338.6 ng/dL but as the 12 hr pre-dose baseline sample of Period 1 was excluded as being one of the 22 reanalysis samples invalidated, the baseline for Subject 96 became 360.2 ng/dL and was excluded in the final BE reanalysis.

As a result the subjects in Table 6 were excluded and 72 subjects were included in the final BE reanalysis per the Division's request. The baseline T concentrations for each subject after reintegration of the chromatograms can be found in Tables A-1-3 and A-1-4 in Section 4.1.1 of this review.

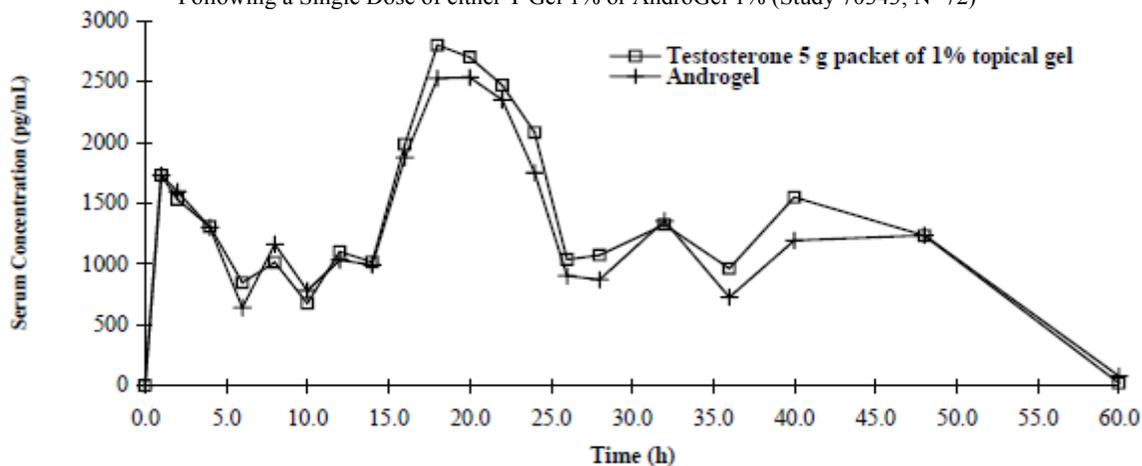
**Table 6:** Subjects who Completed the Study but were Excluded from the BE Reanalysis (N=18)

Subject Number	Reason for Exclusion from Statistical Analysis
24	This subject's samples stability exceeded validation data.
03, 15, 25, 27, 35, 37, 40, 84, 87, 89 and 96	These subjects had a baseline testosterone serum concentration mean in at least one period that was higher than 350 ng/dL
60, 61, 62, 92, 93, and 94	Data from these subjects were found to be invalid due to an error of sample handling

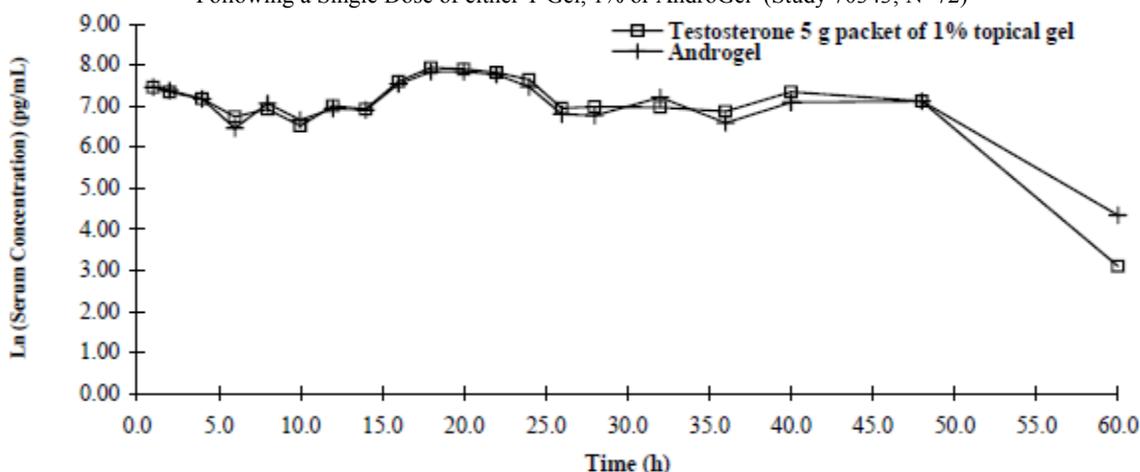
As endogenous T exists in the body and the study objective is to compare the exposure of T by the contribution of the drug products, BE analysis based on baseline corrected PK parameters were selected as the primary parameter for BE analysis.

The plots of the mean serum T levels over the sampling period are presented for both the untransformed and ln-transformed data in Figures 2 and 3 for baseline corrected T, respectively. The mean profiles for both the test and reference formulations are plotted based on the mean serum concentrations calculated per time point.

**Figure 2:** Baseline Corrected Mean T Concentration-Time Profile Following a Single Dose of either T Gel 1% or AndroGel 1% (Study 70343; N=72)



**Figure 3:** Baseline Corrected Ln-transformed Mean T Concentration-Time Profile Following a Single Dose of either T Gel, 1% or AndroGel (Study 70343; N=72)



The Sponsor’s BE analysis results were confirmed to be valid based on this reviewer’s own BE analysis. All analyses of variance (ANOVA) were performed with the SAS (version 9.2 for Windows) General Linear Models (GLM) procedure. Based on pair-wise comparisons of the ln-transformed of AUC(0-t) and C<sub>max</sub> data, the ratios of the least squares means, calculated according to the formula “e<sup>(X-Y)</sup> x 100”, as well as the 90% geometric CIs for ln-transformed AUC(0-t) and C<sub>max</sub> were determined. This reviewer’s BE analysis results are summarized in Table 7 below:

**Table 7:** Reviewer’s Baseline Corrected BE Analysis Results Following a Single Dose of either T Gel 1% or AndroGel 1% (Study 70343; N=72)

	AUC <sub>0-t</sub>	C <sub>max</sub>
Ratio <sup>1</sup>	105.3%	116.2%
90 % Geometric C.I. <sup>2</sup>	96.0% to 115.5%	106.6% to 126.7%
Intra-Subject CV	33.5%	30.8%

<sup>1</sup> Calculated using least-squares means according to the formula: e<sup>(T Gel 1% (A) – AndroGel 1% (B))</sup> X 100

<sup>2</sup> 90% Geometric Confidence Interval using ln-transformed data

For baseline corrected T, a statistically significant difference between treatments was detected using ANOVA for ln-transformed C<sub>max</sub>, but not for ln-transformed AUC(0-t). The 90% geometric CIs were within the BE acceptance range for AUC(0-t) but not for C<sub>max</sub> (i.e., 106.6% to 126.7%).

As the T exposure (i.e., both AUC[0-t] and C<sub>max</sub>) from the T Gel 1% product was shifted to be slightly higher compared to AndroGel<sup>®</sup> 1% there are no concerns regarding the potential lack of efficacy. While the clinical implication of the high 90% geometric CI for C<sub>max</sub> being outside of the BE acceptance range (i.e., 80.00-125.00%) by 1.7% is unknown, there were no additional safety signals for T Gel 1% detected from this single dose BE study and other clinical safety studies submitted in this NDA.

It should be noted that there is a considerable variability in both AUC(0-t) and C<sub>max</sub> of T. For baseline corrected T the intra-subject CVs for AUC(0-t) and C<sub>max</sub> were 34.9% and 31.3%, respectively.

In summary, this reviewer concludes that BE between T Gel 1% and AndroGel<sup>®</sup> 1 % has been established regarding AUC following a single 100 mg dose (2 x 5 g packets) of T to the upper

arms/shoulders (5 g gel applied to each side) of hypogonadal males. However, the upper 90% CI of  $C_{max}$  was slightly higher (by 1.7%) compared to the BE acceptance range (i.e., 80.00-125.00%) but it is still acceptable given that there is no concern regarding the lack of efficacy as it is slightly exceeded the upper limit of the 90% CI of the BE acceptance criteria and there were no additional safety signals detected in the clinical safety studies submitted in this NDA. Details of the BE analysis can be found in Section 4.1.1 of this review.

### 2.2.7 What is the interpersonal transfer potential of T from T Gel 1%?

A single-dose, four-period, four-treatment, crossover study (Study MIFX10001) to assess the interpersonal transfer potential of topical T was conducted. A total of 96 healthy subjects (48 male and female couples) were enrolled in the study and 86 completed. A single 10 g topical dose (i.e., 2 x 5 g packets) of either T Gel 1% or AndroGel<sup>®</sup> 1% applied to the upper arm/shoulder of one side of male subjects either wearing or not wearing a 100% cotton long-sleeved T-shirt. The T baseline in females was characterized by conducting a 24 hour PK measurement. Two hours after dosing to the male subjects, female subjects were instructed to gently rub their arms and shoulders up and down the upper arms and shoulders of their male partners for 15 minutes. For those periods that males were to wear the T-shirts, subjects waited at least 5 minutes for either T Gel 1% or AndroGel<sup>®</sup> 1% to dry before putting clothes over the application area. Then, the T-shirt was worn throughout the study. Female subjects did not shower or bathe until at least 24 hours after the contact period. There was a 7 day washout period between treatment periods.

The PK parameters ( $C_{max}$  and AUC) of total T were calculated and summarized for baseline total T (Day -1) and post-transfer procedure (Day 1) for female subjects that received T Gel 1% through the transfer process in Tables 8 and 9 with the percent difference between the baseline and post-transfer PK parameters. Taking the washing instructions in account, interpersonal transferability of T was assessed based on AUC(0-24) and  $C_{max}$ .

**Table 8:** Summary of Arithmetic Mean (SD) PK parameters for Total T (Pre and Post-transfer) Following the Treatment of 2 x 5 g of T Gel 1% without a T-shirt (Study MIFX10001; N=47)

	24 hour Pre-Transfer (N=47)	24 hour Post-Transfer (n=47)	% Difference
AUC(0-24) (ng·hr/mL)	4.62 (1.84)	13.78 (9.84)	198.32
$C_{max}$ (ng/mL)	0.27 (0.18)	1.02 (0.86)	271.22

**Table 9:** Summary of Arithmetic Mean (SD) PK parameters for Total T (Pre and Post-transfer) Following the Treatment of 2 x 5 g of T Gel 1% with a T-shirt (Study MIFX10001; N=45)

	24 hour Pre-Transfer (N=45)	24 hour Post-Transfer (n=45)	% Difference
AUC(0-24) (ng·hr/mL)	4.78 (2.75)	5.30 (3.22)	10.83
$C_{max}$ (ng/mL)	0.24 (0.17)	0.28 (0.16)	15.52

It should be noted that Subject 24 was withdrawn from the study due to pregnancy and was excluded from all PK analysis. As a result, there were N=47 females included in the PK analysis for the no T-shirt period. In addition, Subjects 28 and 47 were excluded from the PK analysis of the T-shirt on period as Subject 28 showed positive laboratory results (i.e., cocaine) and Subject 47 did not show up at check-in for the T-shirt on period. As a result only N=45 subjects were included in the PK analysis for the T-shirt on period.

As shown in Tables 8 and 9, study results show approximately 11% and 16% increase in T AUC(0-24) and  $C_{max}$ , respectively, compared to baseline in females when males were wearing a T-shirt following a 10 g T Gel 1% application to the upper arm/shoulder of one side. It should be

noted that the interpersonal transfer potential of topical T applied on the abdomen was not assessed and therefore, the same conclusion cannot be extrapolated to when T Gel 1% is applied to the abdomen. This should be clearly reflected on the product label.

The overall percent difference of the PK parameters for females was much lower when males were wearing a T-shirt during the transfer procedure than without a T-shirt, indicating that there is less exposure to T when a T-shirt is covering the application site.

### 2.2.8 What are the findings from hand washing study conducted after T Gel application?

A single-dose, open label, two-period crossover study (Study CRI-00018704) in 48 healthy adult men was conducted to evaluate the residual amount of T topically delivered from T Gel 1% following hand washing procedure. Ten grams (2 x 5 g packets) of either T Gel 1% or AndroGel® 1% was applied to the subject's palm of their dominate hand by the clinical staff. Then subjects applied the dose to their opposing arm and shoulder with monitoring by the clinical staff each time. Approximately 5 minutes after dose application, the subjects washed their hands as described below:

- The subjects wet their hands with warm tap water (35°C ± 5°C) for 10 seconds.
- Two (2) mL of liquid soap was dispensed to the hands (same brand of soap was used throughout the study; brand of soap not specified)
- Subjects washed their hands with a controlled hand scrubbing procedure for 20 seconds
- Subjects rinsed their hands with warm tap water for 20 seconds
- Subjects dried their hands with a dry cotton towel for 30 seconds

There was a 14 day washout period between treatment periods.

Table 10 summarizes the results of the residual T amount following hand washing after application of each test product.

**Table 10:** Residual T Amount following Hand Washing after Application of Each Test Product (Study CRI-00018704)

	T Gel 1% (N=39)	AndroGel® 1% (N=39)
Mean (µg)	284.9	287.1
SD (µg)	131.0	132.2
%CV	46.0	46.0
Minimum (µg)	62.4	98.9
Maximum (µg)	592.5	547.3

The Sponsor did not report the percentage of T removed by the hand washing procedure as the measurement of residual T on the subjects' hands (after applying the drug product to the application site) prior to hand-washing was not carried out. However, considering that the mean residual amount of T Gel 1% is very small compared to the theoretical dose of 100 mg T (i.e., 2.85%) and that it is comparable to the residual amount following hand washing after application of AndroGel® 1%, this reviewer concludes that T Gel 1% is sufficiently removed from the hands following the hand washing procedure.

## 2.3 Intrinsic Factors

### 2.3.1 What is the Sponsor's justification of the pediatric waiver request and is it acceptable?

T production is dormant until the time of puberty, at which time endogenous T levels increase, leading to secondary male sex characteristics. Therefore, there is no therapeutic use for T in the neonate, infant, or child. No pediatric studies were conducted with T Gel 1%.

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable. Because none of these criteria apply to this application, the Division has determined that the Sponsor is exempt from this requirement.

### **2.3.2 Did the Sponsor conduct PK studies in population with renal or hepatic impairment?**

No. The Sponsor did not conduct studies with T Gel 1% in renal and/or hepatic impaired patients. No additional information is available in the labeling of topical drugs in the same drug class (i.e., Testim<sup>®</sup>, Axiron<sup>®</sup>, or AndroGel<sup>®</sup> 1%) regarding this aspect.

## **2.4 Extrinsic Factors**

### **2.4.1 Did the Sponsor conduct any DDI studies?**

No DDI studies were conducted with T Gel 1%. The Sponsor is proposing to use the following publically available information of the RLD (i.e., AndroGel<sup>®</sup> 1%) for their product: Changes in insulin sensitivity or glycemic control may occur in patients treated with androgens. In diabetic patients, the metabolic effects of androgens may decrease blood glucose and, therefore, insulin requirement. Changes in anticoagulant activity may be seen with androgens. More frequent monitoring of INR and prothrombin time is recommended in patients taking anticoagulants, especially at the initiation and termination of androgen therapy. The concurrent use of testosterone with ACTH or corticosteroids may result in increased fluid retention and should be monitored cautiously, particularly in patients with cardiac, renal, or hepatic disease.

## **2.5 General Biopharmaceutics**

### **2.5.1 What is the quantitative composition of the drug products used in the clinical trials of this application?**

T Gel 1% is a colorless hydroalcoholic gel containing 1% T for topical administration to clean, dry, intact skin surface of shoulders and upper arms and/or abdomen. The active ingredient, route of administration, dosage form, and strength for the proposed drug product are the same as those of AndroGel<sup>®</sup> 1%. (

The composition of T Gel 1% is summarized in Table 11 below. b  
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**Table 11:** Composition of T Gel 1% Product

Ingredients	Function	Amount (gm) / 2.5 gm sachet	Amount (gm) / 5 gm sachet	(b) (4)	Amount (% w/w)
Testosterone, USP	Active	0.025	0.05	(b) (4)	1.00
Dehydrated Alcohol, USP	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)
Carbomer Homopolymer Type C	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)
Isopropyl Palmitate, NF	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)
Sodium Hydroxide, NF	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)
Purified Water, USP	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)
<b>Total:</b>	-	<b>2.5</b>	<b>5.0</b>	(b) (4)	<b>100</b>

Initially, T Gel 1% was proposed to be marketed in the following dosage forms: 2.5 g packets, 5 g packets, (b) (4). However, in the Sponsor's July 29, 2011 response to the Division's May 26, 2011 comment (b) (4)

(b) (4)

Studies 70343, CRI-00018704, M1FX10001, and 10936025 were all conducted with the TBM formulation (i.e., T Gel 1%).

**2.6 Bioanalytical Methods**

**2.6.1 Did the Sponsor use validated bioanalytical methods to generate data in the clinical studies?**

Study samples were analyzed for total T concentrations by validated bioanalytical methods. A validated HPLC-UV method was used in Study CRI-00018704. In Studies 70343 and M1FX10001, a validated LC-MS/MS method was used.

An OSI inspection of clinical and bioanalytical sites of the pivotal BE study (Study 70343) has been conducted. In summary, inappropriate conduct of data integration was found during the Agency's OSI inspection and all chromatograms of the BE study were reintegrated as a result. As all of the T concentrations were changed, a revised BE study report was submitted by the Sponsor on September 14, 2011. In addition, data from Subjects 60, 61, 62, 92, 93, and 94 and the repeat analysis of 22 samples were found to be invalid as the bioanalyst responsible these samples made an error during sample handling and further investigation of this bioanalyst's training records revealed that this bioanalyst was not trained properly to conduct sample handling appropriately. Therefore, these 6 subjects were additionally excluded from the BE reanalysis. Details of these OSI inspection findings can be found in Dr. Sripal Mada's OSI consult review dated July 1, 2011 and July 30, 2011 in DARRTS that are also attached to Section 4.2 of this review.

Dynamic ranges varied between the methods used in each individual study. Bioanalytical methods are summarized in Table 12.

**Table 12: Summary of Bioanalytical Methods**

Study Number	Study Title	Biological Matrix	Analyte	Method	Dynamic Range
70343	Single Dose BE Study	Serum	T	LC-MS/MS	59.6-11,916.0 pg/mL
M1FX10001	Interpersonal Transferability Study	Serum	T	LC-MS/MS	0.05-50.0 ng/mL
CRI-00018704	Hand Washing Study	50/50 EtOH/Water	T	HPLC-UV	0.03-2.5 µg/mL

In Study 70343, incurred sample reanalysis (ISR) was performed on 20 (2 samples from 10 subjects; 1 around  $C_{max}$  at 18 hours post-dose and 1 in the elimination phase at 40 hours post-dose) out of 4,135 samples (approximately 0.5%) from 10 out of 93 subjects for T. All of the ISR results met the acceptance criteria of being within (b) (4) of the original reported concentration value for at least 67% of the ISR samples. Based on the reasons stated in Section 4.1.1 of this review, this reviewer concludes that although the number of ISR samples were small compared to the current Agency's standard (i.e., 5-10% of the incurred samples), the Sponsor's ISR data demonstrates that the bioanalytical method used in this study is reproducible.

Bioanalytical method validation and study reports were submitted for all studies that were reviewed. Acceptance criteria and method performance for T concentration measurement was in compliance with the Agency's *Bioanalytical Method Validation Guidance* and the bioanalytical methods were found to be acceptable.

### 3 Detailed Labeling Recommendations

The following Clinical Pharmacology related parts of the Sponsor's proposed label were submitted in this NDA supplement. ~~Strikes~~ are used for deletion and double underline is used for addition for the OCP's preliminary response to the Sponsor's proposal. Please note that Sections illustrated below does not necessarily reflect the entire corresponding Section of the product label.

#### 1 Indications and Usage

##### Important limitations of use:

- Testosterone gel is interchangeable only with approved testosterone gel products that employ the same doses and application sites

**Reviewer's Comment:** *The important limitation of use statement should be added to the Indications and Usage Section of both the Highlights and the Full Prescribing Information of the product label to preclude interchangeable use of Sponsor's T Gel 1% with any T gel product other than a product with the same dose (i.e., mg) of T and same sites of application, which currently includes only AndroGel® 1%. It should be noted that Testim® is also a 1% T gel product with a recommended starting dose of 50 mg T but it is approved for application only on upper arms/shoulders (not abdomen) and therefore, is not interchangeable with the Sponsor's T Gel 1%.*

#### 2 Dosage and Administration

**Reviewer's Comment:** *Regarding the Dosage and Administration and Dose Adjustment instruction recommendations for the T Gel 1% product label, the review team encountered some limitations. Per Regulatory Chief, Jennifer Mercier, the T Gel 1% product label must use the same language from the RLD, AndroGel® 1%. Unless the Sponsor for T Gel 1% has data to support the change of labeling language, the AndroGel® 1% product label must be changed first. This regulation limits the review team to clarify and put additional information regarding Dosage and Administration (i.e., application of 10 g gel on 1-site vs. 2.5 g gel each on 4-sites; necessity of rotation among application sites) and dosage adjustment instructions (e.g., based on single serum T concentration measured in the morning pre-dose vs. 2-8 hours post-dose) that is unclear on the AndroGel® 1% product label.*

#### 12.3 Pharmacokinetics

##### *Absorption*

In a single-dose, two way-crossover clinical study conducted in 72 hypogonadal males under fasting condition, the testosterone exposure (AUC<sub>0-60</sub>) and maximum testosterone concentration (C<sub>max</sub>) following a topical administration of testosterone gel 1% administered as 2 x 50 mg testosterone packets (1 packet applied on each shoulder/upper arm) on a designated area of 500 cm<sup>2</sup> were comparable to those following a topical administration of an approved testosterone gel product.

**Reviewer's Comment:** *Upon completion of the review, this reviewer concludes that T Gel 1% has established BE to the AndroGel® 1 % regarding AUC following a single 100 mg dose (2 x 5 g packets) of T to the upper arms/shoulders (5 g gel applied to each side) of hypogonadal males. However, the upper 90% CI of C<sub>max</sub> was slightly higher (by 1.7%) compared to the BE acceptance range (i.e., 80.00-125.00%) but it is still acceptable given that there was no concern regarding the lack of efficacy as it is slightly exceeded the upper limit of the 90% CI of the BE acceptance criteria and there were no additional safety signals detected in the clinical safety studies submitted in this NDA.*

*It should be noted that while AndroGel® 1 % had upper arms/shoulders and/or abdomen as its approved application sites, the pivotal BE study was only conducted using the upper*

arm/shoulders but not the abdomen. This is still acceptable from the Clinical Pharmacology standpoint as there is relative BA data submitted in the original NDA for AndroGel® 1 % showing the T exposure from the abdomen is not statistically different from the upper arms/shoulders using the RLD. However, this reviewer believes that it is important to clearly state in the product label that (1) the BE study was conducted only using the upper arms/shoulders; (2) the BE study results show the exposure was comparable (but not strictly BE); and (3) listing what it was compared to (in this case it would be "an approved testosterone gel product" per the Associate Director of the Office of Drug Evaluation III, Maria Walsh's recommendation via email on January 6, 2012). This recommendation was fully discussed with the Division Director of DCP-3, Dr. Edward Dennis Bashaw on January 4, 2012 and this reviewer has received his concurrence.

*Testosterone Transfer from Male Patients to Female Partners*

The potential for (b) (4) testosterone transfer following testosterone gel use was evaluated in a clinical study between males dosed with testosterone gel and their untreated female partners. Two (2) (b) (4) hours after testosterone gel (10 g) application to upper arm and shoulder of one side by the male subjects, the couples (N = (b) (4) 48 couples) engaged in (b) (4) a 15 minute sessions of vigorous skin-to-skin contact so that the female partners gained maximum exposure to the testosterone gel application sites. Serum concentrations of testosterone were monitored in the female subjects for 24 hours after the transfer procedure. Under these study conditions, all unprotected female partners had a serum testosterone concentration > 2 times the baseline value (b) (4) derived from a 24 hour testosterone concentration measurement during the study. When a shirt covered the application site. (b) (4) (b) (4) study results show a 11% and 16% increase in testosterone AUC<sub>0-24</sub> and testosterone C<sub>max</sub>, respectively, compared to baseline in these females. The potential for dermal testosterone transfer following testosterone gel 1% application on the abdomen has not been evaluated.

In a separate clinical study conducted to evaluate the effect of hand washing on the residual amount of testosterone, 39 healthy male subjects received 100 mg of testosterone from 10 g (2 x 5 g packets) of testosterone gel 1% on the upper arm and shoulder of one side. Subjects washed their hands with liquid soap and warm tap water 5 minutes after drug application. Then hands were wiped with 3 ethanol dampened gauzes per hand which were then combined together and analyzed for testosterone content. A mean (SD) of 284.9 (131.0) mcg of residual testosterone (i.e., approximately 2.9% of the theoretical dose of 100 mg testosterone administered) was recovered after washing hands with liquid soap and warm tap water.

**Reviewer's Comment:** *This reviewer recommends moving Section 14.3 (i.e., T transfer from Male Patients to Female Partners) to Section 12.3 (i.e., Pharmacokinetics) and substitute the data on product label with data from Studies MIFX10001 (interpersonal transferability study) and CRI-00018704 (hand washing study). It should be clearly stated that the potential for dermal T transfer following T Gel 1% application on the abdomen has not been evaluated. This recommendation was fully discussed with the Division Director of DCP-3, Dr. Edward Dennis Bashaw on January 4, 2012 and this reviewer has received his concurrence.*

## 4 Appendices

### 4.1 Individual Study Reviews

#### 4.1.1 BE Study: Study 70343

**Title:** Randomized, open-label, 2-way crossover, bioequivalence study of T 1% topical gel formulation and AndroGel<sup>®</sup> (reference) following a 100 mg dose in hypogonadal males

**Objective:** To compare the rate and extent of absorption of Teva Pharmaceuticals U.S.A., U.S.A., T Gel 1% and Solvay Pharmaceuticals Inc., U.S.A., T (AndroGel<sup>®</sup> 1%), applied as a single topical dose of 2 x 5 g packets of 1% T Gel (each packet corresponding to 50 mg T for a total dose of 100 mg), under fasting conditions.

**Clinical Study Centers:**

(b) (4)

**Clinical Study Period:** March-November 2008

**Bioanalytical Study Center:** (b) (4)

**Bioanalysis Period:** March 16 - December 17, 2008

**Study Design:**

This was a multiple-center, randomized, single-dose, open-label, 2-way crossover BE study to compare the rate and extent of absorption of a test, T Gel 1% versus AndroGel<sup>®</sup> 1%, the reference T Gel, under fasting conditions.

In each period, subjects reported to the Clinical facility in the morning of Day -1 and remained in the clinical unit until released by the Investigator subsequent to obtaining the 48-hour post-application blood draw. Prior to study commencement, subjects were randomly assigned to a treatment in accordance with the randomization scheme generated by (b) (4). Baseline T measurements were conducted at 12, 6 hrs pre-dose, and immediately before application of the study drug. The treatment phases were separated by a washout period of 7 days. Measurements of treatment compliance were 100%, as study medication was applied to the subjects by the study staff.

**Inclusion Criteria:**

- Male, smoker or non-smoker, 18 years of age and older.
- Healthy subjects (except for their hypogonadal status) or subjects with stable chronic illnesses (stable medication for a minimum of 3 months) which will not interfere in the PK or the bioanalysis of the administered testosterone.
- Body Mass Index (BMI)  $\geq 19.0$  and  $< 35.0$  kg/m<sup>2</sup>.
- Have an average of 2 morning total serum T concentrations (measured on 2 separate days)  $\leq 300$  ng/dL, the lower limit of the normal range for healthy young males (with the two morning individual values no higher than 350 ng/dL).
- Have a normal 12-lead electrocardiogram, without any clinically significant abnormalities of rate, rhythm, or conduction.

- Prostate specific antigen (PSA) between 0 - 2.5 ng/mL for subjects ≤ 50 years of age and between 0-4 ng/mL for subjects > 50 years of age.

**Exclusion Criteria:**

- Incompletely cured pre-existing diseases for which it could be assumed that the absorption, distribution, metabolism, elimination and effects of the study drugs were not be normal
- Clinically significant illness or surgery within 4 weeks prior to gel application.
- Any clinically significant abnormality or abnormal laboratory test results found during medical screening.
- Positive test for hepatitis B, hepatitis C, or HIV at screening.
- ECG abnormalities (clinically significant) or vital sign abnormalities (systolic blood pressure lower than 90 or over 140 mmHg, diastolic blood pressure lower than 50 or over 90 mmHg, or heart rate less than 50 or over 100 bpm) at screening.
- History of significant alcohol abuse or drug abuse within 1 year prior to the screening visit. Regular use of alcohol within six months prior to the screening visit (more than 14 units of alcohol per week [1 Unit = 150 mL of wine, 360 mL of beer, or 45 mL of 40% alcohol]), or positive alcohol breath test at screening. Use of soft drugs (such as marijuana) within 3 months prior to the screening visit or hard drugs (such as cocaine, phencyclidine [PCP] and crack) within 1 year prior to the screening visit or positive urine drug screen at screening.
- Use of any drugs known to induce or inhibit hepatic drug metabolism (examples of inducers: barbiturates, carbamazepine, phenytoin, glucocorticoids, omeprazole; examples of inhibitors: antidepressants [SSRI], cimetidine, diltiazem, macrolides, imidazoles, neuroleptics, verapamil, fluoroquinolones, antihistamines) within 30 days prior to gel application.
- Use of an investigational drug or participation in an investigational study within 30 days prior to gel application.
- Clinically significant history or presence of any gastrointestinal pathology (e.g. chronic diarrhea, inflammatory bowel diseases), unresolved gastrointestinal symptoms (e.g. diarrhea, vomiting), liver or kidney disease, or other conditions known to interfere with the absorption, distribution, metabolism, or excretion of the drug.
- Use of any prohibited prescription medication within 14 days prior to administration of study medication or prohibited over-the-counter products (including natural food supplements, vitamins, garlic as a supplement) within 7 days prior to gel application, except for topical products without systemic absorption.
- Smoking more than 25 cigarettes per day.
- A depot injection or an implant of any drug within 3 months prior to gel application.
- Clinically significant history of renal, hepatic, or cardiovascular disease, tuberculosis, epilepsy, asthma, diabetes, psychosis or glaucoma will not be eligible for this study.
- Have used finasteride, ketoconazole, prednisone, opioids, DHEA (or other T precursors) or other medications which may interfere with the production, metabolism or disposition of T within 30 days prior to the study.
- Have significant dermatitis, scars, tattoos or any other skin disorder at the protocol specified application site that would compromise absorption of the study medications.
- An ALT or AST greater than 1.5 times the upper limit of normal at screening or Day –1 in each dosing period.

**Concomitant Medication:**

Subjects who had been under stable treatment with the same medication for 3 months for a stable chronic condition, with no change in dosage for at least 14 days before first study drug application, and no expected change throughout the study were eligible for the study once their concomitant medication had been approved by a physician and by the study Sponsor as not having possible effects on T concentrations.

Newly prescribed medication was prohibited from 14 days and over-the-counter medication from 7 days prior to drug application until the last sample collection of the study (60 hour post-application), in each period. Subjects were required to abstain from oral or transdermal T replacement therapy from 28 days prior to gel application, and from injection, intramuscular T replacement therapy, or implants from 6 months prior to gel application, until after the last sample collection of the study, in each period. In addition, the use of topical products without systemic absorption on the treated area was prohibited from 48 hours prior to gel application until after the last sample collection of each period.

The following medications were not accepted since they could affect T levels: glucocorticoids (cortisone, prednisone) (topical steroid use was to be evaluated on a case-by-case basis by the investigator), anabolic steroids, opiates (codeine, morphine, hydromorphone), estrogens, digoxin (Lanoxin<sup>®</sup>), spironolactone (Aldactone<sup>®</sup>), barbiturates, anti-androgen (Casodex<sup>®</sup>, Euflex<sup>®</sup>), prostate cancer treatment (Lupron<sup>®</sup>, Zoladex<sup>®</sup>), anti-epileptic drugs (Dilantin<sup>®</sup>), anti-depressants (Paxil<sup>®</sup>, Effexor<sup>®</sup>, Prozac<sup>®</sup>, Zoloft<sup>®</sup>, Luvox<sup>®</sup>, Celexa<sup>®</sup>, Cipralex<sup>®</sup>), antipsychotic agents (Risperdal<sup>®</sup>, Zyprexa<sup>®</sup>, Haldol<sup>®</sup>), propranolol, and insulin.

Any medication assessed as being interfering with the PK or bioanalysis of T was not accepted. The short-term use of a medication for a self-limiting indication (e.g., acetaminophen for a headache) could be authorized by the Investigator. The Investigator could authorize use of such a medication only after consideration of the clinical situation, the potential for making symptoms of a more significant underlying event, and whether the use of the medication could compromise the outcome or validity of the study. Upon entering the study, each subject was instructed to report the use of any medication to the Investigator. Any medication taken by a subject during the course of the study and the reason for use of the medication was recorded.

**Disposition of subjects:**

A total of 96 hypogonadal, male subjects signed the study-specific informed consent form and were confined for Period 1; of these subjects, 93 were enrolled and dosed in the study; 90 of these enrolled subjects completed the study.

The following subjects were withdrawn from the study for the reasons listed below:

- Subject 23: elected to withdraw due to medication taken as treatment for adverse events (AE) (pain at buttock left side and infected hematoma on left buttock)
- Subject 42: withdrawn due to positive urine drug screen result for benzodiazepines
- Subject 91: withdrawn due to the possibility of taking prohibited concomitant medication (medication was found in baggage during check-in; medication not specified)

In addition, the following subjects in Table A-1-1 who completed the study were excluded from the BE analysis by the Sponsor:

**Table A-1-1:** Subjects who Completed the Study but were Excluded from the Original BE Analysis (N=13)

Subject Number	Reason for exclusion from statistical analysis
24	This subject samples stability exceeded validation data.
03, 15, 25, 27, 35, 37, 40, 70, 84, 87, 88, and 89	These subjects had a mean baseline T serum concentration in at least one period that was higher than 350 ng/dL.

The mean age of the 77 subjects that the Sponsor included in their BE analysis was 47 (range: 21-68 years) with a mean BMI of 28.6 kg/m<sup>2</sup> (range: 21.7-35.4 kg/m<sup>2</sup>). There were 70 Caucasians (91%), 2 Asians, 1 Black, and 4 subjects from unspecified race groups.

**Reviewer's Comment:** *Subject 08 was judged eligible to participate in the study although he had a BMI of 35.4 kg/m<sup>2</sup> at screening. It was stated in the study report that a waiver was granted from the Sponsor.*

*In the study protocol it is stated that "if the baseline T serum concentration mean for any study period is higher than 350 ng/dL, all of the study data from that subject will be excluded from the PK analysis."*

*As there was inappropriate conduct of data integration found by the Agency's OSI inspection, all chromatograms of this study was reintegrated and as a result, the baseline T concentrations were changed. Subject 70 was not included in the original BE analysis as its T baseline concentration was 352.9 mg/dL in Period 1. However, the T baseline following reintegration of chromatograms for Subject 70 fell below 350 mg/dL and therefore, was included in the BE reanalysis.*

*Out of the 78 subjects included in the Sponsor's reanalysis, data from Subjects 60, 61, 62, 92, 93, and 94 and the repeat analysis of 22 samples were found to be invalid as the bioanalyst responsible these samples made an error during sample handling and further investigation of this bioanalyst's training records revealed that this bioanalyst was not trained properly to conduct sample handling appropriately. Therefore, these 6 subjects were additionally excluded from the BE reanalysis. Details of these OSI inspection findings can be found in Dr. Sripal Mada's OSI consult reviews in Section 4.2 of this review.*

*In addition, it should be noted that the baseline value for Subject 88 was 351.3 ng/dL but as the -6 hr baseline sample of Period 2 was excluded as being one of the 22 reanalysis samples invalidated, the baseline for Subject 88 became 337.0 ng/dL and was included in the final BE reanalysis. In a similar manner, the baseline value for Subject 96 was 338.6 ng/dL but as the -12 hr baseline sample of Period 1 was excluded as being one of the 22 reanalysis samples invalidated, the baseline for Subject 96 became 360.2 ng/dL and was excluded in the final BE reanalysis.*

*As a result the subjects in Table A-1-2 were excluded and 72 subjects were included in the final BE reanalysis per the Division's request. The baseline T concentrations for each subject after reintegration of the chromatograms can be found in Tables A-1-3 and A-1-4 below.*

**Table A-1-2:** Subjects who Completed the Study but were Excluded from the BE Reanalysis (N=18)

Subject Number	Reason for Exclusion from Statistical Analysis
24	This subject's samples stability exceeded validation data.
03, 15, 25, 27, 35, 37, 40, 84, 87, 89 and 96	These subjects had a mean baseline T serum concentration in at least one period that was higher than 350 ng/dL
60, 61, 62, 92, 93, and 94	Data from these subjects were found to invalid due to an error of sample handling

**Table A-1-3:** Baseline T Concentrations (pg/mL) for Each Subject in Period 1 after Reintegration of Chromatograms

Subject	Pre-Dose			Baseline
	-12 h	-6 h	0 h	
1	(b) (4)			
2				
3				
4				
5				
6				
7				
8				
9				
10				
11				
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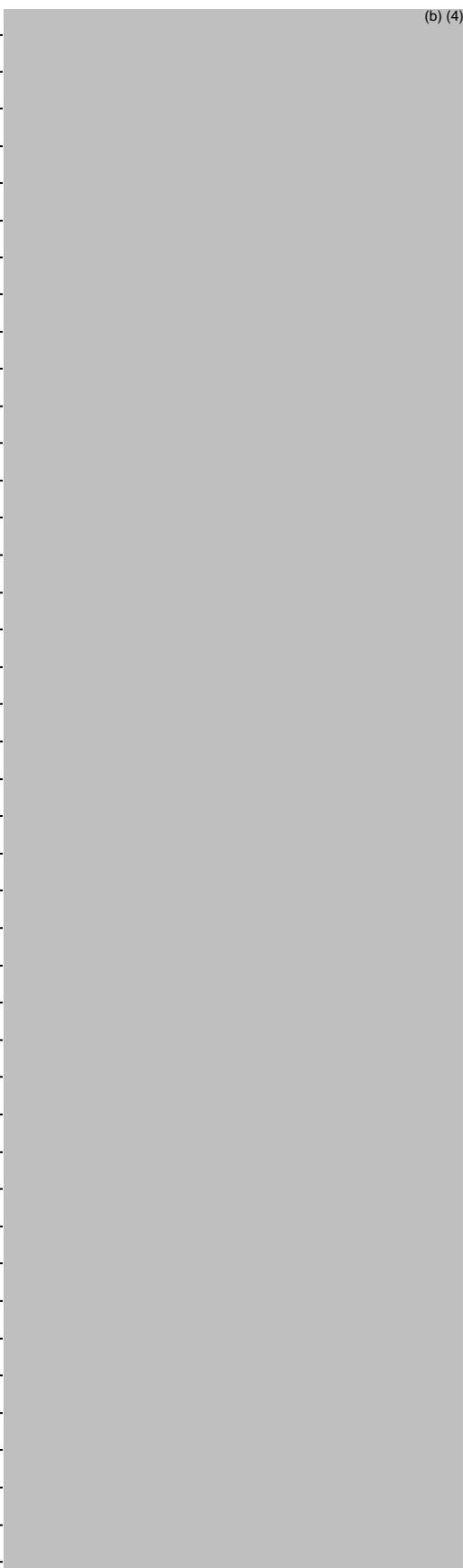
	(b) (4)
83	
84	
85	
86	
87	
88	
89	
90	
95	
96	

NRV: Affected samples by additional invalidation of the 22 repeat samples  
 Subjects with baseline concentration numbers in red fonts are excluded from the BE reanalysis

**Table A-1-4:** Baseline T Concentrations (pg/mL) for Each Subject in Period 2 after Reintegration of Chromatograms

Subject	Pre-Dose			Baseline
	-12 h	-6 h	0 h	
1				(b) (4)
2				
3				
4				
5				
6				
7				
8				
9				
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	(b) (4)
78	
79	
80	
81	
82	
83	
84	
85	
86	
87	
88	
89	
90	
95	
96	

NRV: Affected samples by additional invalidation of the 22 repeat samples  
 Subjects with baseline concentration numbers in red fonts are excluded from the BE reanalysis

#### Treatments, Study Drugs, and Study Drug Administration

Subjects were administered a single topical dose of either the test (T Gel 1%) or reference (AndroGel<sup>®</sup> 1%), as 2 x 5 g packets of topical gel.

**Table A-1-5:** Study Formulations used in Study 70343

Product	Test	Reference
<b>Treatment ID</b>	A	B
<b>Product Name</b>	T (T Gel 1%)	T (AndroGel <sup>®</sup> 1%)
<b>Manufacturer</b>	Manufactured by Cipla Ltd., India for Teva Pharmaceuticals U.S.A.	Manufactured by Laboratoires Besins International, France for Unimed Pharmaceuticals, Inc. a Solvay Pharmaceuticals, Inc. company, U.S.A.
<b>Batch/Lot No.</b>	Batch No.: X028	Batch No.: 31154
<b>Manufacture Date</b>	02/2008	Not available
<b>Expiration Date</b>	01/2010	08/2009
<b>Strength</b>	1%	1%
<b>Dosage Form</b>	topical gel	topical gel
<b>Potency</b>	104.8%	100.8%
<b>Content Uniformity (mean, %CV)</b>	Not available	Not available
<b>Dose Administered</b>	2 x 5 g packets of 1% topical gel, corresponding to 50 mg testosterone each packet, for a total of 100 mg T	2 x 5 g packets of 1% topical gel, corresponding to 50 mg testosterone each packet, for a total of 100 mg T
<b>Route of Administration</b>	topical	topical

In this study, two 5 g packets of T Gel (each containing 50 mg of T; total dose of 100 mg) were applied (one packet applied on each shoulder and upper arm) with a spatula to each hypogonadal subject after a supervised overnight fast of at least 10 hours. Following dosing, subjects fasted for a period of at least 4 hours.

Prior to gel application, the shoulders and upper arms of each subject were washed with warm water and mild soap and were rinsed with clean, warm water, and allowed to dry for approximately 1 hour before gel was applied. Any excessive body hair (judged by the Investigator or a Sub-Investigator to possibly interfere with drug absorption) on the site of application was to be clipped (not shaved) prior to washing.

Within 5 or 10 minutes, before gel application, the topical gel was squeezed out directly onto a weigh boat and approximately 5 g was weighted (in grams out to 2 decimal places). Acceptable range of weight was between 4.70-5.00 g. Extra packets of medication could have been used to complete the range.

In each period, using gloved hands and a spatula applicator, the pre-weighted topical gel was applied directly on the application site by the study staff (5 g per shoulder/arm for a total of 10 g) on the designated area predefined with an individual template (outlining a 500 cm<sup>2</sup> area; each subject was designed his own template) to insure consistent size of the application area between and within subjects. The application site was allowed to dry until after the 30 minutes local irritation evaluation. Subjects were instructed not to touch the application site for at least 4 hours after gel application. After the gel had dried, subjects covered the application site with clothing (e.g., a shirt - type [long or short] not specified) (within ~30 minutes) to avoid transfer to another person. Washing the treated area was prohibited from 2 hours before until 48 hours after gel application, unless required by study procedures. After the 48 hour blood sample collection, subjects had the dosing area washed by clinical staff member to remove any residual, unabsorbed study drug, and were given the option to shower and wear a clean shirt.

**Reviewer's Comment:** *It should be noted that while the approved application sites of AndroGel<sup>®</sup> 1% (NDA 021015) are shoulder/upper arms and/or abdomen, the application sites used in this BE study were shoulders/upper arms but did not include abdomen. However, it should be noted that results from a clinical study with AndroGel<sup>®</sup> 1% (Study UMD-98-012) did not show any statistically significant differences in PK parameters of T following 1-site (left upper arm/shoulder) or 4-site (left upper arm/shoulder, right upper arm/shoulder, left abdomen, and right abdomen).*

*Reference is made to Dr. Dhruba J. Chatterjee's Clinical Pharmacology review dated February 25, 2000 available at [http://www.accessdata.fda.gov/drugsatfda\\_docs/nda/2000/21-015\\_AndroGel\\_BioPharmr.pdf](http://www.accessdata.fda.gov/drugsatfda_docs/nda/2000/21-015_AndroGel_BioPharmr.pdf).*

**PK Characterization:**

Blood samples for PK characterization were taken at 12 and 6 hours pre-dose, and immediately before drug application, and 1, 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 32, 36, 40, 48, and 60 (±0.5) hours post-dose in each period.

Mean baseline T concentrations were calculated for each subject by averaging the 3 pre-dose values (12 and 6 hours pre-dose and immediately before drug application) for each period. The mean of the 3 pre-dose concentrations were attributed to the pre-dose sample as the baseline concentration. All concentrations, including the pre-dose concentration for each subject and period, were corrected for the mean of the 3 pre-dose concentrations for the baseline corrected assessment. Every negative concentration obtained after correction was set equal to zero.

The mean, standard deviation (SD), coefficient of variation (%CV) and range (minimum and maximum) were calculated for serum concentrations of baseline corrected and uncorrected T for each sampling time and treatment. The mean, SD, %CV, range (minimum and maximum), median and inter-quartile range were calculated for the AUC(0-t) (pg-h/mL),  $C_{\max}$  (pg/mL) and  $T_{\max}$  (h). Due to physiological fluctuation of endogenous concentrations of T, the AUC(0-∞) (pg-h/mL) and  $t_{1/2}$  (h) could not be properly characterized for baseline corrected T, for every subjects, and therefore these parameters were not calculated.

#### **Statistical Analysis:**

For both baseline corrected T and baseline uncorrected T, analysis of variance was performed on the ln-transformed data of AUC(0-t) and  $C_{\max}$ . ANOVA was also carried out on the untransformed data of  $T_{\max}$ . All ANOVAs were performed with the SAS (version 8.2 for Windows) GLM Procedure. Based on pair-wise comparisons of the ln-transformed of AUC(0-t) and  $C_{\max}$  data, the ratios of the least squares means, calculated according to the formula “ $e^{(X-Y)} \times 100$ ”, as well as the 90% geometric CIs for ln-transformed AUC(0-t) and  $C_{\max}$  were determined.

#### **Safety Evaluations:**

Physical and gynecological examination, blood pressure, heart rate, and electrocardiogram (ECG) at pre-treatment examination; standard laboratory parameters in blood and urine at pre- and post-treatment examination; recording of AE and concomitant medication during treatment phase

In each period, skin reactions at the gel application site were recorded: prior to gel application, approximately 0.5, 8, 24, and 48 hours post-gel application, and at the return visit for the 60-hour blood sample collection. The local dermal reaction at the gel application site according to the following rating scale (based on Agency's *Guidance For Industry: Skin Irritation and Sensitization Testing of Generic Transdermal Drug Products*; December 1999):

- 0 = no evidence of irritation;
- 1 = minimal erythema, barely perceptible;
- 2 = definite erythema, readily visible; minimal edema or minimal popular response;
- 3 = erythema and papules;
- 4 = definite edema;
- 5 = erythema, edema and papules;
- 6 = vesicular eruption;
- 7 = strong reaction spreading beyond application site.

#### **Bioanalytical Methods:**

Bioanalyses for total T was performed at [REDACTED] <sup>(b) (4)</sup> between March 16, 2008 and December 17, 2008.

The analyte T and its internal standard (IS) T-ds were extracted from a 0.150 mL aliquot of human serum using an Oasis HLB 30 mg, 1 cc solid phase extraction cartridges. The extracted samples were injected into an Atlantis dC18 75 x 4.6 mm, 3 µm column for separation using liquid chromatography. The mobile phase A, reconstitution and autosampler rinsing solution was a mixture of Milli-Q type water / acetonitrile (50/50) and the mobile phase B was a mixture of Milli-Q type water / acetonitrile (10/90). The chromatographic separation was in gradient mode and performed at room temperature at a flow-rate of 1 mL/minutes and 1.5 mL/minutes. Following separation, T concentrations were measured by a triple quadrupole tandem mass spectrometer (API 4000; MDS Sciex). The dynamic range was 59.58-11,916.00 pg/mL.

Mean inter-assay accuracy of back-calculated concentrations in calibrators ranged between 99.3% and 101.5% and precision was 2.6-6.9%. Quality control (QC) samples for T (range: 179.6-8,383.2 pg/mL) had an accuracy of 97.9-101.8 % and a precision of 1.5-12.7%.

Samples were stored at or below -20°C until the time of analysis. All samples were analyzed within 101 days after sample collection. Long term stability for T in unstrapped human serum was established for 105 days at -20°C.

ISR was performed on 20 (2 from Subjects 1-10; 1 around C<sub>max</sub> at 18 hours post-dose and 1 in the elimination phase at 40 hours post-dose) out of 4,135 samples (approximately 0.5%) from 10 out of 93 subjects for T. All of the ISR results met the acceptance criteria of being within ±20% of the original reported concentration value for at least 67% of the ISR samples.

**Reviewer’s Comment:** *The following information request (IR) was sent to the Sponsor on March 8, 2011:*

*“Incurred sample reanalysis (ISR) is recommended to evaluate the accuracy of the incurred samples analyzed. We note that ISR was only conducted in the Bioequivalence Study 70343 for 20 out of 4135 samples (i.e., approximately 0.5%) analyzed. The number of samples for ISR should equal to at least 5% of the total sample size. We request that you either submit additional ISR results or conduct additional ISR to ensure the reliability of the study data.”*

*In the Sponsor’s response of April 21, 2011, the Sponsor acknowledged the number of ISR samples analyzed during the study was small when compared to current Agency’s standards but states that it had followed (b)(4) existing ISR SOP effective at the time of the bioanalysis which required only 20 samples to assess the reproducibility of the bioanalytical method.*

*Given the absence of a definite requirement from the Agency at the time of study (i.e., ISR requirements were under discussion) and the fact that T has considerable number of well established bioanalytical methods with reproducibility demonstrated, this reviewer concludes that although the number of ISR samples were small compared to the current Agency’s standard (i.e., 5-10% of the incurred samples), the Sponsor’s ISR data demonstrates that the bioanalytical method used in this study is reproducible.*

**PK Results:**

Baseline Corrected PK Parameters

Baseline corrected T PK parameters for each treatment are shown in Table A-1-6.

**Table A-1-6:** Mean, SD, and %CV of Baseline Corrected T PK Parameters Following a Single Dose of either T Gel 1% or AndroGel 1% (N=72)

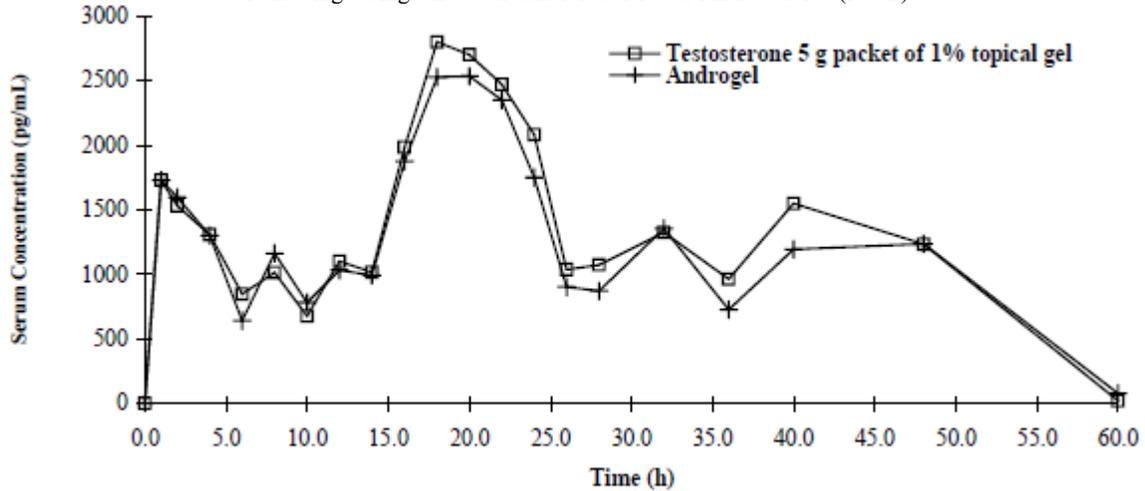
Parameters	Test (5 g packet of T Gel 1% (A))			Reference (AndroGel 1% (B))		
	Mean	SD	CV (%)	Mean	SD	CV (%)
AUC <sub>0-t</sub> (pg/h/mL)	65898.89	34034.54	51.65	61144.45	27227.53	44.53
C <sub>max</sub> (pg/mL)	3826.24	2478.19	64.77	3216.90	1567.72	48.73
T <sub>max</sub> (h)	19.6	10.7	54.74	19.2	10.5	54.89
T <sub>max</sub> * (h)	20.0	4.0	-	20.0	6.0	-

\* Medians and interquartile ranges are presented

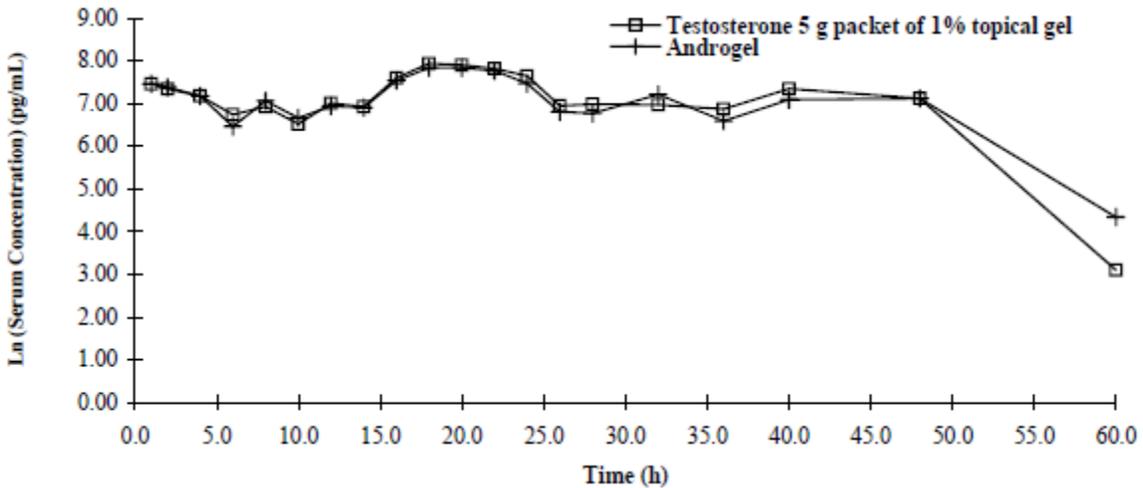
The plots of the mean serum levels over the sampling period are presented for both the untransformed and ln-transformed data in Figures A-1-1 and A-1-2 for baseline corrected T,

respectively. The mean profiles for both the test and reference formulations are plotted based on the mean serum concentrations calculated per time point. Therefore, it should be noted that the maximum concentrations observed in the mean data figures may not reflect the mean  $C_{max}$ , as the  $C_{max}$  and the time of maximum concentration ( $T_{max}$ ) vary between individuals.

**Figure A-1-1:** Baseline Corrected Mean T Concentration-Time Profile Following a Single Dose of either T Gel 1% or AndroGel 1% (N=72)



**Figure A-1-2:** Baseline Corrected Ln-transformed Mean T Concentration-Time Profile Following a Single Dose of either T Gel 1% or AndroGel 1% (N=72)



The ratios of the least-squares means, calculated according to the formula “ $e^{(X-Y)} \times 100$ ”, as well as the 90% geometric CIs for ln-transformed AUC(0-t) and  $C_{max}$  were determined using the ANOVA that excluded the Treatment\*Group factor. These results are summarized in the following Table A-1-7.

**Table A-1-7: Sponsor’s Baseline Corrected BE Analysis Results (N=72)**

	AUC <sub>0-t</sub>	C <sub>max</sub>
Ratio <sup>1</sup>	105.28%	115.72%
90 % Geometric C.I. <sup>2</sup>	95.82 % to 115.67 %	105.95 % to 126.40 %
Intra-Subject CV	34.56 %	32.29 %

<sup>1</sup> Calculated using least-squares means according to the formula:  $e^{(5 \text{ g packet of T Gel 1\% (A)} - \text{AndroGel 1\% (B)})} \times 100$

<sup>2</sup> 90% Geometric Confidence Interval using ln-transformed data

**Reviewer’s Comment:** *As endogenous T exists in the body and the study objective is to compare the exposure of T by the contribution of the drug products, BE analysis based on baseline corrected PK parameters were selected as the primary parameter for BE analysis.*

*The Sponsor’s BE analysis results were confirmed to be valid based on this reviewer’s own BE analysis. All ANOVAs were performed with the SAS (version 9.2 for Windows) GLM procedure. Based on pair-wise comparisons of the ln-transformed of AUC(0-t) and C<sub>max</sub> data, the ratios of the least squares means, calculated according to the formula “ $e^{(X-Y)} \times 100$ ”, as well as the 90% geometric CIs for ln-transformed AUC(0-t) and C<sub>max</sub> were determined. This reviewer’s BE analysis results are summarized in Table A-1-8 below:*

**Table A-1-8: Reviewer’s Baseline Corrected BE Analysis Results (N=72)**

	AUC <sub>0-t</sub>	C <sub>max</sub>
Ratio <sup>1</sup>	105.3%	116.2%
90 % Geometric C.I. <sup>2</sup>	96.0% to 115.5%	106.6% to 126.7%
Intra-Subject CV	33.5%	30.8%

<sup>1</sup> Calculated using least-squares means according to the formula:  $e^{(\text{T Gel 1\% (A)} - \text{AndroGel 1\% (B)})} \times 100$

<sup>2</sup> 90% Geometric Confidence Interval using ln-transformed data

*For baseline corrected T, a statistically significant difference between treatments was detected using ANOVA for ln-transformed C<sub>max</sub>, but not for ln-transformed AUC(0-t). The 90% geometric CIs were within the BE acceptance range for AUC(0-t) but not for C<sub>max</sub> (i.e., 106.6% to 126.7%).*

*While the clinical implication of this is unknown, as there is a shift towards slightly higher exposure from the T Gel 1% product compared to the RLD, AndroGel<sup>®</sup> 1%, there are no concerns regarding the potential lack of efficacy. In addition, there were no additional safety signals for T Gel 1% detected from this single dose BE study.*

*It should be noted that there is a considerable variability in both AUC(0-t) and C<sub>max</sub> of T. For baseline corrected T the intra-subject CVs for AUC(0-t) and C<sub>max</sub> were respectively 34.9% and 31.3%.*

*This reviewer concludes that BE between T Gel 1% and AndroGel<sup>®</sup> 1 % has been established regarding AUC following a single 100 mg dose (2 x 5 g packets) of T to the upper arms/shoulders (5 g gel applied to each side) of hypogonadal males. However, the upper 90% CI of C<sub>max</sub> was slightly higher (by 1.7%) compared to the BE acceptance range (i.e., 80.00-125.00%) but it is still acceptable given that there is no concern regarding the lack of efficacy as it is slightly exceeded the upper limit of the 90% CI of the BE acceptance criteria and there were no additional safety signals detected in the clinical safety studies submitted in this NDA.*

### Baseline Uncorrected PK Parameters

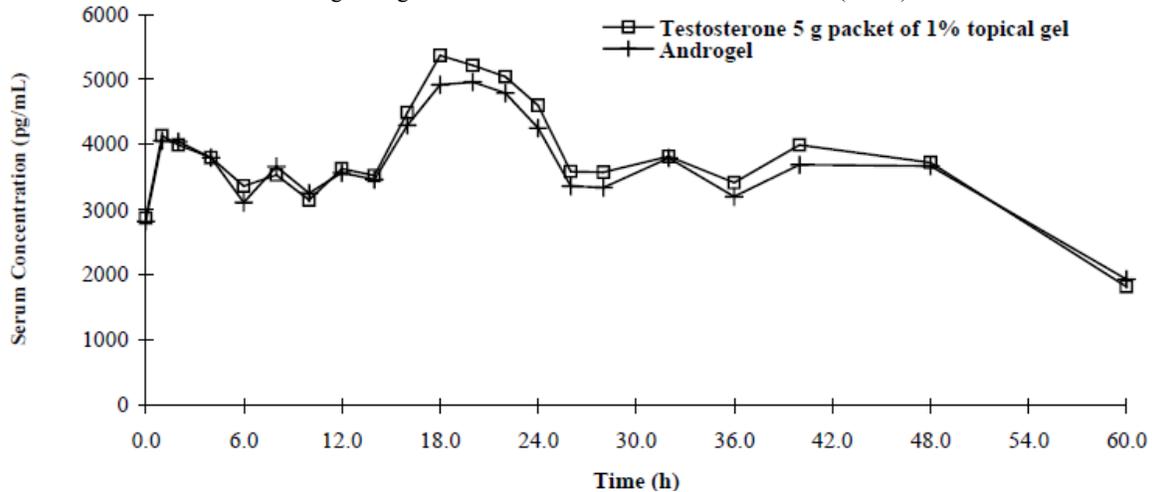
Baseline uncorrected T PK parameters for each treatment are shown in Table A-1-9.

**Table A-1-9:** Mean, SD, and % CV of Baseline Uncorrected T PK Parameters following a Single Dose of either T Gel 1% or AndroGel 1% (N=72)

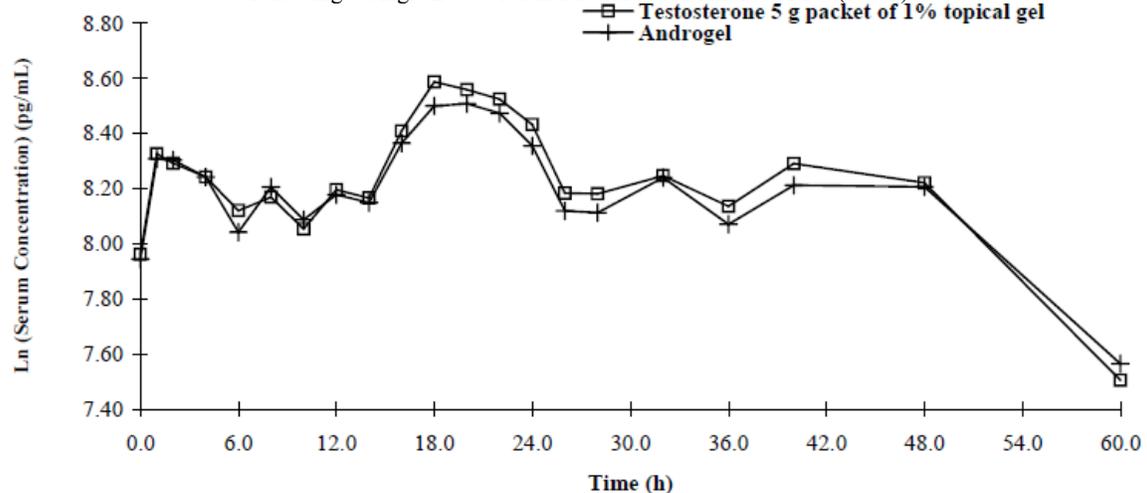
Parameters	Test (5 g packet of T Gel 1% (A))			Reference (AndroGel 1% (B))		
	Mean	SD	CV (%)	Mean	SD	CV (%)
AUC <sub>0-t</sub> (pg h/mL)	218205.72	44320.40	20.31	210616.55	43592.25	20.70
C <sub>max</sub> (pg/mL)	6406.11	2532.93	39.54	5764.91	1796.75	31.17
T <sub>max</sub> (h)	19.6	10.7	54.74	19.2	10.5	54.89
T <sub>max</sub> * (h)	20.0	4.0	-	20.0	6.0	-

\* Medians and interquartile ranges are presented

**Figure A-1-3:** Baseline Uncorrected Mean T Concentration-Time Profile following a Single Dose of either T Gel 1% or AndroGel 1% (N=72)



**Figure A-1-4:** Baseline Uncorrected Ln-transformed Mean T Concentration-Time Profile following a Single Dose of either T Gel 1% or AndroGel 1% (N=72)



The ratios of the least-squares means, calculated according to the formula “ $e^{(X-Y)} \times 100$ ”, as well as the 90% geometric CI for ln-transformed AUC(0-t) and C<sub>max</sub> were determined using the ANOVA that excluded the Treatment\*Group factor. These results are summarized in the following Table A-1-10.

**Table A-1-10: Sponsor's Baseline Uncorrected BE Analysis Results (N=72)**

	AUC <sub>0-t</sub>	C <sub>max</sub>
Ratio <sup>1</sup>	103.50%	109.58%
90 % Geometric C.I. <sup>2</sup>	100.91 % to 106.16 %	104.53 % to 114.88 %
Intra-Subject CV	9.07 %	16.96 %

<sup>1</sup> Calculated using least-squares means according to the formula:  $e^{(T \text{ Gel } 1\% (A) - \text{AndroGel } 1\% (B))} \times 100$

<sup>2</sup> 90% Geometric Confidence Interval using ln-transformed data

**Reviewer's Comment:** *The Sponsor's BE analysis results were confirmed to be valid based on this reviewer's own BE analysis. All ANOVAs were performed with the SAS (version 9.2 for Windows) GLM procedure. Based on pair-wise comparisons of the ln-transformed of AUC(0-t) and C<sub>max</sub> data, the ratios of the least squares means, calculated according to the formula " $e^{(X-Y)} \times 100$ ", as well as the 90% geometric CIs for ln-transformed AUC(0-t) and C<sub>max</sub> were determined. This reviewer's BE analysis results are summarized in Table A-1-9 below:*

**Table A-1-9: Reviewer's Baseline Uncorrected BE Analysis Results (N=72)**

	AUC <sub>0-t</sub>	C <sub>max</sub>
Ratio <sup>1</sup>	103.7%	110.0%
90 % Geometric C.I. <sup>2</sup>	101.0% to 106.4%	105.0% to 115.3%
Intra-Subject CV	9.3 %	16.8%

<sup>1</sup> Calculated using least-squares means according to the formula:  $e^{(T \text{ Gel } 1\% (A) - \text{AndroGel } 1\% (B))} \times 100$

<sup>2</sup> 90% Geometric Confidence Interval using ln-transformed data

*The 90% geometric CIs were within the acceptance range for both baseline uncorrected AUC(0-t) and C<sub>max</sub>.*

### Safety Results:

No deaths or serious adverse events (SAE) were reported during this study. One subject presented 2 significant AEs "Musculoskeletal pain" and "Haematoma infection." The health of this subject was not at risk during the study.

A total of 208 treatment emergent AEs (TEAE) were recorded by 80 subjects during the study: The most commonly reported TEAEs were related to study drug application site, with "Application site erythema" and "Application site pruritus" being reported by 63.4% (n=58) and 12.9% (n=12), respectively.

### Conclusion:

This reviewer concludes that BE between T Gel 1% and AndroGel<sup>®</sup> 1 % has been established regarding AUC following a single 100 mg dose (2 x 5 g packets) of T to the upper arms/shoulders (5 g gel applied to each side) of hypogonadal males. However, the upper 90% CI of C<sub>max</sub> was slightly higher (by 1.7%) compared to the BE acceptance range (i.e., 80.00-125.00%) but it is still acceptable given that there is no concern regarding the lack of efficacy as it is slightly exceeded the upper limit of the 90% CI of the BE acceptance criteria and there were no additional safety signals detected in the clinical safety studies submitted in this NDA.

#### 4.1.2 Interpersonal Transferability Study: Study MIFX10001

**Title:** A Study Comparing the Transfer of T Gel 1% Manufactured by Cipla Ltd. for TEVA Pharmaceuticals USA to AndroGel® 1% by Solvay Pharmaceuticals from a Male Subject to a Female Subject

**Objective:** This study assessed the relative BA of T Gel 1% by TEVA Pharmaceuticals USA compared to that of AndroGel® 1% by Solvay Pharmaceuticals in healthy female subjects following direct transfer from healthy male subjects who received a single topical dose (2 x 5 g of gel for a total of 100 mg T). Transfer from males with a T-shirt and without a T-shirt was assessed.

**Clinical Study Center:** (b) (4)  
**Clinical Study Period:** August 22, 2010 - September 29, 2010

**Bioanalytical Study Center:** (b) (4)  
**Bioanalysis Period:** October 7, 2010 - November 5, 2010

#### Study Design:

This was an open label, single-dose, randomized, four-period, four-treatment, crossover study. The total duration of the study, screening through study exit, was approximately 12 weeks with a 7-day washout period between doses. At study check-in for each period, female subjects reported to the clinical site on Day -2 at least 48 hours prior to Day 1 dosing and were required to stay for 26 hours after Day 1 dosing of the male subjects (i.e., Day 2, 24 hours after dose transfer). Male subjects reported to the clinical site on Day -1 at least 10 hours prior to dosing and were required to stay for at least 4 hours after Day 1 dosing. On study day 1 (Periods I to IV), each subject received either a single topical dose of T Gel 1%, or a single topical dose of AndroGel® 1%. Following the washout period, subjects returned to the clinical facility to be dosed with the alternative treatment as per the randomization. Blood samples were collected from female subjects only, on Day -1 at 0, 2, 4, 6, 8, 10, 12, 16 and 24 hours (such that these times were parallel with respect to sampling times on Day 1) and on Day 1 at 0 (within 10 minutes prior to dose transfer) and 2, 4, 6, 8, 10, 12, 16, and 24 hours after dose transfer while subjects were confined to the clinic.

#### Disposition of subjects:

One hundred and fifty five subjects were screened, and a total of 96 healthy adult subjects (48 couples, male and female) of 18-64 years of age were enrolled and randomized. The randomization scheme utilized a 4-treatment, 4-sequence design. Eighty six subjects (43 females) completed the study and the discontinued subjects are listed in Table A-2-1.

Table A-2-1: Discontinued Subjects

Subject No.	Reason	Gender	Age	Race*
02	Withdrawn at Period IV due to no show of male partner at admission.	Female	28	W
		Male	36	B
20	Withdrawn at Period IV due to no show of male partner at admission.	Female	45	W
		Male	21	B
24	Withdrawn by the principal investigator at Period II due to pregnancy. Male partner was also withdrawn.	Female	19	W
		Male	39	W
38	Withdrawn by the principal investigator due to positive laboratory results (cocaine) at Period III check-in. Male partner was also withdrawn.	Female	26	W
		Male	42	W
47	Subject did not show up for check-in at Period III. Male partner was also withdrawn.	Female	38	W
		Male	18	W

\*W= White; B=Black or African American

The 43 females (41 were Caucasians) completed the study had a mean age of 41.0 years (range: 27-60 years) with a mean BMI of 27.2 kg/m<sup>2</sup> (range: 20.6-33.8 kg/m<sup>2</sup>).

**Inclusion Criteria:**

- Healthy male or female, 18-65 years of age at the time of dosing.
- BMI:  $18 \leq \text{BMI} < 34$  kg/m<sup>2</sup>
- Both males and females with T concentrations in the normal range at screening and at each period check-in. The clinical laboratory defines the normal range as 220-1,000 ng/dL for males and 0-90 ng/dL for females.
- Females of childbearing potential, postmenopausal or surgically sterile. Females of childbearing potential practicing an acceptable method of birth control as judged by the investigator(s). Beginning 2 weeks prior to dosing, throughout the study, and until 7 days following the last dose, female subjects of childbearing potential were instructed not to use hormonal contraceptives for 3 consecutive months and agreed to utilize one of the following methods of contraception:
  - condom and spermicide (foam, cream, gel, sponge)
  - condom and diaphragm
  - diaphragm and spermicide (foam, cream, gel, sponge)
  - non-hormonal intrauterine device (IUD)
  - complete abstinence

Females who were surgically sterile, or who were postmenopausal were of postmenopausal status (no menses) for at least 1 year and if < 55 years of age, had a documented FSH level  $\geq 40$  mIU/mL. Surgically sterile included bilateral tubal ligation, bilateral oophorectomy, or hysterectomy.

- Willing to refrain from excessive consumption of sodium in food or beverage 48 hours prior to and throughout the study.
- Willing to refrain from caffeine/xanthine such as coffee, tea, chocolate, and all caffeine containing soft drinks or energy drinks for 48 hours prior to each period dosing and throughout the study until the last scheduled blood sample collection.

**Exclusion Criteria:**

- Anyone who received any investigational drug within 30 days prior to Period I dosing
- For males, baseline PSA > 2.5 ng/mL. If the volunteer had documentation of a negative prostate biopsy within the past 6 months, a PSA of 2.6-3.74 ng/mL was to be allowed.
- Anyone who had used any over the counter (OTC) medications within 7 days prior to the first dose of study medication or had used any prescription medications or herbal and dietary supplements within 14 days prior to the first dose of study medication. This exclusion was extended to 28 days for any drugs known to induce CYP3A enzymes and 14 days for any drugs known to inhibit CYP3A enzymes or 5 $\alpha$ -reductase, such as finasteride and dutasteride.
- Anyone who reported a history of drug or alcohol addiction or abuse within the past 2 years.
- Anyone who reported smoking or using tobacco products within the last 6 months or was currently using nicotine products (patches, gum, etc)
- Anyone who reported a caffeine intake greater than 500 mg per day (1 cup of coffee contains approximately 85 mg of caffeine).
- Anyone unwilling to abstain from alcohol or caffeine for 48 hours prior to and throughout the study.

- Females that were pregnant, lactating, breastfeeding, or intended to become pregnant over the course of the study.

#### Concomitant Medication:

- No prescription medications or herbal/dietary supplements were allowed for a period of 14 days prior to dosing and no OTC medications/vitamins were allowed for a period of 7 days to dosing with the exception of CYP3A enzyme inducers which were restricted for 28 days, and 14 days for any drug known to inhibit CYP enzyme drug metabolism.
- No subject was allowed to apply any cream, ointment, lotion, moisturizer, etc. to the dosing areas 48 hours prior to study conduct and throughout the study period.
- Hormone replacement therapy (e.g., oral, vaginal insert, patch, injectable, or topical) was not to have been used by female subjects for at least 3 consecutive months prior to Period I dosing and throughout the study. Females on hormonal replacement therapy for at least 3 consecutive months prior to Period I were excluded from the study.
- Caffeine/xanthine such as coffee, tea, chocolate, and all caffeine-containing soft drinks or energy drinks and alcoholic beverages and/or other alcohol containing products were not consumed 48 hours prior to each period dosing and throughout the study until the last scheduled blood sample collection.

#### Treatments and Study Drug Administration

The identity of the test drug products are summarized in Table A-2-2.

**Table A-2-2:** Identity of Treatment Products

Product	Test	Reference
<b>Treatment ID</b>	A	B
<b>Product Name</b>	Testosterone	Androgel
<b>Manufacturer</b>	Cipla Ltd.	Solvay Pharmaceuticals
<b>Lot No.</b>	X145	31848
<b>Manufacture Date</b>	05-2010	N/A
<b>Expiration/Retest Date</b>	04-2012	03-2012
<b>Strength</b>	1%	1%
<b>Dosage Form</b>	Gel	Gel
<b>Dose Administered</b>	2 x 5 g	2 x 5 g
<b>Route of Administration</b>	Topical	Topical
<b>Cumulative Maximum Dose</b>	10 g	10 g

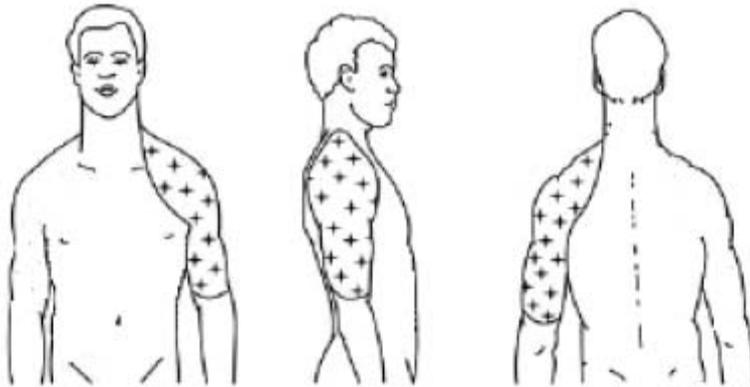
- Treatment A: 2 x 5 g of T Gel 1% without a T-shirt (Lot #: X145);
- Treatment B: 2 x 5 g of T Gel 1% with a T-shirt (Lot #: X145);
- Treatment C: 2 x 5 g of AndroGel® 1% without a T-shirt (Lot #: 31848);
- Treatment D: 2 x 5 g of AndroGel® 1% with a T-shirt (Lot #: 31848);

Dose application for each male subject occurred at the same time and at the same application site/body part for each treatment period under the supervision of the clinical research staff. Additionally the same areas of the female were used during the transfer process.

On study Day 1 (Periods I to IV), either a single 10 mg dose (2 × 5 mg gel) of T Gel 1%, or a single 10 mg dose (2 × 5 mg gel) of AndroGel® 1% was administered to study subjects. One (1) hour prior to the targeted time of dose application, male subjects showered and washed the application site with soap and water. Subjects did not remain in the shower for longer than 10 minutes. The designated area for gel application was thoroughly dried.

Each packet containing the gel was weighed prior to being opened and the exact weight was recorded in the source documentation. The gel was dispensed directly from the packet into the male subject's dominant hand to be applied to the opposite arm and shoulder. The subject's dominant hand was recorded in the source documents. The subject rubbed the product into the skin of the designated application site using his hand. The gel was not rubbed or massaged excessively. This process was repeated with a second 5 g volume amount to the palm, and then to the same arm and shoulder. A staff member monitored the applications to ensure that the gel was evenly dispersed across the entire designated area. Within 5 minutes after dispensing the contents of the packet to the subject's hand the packet was weighed and the exact weight was recorded in the source documentation.

**Figure A-2-1:** An Example of Dose Application Site



Male subjects thoroughly washed their hands with soap and water immediately after gel application was completed. Following the last incremental gel application, for those subjects assigned to wear a T-shirt, the T-shirt (a 100% cotton long-sleeved T-shirt, heavy weight 6.1 oz.) was worn 5 minutes after the gel had been applied and after they had washed their hands. The T-shirts were not washed prior to wearing, and were used only once (i.e., a new shirt for each period requiring a T-shirt) to prevent the possibility of any residual hormone to be left on the material.

**Reviewer's Comment:** *The highest of dose level of T Gel 1% and AndroGel® 1% were investigated in this study as this represents the worst case scenario in terms of interpersonal transfer.*

### **Transfer Process**

Females had a 100% cotton T-shirt (heavy weight 6.1 oz) over the tube tops until the time of dose transfer. The T-shirt was not washed prior to wearing, and was used only once (i.e. a new shirt for each period) to prevent the possibility of any residual hormone to be left on the material. The antecubital region of the females' arms was covered prior to the contact period to prevent potential blood sample contamination.

Prior to the contact process, female subjects were to be asked to remove all upper body clothing with the exception of the tube top. For skin contact with the upper arms and shoulders application site, 2 hours after the gel application female subjects were instructed to rub their upper arms and shoulders up and down the upper arms and shoulders of their male partner during the 15 minute contact period. Female subjects were instructed to gently rub (for approximately 10 seconds per stroke) their arms and shoulders up and down the upper arms and shoulders of their

male partner for 1 minutes intervals. 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 were completed. Each couple was to be monitored and coached by one staff member throughout the contact period.

Female subjects thoroughly washed their hands with soap and water immediately after the skin contact period was complete. Five minutes after the completion of the contact period, female subjects re-clothed with their T-shirt. Female subjects did not shower or bathe until at least 24 hours after the contact period. For those periods where the male was to wear a T-shirt, the T-shirt was worn throughout the contact rubbing session.

**Reviewer's Comment:** *Taking the washing instructions in account, interpersonal transferability was assessed based on AUC(0-24) and C<sub>max</sub>.*

**PK Characterization:**

Serum concentrations of T pre-transfer (baseline) and post-transfer from females after single dose administration were measured. Blood samples for PK characterization were taken as following:

- Baseline: at 0, 2, 4, 6, 8, 10, 12, 16, and 24 hours on Day -1
- Post-transfer: at 0 (within 10 minutes prior to dose transfer) and 2, 4, 6, 8, 10, 12, 16, and 24 hours on Day 1

The following PK parameters for total T were characterized: AUC(0-t), C<sub>max</sub>, and T<sub>max</sub>

**Safety Evaluations:**

Physical examination, blood pressure, heart rate and ECG at pre-treatment examination; standard laboratory parameters in blood and urine at pre- and post-treatment examination; recording of AEs and concomitant medication during treatment phase

**Bioanalytical Method:**

Bioanalyses for total T were performed at (b) (4) between October 7, 2010 and November 5, 2010. Serum concentrations of T were measured by a validated LC-MS/MS method. The dynamic range was 0.05-50.0 ng/mL.

T (lot number FE030110-03) and the IS, T-d3 (lot number FE042810-01) were obtained from (b) (4). T is an androgen, secreted by the glands of both male and female humans. Due to the presence of endogenous T in female human serum, the calibration standard curve, lower limit of quantitation (LLOQ), low quality control-1 (LQC-1) and upper limit of quantitation (ULOQ) samples are prepared in 10% bovine serum albuminates (BSA) in 10% phosphate buffer saline (PBS) solution in water and the LQC-2, mid-quality control-1 (MQC-1), MQC-2, and high quality control (HQC) samples containing T are prepared in female human serum. The serum QC samples contain at least 95% blank female human serum. The analyte was quantitated using a liquid-liquid extraction (LLC) procedure.

Following extraction, a 10 µL aliquot was injected onto an API 4000 LC-MS/MS system, equipped with Turbo Ionspray<sup>®</sup> for analysis. The positive ions were measured in multiple reaction monitoring (MRM) mode.

Mean inter-assay accuracy of back-calculated concentrations in calibrators ranged between 97% and 101.5% and precision was ≤ 4.4%. QC samples for T (range: 0.15-37.5 ng/mL) had an accuracy of 97.9-101.5% and a precision of ≤ 5.7%. ISR was performed on 222 out of 3,098 samples and 215 (96.8%) were within ±20% of the original value.

Samples were stored at -20°C until the time of analysis. All samples were analyzed within 74 days after sample collection. Long term stability was established for 79 days at -20°C.

### PK/Transferability Results:

The PK parameters ( $C_{max}$  and AUC) of total T were calculated and summarized for baseline total T (Day -1) and post-transfer procedure (Day 1) for female subjects that received T Gel 1% through the transfer process in Tables A-2-3 and A-2-4 with the percent difference between the baseline and post-transfer PK parameters.

**Table A-2-3:** Summary of Arithmetic Mean (SD) PK parameters for Total T (Pre and Post-transfer) Following the Treatment of 2 x 5 g of T Gel 1% without a T-shirt (N=47)

	24 hour Pre-Transfer (N=47)	24 hour Post-Transfer (n=47)	% Difference
AUC(0-24) (ng·hr/mL)	4.62 (1.84)	13.78 (9.84)	198.32
$C_{max}$ (ng/mL)	0.27 (0.18)	1.02 (0.86)	271.22

**Table A-2-4:** Summary of Arithmetic Mean (SD) PK parameters for Total T (Pre and Post-transfer) Following the Treatment of 2 x 5 g of T Gel 1% with a T-shirt (N=45)

	24 hour Pre-Transfer (N=45)	24 hour Post-Transfer (n=45)	% Difference
AUC(0-24) (ng·hr/mL)	4.78 (2.75)	5.30 (3.22)	10.83
$C_{max}$ (ng/mL)	0.24 (0.17)	0.28 (0.16)	15.52

**Reviewer’s Comment:** *In the original NDA submission, the Sponsor compared the interpersonal transferability of their T Gel 1% product with AndroGel® 1%. As the primary analysis of this study should be the comparison of PK parameters (i.e.,  $C_{max}$  and AUC) obtained from female partners at baseline to PK parameters obtained after the rubbing procedure with men who used the Sponsor’s T Gel 1% product, the Division requested the Sponsor to submit the 24 hour baseline of total T measured on Day -1 (for females in both groups with male partners either with or without T-shirts on during the transfer procedure) and a comparison between the baseline and the post-rubbing procedure PK parameters of the Sponsor’s T Gel 1% product including the calculated percent difference between the baseline and the post-rubbing procedure PK parameters for each individual in the Filing Communication Letter dated March 28, 2011 available in DARRTS. Subsequently, the Sponsor submitted the requested information to the Division in their June 10, 2011 submission.*

*It should be noted that Subjects 02 and 20 have completed T Gel 1% treatment periods but not AndroGel® 1% treatment periods during the study. Therefore, these 2 subjects were included in interpersonal transferability analysis. As indicated in Table A-2-1, Subject 24 was withdrawn from the study due to pregnancy and was excluded from all PK analysis. As a result, there were N=47 females included in the PK analysis for the no T-shirt period. In addition, Subjects 28 and 47 were excluded from the PK analysis of the T-shirt on period as Subject 28 showed positive laboratory results (i.e., cocaine) and Subject 47 did not show up at check-in for the T-shirt on period. As a result only N=45 subjects were included in the PK analysis for the T-shirt on period.*

As shown in Tables A-2-3 and A-2-4, study results show approximately 11% and 16% increase in T AUC(0-24) and  $C_{max}$ , respectively, compared to baseline in females when males were wearing a T-shirt.

The overall percent difference of the PK parameters for females was much lower when males were wearing a T-shirt during the transfer procedure than without a T-shirt, indicating that there is less exposure to T when a T-shirt is covering the application site.

**Reviewer's Comment:** *Reference is made to Dr. Chongwoo Yu's Clinical Pharmacology reviews of Axiron<sup>®</sup> (NDA 022504, approved on November 23, 2010) dated November 1, 2010 and November 17, 2010 available in DARRTS. This study result was comparable with the interpersonal transferability study results of Axiron<sup>®</sup> (Study MTE12) where the study results showed a 13% and 17% increase in T exposure (AUC[0-24]) and C<sub>max</sub>, respectively, compared to baseline in females when males were wearing a T-shirt during the transfer procedure.*

*It should be noted that the interpersonal transferability of T from AndroGel<sup>®</sup> 1% could not be assessed as the Sponsor did not submit the 24 hour baseline of total T measured on Day -1 (for females in both groups with male partners either with or without T-shirts on during the transfer procedure) and a comparison between the baseline and the post-rubbing procedure PK parameters of AndroGel<sup>®</sup> 1% product including the calculated percent difference between the baseline and the post-rubbing procedure PK parameters for each individual.*

*Despite the increase over baseline in mean total T concentrations following the transfer procedure, serum levels from this study remain within the normal range for females of approximately 10-80 ng/dL (Javanbakht et al., J. Clin. Endocrinol. Metabol., 2000) when males were wearing a T-shirt during the transfer procedure.*

*It should be noted that the interpersonal transfer potential of topical T applied on the abdomen was not assessed and therefore, the same conclusion cannot be extrapolated to when T Gel 1% is applied to the abdomen. This should be clearly reflected on the product label.*

**Safety Results:**

No SAEs were reported during this study. Overall, the most common AE reported was headache. Headache occurred on at least 1 occasion in 4 subjects (4.17%) and generally was considered by the investigator to be probably related to the treatment. Overall, the T Gel 1% was tolerated well by all subjects.

**Conclusion:**

Increases in total T exposure were observed following the transfer procedure compared to that observed at baseline. Although some T transfer is still anticipated even with a T-shirt on, it helps reducing the potential of interpersonal transfer of T.

#### 4.1.3 Hand Washing Study: Study CRI-00018704

**Title:** A Pivotal Study to Evaluate the Residual Amount of Topically Delivered Testosterone Gel 1% Present on Normal Skin of the Hand, in Healthy Adult Male Subjects Following Hand Washing Procedures

**Objective:** To quantify and compare the amount of residual drug remaining on the hands between T Gel 1% manufactured by Cipla Ltd. for Teva Pharmaceuticals USA and AndroGel® 1% manufactured by Solvay Pharmaceuticals, Inc. following a hand washing procedure.

**Clinical Study Center:** (b) (4)

**Clinical Study Period:** August 29 - September 12, 2010

**Bioanalytical Study Center:** (b) (4)

**Bioanalysis Period:** September 28 - October 5, 2010

#### **Study Design:**

This was an open label, two-period, crossover study on healthy adult males. A total of 48 healthy adult male subjects were enrolled in the study. The total duration of the study, screening through study exit, was approximately 4 weeks with a 14-day washout period between doses.

#### **Disposition of subjects:**

Fifty three males checked in for Period 1 from which a total of 48 subjects were enrolled and 46 subjects completed.

Data from 39 of 48 males were used in data analysis. Subjects 21 and 40 withdrew the study consent prior to Period 2 check-in due to schedule conflict. Subjects 1, 2, 3, 10, 11, 12, and 16 were not included in data analysis due to missing samples (i.e., Sponsor reports that samples were lost in processing)

All 39 males that were included in data analysis were Caucasians with a mean age of 28.3 years (range: 18-57 years) and a mean BMI of 26.2 kg/m<sup>2</sup> (range: 19.1-33.5 kg/m<sup>2</sup>).

#### **Inclusion Criteria:**

- Healthy, non-smoking (at least for 14 days) adult males (age: 18-65 years)
- BMI:  $18 \leq \text{BMI} < 34$  kg/m<sup>2</sup>
- Subject's hands, arms, and shoulders were free from scars, cuts, excessively thick calluses or skin diseases that may have affected absorption or interfere with evaluation of the test site.
- Willingness to follow study restrictions including taking a shower using the same soap/cleansers between the Screening Visit and until completion of study related activities.

#### **Exclusion Criteria:**

- Reported participating in another investigational drug, medical device, or biologics study within 30 days prior to dosing.
- Reported participating in a topical or oral T study, or having received supplemental T by topical, oral, or injection within 60 days prior to dosing.
- 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 using a tobacco product within 14 days of study conduct.
- Demonstrated a positive urine drug screen.

**Concomitant Medication:**

Concomitant medication was not allowed during the study. Any concomitant medication, other than the test product, that was taken by or administered to a subject during the course of this study was recorded.

**Treatments, Study Drugs, and Study Drug Administration**

Table A-3-1 presents a brief description of the 2 products administered over the course of the study. The sequence of drug administration (AB or BA) was generated in a 1:1 ratio. Half of the subjects received Treatment A followed by treatment B, and the other half received Treatment B followed by Treatment A.

**Table A-3-1: Identity of Products used in the Study**

Treatment ID	A	B
Product Name	T Gel 1%	AndroGel <sup>®</sup> 1%
Manufacturer	CIPLA, LTD.	Solvay Pharmaceuticals, Inc.
Batch/Lot No.	X145	31848
Manufacture Date	05/2010	N/A
Expiration Date	N/A	03/12
Strength	1%	1%
Dosage Form	Gel	Gel
Dose Administered	5 grams x 2	5 grams x 2
Route of Administration	Topical	Topical
Cumulative Maximum Dose	10 grams	10 grams

At study check-in for each period, the subjects reported to the clinical site at least 1 hour prior to Day 1 dosing and were required to stay until all study related activities were completed on Day 1. On study Days 1 (Period I) and 15 (Period II), subjects entered the clinic, had their hands washed and wiped each with 3 ethanol dampened gauze wipes, 1 for palm, 1 for dorsal hand surface, and 1 for digit surface (blank control sample) approximately 15 minutes prior to dosing. The 3 gauze wipes per hand were combined into one vial, with a second vial for the 3 gauze wipes from the other hand. Subsequently, 2 sequential 5 gram doses of one of the T formulations were applied to the subject’s palm of their dominate hand and the subjects applied each dose to their opposing arm and shoulder (i.e., all 10 g applied on one upper arm/shoulder). Dosing was completed under the direct supervision of the (b)(4) staff to ensure treatment compliance and proper drug administration. At 5 minutes after dose application, the subjects washed their hands as described below:

- The subjects wet their hands with warm tap water (35°C ± 5°C) for 10 seconds.
- Two (2) mL of liquid soap was dispensed to the hands (same brand of soap was used throughout the study)
- Subjects washed their hands with a controlled hand scrubbing procedure for 20 seconds
- Subjects rinsed their hands with warm tap water for 20 seconds
- Subjects dried their hands with a dry cotton towel for 30 seconds

Following the hand wash, the subject's hands were wiped with 3 ethanol dampened gauze per hand (sample for assessment). The 3 gauze wipes per hand were combined into one vial, with a second vial for the 3 gauze wipes from the other hand.

This process was repeated 14 days later with the other test product. The gauze was retained for analytical quantification of recovered T. All subjects were evaluated for the amount of residual T that may have remained on the hands following the hand washing procedure.

**Safety Evaluations:**

The subjects were monitored throughout the confinement portion of the study. Additional measurements were obtained at the discretion of the investigator(s) or clinical staff. The staff recorded all AEs observed, queried, or spontaneously volunteered by the subjects. Subjects who experienced AEs were to be followed until the event(s) resolved to the satisfaction.

**Bioanalytical Method:**

Inverted gloves were filled with 100 mL ethanol and extracted overnight at room temperature with gentle horizontal rotation. They were subsequently diluted 1:1 (500 µL sample + 500 µL 50:50 ethanol:water) for analysis. Gauze hand wipe samples were placed within a screw-capped glass jar and were extracted with 30 mL ethanol, overnight, on a horizontal shaker at room temperature. Extracts were subsequently diluted 1:1 as 500 µL sample with 500 µL 50:50 ethanol:water.

Samples were run on an Agilent 1100 LC-UV system with an isocratic solvent system based on 25:75 water:methanol using a Phenomenex Luna C18 (3µ, 4.6 x 100 mm) reverse phase column. Diode array detection was conducted at a wavelength of 245 nm (5 nm) referenced to 450 nm (50 nm).

The dynamic range was 0.03-2.5 µg/mL from a 30 µL sample + 5 µL water injection. Blank samples, used in preparation of calibration and QC standards were prepared in 50:50 ethanol:water (v/v). Mean inter-batch accuracy of back-calculated concentrations in calibrators ranged between 99.7% and 101.4% and precision was 1.4-4.0%. QC samples had an accuracy of 102.3-115.8 % and a precision of 1.4-4.0%. Samples were stored at nominal -20 °C or lower until analysis. Long term stability was established for 42 days at -20°C.

**Residual T Analysis Results:**

Table A-3-2 summarizes the results of the residual T amount following hand washing after application of each test product.

**Table A-3-2:** Residual T Amount following Hand Washing after Application of Each Test Product

	T Gel 1% (N=39)	AndroGel <sup>®</sup> 1% (N=39)
Mean (µg)	284.9	287.1
SD (µg)	131.0	132.2
%CV	46.0	46.0
Minimum (µg)	62.4	98.9
Maximum (µg)	592.5	547.3

**Reviewer's Comment:** *In the study report submitted, the Sponsor did not calculate the percentage of T removed by the hand washing procedure.*

*The following comment was sent to the Sponsor as a part of the 74-day filing communication on March 28, 2011: "In the hand-washing study, the measurement of residual testosterone on the*

*subjects' hands prior to hand-washing, after applying the drug product to the application site, was not conducted. Therefore, it is not possible to calculate the percentage of the testosterone removed by the hand washing procedure (a "wash-off percentage"). Lacking a "wash-off percentage," explain how this study provides sufficient evidence to conclude that the product is largely removed from the hands by washing.*

*In the Sponsor's June 10, 2011 response, the Sponsor stated that "This study was not designed to determine a "wash-off percentage" however, it is believed that the design still shows that Teva's product is removed from the hands following a hand-washing procedure."*

*While it is impossible to calculate the percentage of T removed by the hand washing procedure as measurement of residual T on the subjects' hands prior to hand-washing, after applying the drug product to the application site, was not conducted, considering that the mean residual amount of T is very small compared to the theoretical dose of 100 mg T (i.e.,  $[284.9 \mu\text{g}/100000 \mu\text{g}] \times 100 = 2.85\%$ ) and that it is comparable to the residual amount following hand washing after application of AndroGel® 1% it appears that T Gel 1% was sufficiently removed from the hands following a hand washing procedure.*

**Safety Results:**

No SAEs were reported and 1 subject experienced one AE over the course of the study. The AE was moderate in intensity. Subject 23 experienced a joint sprain prior to Period II activities that was deemed by the investigator as having no reasonable possibility of being related to the administration of study drug.

In general, the clinical portion of the study was completed without any significant sequelae attributable to the investigational drug. The safety monitoring was completed to the satisfaction of the clinical investigators. Overall, T Gel, 1% was well tolerated as a repeated 5 g dose.

**Conclusion:**

This study demonstrates that T Gel 1% was sufficiently removed from the hands following a hand washing procedure.

#### 4.2 Office of Scientific Investigations Consult Report

The following are the original OSI Consult review and addendum:

**M E M O R A N D U M**

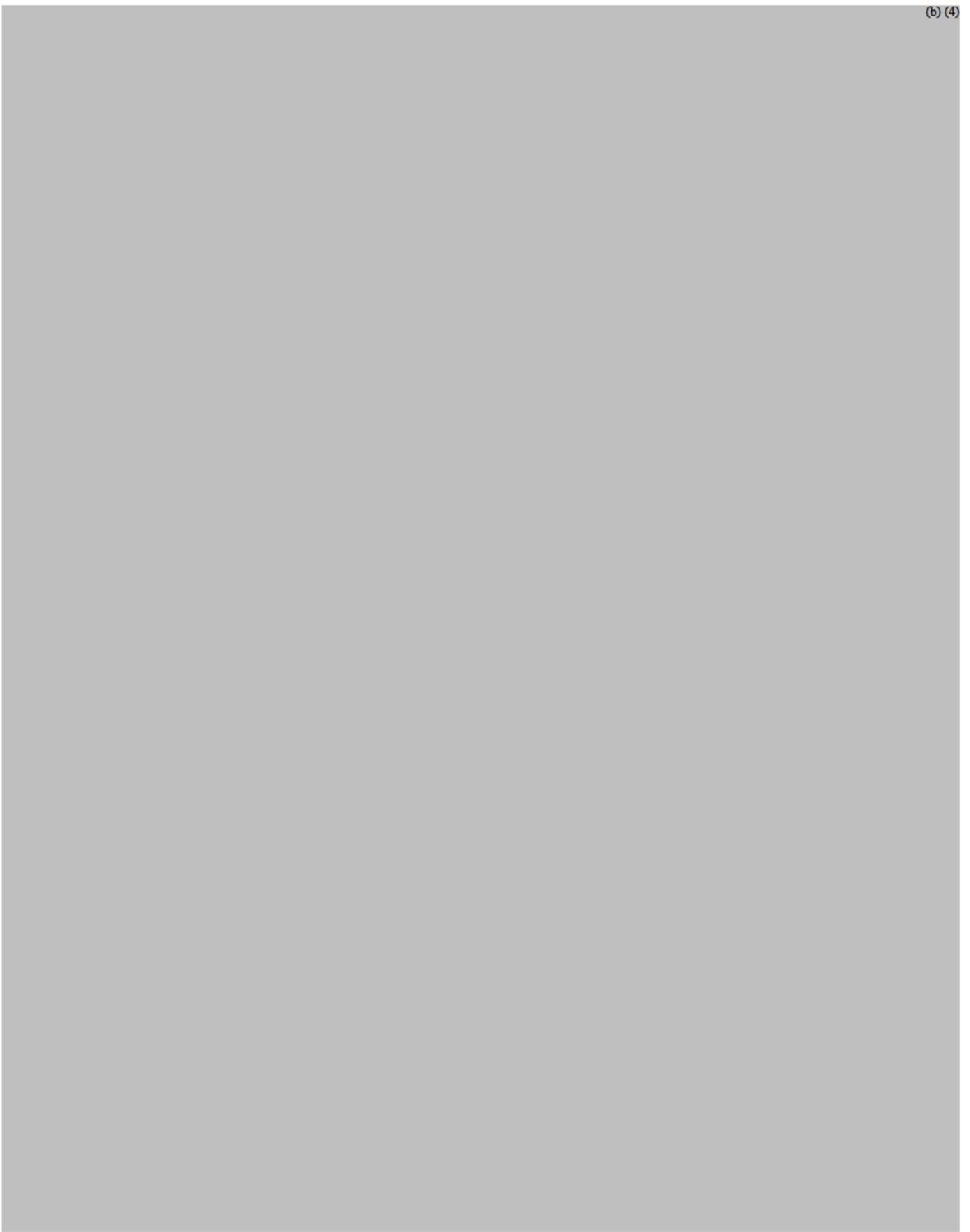
**DEPARTMENT OF HEALTH AND HUMAN SERVICES  
PUBLIC HEALTH SERVICE  
FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH**

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The following 22 pages of EIR Reviews, including this page and attachments, have been removed. A duplicate of this review dated July, 1, 2011 and July 29, 2011 can be found in "Other Reviews" at e-page 50.

### 4.3 Clinical Pharmacology Filing Memo

(b) (4)



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/s/  
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CHONGWOO YU  
01/18/2012

LAI M LEE  
01/19/2012

## OFFICE OF CLINICAL PHARMACOLOGY REVIEW ADDENDUM

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NDA: 202763	Submission Date(s): 1/14/2011, 4/21/2011, 5/18/2011, 6/10/2011, 7/29/2011, 9/14/2011, 11/3/2011, 12/5/2011, and 1/30/2012
Brand Name:	Testosterone (T) Gel 1% (No name proposed)
Generic Name:	T Gel 1%
Clinical Pharmacology Primary Reviewer:	Chongwoo Yu, Ph.D.
Clinical Pharmacology Secondary Reviewer:	LaiMing Lee, Ph.D.
OCP Division:	Division of Clinical Pharmacology 3 (DCP3)
OND Division:	Division of Reproductive and Urologic Products (DRUP)
Sponsor:	Teva Pharmaceuticals
Submission Type:	Original
Formulation, Strength(s), and Dosing Regimen:	Gel; 1%; 50 mg, (b) (4) T once daily
Indication:	Treatment of male hypogonadism

---

The purpose of this addendum is to address the Office of Clinical Pharmacology (OCP)'s recommendations on the Sponsor's proposed product labeling that were not addressed or revised from the original Clinical Pharmacology review of NDA 202763 dated January 19, 2012 in DARRTS.

### 1. OCP's Recommendations on the Product Labeling

#### Important Limitations of Use

The important limitation of use statement in the Indications and Usage Section of both the Highlights and the Full Prescribing Information (Section 1) of the product label has been modified as the following:

- *Safety and efficacy of testosterone gel in males < 18 years old have not been established*
- *Topical testosterone products may have different doses, strengths, or application instructions that may result in different systemic exposure*

#### Residual Testosterone Amount following Hand Washing Study

In Section 12.3 Pharmacokinetics, a typographical error of 2.85% was corrected to 0.29% and the text now reads as the following:

*Then hands were wiped with 3 ethanol dampened gauzes per hand which were then combined together and analyzed for testosterone content. A mean (SD) of 284.9 (131) mcg of residual testosterone (i.e., approximately 0.29% of the theoretical dose of 100 mg testosterone administered) was recovered after washing hands with liquid soap and warm tap water.*

This correction also applies to the same typographical errors on Pages 4, 16, 21, and 48 of the original Clinical Pharmacology review of NDA 202763 dated January 19, 2012 in DARRTS.

The final agreed upon product label between the Sponsor and the DRUP will be attached to the Approval Letter. There are no outstanding Clinical Pharmacology labeling issues.

## **2. Recommendation**

The DCP3, OCP finds NDA 202763 acceptable from the Clinical Pharmacology perspective.

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/s/  
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CHONGWOO YU  
02/09/2012

LAI M LEE  
02/09/2012

## ONDQA (Biopharmaceutics) Memo

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**NDA:** 202-763  
**Submission Date:** 01/14/2011  
**Product:** Testosterone Gel, 1%  
**Type of Submission:** Original NDA  
**Applicant:** TEVA  
**Reviewer:** Tapash K. Ghosh, Ph.D.

---

### **BACKGROUND:**

The proposed product was initially submitted to the Office of Generic drugs (OGD) under ANDA (b) (4) for Testosterone Gel, 1% on December 29, 2008, and the Agency issued a "Refuse to Receive Letter" dated April 7, 2009 for this product. The basis for the refusal letter was that TEVA's formulation contained different ingredients than those contained in the RLD. (b) (4)

(b) (4)

(b) (4)

### **SUBMISSION:**

TEVA Pharmaceuticals USA submitted this New Drug Application, NDA 202-763 for Testosterone Gel, 1% seeking approval for the treatment of hypogonadism. The Applicant used AndroGel® (1%, w/w) marketed by Solvay Pharmaceuticals Inc. as the reference listed drug (RLD). The drug product under review is a 1% testosterone gel that will be available in two presentations: a 2.5 g sachet, a 5.0 g sachet. Each 2.5 g sachet provides 25 mg of testosterone and each 5 g sachet provides 50 mg of testosterone. The product was developed (b) (4) Cipla Ltd., (b) (4) for TEVA.

To support the approval of this NDA submission, the Applicant conducted a single *in vivo* Bioequivalence study under fasting conditions comparing the Testosterone Gel 1% manufactured by Cipla for TEVA, to the reference listed drug, AndroGel® (testosterone gel) 1% (*Study No. 70343*). Additionally, this application also contains; 1) an Irritation and

Sensitization Study (Study No. 10936025), 2) a Hand Washing Study (Study No. CRI-00018704) and 3) a BA Transfer Study (Study No. M1FX10001). (b) (4)

**Comparison of Excipients present in RLD & Cipla Product**

Reference Listed Drug	Proposed generic Drug Product	Function
Testosterone	Testosterone	Active
Ethanol	Dehydrated alcohol	(b) (4)
Carbopol 980 NF	Carbomer Homopolymer Type C (b) (4)	(b) (4)
Isopropyl Myristate	Isopropyl Palmitate	(b) (4)
Sodium Hydroxide	Sodium Hydroxide	(b) (4)
Purified water	Purified Water	(b) (4)

***In Vivo Bioequivalence Study:*** Study No. 70343 is a Single-dose BE study under fasting conditions comparing the T gel, 1% manufactured by Sponsor, to the RLD, Androgel® (T gel) 1%. The Applicant reported that for the log-transformed Testosterone data, the 90% confidence intervals about the ratio of the Test geometric mean to Reference geometric mean are within 80% to 125% limits for AUC<sub>0-t</sub>, C<sub>max</sub>. Based on these results for Testosterone, the Testosterone 5 g packets of 1% topical gel (manufactured by Cipla Ltd., India for TEVA Pharmaceuticals USA) and the Testosterone (Androgel®) 5 g packets of 1% topical gel are bioequivalent (*for details see the Clinical Pharmacology Review*)

**ASSESSMENT:**

ONDQA-Biopharmaceutics considers that the approval of this product is based on the demonstration of bioequivalence (BE) to the RLD product. Also, the Applicant conducted other clinical studies as required by the Agency.

Since the provided *in-vitro* release information does not have any regulatory utility and the *in vitro* drug release test is not part of the product’s quality tests, Biopharmaceutics considers that the evaluation of the IVRT information is unnecessary and therefore, ONDQA-Biopharmaceutics will not provide any comments regarding the filing and approvability of this product.

**CONCLUSION:**

A Biopharmaceutics Review for NDA 202-763 is deemed unnecessary.

Tapash K. Ghosh, Ph. D.  
 Primary Biopharmaceutics Reviewer  
 Office of New Quality Assessment

FT Initialed by Angelica Dorantes, Ph. D. \_\_\_\_\_

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/s/  
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TAPASH K GHOSH  
09/11/2011

ANGELICA DORANTES  
09/11/2011

# CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

On **initial** review of the NDA/BLA application for filing:

	Content Parameter	Yes	No	N/A	Comment
<b>Criteria for Refusal to File (RTF)</b>					
1	Has the applicant submitted bioequivalence (BE) data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?	x			A 10 mg single dose BE study using upper arm and shoulder as the site of application
2	Has the applicant provided metabolism and drug-drug interaction information?			x	Refers to distribution, metabolism, and excretion information publically available (i.e., Androgel <sup>®</sup> label)
3	Has the sponsor submitted bioavailability data satisfying the CFR requirements?	x			
4	Did the sponsor submit data to allow the evaluation of the validity of the analytical assay?	x			
5	Has a rationale for dose selection been submitted?	x			BE approach to a reference product (i.e., Androgel <sup>®</sup> )
6	Is the clinical pharmacology and biopharmaceutics section of the NDA organized, indexed and paginated in a manner to allow substantive review to begin?	x			
7	Is the clinical pharmacology and biopharmaceutics section of the NDA legible so that a substantive review can begin?	x			
8	Is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work?	x			
<b>Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality)</b>					
<b>Data</b>					
9	Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?	x			No pre-submission discussions were held
10	If applicable, are the pharmacogenomic data sets submitted in the appropriate format?			x	
<b>Studies and Analyses</b>					
11	Is the appropriate pharmacokinetic information submitted?	x			
12	Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?			x	BE approach to a reference product (i.e., Androgel <sup>®</sup> )
13	Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?			x	BE approach to a reference product (i.e., Androgel <sup>®</sup> )
14	Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need			x	BE approach to a reference product (i.e., Androgel <sup>®</sup> )

## CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

	for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?				
1 5	Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?			x	BE approach to a reference product (i.e., AndroGel <sup>®</sup> )
1 6	Did the applicant submit all the pediatric exclusivity data, as described in the WR?			x	BE approach to a reference product (i.e., AndroGel <sup>®</sup> )
1 7	Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the label?	x			
<b>General</b>					
1 8	Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	x			
1 9	Was the translation (of study reports or other study information) from another language needed and provided in this submission?			x	

**IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE?** \_\_\_ Yes \_\_\_

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

- *The following review issues were identified:*
  - *In the interpersonal transfer study, Sponsor compared the interpersonal transferability between the Sponsor's testosterone (T) gel and the reference listed drug (RLD). However, the primary endpoint of the interpersonal transfer study should be the comparison between the baseline and post-transfer PK parameters (i.e., C<sub>max</sub> and AUC) of Sponsor's T gel product in female partners. The potential for secondary exposure of T to women and children will be further considered. Additional information in labeling may be needed, including information directed to patients to assure safe use.*
  - *In the hand washing study, the residual T amount before hand washing was not measured and the RLD was used as a comparator. However, the primary endpoint of the hand washing study should be the comparison between residual T amount of the control (i.e., no washing) and post-washing following application of the test product (i.e., your T gel). The review will focus on the hand washing aspects of the Sponsor's T gel.*
  - *We note that there was no application site washing study submitted. We believe that a study evaluating the wash-off of the product from the application site is needed in addition to the wash-off evaluation from the hands. We believe that the application site washing study is needed to support labeling language indicating that washing the application site will limit the potential for interpersonal transfer. This study should be done at two hours after T gel application. This might result in becoming a post-marketing requirement.*
- *We request the Sponsor to submit the following information regarding the interpersonal transfer study:*
  - *The 24 hour baseline of total T measured on Day -1.*
  - *Comparison between the baseline and post-transfer PK parameters (i.e., C<sub>max</sub> and AUC) of the Sponsor's T gel product in female partners. This information should include the % calculation of difference between the baseline vs. post-transfer PK parameters (i.e., C<sub>max</sub> and AUC) for each individual.*

**CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS  
FILING FORM/CHECKLIST FOR NDA/BLA or Supplement**

*Chongwoo Yu*

*2/24/2011*

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Reviewing Clinical Pharmacologist

Date

*MyongJin Kim*

*2/24/2011*

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Team Leader/Supervisor

Date

**CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS  
FILING FORM/CHECKLIST FOR NDA/BLA or Supplement**

**Filing Memo**

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**Clinical Pharmacology Review**

**NDA:** 202763  
**Compound:** Testosterone (T) gel, 1%  
**Sponsor:** Teva Pharmaceuticals

**Date:** 2/24/2011  
**Reviewer:** Chongwoo Yu, Ph.D.

**Introduction:**

Teva Pharmaceuticals USA submitted New Drug Application (NDA) 202763 for T gel, 1% in accord with Section 505 (b)(2) on January 13, 2011 to seek an approval for the treatment of hypogonadism. Sponsor used AndroGel® (1%, w/w) marketed by Solvay Pharmaceuticals Inc. as the reference listed drug (RLD).

T gel was manufactured, (b)(4) at Cipla Ltd., India, a contract manufacturer for the Sponsor. The active ingredient, route of administration, dosage form, and strength for the proposed drug product are the same as those of the RLD. (b)(4)

The recommended starting dose of T gel, 1% is 5 g once daily (preferably in the morning) to clean, dry, intact skin of the shoulders and upper arms and/or abdomen (area of application should be limited to the area that will be covered by the patient's short sleeve t-shirt). T gel, 1% for topical use is available in either unit-dose packets (b)(4)

will be available in the following (b)(4) package containers:  
2.5 g packet, or 5 g packet.

T gel  
(b)(4)  
(b)(4)  
(b)(4)

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

(b)(4)

Serum T concentrations should be measured at intervals for dose adjustments. For the RLD, serum T concentrations were measured on Day 60 and dose adjustment took place on Day 91 in the Phase 3 clinical study. There was no specific recommendation in the RLD product labeling regarding applications sites (e.g., for the 10 g dose, 5 g on each upper arm/shoulder vs. 10 g on one side upper arm/shoulder). If the serum T concentration is below the normal range, the daily T gel dose may be increased from 5 g to 7.5 g and from 7.5 g to 10 g for adult males as instructed by the physician. If the serum T concentration exceeds the normal range, the daily T gel dose may be decreased. If the serum T concentration consistently exceeds the normal range at a daily dose of 5 g, T gel therapy should be discontinued.

# CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

## Regulatory History

Reference is made to Sponsor's original ANDA (b) (4) for T Gel, 1% submitted to the Office of Generic Drugs (OGD) on December 29, 2008 and the OGD's Refuse to Receive Letter dated April 7, 2009. The basis for the letter was that Sponsor's formulation contained different ingredients than those contained in the RLD. (b) (4)

## Clinical Development of T gel

This application contains a full report of:

- Single-dose BE study under fasting conditions that compares the T gel, 1% manufactured by Sponsor, to the RLD, AndroGel® (T gel) 1% (Study No. 70343)
- Irritation and sensitization study (Study No. 10936025)
- Hand washing study (Study No. CRI-00018704)
- Transfer study (Study No. MIFX10001)

These studies are summarized in the Table below:

Type of Study	Study Identifier	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
Bioequivalence	70343	Determine the bioequivalence between a new (generic) drug product and a marketed reference product under fasting conditions	Multiple-centre, Bioequivalence, Open-label Randomized, 2-way crossover study.	Testosterone 1% Topical Gel	93 (90 Completed)	Hypogonadal Adult Male Subject	Single-Dose	Completed
Irritation and Sensitization	10936025	Compare cumulative skin irritation and sensitization potential between two new (generic) products and two marketed reference products.	Multiple Site, Multiple-Application, Double-Blind, Randomized, Two Phase Irritation and Sensitization Study	Testosterone 1% Topical Gel	265 (233 included in PPPI and 222 included in PPPS)	Healthy Adult Male Subjects	Multiple-Dose	Completed
Hand-Washing	CRI-00018704	Quantify and compare the amount of residual drug remaining on the hands between a new (generic) product and a marketed reference product.	Open-label, Two Period, Crossover, pivotal study on healthy adult male subjects	10 g of Testosterone 1% Topical Gel in each study period, topical	48 (46 Completed)	Healthy Adult Male Subjects	Single-Dose	Completed
BA Transfer	MIFX10001	Quantify and compare the relative bioavailability between a new (generic) product and a marketed reference product in female subjects following direct transfer from healthy male subjects	Open-label, Randomized, Four Period, Four Treatment Crossover Study.	Testosterone 1% Topical Gel	A vs. C 48 male and female couples (47 couples completed)	Healthy Adult Male and Female Subjects	Single-Dose	Completed
				Testosterone 1% Topical Gel	B vs. D 48 male and female couples (43 couples completed)			

## Drug Product Formulation:

The composition of the drug product is summarized in the Table below.

## CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

Ingredients	Function	Amount (gm) / 2.5 gm sachet	Amount (gm) / 5 gm sachet	(b) (4)	(b) (4)	Amount (% w/w)
Testosterone, USP	Active	0.025	0.05			1.00
Dehydrated Alcohol, USP	(b) (4)	(b) (4)	(b) (4)			(b) (4)
Carbomer Homopolymer Type C (b) (4)	(b) (4)					(b) (4)
Isopropyl Palmitate, NF	(b) (4)					(b) (4)
Sodium Hydroxide, NF	(b) (4)					(b) (4)
Purified Water, USP	(b) (4)					(b) (4)
<b>Total:</b>	-	<b>2.5</b>	<b>5.0</b>			<b>100</b>

The Table below compares the Sponsor's formulation to the RLD formulation:

Androgel® 1% (Testosterone Gel) Solvay Pharmaceuticals, Inc.	Testosterone Gel 1% TEVA Pharmaceuticals USA
Testosterone, USP	Testosterone, USP
Dehydrated Alcohol, USP	Dehydrated Alcohol, USP
Carbopol 980, NF	Carbomer Homopolymer Type C (b) (4)
Isopropyl Myristate, NF	--
--	Isopropyl Palmitate, NF
Sodium Hydroxide, NF	Sodium Hydroxide, NF
Purified Water, USP	Purified Water, USP

### BE Assessment

A multi-center, randomized, single-dose, two way-crossover pivotal BE study was conducted to compare the Sponsor's T gel product and the RLD (i.e., Androgel®, 1 % w/w) under fasting condition. Ninety three hypogonadal men were enrolled and 90 men completed the study. The T baseline measurements occurred at -12 hr, -6 hr, and immediately before drug administration. A single topical dose of either the test or RLD was administered as 2 x 5 g packets (1 packet applied on each shoulder and upper arm) on the designated area predefined with an individual template (outlining a 500 cm<sup>2</sup> area) to ensure constant application area between and within subjects. The treatment periods were separated by a 7 day washout period between treatment periods.

### Absorption, Distribution, Metabolism, and Excretion (ADME)

Specific studies describing the ADME of T were not conducted. The Sponsor is proposing to use the publically available information of the RLD (i.e., Androgel®, 1 % w/w) for their product.

### Transfer Potential Assessment

A Single-dose, four-period, four-treatment crossover study to assess the interpersonal transfer potential was conducted. A total of 96 healthy subjects (48 male and female couples) were enrolled in the study and 86 completed. A single topical dose (i.e., 2 x 5 g packets) of either T gel or the RLD with or without males wearing a T-shirt was applied to the male subjects. The T baseline in females was characterized by conducting a 24 hr PK measurement. Two hr after dosing to the male subjects, female subjects were instructed to gently rub their arms and shoulders up and down the upper arms and shoulders of their male partners for 15 min. For those periods that males were to wear the T-shirts, subjects waited at least 5 min for the T gel to dry before putting clothes over the application area. Then, the T-shirt was worn throughout the study. There was a 7 day washout period between treatment periods.

### Hand Washing Study

A single-dose, open label, two-period crossover study in healthy adult men was conducted to evaluate the residual amount of topically delivered T gel following hand washing procedure. Forty eight subjects were enrolled in the study and 46 completed. On Day 1 of each treatment period, approximately 30 min prior to dosing, subjects had their hands washed with warm tap water and liquid soap for 50 sec followed by drying their hands with a dry cotton towel for 30 sec and

# CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

wiped each with 3 ethanol dampened gauzes (controls). Subsequently, 10 g (2 x 5 g packets) of either the T gel or the RLD was applied to the subject's palm of their dominant hand by the clinical staff. Then subjects applied the dose to their opposing arm and shoulder with monitoring by the clinical staff each time. Approximately 5 min after dose application, subjects washed their hands with warm tap water and liquid soap for 50 sec followed by drying their hands with a dry cotton towel for 30 sec. Following the hand wash, the subject's hands were wiped with 3 ethanol dampened gauze per hand (test sample). There was a 14 day washout period between treatment periods.

## **Drug-Drug Interactions:**

No DDI studies were conducted with T gel.

## **Specific Populations:**

- Pediatric use: No pediatric studies were conducted
- 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:**

- Serum samples were analyzed for total T by validated bioanalytical methods. A validated high performance liquid chromatography with ultraviolet detector (HPLC-UV) was used in Study CRI-00018704. In Studies 70343 and M1FX10001, a validated liquid chromatography-tandem mass spectrometry (LC-MS/MS) method was used. A DSI consult requesting inspections of the clinical and bioanalytical sites of the pivotal BE study has been requested (signed off in DARRTS by Dr. Dennis Bashaw on March 7, 2011).

## **Recommendation:**

The Office of Clinical Pharmacology/Division of Clinical Pharmacology 3 finds that the Clinical Pharmacology section for NDA 202763 is fileable.

## **Comments for the Sponsor:**

- *The following review issues were identified:*
  - *In the interpersonal transfer study, Sponsor compared the interpersonal transferability between the Sponsor's testosterone (T) gel and the reference listed drug (RLD). However, the primary endpoint of the interpersonal transfer study should be the comparison between the baseline and post-transfer PK parameters (i.e.,  $C_{max}$  and AUC) of Sponsor's T gel product in female partners. The potential for secondary exposure of T to women and children will be further considered. Additional information in labeling may be needed, including information directed to patients to assure safe use.*
  - *In the hand washing study, the residual T amount before hand washing was not measured and the RLD was used as a comparator. However, the primary endpoint of the hand washing study should be the comparison between residual T amount of the control (i.e., no washing) and post-washing following application of the test product (i.e., your T gel). The review will focus on the hand washing aspects of the Sponsor's T gel.*
  - *We note that there was no application site washing study submitted. We believe that a study evaluating the wash-off of the product from the application site is needed in addition to the wash-off evaluation from the hands. We believe that the application site washing study is needed to support labeling language indicating that washing the application site will limit the potential for interpersonal transfer. This study should be done at two hours after T gel application. This might result in becoming a post-marketing requirement.*
- *We request the Sponsor to submit the following information regarding the interpersonal transfer study:*
  - *The 24 hour baseline of total T measured on Day -1.*
  - *Comparison between the baseline and post-transfer PK parameters (i.e.,  $C_{max}$  and AUC) of the Sponsor's T gel product in female partners. This information should include the % calculation of difference between the baseline vs. post-transfer PK parameters (i.e.,  $C_{max}$  and AUC) for each individual.*

# CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

Office of Clinical Pharmacology New Drug Application Filing and Review Form				
General Information About the Submission				
	Information		Information	
NDA Number	202763	Brand Name	Pending	
OCP Division	DCP3	Generic Name	Testosterone	
Medical Division	DRUP	Drug Class	Steroid	
OCP Reviewer	Chongwoo Yu, Ph.D	Indication(s)	Treatment of male hypogonadism	
OCP Team Leader	Myong Jin Kim, Pharm. D.	Dosage Form	Gel 1% (5 g, (b) (4) g daily)	
Secondary Reviewer	Myong Jin Kim, Pharm. D.	Dosing Regimen	Starting dose at 5 g testosterone) and dose adjust appropriately	
Date of Submission	January 14, 2011	Route of Administration	Transdermal	
Estimated Due Date of OCP Review	September 14, 2011	Sponsor	Teva Pharmaceuticals	
PDUFA Due Date	November 14, 2011	Priority Classification	Standard	
Division Due Date	October 24, 2011			
Clin. Pharm. and Biopharm. Information				
	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
<b>STUDY TYPE</b>				
Table of Contents present and sufficient to locate reports, tables, data, etc.	X			
Tabular Listing of All Human Studies	X			
HPK Summary	X			
Labeling	X			
Reference Bioanalytical and Analytical Methods	X			
<b>I. Clinical Pharmacology</b>				
<b>Mass balance:</b>				
<b>Isozyme characterization:</b>				
<b>Blood/plasma ratio:</b>				
<b>Plasma protein binding:</b>				
<b>Pharmacokinetics (e.g., Phase I) -</b>				
<b>Healthy Volunteers-</b>				
single dose:	X	2		CRI-00018704, M1FX10001
multiple dose:				
<b>Patients-</b>				
single dose:				
multiple dose:				
<b>Dose proportionality -</b>				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
<b>Drug-drug interaction studies -</b>				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
<b>Subpopulation studies -</b>				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				

## CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

renal impairment:				
hepatic impairment:				
<b>PD:</b>				
Phase 1:				
Phase 2:				
Phase 3:				
<b>PK/PD:</b>				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
<b>Population Analyses -</b>				
PK:				
PD:				
<b>II. Biopharmaceutics</b>				
<b>Absolute bioavailability:</b>				
<b>Relative bioavailability -</b>				
solution as reference:				
alternate formulation as reference:				
<b>Bioequivalence studies -</b>				
traditional design; single / multi dose:	X			70343
replicate design; single / multi dose:				
<b>Food-drug interaction studies:</b>				
<b>Dissolution:</b>				
<b>(IVIVC):</b>				
<b>Bio-wavier request based on BCS</b>				
<b>BCS class</b>				
<b>III. Other CPB Studies</b>				
<b>Irritation and sensitization</b>	X			10936025
<b>Genotype/phenotype studies:</b>				
<b>Chronopharmacokinetics</b>				
<b>Pediatric development plan</b>				
<b>Immunogenicity profile</b>				
<b>Thorough QT study</b>				
<b>Literature References</b>				
<b>Total Number of Studies</b>		4		
<b>Other comments</b>				
	<b>Comments</b>			
<b>QBR questions (key issues to be considered)</b>	<ol style="list-style-type: none"> <li>1. Establishment of BE between T gel and the RLD</li> <li>2. Assessment of transfer potential and washing potential</li> <li>3. Acceptability of the study designs</li> <li>4. DSI inspection on clinical and bioanalytical sites for the pivotal BE study</li> <li>5. Acceptability of bioanalytical assay validation and performance</li> </ol>			
<b>Other comments or information not included above</b>	<ul style="list-style-type: none"> <li>• A formal DSI consult on clinical and bioanalytical study sites has been requested (signed off in DARRTS by Dr. Dennis Bashaw on March 7, 2011).</li> </ul>			

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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CHONGWOO YU  
03/15/2011

MYONG JIN KIM  
03/15/2011