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APPLICATION NUMBER:

204399Orig1s000

MEDICAL REVIEW(S)

Clinical Review of NDA Resubmission

Application Number:	NDA 204399
Date of Submission:	December 4, 2013
PDUFA Date:	June 4, 2014
Reviewer Name:	Martin Kaufman, D.P.M., M.B.A.
Review Completion Date:	May 12, 2014
Product:	Vogelxo (testosterone) gel
Indication:	Testosterone replacement therapy in adult males for conditions associated with a deficiency or absence of endogenous testosterone: • Primary hypogonadism (congenital or acquired) • Hypogonadotropic hypogonadism (congenital or acquired)
Applicant:	Upsher-Smith Laboratories, Inc.

Executive Summary

On December 4, 2013, the applicant submitted a class 2 resubmission in response to the tentative approval of NDA 204399 on August 16, 2013. The submission contains documentation that the patent infringement lawsuit filed during the initial review cycle was decided in favor of the applicant, allowing final approval of the NDA. In the submission, the applicant confirms that there have been no changes in the conditions under which the application was tentatively approved and that there is no additional safety information since the tentative approval. The applicant submitted a risk evaluation and mitigation strategy (REMS) for Vogelxo and its authorized generic that is acceptable to the Division of Risk Management (DRISK). Labeling negotiations were completed and an agreement was reached on the content and the language in the package insert and Medication Guide. From a clinical perspective, NDA 204399 should be approved.

Background

Upsher-Smith Laboratories, Inc. (USL) submitted NDA 204399 (testosterone gel for replacement therapy in males for conditions associated with a deficiency or absence of endogenous testosterone) on October 18, 2012. The NDA was submitted under section 505(b)(2) of the Federal Food, Drug and Cosmetic Act (FDCA) and relies, in part, on the Agency's finding of safety and efficacy for Testim 1% (testosterone gel) (NDA 021454), the reference listed drug (RLD) for the NDA. The patent certification submitted with the NDA included Paragraph IV certifications for each of the ten patents listed in the Orange Book for Testim 1%.

On February 12, 2013, USL submitted an amendment to the NDA notifying the Division that the holder of the NDA for the RLD and the owner of the patents referenced in the patent certification had initiated a patent infringement lawsuit against USL. The lawsuit was still ongoing when the Division issued its action letter for the initial review cycle.

During the initial review cycle, the review team conducted a thorough review of NDA 204399 and concluded that the NDA should be approved. However, because the patent infringement lawsuit had not been resolved, the Division issued a tentative approval letter for the NDA on August 16, 2013. The letter explained that final approval of the NDA could not be granted until (1) expiration of the 30-month stay of approval provided by the Hatch-Waxman Amendments, or (2) the date the court decides that the patents listed in the application's patent certification are invalid or not infringed, or (3) the listed patents expire. The letter also indicated that final approval would be contingent upon there being no new information, since the tentative approval, which would preclude granting final approval of the application.

Current Submission

The current submission (SDN 23), received on December 5, 2013, is a class 2 resubmission that responds to the Division's tentative approval letter issued on August 16, 2013. The submission includes:

- a Memorandum Opinion and Order, pertaining to the patent infringement lawsuit, issued by the U.S. District Court for the District of Delaware on December 4, 2013;
- proposed risk evaluation and mitigation strategy (REMS) for Vogelxo;
- proposed labeling (package insert and Medication Guide) for Vogelxo.

In addition, the submission states that the applicant intends to market an authorized generic[1] with manufacture, packaging and testing that are identical to Vogelxo, and includes proposed REMS and labeling for that product.

Patent Infringement Litigation

In the patent certification for NDA 204399, USL certified that the ten Orange Book listed patents for Testim 1%, the NDA's RLD, would not be infringed by the manufacture, use, or sale of Vogelxo. After submitting the NDA, USL provided Paragraph IV notification to the holder of the NDA for the RLD and to the owner of the Orange Book listed patents. Subsequent to receiving that notification, both parties filed suit against USL for patent infringement in the U.S. District Court for the District of Delaware (Docket #13-CV-148-SLR).

[1] An "authorized generic drug" is a listed drug that has been approved under subsection 505(c) of the FDCA and is marketed, sold, or distributed directly or indirectly to retail class of trade with either labeling, packaging, product code, labeler code, trade name, or trade mark that differs from that of the listed drug (21 C.F.R. §314.3).

In the current submission, USL submitted two district court documents that pertain to the patent infringement lawsuit: A Memorandum Opinion and an Order both dated December 4, 2013. A third district court document, a Stipulated Final Judgment of Non-Infringement dated December 30, 2013, was submitted on December 31, 2013. The documents dated December 4 granted USL's motion for summary judgment of non-infringement of the Orange Book listed patents, and the document dated December 30 entered a judgment of non-infringement in favor of USL and against the plaintiffs in the lawsuit.

Reviewer Comment: Based on the court documents submitted by the applicant, final approval of NDA 204399 may now be granted provided there is no new information, since the tentative approval, which would preclude final approval of the NDA.

Efficacy

For full review of efficacy see my memo for Tentative Approval dated August 12, 2013.

Safety Update

The current submission contains the applicant's statement confirming that there is no additional safety information for Vogelxo since the tentative approval. This statement is consistent with information provided in the annual reports for IND 76654, the IND USL opened to conduct clinical trials for Vogelxo. The annual reports indicate that (1) all clinical data collected under the IND were submitted in NDA 204399, (2) no clinical trials were ongoing at the time the NDA was submitted, and (3) no clinical trials were initiated since the NDA was submitted.

Although there was no additional safety information specifically for Vogelxo since the tentative approval, additional safety information for the testosterone products in general became available during this timeframe. (b) (4)

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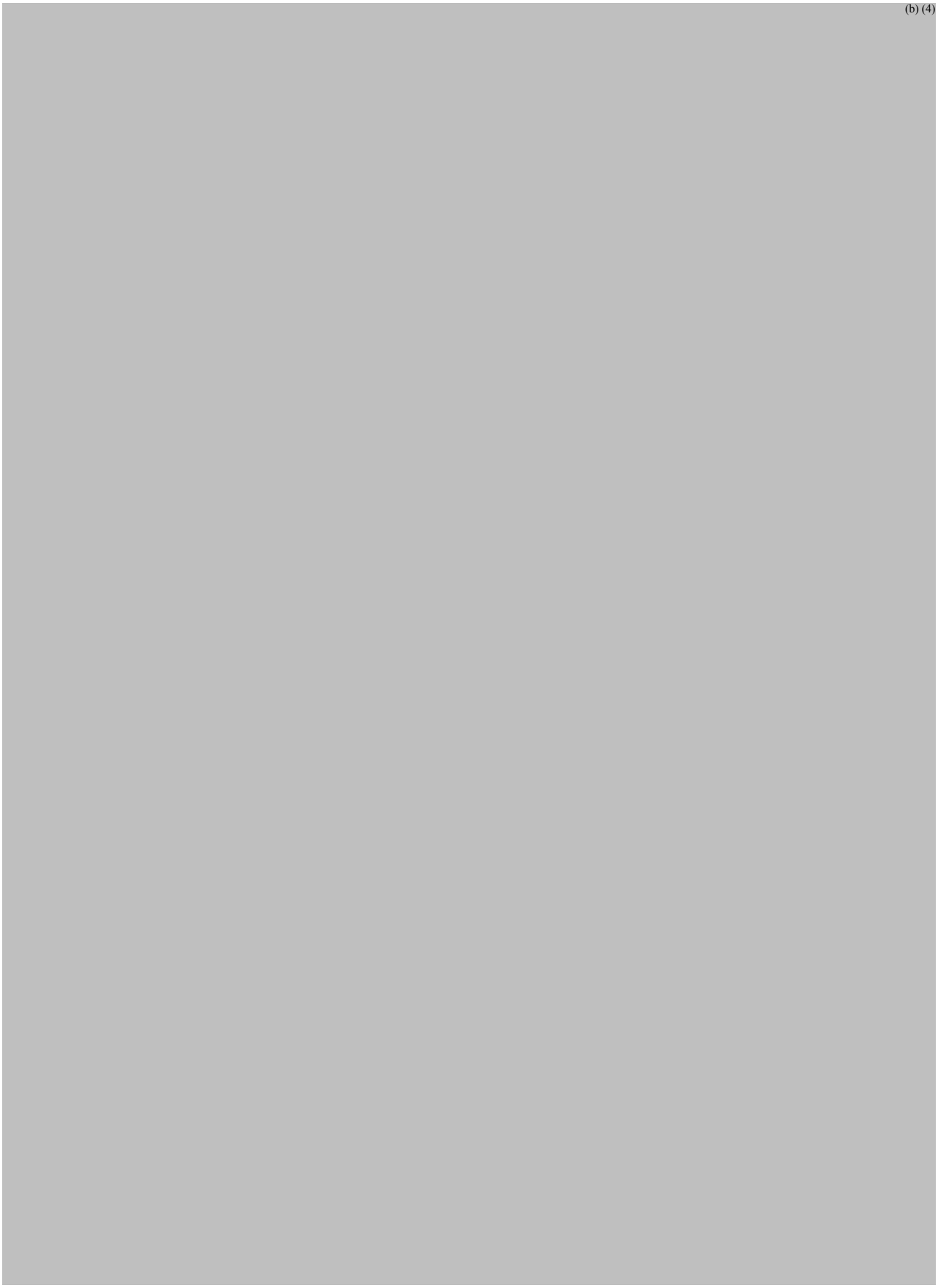
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Risk Evaluation and Mitigation Strategy (REMS)

The current submission contains two proposed REMS documents: one for Vogelxo and one for the authorized generic. Both proposed REMS include a Medication Guide and timetable for submission of assessments 18 months, 3 years, and 7 years after approval of the REMS.

The issue of whether REMS that include both a brand and an authorized generic should have two REMS documents (one for the brand and one for the authorized generic) or a single document for both products was discussed with the Division of Risk Management (DRISK) and the CDER Safety Requirements Team. It was decided that a single REMS document for the brand and authorized generic products would facilitate administrative processes and future REMS modifications. The applicant was informed of this decision and amended the application to include a single REMS supporting document on April 9, 2014, and a single REMS document on May 8, 2014.

DRISK reviewed the proposed REMS for Vogelxo and the authorized generic, including the amendments submitted on April 9 and May 8, 2014, and found it acceptable.

Labeling

The current submission includes proposed labeling (package insert and Medication Guide) for Vogelxo that is identical to that which was tentatively approved on August 16, 2013.

All disciplines provided input to the label language and all recommended changes were incorporated in the final negotiated label.

During the labeling negotiations, the applicant agreed to include the new safety information regarding the risk of VTE and testosterone use that the Division requested in the Safety Labeling Change for the approved testosterone products (see Safety Update).

Highlights of Prescribing Information:
"Venous thromboembolism (VTE), including deep vein thrombosis (DVT) and pulmonary embolism (PE) have been reported in patients using testosterone products. Evaluate patients with signs or symptoms consistent with DVT or PE."

Full Prescribing Information:
"There have been postmarketing reports of venous thromboembolic events, including deep vein thrombosis (DVT) and pulmonary embolism (PE), in patients using testosterone products, such as Vogelxo. Evaluate patients who report signs and symptoms of pain, edema, warmth and erythema in the lower extremity for DVT and those who present with acute shortness of breath for PE. If a venous thromboembolic event is suspected, discontinue treatment with Vogelxo and initiate appropriate workup and management."

Labeling negotiations for Vogelxo are complete and a final agreement was reached between the Division and the applicant on the content of the package insert and Medication Guide on May 29, 2014. The authorized generic will have labeling that is materially the same as the labeling approved for Vogelxo.

Recommended Regulatory Action

From a clinical perspective, NDA 204399 should be approved.

The clinical review for the initial review cycle of NDA 204399, dated August 12, 2013, is appended.

CLINICAL REVIEW

Application Type	NDA [505(b)(2)]
Application Number(s)	204,399
Priority or Standard	Standard
Submit Date(s)	October 17, 2012
Received Date(s)	October 18, 2012
PDUFA Goal Date	August 18, 2013
Division / Office	DRUP/ODE III
Reviewer Name(s)	Martin Kaufman, D.P.M.
Review Completion Date	July 22, 2013
Established Name	Testosterone Gel
Trade Name	Vogelxo
Therapeutic Class	Testosterone replacement
Applicant	Upsher-Smith Laboratories, Inc.
Formulation(s)	Gel for transdermal use
Dosing Regimen	Once daily
Indication(s)	Treatment of male hypogonadism
Intended Population(s)	Males 18 years of age and older with hypogonadism

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

From a clinical perspective, this reviewer recommends that Vogelxo be approved for the indication of testosterone replacement therapy in adult males for conditions associated with a deficiency or absence of endogenous testosterone: Primary hypogonadism (congenital or acquired), or hypogonadotropic hypogonadism (congenital or acquired).

The recommendation of approval for this 505(b)(2) application is based on the demonstration of bioequivalence between Vogelxo and Testim, a FDA approved testosterone gel, which is the reference listed drug (RLD) for the application. Additionally, the three safety studies conducted by the Sponsor demonstrated an acceptable safety profile for Vogelxo in terms of formulation dependent safety parameters,

1.2 Risk Benefit Assessment

NDA 204399 was submitted as a 505(b)(2) application, which relied on the Agency's previous finding of safety and efficacy for Testim, the reference listed drug (RLD). The Sponsor conducted a pivotal bioequivalence study (Study P06-011) to establish the "bridge" between Vogelxo and Testim. Establishing bioequivalence was considered sufficient to support the conclusion that Vogelxo would be effective for the same indication as the RLD.

However, because the inactive ingredients of Vogelxo are not identical to those of the RLD, bioequivalence alone was not considered sufficient to establish the safety of Vogelxo. In addition to bioequivalence, the Sponsor was required to address the formulation dependent safety concerns of skin irritation and sensitization, ability of washing to remove the gel from the hand used to apply the gel, and interpersonal transfer of testosterone from dosed men via skin contact.

The Sponsor conducted Study P06-011 to demonstrate that Vogelxo and Testim are bioequivalent. The study was a single-dose, open-label, randomized, 2-treatment 4-way replicate crossover bioequivalence study conducted under fasting conditions comparing equal doses (100 mg testosterone) of Vogelxo (test) and Testim (reference). The Sponsor reported that for the ln-transformed baseline-corrected data, the 90% confidence intervals about the ratio of the test (Vogelxo) geometric mean to the reference (Testim) geometric mean were within the 80.00% to 125.00% limits for AUC_{0-t}, AUC_{0-24} and C_{max}. Based on the results of this study, bioequivalence of Vogelxo with Testim was established.

The Sponsor conducted Study P08-001 to evaluate the cumulative irritation produced by Vogelxo compared to the cumulative irritation produced by Testim on intact skin of healthy adult male subjects. The study also evaluated the sensitization potential of Vogelxo compared to Testim. The study was a randomized, double-blind study of healthy adult male subjects. Irritation was evaluated during the 21 day induction phase of the study. The induction phase was followed by a 14 – 17 day rest phase, after which the subjects were dosed and evaluated for sensitization. Subjects with reactions suggestive of sensitization were rechallenged 3 – 4 weeks after resolution of the original reactions.

Statistical analysis of the data comparing the converted cumulative irritation evaluation scores indicated that Vogelxo is no more irritating than Testim when topically applied over a continuous 21-day period. Results from the sensitization data for all subjects indicate that both Vogelxo and Testim demonstrate an equal propensity for inducing sensitization. Based on the results of this study, it is reasonable to conclude that the irritation and sensitization potential of Vogelxo is similar to that of Testim.

The Sponsor conducted Study P10-002 to determine if washing the hands following application of Vogelxo removed testosterone from the surface of the skin. The study was a randomized, open-label, 3-way crossover study to assess the removal of Vogelxo from the hands, after being washed with soap and water. This study showed that washing was effective in removing approximately 99% of the testosterone remaining on the skin of the hand used to apply Vogelxo. This result was consistent regardless of whether or not the gel remaining on the hand after application was allowed to dry, or the method (towel or air dry) used to dry the hands after washing.

The Sponsor conducted Study P10-003 to determine the extent of skin-to-skin testosterone transfer from male subjects dosed with Vogelxo to non-dosed female subjects under the following conditions: in the presence of clothing, in the absence of clothing, and after the application site had been washed. The study showed that testosterone is transferred from a male treated with Vogelxo to a non-dosed female through skin-to-skin contact. Based on the data from the study, it is reasonable to conclude that covering the application site with clothing or washing the application site before contact are effective methods for preventing clinically significant testosterone transfer from a treated male to a non-treated female.

In summary, the information submitted in this application is adequate to conclude that Vogelxo is effective and safe for the indication of testosterone replacement therapy in adult males for conditions associated with a deficiency or absence of endogenous testosterone.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

Based on the transference study (Study P10-003) submitted by the Sponsor, it is expected that interpersonal, skin-to-skin transfer of testosterone will occur unless appropriate steps, such as washing the application site or covering it with clothing, are taken to mitigate transfer. Because the potential for interpersonal transfer is expected to be similar to that of other testosterone gel products, this reviewer recommends that Vogelxo be subject to a risk evaluation and mitigation strategy (REMS) that is similar to the REMS for the other testosterone gel products.

The goal of the REMS should be to inform patients about the serious risks associated with Vogelxo. The REMS elements should include a Medication Guide and a timetable for submission of assessments. The assessments should be submitted 18 months, 3 years, and 7 years from the date of approval.

1.4 Recommendations for Postmarket Requirements and Commitments

No postmarketing requirements or commitments are recommended for this application.

2 Introduction and Regulatory Background

2.1 Product Information

Vogelxo (testosterone gel) is a clear, translucent, alcohol-based testosterone gel intended for topical administration. The drug product contains 1% testosterone in dissolved form and the formulation is intended to release the testosterone for absorption through the skin.

The active ingredient, testosterone, is a naturally occurring hormone with a well-established clinical profile. Testosterone is the predominant circulating androgen in males and is responsible for the development and maintenance of male reproductive functions and secondary sex characteristics. Testosterone replacement therapy is used to normalize serum testosterone in hypogonadal men.

The Sponsor submitted this NDA under section 505b(2) of the Federal Food Drug and Cosmetic Act and is substantially relying on the Agency's findings of safety and efficacy for Testim (NDA 021454), the referenced listed drug (RLD). Although both Testim and Vogelxo contain the same active ingredient (testosterone), in the same strength (1%), in the same dosage form (topical gel), and with the same route of administration (transdermal); the composition of each product differs with respect to the inactive ingredients used. Table 1 presents the composition of Vogelxo and Testim.

Table 1: Composition of Vogelxo and Testim Formulations

Component	Vogelxo (mg/g)	Testim (mg/g)
Testosterone	10.00	10.00
Alcohol (USP)	(b) (4)	
Glycerin (USP)		
Diisopropyl Adipate		
Methyl Laurate		
Oleyl Alcohol		
Carbomer Homopolymer Type C		
Carbomer Copolymer Type B		
Propylene Glycol		
Polyethylene Glycol		
Purified Water		
Tromethamine		
(b) (4)		

Source: NDA 204399, Module 3.2.P.1, Table 2, pp.2-3; Chemistry Review for NDA 021454, pp. 14-15.

***Reviewer's Comment**: Because the inactive ingredients of Vogelxo are not identical to those of Testim, the Sponsor was required to conduct an irritation and sensitization study (Study P08-001), a hand washing study (Study P10-002), and a skin-to-skin transferability study (Study P10-003) to address formulation dependent safety.*

2.2 Tables of Currently Available Treatments for Proposed Indications

Table 2: Currently Available Products for the Treatment of Male Hypogonadism

Route of Administration	Trade/Generic Name	Dose	NDA	ANDA
Parenteral	Depo-testosterone/ testosterone cypionate	50–400 mg every 2 – 4 weeks		085635
	testosterone cypionate	50–400 mg every 2 – 4 weeks		090387 091244 040652 040530 040615 086030 201720
	Delatestryl/testosterone enanthate	50–400 mg every 2 – 4 weeks	009165	
	testosterone enanthate	50–400 mg every 2 – 4 weeks		009165 091120 040647 040575 085598
Oral	Testred/methyltestosterone	10-50 mg daily		083976
	Android/methyltestosterone	10-50 mg daily		086450 087147
	methyltestosterone	10-50 mg daily		080767 084310
	Androxy/fluoxymesterone	5-20 mg daily		088342
Implant	Testopel/testosterone	150 mg-450 mg every 3 to 6 months		080911
Transbuccal	Striant/testosterone	30 mg twice daily	021543	
Transdermal Patch	Androderm/testosterone	2-6 mg daily	020489	
Transdermal Gel	Androgel/testosterone 1.62%	20.25-81 mg daily	022309	
	Androgel/testosterone 1%	50-100 mg daily	021015	
	Testim/testosterone 1%	50-100 mg daily	021454	
	Fortesta/testosterone	10-70 mg daily	021463	
	testosterone gel (Teva)	50-100 mg daily	202763	
	testosterone gel (Perrigo)	50-100 mg daily	203098	
Transdermal Solution	Axiron/testosterone	30-120 mg daily	022504	

Source: Approved Drug Products with Therapeutic Equivalence Evaluations (Orange Book), electronic version accessed June 24, 2013.
Product labeling accessed at the DailyMed website and the FDA Document Archiving, Reporting and Regulatory Tracking System (DARRTS) on June 24, 2013.

2.3 Availability of Proposed Active Ingredient in the United States

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

2.4 Important Safety Issues with Consideration to Related Drugs

Labeled risks of testosterone administration in hypogonadal men include worsening of clinical symptoms of BPH, polycythemia, induction or exacerbation of sleep apnea, breast tenderness or enlargement, liver toxicity (with high doses of orally active 17-alpha-alkyl androgens such as methyltestosterone), and acne. Two major areas of concern in older men with aging-associated decline in serum testosterone are the effects of long-term testosterone administration on the risks of prostate cancer and progression of atherosclerotic heart disease.

Transdermal testosterone preparations, which are applied to the skin, have been associated with secondary exposure of testosterone in women and children via direct skin-to-skin transfer. On September 18, 2009, the transdermal testosterone products that were being marketed at that time were required to include a Boxed Warning in product labeling and adhere to a risk evaluation and mitigation strategy (REMS) to address the serious risk of secondary transfer of testosterone to women and children. All transdermal testosterone products approved since that time have also been subject to the Boxed Warning and REMS requirements.

2.5 Summary of Pre-submission Regulatory Activity Related to Submission

During the development program for the proposed product, the applicant had three meetings with the Division of Bone, Reproductive and Urologic Products. In addition, the Division reviewed and provided comments on draft protocols for the irritation and sensitization, hand washing, and transferability studies (P08-001, P10-002, and P10-003, respectively).

- **Type B, Pre-IND Meeting on 08 November 2007:** The objective of this meeting was to discuss the submission of a New Drug Application (NDA) for Testosterone Gel 1% pursuant to Section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act. During this meeting, the Division asked that a cumulative skin irritation and sensitization study be conducted. The Division determined that no further evidence of safety, beyond information from the Inactive Ingredient Database and, in the case of ethyl alcohol and diisopropyl adipate, evaluations of safety based reviews of the available literature, was required to support the use of the inactive ingredients in Vogelxo.

- **FDA protocol comments dated 03 April 2008:** Comments pertaining to the Phase 1 skin irritation and sensitization study (P08-001) were provided by the Division.
- **Type C, Guidance Meeting on 11 September 2009:** The objective of this meeting was to obtain guidance related to the format and content of the planned NDA submission for Testosterone Gel 1%. During this meeting, the Division asked that hand washing and transferability studies be conducted, and the Division agreed with USL's proposal to use drug product packaged in tubes, only.
- **FDA protocol comments dated 30 June 2010:** Comments pertaining to the Phase 1 hand washing and transferability studies (P10-002 and P10-003, respectively) were provided by the Division. In particular, the Division provided guidance on the cohorts to be used, use of a washout phase, the PK parameters to be evaluated, and evaluation of transfer after washing the application site.
- **FDA protocol comments dated 04 August 2010:** Additional comments pertaining to the Phase 1 transferability study (P10-003) were provided by the Clinical Pharmacology Reviewer. In particular, the Reviewer specified that the application site washing should reflect a real-life scenario (i.e., full-body showering), and USL incorporated this consideration into the final protocol. In considering the Division's recommendation to include 15 minutes of continuous rubbing in each treatment arm, USL focused on an effort to mimic a potential real-life scenario and to limit the potential for significant skin irritation due to the skin-to-skin rubbing between male and female partners. In order to achieve these goals but also to maintain consistency with the 15 minutes of skin contact in the Testim label, the rubbing technique employed in the study consisted of 5 minutes of active rubbing followed by 10 minutes of skin-to-skin contact (15 minutes total contact).
- **Type B, Pre-NDA Meeting on 02 August 2011:** The objective of the meeting was to discuss the completeness of the Vogelxo development program prior to submission of a 505(b)(2) application. The Division agreed that no additional nonclinical studies were necessary, an integrated PK analysis was not required, and a literature search or analysis of the Adverse Event Reporting System database was not required. The Division requested that a summary of all adverse events from studies be compiled in tabular format.

Reviewer's Comment*: The Sponsor originally submitted the pivotal bioequivalence study (Study P06-011) and cumulative skin irritation and sensitization study (Study P08-001) to the Office of Generic Drugs (OGD) in ANDA 79-178.* (b) (4) [redacted]

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

The submission is of good quality and no concerns have been raised about the integrity of the processes that were used by the Sponsor to generate this submission.

3.2 Compliance with Good Clinical Practices

The Sponsor has indicated that their studies were conducted in compliance with Good Clinical Practice Rules (GCP) as referenced in the International Conference on Harmonisation (ICH) guidelines (ICH E6), the U.S. Code of Federal Regulations Guidelines for Good Clinical Practice, and the Declaration of Helsinki.

3.3 Financial Disclosures

The Sponsor certified that the compensation of all clinical investigators was independent of the study outcome and that no investigator had a financial interest in the product or the Sponsor. The Sponsor could not obtain a financial disclosure statement for the Clinical Project Coordinator for Study P10-003 because she was no longer employed by (b) (4), the Contract Research Organization (CRO) and had not signed one during the study.

Reviewer's Comment*: This reviewer believes it is unlikely that the Clinical Project Coordinator could have materially influenced the results of Study P10-003.*

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

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

The CMC reviewer has recommended approval in a review dated August 9, 2013.

4.2 Clinical Microbiology

A microbiology review of the application was not conducted.

4.3 Preclinical Pharmacology/Toxicology

A toxicology review of the application has been conducted. The applicant submitted no new nonclinical information, and is relying on the FDA findings of safety and efficacy for Testim, testosterone gel 1% (NDA 21-454) and published studies on testosterone for Approval. The overall toxicological profile of testosterone is well established. Nonclinical toxicities are not relevant for approval due to the preponderance of clinical data for testosterone that supersedes any nonclinical findings. A scientific rationale for the reliance on Testim supports the nonclinical sections of the labeling. While the formulation is different from other FDA-approved testosterone gel products, the components are at or below the levels in other FDA-approved products.

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

4.4 Clinical Pharmacology

A clinical pharmacology review of the application has been conducted. The clinical pharmacology review team concluded that overall the clinical pharmacology information submitted to support the NDA is acceptable provided that a satisfactory agreement is reached regarding the labeling language.

4.4.1 Mechanism of Action

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

4.5 Office of Scientific Investigations

The Division of Bioequivalence and GLP Compliance, Office of Scientific Investigations conducted an inspection of the analytical portion of the pivotal bioequivalence study (Study P06-011). Following the inspection, a Form FDA 483 was issued with the following observation:

> Your firm failed to apply uniform integration parameters to all chromatograms in a run. Calibrators, quality control samples, and subject samples were individually re-integrated without proper documentation.

After evaluating the site's response to the observation noted in the Form FDA 483, the inspection team concluded:

> Although inconsistent integration in chromatogram processing is objectionable, the inspection did not identify any incidents in which integrity or accuracy of data was compromised.

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

This 505(b)(2) application is supported by five clinical studies: a pilot bioavailability study (Study P06-001), a pivotal bioequivalence study (Study P06-011), an irritation and sensitization study (Study P08-001), a hand washing study (Study P10-002), and a skin-to-skin transferability study (Study P10-003). The studies are summarized in Table 3.

Table 3: Studies Submitted To Support the Application

Type of Study	Study Number	Study Objective	Study Design	Test Product	N	Type of Subjects
Bioavailability	P06-001	Evaluate the bioavailability of three pilot formulations of Vogelxo versus Testim	Single-dose, randomized, open-label, 4-way crossover study	Three formulations of testosterone gel and Testim	32	Hypogonadal males
Bioequivalence	P06-011	To evaluate the bioequivalence of Vogelxo versus Testim	Single-dose, open-label, randomized, 2-treatment 4-way replicate crossover	Vogelxo Testim	84	Hypogonadal males
Skin Irritation and Sensitization	P08-001	To evaluate the cumulative irritation and sensitization produced by Vogelxo compared with Testim on the skin	Randomized, double-blind	Vogelxo Testim	225	Healthy male volunteers
Residual Testosterone after Hand Washing	P10-002	To assess the removal of Vogelxo from hands after washing with soap and water.	Randomized, open-label, 3-way crossover study	Vogelxo	36	Healthy male volunteers
Interpersonal Transfer of Testosterone	P10-003	Evaluate the transfer of testosterone from a treated male to an untreated female via skin contact	Randomized, open-label, 3-way crossover study	Vogelxo	48 dosed males 48 non-dosed females	Healthy male and female volunteers

5.2 Review Strategy

This 505(b)(2) application relies on FDA's finding of safety and efficacy for Testim, the RLD. The Sponsor conducted Study P06-011 to demonstrate the bioequivalence of Vogelxo to Testim. This study will be reviewed to determine whether the two drug products are bioequivalent. If bioequivalence is established between Vogelxo and the RLD, it will be considered adequate evidence that Vogelxo is effective.

However, because the inactive ingredients of Vogelxo are not identical to those of Testim, bioequivalence alone is not sufficient to establish the safety of Vogelxo. In addition to bioequivalence, the Sponsor needs to address the formulation dependent safety concerns of skin irritation and sensitization, ability of washing to remove the gel from the hand used to apply the gel, and interpersonal transfer of testosterone from dosed men via skin contact. The Sponsor conducted three safety studies to address these concerns: an irritation and sensitization study (Study P08-001), a hand washing study (Study P10-002), and a male to female, skin-to-skin transfer study (Study P10-003). The studies are summarized in Table 4. The three safety studies will be reviewed to determine if Vogelxo is safe in terms of the formula dependent safety parameters. Demonstrating that Vogelxo is safe in the three safety studies, in addition to being bioequivalent to Testim, will be considered adequate evidence that Vogelxo is safe.

Table 4: Studies Performed to Evaluate Formulation Dependent Safety

Type of Study	Study Number	Study Objective
Cumulative Skin Irritation and Sensitization	P08-001	To evaluate the cumulative irritation and sensitization produced by Vogelxo compared with Testim on the skin
Residual Testosterone after Hand Washing	P10-002	To evaluate the removal of Vogelxo from hands after washing with soap and water.
Interpersonal Transfer of Testosterone	P10-003	To evaluate the transfer of testosterone from a treated male to an untreated female via skin contact

5.3 Discussion of Individual Studies/Clinical Trials

5.3.1 Bioavailability/Bioequivalence Study P06-001

Study P06-001 was a randomized, open-label, 4-way crossover pilot study to compare the relative bioequivalence of three different testosterone 1% topical gel formulations by Upsher-Smith Laboratories versus Testim in hypogonadal male volunteers.

Study Design
This was a pilot, single center, single-dose, open-label, randomized, 4-way crossover bioequivalence study to compare the rate and extent of absorption of three different testosterone 1% topical gel formulations (tests A, B, and C) by Upsher-Smith Laboratories, Inc., U.S.A., versus Testim (reference) by Auxilium Pharmaceuticals, Inc., U.S.A., applied as a single topical dose (1 x 50 mg) in hypogonadal male subjects.

In each period a total of 25 blood samples was collected at -24.0, -20.0, -16.0, -12.0, -8.00, -4.00-hour, immediately before the gel application, and at 1.00, 2.00, 4.00, 6.00, 8.00, 12.0, 16.0, 18.0, 20.0, 22.0, 24.0, 26.0, 28.0, 32.0, 36.0, 48.0, 60.0, and 72.0-hour post-gel application. Subjects were confined to the (b) (4) from the morning (approximately 8:00 AM) of Day -2 until after the 48-hour post-dose

blood draw (on Day 3), in each period. The treatment phases were separated by washout periods of 7 days.

Inclusion Criteria
Subjects who met the following criteria were included in the study:

1. Male, smoker (limited to < 20 cigarettes per day) or non-smoker, ≥18 and ≤ 70 years of age.
2. Able to communicate effectively with the study personnel.
3. BMI ≥19.0 and <30.0 kg/m2, and weigh at least 110 lbs.
4. Total serum testosterone documented by a morning testosterone level ≤300 ng/dL, the lower limit of the normal range for healthy young male.
5. No significant disease (except hypogonal status) or abnormal laboratory values as determined by medical history, physical examination or laboratory evaluations, conducted at the screening visit or on admission to the clinic.
6. A normal 12-lead electrocardiogram, without any clinically significant abnormalities of rate, rhythm or conduction.
7. Adequately informed of the nature and risks of the study and gave written informed consent prior to receiving study medication.

Exclusion Criteria
Subjects who met any of the following criteria were excluded from the study:

1. Clinically significant illnesses or surgery within 4 weeks prior to gel application.
2. Any clinically significant abnormality or abnormal laboratory test results found during medical screening.
3. Any reason which, in the opinion of the Qualified Investigator or Clinical Sub-Investigator, would have prevented the subject from participating in the study.
4. Positive testing for hepatitis B, hepatitis C, or HIV at screening.
5. 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.
6. History of significant alcohol abuse or drug abuse within one year prior to the screening visit.
7. Regular use of alcohol within six months prior to the screening visit (more than fourteen units of alcohol per week [1 Unit = 150 mL of wine, 360 mL of beer, or 45 mL of 40% alcohol]).
8. 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 or urine alcohol test at screening and during any dosing period.
9. History of allergic reactions to testosterone, testosterone USP (which may be synthesized from soy) or other related drugs, or hypersensitivity to topical alcohol.
10. 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 administration of the study medication.

11. Use of an investigational drug or participation in an investigational study within 30 days prior to gel application.
12. 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.
13. Any clinically significant history or presence of neurological, endocrinal, cardiovascular, pulmonary, hematologic, immunologic, psychiatric, or metabolic disease.
14. Use of prescription medication within 14 days prior to administration of study medication or over-the-counter products (including natural food supplements, vitamins, garlic as a supplement) within 7 days prior to administration of study medication, except for topical products without systemic absorption.
15. Smoking more than 20 cigarettes per day.
16. Any food allergy, intolerance, restriction or special diet that, in the opinion of the Medical Sub-Investigator, could have contraindicated the subject's participation in this study.
17. A depot injection or an implant of any drug within 3 months prior to administration of study medication.
18. Donation of plasma (500 mL) within 7 days prior to drug administration. Donation or loss of whole blood (excluding the volume of blood that will be drawn during the screening procedures of this study) prior to administration of the study medication as follows:
    - 50 mL to 499 mL of whole blood within 30 days,
    - more than 499 mL of whole blood within 56 days prior to drug administration.
19. 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.
20. Clinically significant history of sleep apnea or known risk factors such as chronic lung disease.
21. Had evidence by physical examination or symptoms indicative of breast or prostate cancer and/or clinically significant benign prostatic hyperplasia.
22. Had used finasteride, ketoconazole, prednisone, opioids, DHEA (or other testosterone precursors) or other medications which could have interfered with the production, metabolism or disposition of testosterone within 30 days prior to the study.
23. Had significant dermatitis, excessive body hair, scars, tattoos or any other skin disorder at the protocol specified application site that would have compromised absorption of the study medications.
24. History of cancer other than basal cell with clear margins.

25. An ALT or AST greater than 1.5 times the upper limit of normal at screening or Day –2 in each dosing period.

Study Drugs
The four test formulations of testosterone 1% topical gel tested were identified in the study report as:

A. Upsher-Smith Laboratories, Inc., U.S.A., testosterone 5 g tube of 1% topical gel (50 mg): clear translucent gel. (Lot No.: 42956; Manufacturing date: March 01, 06).
B. Upsher-Smith Laboratories, Inc., U.S.A., testosterone 5 g tube of 1% topical gel (50 mg): clear translucent gel. (Lot No.: 42400; Manufacturing date: February 01, 06).
C. Upsher-Smith Laboratories, Inc., U.S.A., testosterone 5 g tube of 1% topical gel (50 mg): clear translucent gel. (Lot No.: 42910; Manufacturing date: February 27, 06).
D. Auxilium Pharmaceuticals, Inc. U.S.A. (Manufactured by (b) (4) .) Testim, testosterone 5 g tube of 1% topical gel (50 mg): clear translucent gel. (Lot No.: WLCD; Expiry December 2007).

Reviewer's Comment*: The formulation of lot number 42956, Test Formulation A in this study, is Vogelxo. This formulation was used in all clinical trials conducted after Study P06-001 and is the to-be-marketed formulation. Other than Study P06-001, the NDA does not contain any additional information regarding Test Formulation B or Test Formulation C.*

Study Endpoint
This study compared the relative bioavailability (rate and extent of absorption) of three different testosterone 1% topical gel formulations (Test Formulations A, B, and C) by Upsher-Smith Laboratories, Inc., U.S.A., versus Testim (reference) by Auxilium Pharmaceuticals, Inc., U.S.A., applied as a single topical dose (1 x 50 mg) in hypogonadal male subjects.

The hypothesis of bioequivalence of the formulations was accepted if the 90% geometric confidence intervals of the ratio of least-squares means of the test to reference product of ln-transformed AUC_{0-t} and C_{max} were within the acceptance range of 80.00% to 125.00%, for baseline corrected data without dose normalization. As per protocol, due to physiological fluctuation of endogenous levels of testosterone, the elimination rate constant could not be properly estimated. Therefore, AUC_{0-inf} was calculated but not included in the assessment of bioequivalence.

Safety Endpoints
Adverse events that occurred following drug administration were collected and tabulated.

In addition, prospective evaluations of application site irritation were conducted, but the data were not analyzed statistically in the final study report. In each period, skin reactions at the gel application site were recorded prior to gel application, approximately 0.5, 24, 60, and 72 hours post-gel application. A trained blinded study staff checked and recorded the dermal reaction at the gel application site using the following scale:

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

Study Results
The results of this study are discussed in section 6.1 Bioequivalence Study.

5.3.2 Bioequivalence Study P06-011

This was a single-dose, open-label, randomized, 2-treatment 4-way replicate crossover bioequivalence study conducted under fasting conditions comparing equal doses of Vogelxo and Testim. The study was conducted at the (b) (4) from January 19 to April 24, 2007. Blood samples collected during the study were processed and frozen serum obtained from the processed blood samples was sent to the (b) (4) for analysis.

Study Design
This was a single center, single-dose, open-label, randomized, 2-treatment 4-way replicate crossover bioequivalence study conducted under fasting conditions comparing equal doses (100 mg testosterone) of the test (Vogelxo) and reference (Testim) products.

In each period a total of 27 blood samples was collected at -12.0, -8.00, -4.00-hour, immediately before the gel application, and at 1.00, 2.00, 4.00, 6.00, 8.00, 10.0, 12.0, 14.0, 16.0, 18.0, 19.0, 20.0, 21.0, 22.0, 24.0, 26.0, 28.0, 32.0, 36.0, 40.0, 48.0, 60.0, and 72.0-hour post-gel application. Subjects were confined to the (b) (4) from the morning of Day -1 until after the 48.0-hour post-dose blood draw (on Day 3), in each period. They returned to the clinical facility for the scheduled blood sample collections at study hours 60.0 and 72.0. The treatment phases were separated by washout periods of 7 days.

Inclusion Criteria
Subjects who met the following criteria were included in the study:

1. Male, smoker (limited to ≤ 20 cigarettes per day) or non-smoker, 18 years of age and older.
2. Healthy subjects (except for their hypogonadal status) or subjects with stable chronic illnesses (stable medication for a minimum of 3 months) which did not interfere in the pharmacokinetics or the assay of the administered testosterone.
3. Be able to communicate effectively with the study personnel.
4. BMI ≥19.0 and <35.0 and weight at least 110 lbs.
5. Have an average of two morning total serum testosterone levels (measured on two separate days) ≤ 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).
6. 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.
7. Have a normal 12-lead electrocardiogram, without any clinically significant abnormalities of rate, rhythm or conduction.
8. Be adequately informed of the nature and risks of the study and give written informed consent prior to receiving study medication.

Exclusion Criteria
Subjects who met any of the following criteria were excluded from the study:

1. Clinically significant illness or surgery within 4 weeks prior to gel application.
2. Any clinically significant abnormality or abnormal laboratory test results found during medical screening.
3. Any reason which, in the opinion of the Clinical Sub-Investigator, would have prevented the subject from participating in the study.
4. Positive test for hepatitis B, hepatitis C, or HIV at screening.
5. 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.
6. History of significant alcohol abuse or drug abuse within one year prior to the screening visit.
7. Regular use of alcohol within six months prior to the screening visit (more than fourteen units of alcohol per week [1 Unit = 150 mL of wine, 360 mL of beer, or 45 mL of 40% alcohol]), or positive urine alcohol test at screening or at check-in of any dosing period.
8. Use of soft drugs (such as marijuana) within 3 months prior to the screening visitor hard drugs (such as cocaine, phencyclidine [PCP], and crack) within 1 year prior to the screening visit or positive urine drug screen at screening and during any dosing period.
9. History of allergic reactions to exogenous testosterone, soy, soy beans, soya lecithin, testosterone USP (which may be synthesized from soy), or other related drugs, or hypersensitivity to topical alcohol.

10. 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 administration of the study medication.
11. Use of an investigational drug or participation in an investigational study within 30 days prior to gel application.
12. 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.
13. Any clinically significant history or presence of neurological, endocrine, cardiovascular, pulmonary, hematological, immunologic, psychiatric, or metabolic disease.
14. 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 administration of study medication, except for topical products without systemic absorption.
15. Smoking more than 20 cigarettes per day.
16. Any food allergy, intolerance, restriction or special diet that, in the opinion of the Clinical Investigator or Sub-Investigator, could have contraindicated the subject's participation in this study.
17. A depot injection or an implant of any drug within 3 months prior to administration of study medication.
18. Donation of plasma (500 mL) within 7 days prior to drug administration. Donation or loss of whole blood (excluding the volume of blood that was drawn during the screening procedures of this study) prior to administration of the study medication as follows: 50 mL to 499 mL of whole blood within 30 days, or more than 499 mL of whole blood within 56 days prior to drug administration.
19. Clinically significant history of sleep apnea or known risk factors such as chronic lung disease.
20. Have evidence by physical examination or symptoms indicative of breast or prostate cancer and/or clinically significant benign prostatic hyperplasia.
21. Have used finasteride, ketoconazole, prednisone, opioids, DHEA (or other testosterone precursors) or other medications which may interfere with the production, metabolism or disposition of testosterone within 30 days prior to the study.
22. Have significant dermatitis, scars, tattoos or any other skin disorder at the protocol specified application site that would compromise absorption of the study medications.
23. History of cancer other than basal cell with clear margins.

24. An ALT or AST greater than 1.5 times the upper limit of normal at screening or Day –1 in each dosing period.
25. History of paraphilia.
26. Acute disease at the time of enrolment (screening).
27. Any confirmed or suspected immunosuppressive or immunodeficient condition.
28. Active neurological disorder.
29. Coagulation disorders or anticoagulant therapy.
30. Diabetes mellitus (even if on stable dose(s)) of medication.
31. History or presence of heart failure, myocardial infarct or coronary heart disease.
32. Chronic liver, renal or inflammatory bowel disease or collagen vascular disease.

Study Drugs
The two drugs tested were identified in the study report as:

1. testosterone gel 1% 5 g tube (corresponding to 50 mg of testosterone); Upsher-Smith Laboratories, Inc., U.S.A. (Batch/Lot No.: 46322)
2. Testim (testosterone) testosterone gel 1% 5 g tube (corresponding to 50 mg of testosterone); Auxilium Pharmaceuticals, Inc., U.S.A. (Lot No.: XFAL; Exp. Date: 6/2008)

Reviewer's Comment*: According to the Sponsor's submission, the formulation of the batch (Lot no. 46322) used in the study is Vogelxo. This formulation was used in all clinical trials conducted after Study P06-011 and is the to-be-marketed formulation.*

Study Endpoint
This study compared the rate and extent of absorption of Vogelxo (test) versus Testim (reference) applied as a single dose (2 x 50 mg of testosterone) in hypogonadal male subjects. The endpoint of the study was bioequivalence based on a comparison of the pharmacokinetics of Vogelxo to Testim over a 72 hour period following a single administration of each product.

Bioequivalence was evaluated using baseline-corrected, non-dose-normalized ln-transformed AUC_{0-24} and C_{max}. To establish bioequivalence, the 90% confidence intervals about the ratio of the test geometric mean to the reference geometric mean should be within the 80.00% to 125.00% range for the pharmacokinetic parameters C_{max} and AUC_{0-24} of the ln-transformed baseline-corrected data.

Safety Endpoint
Adverse events that occurred following drug administration were collected and tabulated.

In addition, during each period, skin reactions at the gel application site were recorded prior to gel application, approximately 0.5, 24, 48, 60, and 72 hours post-gel application. A trained blinded study staff checked and recorded the dermal reaction at the gel application site using the following scale:

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

Study Results
The results of this study are discussed in section 6.2 Bioequivalence Study.

5.3.3 Skin Irritation and Sensitization Study P08-001

This was a single-site, randomized, double-blind study of healthy adult male subjects. During the induction phase, Vogelxo, Testim, a positive control, and a low irritant control were applied under occlusive conditions to 4 sites on both upper outer arms and evaluated for irritation response for 21 days. Following a rest phase, the subjects were dosed with all four treatments on four sites on the upper back, which were evaluated for sensitization to Vogelxo and Testim.

Study Objective
The primary objective of this study was to evaluate the cumulative irritation produced by Vogelxo compared to the cumulative irritation produced by Testim on intact skin of the healthy adult male subjects. The secondary objectives were to evaluate the sensitization potential of Vogelxo compared to Testim and the general safety of the test articles.

Study Design
This was a single-site, randomized, double-blind study of healthy adult male subjects. Two hundred fifty-five (255) subjects (to achieve approximately 200 evaluable subjects) had four 3.14 cm^2 sites demarcated on the upper outer region of both arms. These sites were evaluated for irritation response for 21 days. Each of the four treatments (Vogelxo, Testim, positive control, and low irritant control) was applied under occlusive conditions during the induction phase and was evaluated for irritation response. Following a rest phase, the subjects were dosed with all four treatments on four 3.14 cm^2 sites on the upper back, which were evaluated for sensitization. Skin assessments of each treatment application were examined and scored under light supplied by a 100-watt incandescent blue bulb. Assessments were made no less than 20 minutes and no more than 30 minutes following each test article removal during the induction phase. For the skin sensitization portion of the study, skin assessments to each treatment application were examined and scored under light supplied by a 100-watt incandescent blue bulb at

30 minutes following removal, and then 24, 48, and 72 hours after test article removal for the appearance of skin reactions indicative of sensitization.

This was a double-blinded study using a within-subject randomized design where each subject received all test materials. A single, trained skin irritation evaluator was blinded to the identity of the test materials and performed the scoring on all subjects. Subjects received twenty-one applications of the test articles to the same skin site over a three week period to achieve 21 continuous days of skin contact. A molded plastic chamber, flexible enough to conform to the contour of the skin was used to administer the test articles.

Approximately 80 µl of the Vogelxo and Testim test articles was applied to the patch material. The product was spread over the designated patch using a glass rod and allowed to dry completely (a minimum of 15-20 minutes). The occlusive patch was then applied to the same designated skin sites (separate sites on the upper outer arm which have been marked with a skin marker) on an area of approximately 3.14 cm^2. A dose of 0.2 mL of the positive irritant control and low irritant control test articles were dispensed by pipette or syringe by study staff to the occlusive patch material and applied (without drying) to separate sites on the upper arm (which have been marked by a skin marker) on an area of approximately 3.14 cm^2.

Subjects had all four test articles applied under occlusive conditions: Vogelxo, Testim, a positive irritant control, and a low irritant control. Each application contacted the skin for approximately 24 hours (± 2 hours). Scoring for skin reaction was conducted at each visit no less than 20 minutes and no more than 30 minutes following test article removal. Following a 14-17 day rest phase, subjects received an additional application, which contacted the skin for approximately 48 hours (± 2 hours). Scoring for skin reaction was conducted at 30 minutes, and then 24, 48, and 72 hours after test article removal. Subjects were also queried for adverse events and concomitant medication usage at each visit.

Inclusion Criteria
Subjects who met the following criteria were included in the study:

1. Subjects who were informed of the nature of the study and agreed to and were able to read, review and sign the informed consent document for study participation. The informed consent document was written in English, therefore the subject must have had the ability to read and communicate in English.
2. Subjects who completed the screening process within 8 weeks prior to dosing.
3. Subjects were healthy male subjects 18-65 years of age, inclusive, at the time of consent.
4. Subjects who had a body mass index (BMI) between 18.5-40 kg/m2, inclusive.
5. Subjects who were generally healthy as documented by the medical history, physical examination (including but not limited to an evaluation of the cardiovascular, gastrointestinal, respiratory and central nervous systems), vital

sign assessments, clinical laboratory assessments including a prostate-specific antigen (PSA) analysis, and by general observations. Any abnormalities/deviations from the acceptable range that were considered clinically relevant by the study physician were evaluated as individual cases, documented in study files, and agreed upon by the principal investigator (or sub-investigator) and sponsor prior to enrolling the subject in this study.

6. Subjects who were willing to shower using the same soap/cleanser/lotions/creams/topicals between the Screening Visit and Study Day 1.

Exclusion Criteria

Subjects who met any of the following criteria were excluded from the study:

1. Subjects with diabetes mellitus, clinically significant hypertension or circulatory disease.
2. Subjects who were planning to use any exclusionary over-the-counter (OTC) medications including antihistamines, H2 antagonists, corticosteroids, immunosuppressants, aspirin, ibuprofen, or naproxen within 48 hours prior to or throughout the study.
3. Subjects who were planning to use any exclusionary prescription medications (e.g. estrogen therapy, androgenic medications, HGH, LHRH, and sildenafil and similar drugs, DHEA, NSAIDs, apomorphine) within 48 hours prior to or throughout the study.
4. Subjects who intended to start, stop or change dose of any prescription or OTC medication within 48 hours prior to or throughout the study. Acetaminophen may be administered if needed.
5. Subjects who had used prescription or OTC topical medications on the test sites within 1 month prior to study conduct.
6. Subjects who had a history of sensitivity/allergy to exogenous testosterone, soy, soybeans, soya lecithin, testosterone USP (which may be synthesized from soy) or other related drugs or to the ingredients found in the test formulations.
7. Subjects who had a significant history or allergy to soaps, lotions, emollients, ointments, creams, cosmetics, adhesives, latex, tapes, or transdermal systems.
8. Subjects who had a history of significant skin conditions or disorders, for example, psoriasis, atopic dermatitis, etc., that might interfere with the evaluation of the test site reaction.
9. Subjects who had a systolic blood pressure above 140 mmHg or a diastolic blood pressure higher than 90 mmHg were excluded from the study.
10. Subjects who had 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.
11. Subjects who had a history of prostate cancer or benign prostatic hyperplasia (BPH).
12. Subjects who had a history of diabetes.

13. Subjects who had an obvious difference in skin color between arms or the presence of a skin condition, excessive hair at the application site(s), scar tissue, tattoo or coloration that would interfere with placement of the test sites, their assessments, and their reaction to drug or could compromise the safety of the subject.
14. Subjects who had an open sore(s) at the applications site(s).
15. Subjects who had used a tobacco product within 14 days of study conduct
16. Subjects who had a clinically significant history of drug abuse or alcoholism
17. Subjects whose caffeine intake was greater than 500 mg per day (1 cup of coffee contains approximately 85 mg of caffeine).
18. Subjects who were unwilling to abstain from alcohol for 48 hours prior to and throughout the study.
19. Subjects who had participated in another investigational drug, medical device, or biologics study within 30 days prior to dosing.
20. Subjects who had significantly abnormal laboratory values upon screening.

Study Drugs

- Investigational Product
  - Product: Vogelxo
  - Lot No. 46322
  - Manufacturer: Upsher-Smith Laboratories, Inc.
- Reference Product
  - Product: Testim
  - Lot No: ZKAF
  - Manufacturer: Auxilium Pharmaceuticals, Inc.
- Positive Irritant Control
  - Product: Sodium Lauryl Sulfate Solution (0.05% w/v)
- Low Irritant Control
  - Product: 0.9% Sodium Chloride Injection, USP

Irritation Evaluations

Subjects were evaluated using the Skin Irritation Scale described by Berger and Bowman. Each of the scores represented the presence of a visible or palpable dermal reaction that was localized in the active test system portion of the application area. If a test site exhibited a strong reaction (numerical score of ≥ 3 or letter grade of F, G, or H) that test site was discontinued from further use.

The test sites were evaluated for irritation on study days 1-21 no less than 20 minutes and no more than 30 minutes after test system removal, following adverse event and concomitant medication queries. Subjects who exhibited a strong reaction warranted application of the test article to the Move-1 or Move-2 site and residual scores were collected through the end of the study for all previously exposed sites. The skin reactions observed at such application sites were scored and recorded at each remaining scheduled visit, but for purposes of statistical evaluation, the observed scores

were converted to a 3 and were carried forward for irritation evaluation. A strong reaction was defined as:

- Any numerical score that has been appended with a letter grade of F, G, or H
- An actual or converted score of 3, 4, 5, 6, or 7 regardless of the possible letter grade combination.

The grading scales used to assess skin response to the test articles used in the study are summarized in Tables 5 and 6.

Table 5: Inflammatory Response Scores (Irritation)

Score	Reaction
0	No evidence of irritation
1	Minimal erythema, barely perceptible
2	Definite erythema, readily visible; minimal edema or minimal papular response
3	Erythema and papules
4	Definite edema
5	Erythema, edema and papules
6	Vesicular eruption
7	Strong reaction spreading beyond test site

Source: NDA 204399, Module 5.3.3.1, CSR P08-001, p.36.

Table 6: Superficial effects (Irritation)

Letter Grade	Score	Reaction
A	0	Slight glazed appearance
B	1	Marked glazed appearance
C	2	Glazing with peeling and cracking
F	3	Glazing with fissures
G	3	Film of dried serous exudate covering all or part of the patch site
H	3	Small petechial erosions and/or scabs

Source: NDA 204399, Module 5.3.3.1, CSR P08-001, p.36.

Sensitization Evaluations

Following a 14-17 day rest period, subjects entered the challenge phase and received an additional application of test article, which was removed after 48 ± 2 hours. The test sites were then evaluated for irritation at approximately 30 minutes, 24, 48, and 72 hours after test system removal. The skin reactions observed at the application sites were scored and recorded.

In the challenge phase any subject with a converted score of 2 of more at 48 hours post patch removal was considered to be potentially sensitized and was re-challenged at least 3-4 weeks after the conclusion of the challenge phase to confirm the sensitization reaction. A converted score was calculated by adding together the numeric score and the numeric score assigned to the letter grades. The grading scales used in the sensitization evaluations are summarized in Tables 7, 8, and 9.

Table 7: Inflammatory Response Scores (Sensitization)

Score	Response
0	Visible reaction
0.5	Slight, confluent or patchy erythema
1	Mild erythema (pink)
2	Moderate erythema (definite redness)
3	Strong erythema (very intense redness)

Source: NDA 204399, Module 5.3.3.1, CSR P08-001, p.36.

Table 8: Definition of Appended Letter Grades (Sensitization)

Letter Grade	Score	Response
E	0	Edema-swelling, spongy feeling when palpated
P	1	Papule-red, solid, pinpoint elevation
V	1	Vesicle-small elevation containing fluid
B	1	Bulla reaction-fluid-filled lesion (blister)
S	1	Spreading-evidence of the reaction beyond the pad area
W	1	Weeping-result of a vesicular or bulla reaction-serous exudate
I	1	Induration-solid, elevated, hardened, thickened skin

Source: NDA 204399, Module 5.3.3.1, CSR P08-001, p.36 - 37.

Table 9: Superficial effects (Sensitization)

Letter Grade	Score	Response
g	0	Glazing
y	0	Peeling
c	1	Scab, dried film of serous exudate of vesicular or bulla reaction
d	0	Hyperpigmentation (reddish-brown discoloration of test site)
h	0	Hypopigmentation (loss of visible pigmentation at test site)
f	1	Fissuring-grooves in the superficial layers of the skin

Source: NDA 204399, Module 5.3.3.1, CSR P08-001, p.37.

Data Analysis

Irritation Phase

The irritation potential for each test article was determined by the scores obtained during the induction phase of the study. A converted score was calculated by adding together the numeric score and the numeric score assigned to the letter grade. If a converted score of 3 or greater is reached and the test article had to be moved to a new treatment site, a score of 3 was carried across the remainder of the induction time points for purposes of determining the irritation potential for that particular test article. Descriptive statistics such as the mean and standard deviation were computed for each test article on a daily basis as well as a on a cumulative basis.

A standard approach for scoring and classifying cumulative irritation was used to analyze the dermatological evaluation data. The actual test score was a combination of a numerical and letter score. Letter grades were converted into numerical equivalents, which were considered additive to any numerical score.

The irritation scores for the test articles were summed across the twenty-one (21) days of observation to provide a cumulative irritation score for each subject and for each test article. Descriptive statistics included the mean values for the test and reference products (μ_T, μ_R, respectively). A hypothesis test was used to determine if the test product is no more irritating than the reference product when applied over a continuous 21-day period. Assuming that $\mu_R > 0$, the null and alternative hypotheses were:

H_0: $\mu_T/\mu_R > 1.25$
H_1: $\mu_T/\mu_R \leq 1.25$

which implies:

H_0: $\mu_T - 1.25\ \mu_R > 0$
H_1: $\mu_T - 1.25\ \mu_R \leq 0$

The cumulative scores were evaluated using a randomized, complete block design ANOVA with treatment (test articles) and site (right or left side application) as fixed effects and subject as a random effect. The upper bound of a one-sided 95% confidence interval on $\mu_T - 1.25\ \mu_R$ was used to establish the non-inferiority of the test product compared to the reference product. If the upper bound of the 95% confidence interval for the difference between the test and 1.25 times the reference mean was less than or equal to zero, the test product was deemed to be non-inferior in irritation to the reference product. Also, the following were calculated for each product:

- The total number of subjects with a maximum irritation score for each product.
- The number of subjects with patch removed due to test article irritation.

- The number of days from patch application to patch removal due to test article irritation.

In addition, a frequency chart showing the number of applications of each test article with each irritation score on each day was provided. These analyses were presented for both numeric scores and converted scores.

Sensitization Phase

The interpretation of data was based on the pattern of reactivity to the test article during induction when compared to the severity and persistence of the reaction(s) observed at challenge. Increased reactivity noted during the first week of induction to test articles that are considered non-irritating or minimally irritating generally indicates a pre-sensitized condition. Comparable reactivity during the third week, if it appeared suddenly, would be suggestive of the initiation of sensitization. Cumulative irritation would generally develop more gradually and would resolve with a comparable time sequence after patch removal.

Positive reactions, at challenge, would generally be more intense and persistent than reactions noted during the induction period, particularly those noted early in the test. Characteristically, they may be eczematous (papulovesicular, edematous) rather than strictly erythematous with surface damage. These comparisons, however, are not always diagnostic and borderline or suggestive responses should be re-challenged. Therefore, a score of 1 or less at the 48 hour post patch removal time point of the challenge phase was not considered a sensitization reaction. Re-challenges were conducted 3-4 weeks after resolution of the original reactions, in order to avoid the conditioned response (angry-back syndrome). The immune response would retain its specificity and sensitivity for an extended period, where as hyperirritability should have subsided.

A frequency chart showing the number of applications of each product with each irritation score on each day was provided. These results were presented for both challenge and re-challenge data. The number of subjects exhibiting contact sensitization was summarized by treatment. The percentage of subjects sensitized was computed based on the challenge and rechallenge data.

For the sensitization observed, there are no statistical evaluations, only the number observed and severity is reported. The investigator interpreted the reactions at challenge and re-challenges to confirm sensitization.

Adverse Events

Adverse events were coded using the MedDRA dictionary version 11 and summarized for the number of subjects reporting the adverse event and the number of adverse events reported. A by-subject adverse event data listing including verbatim term, coded term, and severity were provided.

Study Results
The results of this study are discussed in section 7.4.5.1 Skin Irritation and Sensitization Study.

5.3.4 Hand Washing Study P10-002

This was a single-center, randomized, open-label, 3-way crossover study to assess the removal of Vogelxo from the hand used to apply the gel, after being washed with soap and water.

Study Objective
The primary objective was to determine if washing the hands following application of Vogelxo removed testosterone from the surface of the skin.

Study Design
This was a single-center, randomized, open-label, 3-way crossover study to assess the removal of Vogelxo from the hands, after being washed with soap and water. A total of 36 healthy, male subjects who met enrollment criteria were included in this study. Prior to entering the trial, subjects underwent screening assessments to establish eligibility, within 28 days before study drug application. Upon arrival for confinement, subjects were randomized to receive a single dose of testosterone in accordance with the randomization scheme. Subjects reported to the study center on Day-1 and were confined up to 24 hours post-dose. The treatment phases were separated by washout periods of 7 days.

Subjects self-applied the entire contents of one 5 g tube (50 mg of testosterone) over a 500 cm^2 area of the upper shoulder/arm that was opposite of the subject's dominant hand. Self-application by the subjects was intended to mimic the true application of the product according to the labeling instructions. The 5 g dose of Vogelxo was selected in order to limit drug exposure in healthy volunteers. This dose also confined the application site to a single shoulder/upper arm; therefore, reducing the amount of variability in subject self-application and in the swabbing method.

During this study, the contents of the tube were squeezed into the palm of the subject's hand by study staff, and the hand was then used to rub the dose onto the application site. Therefore, the hand was chosen as the site for analysis of testosterone on the skin, before and after washing with soap and water, in order to correspond with current labeling and patient instructions for marketed testosterone gel products.

Treatment methods were as follows:

- Treatment A: After application of Vogelxo, hands were allowed to dry for 3 minutes, washed and rinsed, and dried with a cloth towel;

- Treatment B: After application of Vogelxo, hands were allowed to dry for 3 minutes, washed and rinsed, and air dried for 9 minutes;
- Treatment C: After application of Vogelxo, hands were not allowed to dry, washed and rinsed, and dried with a cloth towel.

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

Inclusion Criteria

Subjects who met all of the following criteria were included in the study:

1. Healthy male subjects 18-65 years of age, inclusive, at the time of consent;
2. Had a body mass index (BMI) between 18 and 35 kg/m2, inclusive, and weight of at least 110 lbs (49.9 kg);
3. Generally healthy, as documented by the medical history, physical examination (PE, including, but not limited to, an evaluation of the cardiovascular, gastrointestinal, respiratory and central nervous systems), vital sign assessments, clinical laboratory assessments, including a prostate specific antigen (PSA) analysis, and by general observations. Any abnormalities/deviations from the acceptable range that might have been considered clinically relevant by the study physician was evaluated as individual cases, documented in study files, and agreed upon by the QI (or Sub-Investigator) and Sponsor prior to enrolling the subject in this study;
4. Had a screening prostate specific antigen (PSA) between 0-2.5 ng/mL for subjects ≤50 years of age and between 0-4 ng/mL >50 years of age;
5. Had not used tobacco products within 90 days prior to screening and willing to abstain from use of tobacco products through final study visit;
6. Was willing to participate in each study period;
7. Was able to communicate effectively with study personnel and was considered reliable, able, willing and cooperative with regard to complying with protocol-defined requirements as assessed by the study investigator;
8. Could voluntarily give written informed consent to participate in the study prior to the completion of any study-related procedures.

Exclusion Criteria

Subjects who met any of the following criteria were excluded from the study:

1. A clinically relevant illness (within 4 weeks prior to dosing) or history that would have interfered with the subject's ability to complete the study or would have confounded the results of this study, as determined by the clinical investigator(s), including diabetes mellitus, clinically significant (CS) hypertension or circulatory disease;
2. Subject had a history of significant skin conditions or disorders on or around the application site, for example, psoriasis, atopic dermatitis, etc.;
3. Subject had significant dermatitis, tattoos, scars or any other skin disorder at the application site;
4. Subjects who had an open sore(s) or abrasion(s) on the hand or application site;

5. Subject had a history of sensitivity/allergy to exogenous testosterone, soy, soybeans, soya lecithin, testosterone USP (which may be synthesized from soy) or other related drugs or to the ingredients found in the test formulations;
6. Subject had a significant history of sensitivity/allergy to soaps, lotions, emollients, ointments, creams, cosmetics, or topical alcohol;
7. Subject had 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;
8. Subject had used prescription or over-the-counter (OTC) topical medications on the test sites within 1 month prior to dosing;
9. Subject was planning to use any exclusionary prescription medications (glucocorticoids [cortisone, prednisone] [topical steroid use was evaluated on a case-by-case basis by the investigator]; anabolic steroids; opiates [codeine, morphine, hydromorphone]; estrogens; digoxin [Lanoxin]; spironolactone [Aldactone]; barbiturates; anti-androgen [Casodex, Euflex]; prostate cancer treatment [Lupron, Zoladex]; anti-epileptic drugs [Dilantin]; antidepressants [Paxil, Effexor, Prozac, Zoloft, Luvox, Celexa, Cipralex]; antipsychotic agents [Risperdal, Zyprexa, Haldol], propranolol, and insulin) within 48 hours prior to dosing or throughout the study;
10. History of coagulation disorders or use of anticoagulant therapy;
11. Had a history of carcinoma of the breast;
12. Had a history of prostate cancer or benign prostatic hyperplasia (BPH); if over the age of 50, had a history of BPH symptoms (urinary hesitancy, urinary urgency, or weak stream, dysuria, frequent urination);
13. ECG abnormalities (CS), or systolic blood pressure of ≥140 mm Hg or diastolic blood pressure of ≥90 mm Hg, or heart rate <50 or >100 bpm at screening;
14. History of malignancy;
15. Had a history of nephrolithiasis or ureterolithiasis;
16. Had a positive test for human immunodeficiency virus (HIV), hepatitis B, or hepatitis C;
17. Took oral or transdermal testosterone replacement therapy from 28 days prior to gel application;
18. Took an injectable or intramuscular testosterone replacement therapy or implants from 6 months prior to gel application;
19. Participated in another clinical trial with an investigational drug within 30 days prior to the first study period;
20. Subject had significantly abnormal laboratory values upon screening;
21. Regularly used alcohol within six months prior to the screening visit (more than fourteen units of alcohol per week [1 Unit = 150 mL of wine, 360 mL of beer, or 45 mL of 40% alcohol]), or positive urine alcohol test at screening or at check-in of the dosing period;
22. Used 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 or at check-in of the dosing period.

Study Drug
Vogelxo (testosterone) gel (50 mg testosterone per 5 g tube) applied topically as a single dose, batch number 64540A.

Drug Concentration Measurements
A dry, porous swab was used for the purpose of measuring testosterone on the surface of the skin. The bioanalytical method was developed to ensure proper recovery of testosterone from this type of swab. A wet swab was not chosen as it may pull testosterone back out of the skin's reservoir after it has been absorbed.

The percentage of testosterone dose remaining on the hand before and after washing and the percentage of testosterone removed from the skin surface by washing were determined from the skin swab data.

Statistical and Analytical Plan
For each treatment, baseline was defined as the results obtained prior to dosing in each period. Baseline corrected testosterone levels were calculated for each subject and treatment at both post-dose time points, before and after washing. Negative baseline-corrected values were considered as 0 for the purpose of the statistical analysis.

Summary statistics (sample size [N], mean, median, standard deviation [SD], coefficient of variation [CV], minimum [Min], and maximum [Max]) were presented by treatment for uncorrected and baseline-corrected testosterone for each skin swab sample collection time.

To evaluate testosterone levels on the skin surface of the hand, two types of percentages were computed and summarized with descriptive statistics. For each subject in each period, the percentage of testosterone removed from the skin surface by washing was calculated as follows:

$$100 \times \frac{\text{(Baseline-corrected level before washing — Baseline-corrected level after washing)}}{\text{Baseline-corrected level before washing}}$$

For each treatment and for both post-dose time points (before and after washing), the percentage of testosterone dose remaining on the skin surface of the hand was calculated by dividing the testosterone level found on the palm of the dominant hand by the testosterone total dose applied (the result was then multiplied by 100). The testosterone total dose applied for each subject in each period was fixed, i.e., 50 mg (equivalent to 5000 µg). The dominant hand for each subject was divided into four equal areas of 10 cm^2, using a template; for each time point, a single skin swab sample was collected from randomly selected area, in accordance with the randomization scheme.

The testosterone level (baseline-corrected) obtained from this sample was then multiplied by four to obtain the total testosterone level remaining on the entire hand (in µg). For each subject in each period, the percentage of testosterone dose remaining on the hand before and after washing was calculated as follows:

$$100 \times \frac{\text{(Baseline-corrected level before or after washing x 4)}}{5000}$$

Individual uncorrected and baseline-corrected testosterone levels, as well as calculated percentages were also presented.

Adverse Events
All adverse events were captured and recorded from the time the written study-specific informed consent was obtained until completion of the final study visit. Information collected on these adverse events included the nature, date and time of onset, date and time of resolution, intensity, duration, relationship, and outcome of the event. The study center recorded all adverse events observed, queried, or spontaneously volunteered by the subjects. Regardless of whether an adverse event was assessed by the Investigator as not being reasonably attributable to the study medication, its occurrence was recorded in the source documents and captured in the database.

Study Results
The results of this study are discussed in section 7.4.5.2 A Randomized, Single-Center, Open-Label, Three-Way Crossover Study of the Removal of Upsher-Smith Laboratories, Inc. Testosterone Gel 1% by Hand Washing (P10-002).

5.3.5 Transferability During Skin-to-Skin Contact Study P10-003

This study was a randomized, single-center, open-label, three-way, crossover study of the transferability of Vogelxo during skin-to-skin contact with clothing, without clothing, and after washing.

Study Objective
The primary objective was to determine the extent of skin-to-skin testosterone transfer from male subjects dosed with Vogelxo to non-dosed female subjects under the following conditions: in the presence of clothing, in the absence of clothing, and after the application site had been washed.

Study Design
This was a randomized, single-center, open-label, three-way, crossover study to assess the transferability of Vogelxo during skin-to-skin contact after application site washing, and with and without clothing in 48 healthy male and 48 healthy female subjects who met all enrollment criteria. Prior to entering the study, subjects underwent screening assessments to establish eligibility within 28 days before the first study drug application.

Upon arrival for confinement in Period 1, subjects were randomized in pairs (a dosed male and a non-dosed female) to apply a single dose of testosterone in each study period in accordance with the randomization scheme. The subjects were matched in pairs for the duration of the study. The subjects reported to the study center on Day-1 of each study period and were confined from at least 24 hours prior to drug administration and up to 30 hours post-dose. The treatment periods were separated by a washout of at least 14 days.

In each period, the entire contents of one 5.0 g tube of Vogelxo (50 mg testosterone) was applied topically by study staff with gloved hands and a spatula (applicator) on a 500 cm^2 area of the upper shoulder/arm of a single side of subject's body. Thereafter, skin contact between the dosed male subjects' upper shoulder/arm and the non-dosed female subjects' forearm was performed according to the randomization scheme (i.e., with a clothing barrier, without a clothing barrier, after washing application site).

Treatment methods were as follows:

- Treatment A: After application of Vogelxo, the application site was covered with a long-sleeve 100% cotton shirt (clothing barrier);
- Treatment B: After application of Vogelxo, the application site remained uncovered (without clothing barrier);
- Treatment C: After application of Vogelxo, the application site was washed (application site washed).

Inclusion Criteria

Subjects who met all of the following criteria were included in the study:

1. Non-smokers aged 18 to 65 years, inclusive.
2. Subjects were male (dosed) and non-pregnant and not breast feeding females (non-dosed only). Non-pregnancy was confirmed by a serum pregnancy test conducted at screening and prior to entering the clinic on Day -1.
3. Female subjects were:
    a. Postmenopausal (no menses) for at least 1 year and having a follicle stimulating hormone (FSH) level 40 mIU/mL; or
    b. Surgically sterile (bilateral tubal ligation, bilateral oopherectomy, or hysterectomy at least 6 months prior to study drug administration).
4. Had a body mass index (BMI) between 18 and 32 kg/m2, inclusive, and weighed at least 110 lbs.
5. Generally healthy as documented by the medical history, physical examination (PE; including but not limited to an evaluation of the cardiovascular, gastrointestinal, respiratory, and central nervous systems and a digital rectal exam for males only), vital sign assessments, clinical laboratory assessments including a prostate-specific antigen (PSA) analysis for males, and by general observations. Any abnormalities/deviations from the acceptable range that might have been considered clinically relevant by the study physician were evaluated on an individual basis, documented in study files, and agreed upon by the

Qualified Investigator (QI; or Sub- Investigator) and Sponsor prior to enrolling the subject in this study.
6. Male subjects had a screening PSA between 0-2.5 ng/mL for subjects ≤50 years of age and between 0-4 ng/mL >50 years of age.
7. Was willing to participate in each study period.
8. Female subjects were deemed to have adequate venous access for drawing blood.
9. Was able to communicate effectively with study personnel and was considered reliable, able, willing and cooperative with regard to complying with protocol-defined requirements as assessed by the study investigator.
10. Voluntarily gave written informed consent to participate in the study prior to the initiation of any study-related procedures.

Exclusion Criteria
Subjects who met any of the following criteria were excluded from the study:
1. Had a clinically relevant current illness (within 4 weeks prior to dosing) or history that would have interfered with the subject's ability to complete the study or would have confounded the results of this study, as determined by the clinical investigator(s), including diabetes mellitus, clinically significant (CS) hypertension, or circulatory disease.
2. Had a history of significant skin conditions or disorders on or around the application site, for example, psoriasis, atopic dermatitis, etc.
3. Had significant dermatitis, tattoos, scars or any other skin disorder at the protocol-specified application/rubbing site.
4. Had an open sore(s) or abrasion(s) at the skin contact site(s).
5. Had a history of sensitivity/allergy to exogenous testosterone, soy, soybeans, soya lecithin, testosterone USP (which may be synthesized from soy) or other related drugs or to the ingredients found in the test formulations.
6. Had a significant history of sensitivity/allergy to soaps, lotions, emollients, ointments, creams, cosmetics, or topical alcohol.
7. Had 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.
8. Had used prescription or over-the-counter (OTC) topical medications on the test sites within 1 month prior to dosing.
9. Had taken a prescription medication within 14 days prior to dosing or taken OTC oral preparations, including dietary and herbal supplements, within 3 days prior to dosing.
10. Had taken oral or transdermal testosterone replacement therapy or estrogens within 30 days prior to dosing.
11. Had used any drugs known to induce or inhibit hepatic drug metabolism (examples of inducers: barbiturates, carbamazepine, phenytoin, glucocorticoids [topical steroid use was evaluated on a case-by-case basis by the Investigator], omeprazole; examples of inhibitors: antidepressants [SSRI], cimetidine,

diltiazem, macrolides, imidazoles, neuroleptics, verapamil, fluoroquinolones, antihistamines) within 30 days prior to dosing or throughout the study.

12. Had taken an injectable or intramuscular testosterone replacement therapy or implants, anabolic steroids, anti-androgens (Casodex, Euflex), or prostate cancer treatment (Lupron, Zoladex) within 6 months prior to dosing.
13. Had used finasteride, ketoconazole, prednisone, opioids, dehydroepiandrosterone (DHEA; or other testosterone precursors) or other medications, which may have interfered with the production, metabolism or disposition of testosterone within 30 days prior to dosing.
14. Was planning to use any exclusionary prescription medications that may have affected testosterone levels (digoxin [Lanoxin]; spironolactone [Aldactone]; barbiturates; anti-epileptic drugs [Dilantin]; anti-depressants [Paxil, Effexor, Prozac, Zoloft, Luvox, Celexa, Cipralex]; antipsychotic agents [Risperdal, Zyprexa, Haldol], propranolol, and insulin) within 14 days prior to dosing or throughout the study.
15. Had participated in another clinical trial with an investigational drug within 30 days prior to dosing.
16. Had a history of coagulation disorders or use of anticoagulant therapy.
17. Had a history of carcinoma of the breast.
18. Male subjects having a history of prostate cancer or benign prostatic hyperplasia (BPH); if over the age of 50, having a history of BPH symptoms (urinary hesitancy, urinary urgency, or weak stream, dysuria, frequent urination).
19. Had electrocardiogram (ECG) abnormalities (CS), or systolic blood pressure of 140 mm Hg or diastolic blood pressure of □90 mm Hg, or heart rate <50 or >100 bpm.
20. Had a history of malignancy.
21. Had diabetes mellitus (even if on stable dose[s] of medication).
22. Had a history of nephrolithiasis or ureterolithiasis.
23. Had an alanine aminotransferase (ALT) or aspartate aminotransferase (AST) greater than 1.5 times the upper limit of normal.
24. Had an active neurological disorder.
25. Female subjects having a history of complications from venipunctures.
26. Had a positive test for human immunodeficiency virus (HIV), hepatitis B, or hepatitis C.
27. Female subjects having donated plasma (500 mL) within 7 days prior to drug administration. Donation or loss of whole blood (excluding the volume of blood drawn during the screening procedures of this study) prior to administration of the study medication corresponded as follows: 50 mL to 499 mL of whole blood within 30 days, or more than 499 mL of whole blood within 56 days prior to drug administration.
28. Had CS abnormal laboratory values.
29. Had regularly used alcohol within six months prior to the screening visit (more than fourteen units of alcohol per week [1 Unit = 150 mL of wine, 360 mL of beer, or 45 mL of 40% alcohol]), or positive urine alcohol screen.

30. Had used 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.

Study Drug
Vogelxo (testosterone) gel (50 mg testosterone per 5.0 g tube) applied topically as a single dose on dosed subjects, batch number 64540A.

Statistical and Analytical Plan
Serum sample data were analyzed to evaluate testosterone concentrations in non-dosed female subjects after skin-to-skin contact with the dosed male subject, in the presence and absence of clothing on the application site, and after the application site had been washed. Uncorrected and baseline-corrected testosterone concentrations obtained from serum samples were presented for each scheduled time point. Baseline-corrected levels of testosterone concentrations obtained from serum samples were summarized, in the presence of clothing, in the absence of clothing, and after the application site had been washed, using descriptive statistics.

Adverse Events
All adverse events were captured and recorded from the time the written study-specific informed consent was obtained until completion of the final study visit. Information collected on these adverse events included the nature, date and time of onset, date and time of resolution, severity, duration, relationship, and outcome of the event. The study center recorded all adverse events observed, queried, or spontaneously volunteered by the subjects. Regardless of whether an adverse event was assessed by the Investigator as not being reasonably attributable to the study drug, its occurrence was recorded in the source documents and captured in the database.

Study Results
The results of this study are discussed in section 7.4.5.3 A Randomized, Single-Center, Open-Label, Three-Way, Crossover Study of the Transferability of Upsher-Smith Laboratories, Inc. Testosterone Gel 1% During Skin-to-Skin Contact With Clothing, Without Clothing, and After Washing (Study P10-003).

6 Review of Bioequivalence

Summary

The efficacy of Vogelxo was not evaluated in a clinical study. Instead, the efficacy of Vogelxo was established by the pivotal bioequivalence study (Study P06-011) showing that it is bioequivalent to Testim, the reference listed drug. Testim is a FDA approved testosterone gel that was shown to be an effective treatment for hypogonadal males in an active and placebo controlled study of 406 adult males with morning testosterone levels less than or equal to 300 ng/dL. A study showing that Vogelxo provides

equivalent blood levels of testosterone to Testim is reasonable support for the conclusion that Vogelxo is also an effective treatment for this indication.

6.1 Pilot Bioequivalence Study P06-001

Before conducting the pivotal bioequivalence study, the Sponsor studied three preliminary testosterone 1% topical gel formulations, which included Vogelxo. Study P06-001 was a randomized, open-label, 4-way crossover pilot study to compare the bioavailability of three different testosterone 1% topical gel formulations by Upsher-Smith Laboratories versus Testim in hypogonadal male volunteers.

Study Results
In this study, bioequivalence was to be concluded if the 90% geometric confidence intervals of the ratio (testosterone 1% topical gel test formulation/Testim) of the least-squares means for ln-transformed area under the concentration-time curve from time 0 to the last measured concentration (AUC_{0-t}) and maximum serum concentration (C_{max}) were within the acceptable range of 80.00% to 125.00% for baseline-corrected, dose non-normalized data.

The study met the bioequivalence criteria for Test Formulation A (Vogelxo) compared to the reference product (Testim) as the 90% geometric confidence intervals were within the acceptance range for AUC_{0-t} and C_{max}. Neither Test Formulation B nor Test Formulation C met the bioequivalence criteria. The pharmacokinetic parameters for baseline corrected data, least squares means ratios, and 90% geometric confidence intervals for Test Formulation A (Vogelxo) and the reference product (Testim) are summarized in Tables 10 and 11.

Table 10: Pharmacokinetic Parameters for Baseline Corrected Data (Study P06-001)

Parameter	Vogelxo	Testim
AUC_{0-t} (SD) pg·h/mL	40063.98 (26722.49)	37390.26 (20804.00)
C_{max} (SD) pg/mL	2375.21 (1283.01)	2514.33 (1292.35)

Source: NDA 204399, Module 5.3.1.2, CSR P06-001, Tables 1 and 2, pp. 66-67.

Table 11: Least Squares Means Ratios, 90% Geometric CI (Study P06-001)

	Ratio[1]	90% Geometric CI[2]
AUC_{0-t} (Vogelxo vs Testim)	103.41%	87.10, 122.78
C_{max} (Vogelxo vs Testim)	94.77%	81.45, 110.27

[1]Calculated using least-squares means of Vogelxo/Testim.
[2]90% Geometric Confidence Interval using ln-transformed data.
Source: NDA 204399, Module 5.3.1.2, CSR P06-001, Tables 2 and 4, pp. 67-68.

***Reviewer's Comment**: This study provides support that a 50 mg dose of Vogelxo is bioequivalent to a 50 mg dose of Testim.*

Adverse Events
No deaths or serious adverse events were reported during this study.

A total of 78 post-dose adverse events occurred during the study. Of these adverse events, 61 were judged to be potentially related to the study medication.

The most commonly reported treatment-emergent adverse event (TEAE) across treatments (Test Formulations A, B, and C and Testim) was application site erythema, all of which were considered to be at least possibly related to treatment.

TEAEs that occurred at a higher incidence for Test Formulation A (Vogelxo) compared with Test Formulation D (Testim) were application site erythema (5 subjects [20.0%] vs. 2 subjects [8.3%]), blood pressure increased (3 subjects [12.0%] vs. 1 subject [4.2%]), and headache (2 subjects [8.0%] vs. 0).

A total of four individual TEAEs (by preferred term) were considered to be at least possibly related to Vogelxo or Testim, including application site erythema (5 subjects [20.0%] vs. 2 subjects [8.3%]), blood pressure increased (3 subjects [12.0%] vs. 1 subject [4.2%]), headache (2 subjects [8.0%]), and ALT increased (0 vs. 1 subject [4.2%];). The most commonly reported treatment-related TEAE across the Vogelxo or Testim treatment groups was application site erythema (7 events), all of which were mild in severity.

Reviewer's Comment*: The number of subjects reporting "Application Site Erythema" in the Vogelxo treatment group was higher than in the Testim treatment group (5 vs. 2). The severity of each of the 7 cases was assessed as mild by the investigator and resolved spontaneously. Application site irritation was further assessed by the prospective evaluations of application site irritation discussed below.*

Because of the small number of adverse events reported for each preferred term, it is difficult to draw any conclusions from the comparison of adverse events between Vogelxo and Testim.

Application Site Irritation
This study included prospective evaluations of application site irritation, but the data was not analyzed statistically. The irritation scores are summarized in Table 12.

Table 12: Summary of Irritation Evaluation Scores Post-Dosing (Study P06-001) (Safety Population)

Treatment	Total Number of Application Sites Scored	Scores, n (%)			
		0	1	2	3
Vogelxo	123	115 (93.5)	8(6.5)	0	0
Testim	117	114(97.4)	3(2.6)	0	0

Source: NDA 204399, Module 2.7.4, Summary of Clinical Safety, Table 21, p. 55.

***Reviewer's Comment**: The irritation scores for Vogelxo and Testim were similar. There was no score greater than 1 (minimal erythema, barely perceptible) for either product.*

Conclusions
The study met the bioequivalence criteria following the comparison of Test Formulation A (Vogelxo) and the reference product (Testim) as the 90% geometric confidence intervals were within the acceptance range for AUC_{0-t} and C_{max}.

All formulations were well tolerated, with no major side effects and no relevant differences in safety profiles were observed between the preparations, particularly with respect to the number and pattern of adverse events.

***Reviewer's Comment**: This was a pilot bioavailability/bioequivalence study to assess three formulations of testosterone gel 1% by the Sponsor. Only one of the formulations, Vogelxo, was found to have acceptable bioequivalence to Testim in this study.*

The adverse events reported during Study P06-001 did not raise any new safety issues regarding Vogelxo. The prospective evaluations of application site irritation were similar for Vogelxo and Testim. No score for either product indicated irritation that was greater than minimal, barely perceptible erythema.

Bioequivalence was demonstrated in the pivotal bioequivalence study (Study P06-011) using a 100 mg (two 5 gm tubes) dose of the test products. The current study provides data which support that a 50 mg dose of Vogelxo is bioequivalent to a 50 mg dose of Testim.

6.2 Bioequivalence Study P06-011

The Sponsor submitted Study P06-011 as evidence that Vogelxo and Testim are bioequivalent. The study design is discussed in Section 5.3.2 *Bioequivalence Study P06-011*. The results of the study are discussed in this section.

6.2.1 GCP and GLP Certification

Serge St. Lauren, M.Sc., the Director of Quality Assurance, certified that the study was conducted in accordance with Good Clinical Practice (GCP) and Good Laboratory Practices (GLP).

6.2.2 Demographics

The demographics of the study subjects are presented in Table 13.

Table 13: Summary of Subject Demographics (Study P06-011)

Parameter	Age (years)	Height (cm)	Weight (kg)	BMI (kg/m2)
Mean (SD)	47 (10)	173.9 (6.4)	85.7 (10.2)	28.3 (2.6)
Range	25 - 66	160.5 – 190.5	67.1 – 107.5	22.3 – 34.4
Median	47	173.2	84.7	28.4

Source: NDA 204399, Module 5.3.1.2, CSR P06-011, Table 11.1, p. 52.

***Reviewer's Comment**: The subjects studied were reasonably representative of the patient population expected to use Vogelxo.*

6.2.3 Subject Disposition

Eighty-four (84) male subjects were randomized and applied the study medication on at least one occasion. Of those 84, 73 subjects completed the study; their serum samples were then assayed for testosterone. Fifteen (15) of the 73 subjects completing the study had a mean baseline serum testosterone concentration greater than 350 ng/dL for at least one period and were, therefore, excluded from the statistical analysis. The disposition of subjects in the study is summarized in Table 14.

Table 14: Summary of Subject Disposition (Study P06-011)

Disposition	n	
Subjects Randomized		84
Subjects Withdrawn by the Investigator or Sponsor	5	
Subjects Who Withdrew Consent	6	
Subjects Who Successfully Completed the Study		73

Source: NDA 204399, Module 5.3.1.2, CSR P06-011, Table 10.2, p. 47.

Of the 5 subjects that were withdrawn by the investigator or Sponsor, 2 (Subjects 74 and 77) were withdrawn due to an adverse event, 2 (Subjects 39 and 58) were withdrawn due to a positive drug test, and 1 (Subject 46) was withdrawn due to bad veins.

Subject 74 was withdrawn due to an ALT of 84 U/L (normal range 0-41 U/L) at check-in for period 3. The subject's ALTs were 45, 51, and 39 U/L at screening, check-in for period 1, and check-in for period 2, respectively. The subject's ALT returned to 45 U/L at the post-study assessment.

Subject 77 was withdrawn due to an ALT of 83 U/L (normal range 0-41 U/L) at check-in for period 4. The subject's ALTs were 48, 51, 41, and 41 U/L at screening, check in for period 1, check-in for period 2, and check-in for period 3, respectively. The subject's ALT was 49 U/L at the post-study assessment.

Reviewer's Comment*: Both Subject 74 and Subject 77 were withdrawn due to an ALT level that was greater than 1.5 times the upper limit of normal, which was an exclusion criterion for the study (Exclusion Criterion #24). It is not possible to determine causality to the study drug from the information provided in the study report, but it cannot be ruled out either.*

6.2.4 Pharmacokinetic Procedures

Eighty-four (84) subjects were applied the study medication on at least one occasion. Seventy-three (73) individuals completed the study. The serum samples from these 73 subjects were assayed for testosterone. Subjects 03, 04, 05, 10, 15, 20, 24, 36, 40, 45, 49, 50, 65, 71, and 76 had a mean baseline testosterone serum concentration higher than 350 ng/dL for at least one period. Therefore, these subjects were excluded from the statistical analysis.

Statistical and pharmacokinetic analyses for testosterone were performed on data from 58 subjects: subjects 01 to 28 were dosed in group 1, subjects 29 to 54 were dosed in group 2, and subjects 55 to 84 were dosed in group 3.

Scheduled sampling times were used to calculate pharmacokinetic parameters when the difference between the scheduled and actual sampling times was less than 1 minute. If the difference exceeded this time limit, the actual sampling times were used to calculate pharmacokinetic parameters, except for pre-dose samples.

For any sample, when no concentration was reported, NRV (no reportable value) was recorded in concentration tables. Samples that were not available were recorded as SNO (sample not obtained) in the concentration tables. Samples that were judged unacceptable were recorded as DEV (unacceptable sample due to a protocol deviation) in the concentration tables. All of these samples were set as missing for pharmacokinetic and statistical analyses.

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

Mean baseline testosterone concentrations were calculated for each subject by averaging the 4 pre-dose values (-12.0, -8.00, -4.00 hours and pre-dose (0 hour)) for each period. All concentrations, including the pre-dose concentration for each subject

and period, were corrected for the mean of the 4 pre-dose concentrations. Any negative concentration obtained after correction was set equal to zero.

Drug concentration-time data were used to calculate the following pharmacokinetic parameters:

AUC_{0-24}	Area under the concentration versus time curve from time 0 to the 24 hour concentration; calculated using linear trapezoidal rule.
AUC_{0-t}	Area under the concentration versus time curve from time 0 to the last measured concentration (C_{last}); calculated using linear trapezoid rule.
AUC_{0-inf}	Area under the concentration versus time curve from time 0 to infinity; calculated as $AUC_{0-t} + C_{last}/ K_{el}$, where C_{last} is the last concentration above the lower limit of quantitation for the assay.
C_{max}	Maximum serum concentration; the highest concentration observed during a dosage interval.
$AUC_{t/inf}$	The ratio of AUC_{0-t} on AUC_{0-inf}
T_{max}	Time of observed C_{max}. In the event that C_{max} occurs at more than one time point, the earliest value will be reported
$T_{1/2el}$	Terminal elimination half-life; calculated as $ln(2)/ K_{el}$
K_{el}	The terminal elimination rate constant; calculated using linear regression on the terminal portion of the ln-concentration versus time curve.

6.2.5 Statistical Analyses

For baseline-corrected data of testosterone, ln-transformed AUC_{0-24}, AUC_{0-t}, AUC_{0-inf} and C_{max} and untransformed T_{max}, K_{el} and $T_{1/2\ el}$ were analyzed using PROC MIXED in SAS.

Due to physiological fluctuation of endogenous levels of testosterone, the elimination rate constant was not properly characterized for 55 of the 58 eligible subjects, for baseline-corrected data. Therefore, no statistical analysis was done on ln-transformed AUC_{0-inf} and untransformed K_{el} and $T_{1/2\ el}$.

Bioequivalence was evaluated using baseline-corrected, non-dose-normalized ln-transformed AUC_{0-24} and C_{max}. The 90% geometric confidence intervals of the ratio (A/B) of least-squares means from the linear mixed effect analysis of the ln-transformed AUC_{0-24}, and C_{max} should be within 80.00% to 125.00%.

6.2.6 Results

Eighty-four (84) subjects began the study and 73 subjects completed the clinical portion of the study in its entirety. Fifteen (15) subjects had a mean baseline testosterone serum concentration greater than 350 ng/dL during at least one dosing period. Therefore, these subjects were excluded from the pharmacokinetic analysis. The serum samples from 58 subjects with a mean baseline testosterone concentration < 350 ng/dL

(3500 pg/mL) during all four dosing periods were included in the determination of bioequivalence.

The results for the ln-transformed baseline-corrected data for Vogelxo (Test A) and Testim (Test B) are summarized in Table 15.

Table 15: Summary of Ln-Transformed PK Parameters (Study P06-011)

	Ratio[1]	90% Geometric CI[2]	
		Lower	Upper
AUC_{0-t}	110.64%	104.19%	117.49%
AUC_{0-24}	110.42%	104.55%	116.61%
C_{max}	103.79%	96.90%	111.18%

[1]Calculated using least-squares means.
[2]90% Geometric CI using ln-transformed data
Source: NDA 204399, Module 5.3.1.2, CSR P06-011, Table 11.2, p. 56.

The 90% confidence intervals about the ratio of the test (Vogelxo) geometric mean to the reference (Testim) geometric mean were within the 80.00% to 125.00% limits for AUC_{0-t}, AUC_{0-24} and C_{max}.

Adverse Events
No deaths or other serious adverse events occurred during the study.

Overall, a total of 201 treatment emergent adverse events (TEAEs) occurred over the course of the study. The incidence of TEAEs was similar between treatment groups (60.5% for Vogelxo [Treatment A] and 60.2% for Testim [Treatment B]. All TEAEs that were assigned a severity grading were mild or moderate in severity.

For both treatment groups, TEAEs were most commonly reported in the System Organ Class (SOC) of General Disorders and Administrative Site Conditions (48.1% for Vogelxo and 36.1% for Testim). The most commonly reported TEAEs across all treatments were application site erythema (25 subjects, 28 events) and application site reaction (21 subjects, 24 events).

Of the 201 post-dose TEAEs reported, the majority (134 of 203 events, 66.7%) were considered to be not related (70 events) or unlikely related (64 events) to study drug. Forty-eight (48) TEAEs were considered to be possibly related and 19 were considered probably related to the study drugs by the Investigator.

The incidence of treatment-related TEAEs (possibly or probably related) was similar between Vogelxo (33.3%) and Testim (30.1%). The most commonly reported treatment-related TEAE in both groups was application site erythema, which occurred at a similar incidence in the Vogelxo (13.6%) and Testim (12.0%) groups.

***Reviewer's Comment**: Five subjects reported 5 events of "blood pressure increased" that were considered treatment-related by the investigator (4 for Vogelxo, 1 for Testim). For each of the 5 events, resolution was reported as "spontaneous" and the maximal severity was considered "mild" by the investigator.*

The adverse events reported during Study P06-011 did not raise any new safety issues for Vogelxo.

Application Site Irritation
This study included prospective evaluations of application site irritation. Application site irritation was evaluated for subjects in the Safety Population (N=84) after administration of both Vogelxo and Testim. The irritation scores are summarized in Table 16.

Table 16: Summary of Irritation Evaluation Scores Post-Dosing (Study P06-011) (Safety Population)

Treatment	Total Number of Application Sites Scored	Scores, n (%)			
		0	1	2	3
Vogelxo	1539	1482 (96.3)	50 (3.25)	7 (0.45)	0 (0)
Testim	1533	1590 (96.4)	47 (3.0)	8 (0.5)	2 (0.1)

Source: NDA 204399, Module 2.7.4, Summary of Clinical Safety, Table 22, p. 56.

***Reviewer's Comment**: In this study, the irritation scores for Vogelxo and Testim were similar. No score was greater than 2 (definite erythema, readily visible; minimal edema or minimal papular response) for Vogelxo.*

6.2.7 Bioequivalence Conclusions
Based on the data submitted in this application, it is this reviewer's opinion that this study provided acceptable evidence of bioequivalence of Vogelxo and Testim.

In addition, the adverse events reported during the study and the evaluation of application site irritation conducted during the study did not raise any new safety concerns for Vogelxo.

7 Review of Safety

Safety Summary

The safety of Vogelxo was not evaluated in a clinical trial. Instead, the safety of the drug product was established by demonstrating its bioequivalence to Testim, the reference listed drug (RLD), in the pivotal bioequivalence study (Study P06-011). Testim was approved in 2002 under NDA 021454. It was evaluated in a randomized multicenter, multi-dose, active and placebo controlled 90-day study in 406 adult males with morning testosterone levels $\leq$ 300 ng/dL and found to be safe and effective for testosterone replacement therapy in adult males with primary hypogonadism and hypogonadotropic

hypogonadism. A study showing that Vogelxo is bioequivalent to Testim provides reasonable support for the conclusion that Vogelxo is safe for testosterone replacement therapy in adult males with primary hypogonadism and hypogonadotropic hypogonadism.

In addition, because the formulation of Vogelxo differs from the RLD with respect to only inactive ingredients, three safety studies were conducted to assess formulation dependent areas of safety. Study P08-001 evaluated the cumulative irritation and sensitization of the skin produced by Vogelxo compared with Testim, Study P10-002 evaluated the removal of Vogelxo from the hand used for application after washing with soap and water, and Study P10-003 evaluated the transfer of testosterone from a treated male to an untreated female via skin contact.

Thus, the safety of Vogelxo was determined by demonstrating it was bioequivalent to Testim in Study P06-011 and that the formulation dependent safety parameters were acceptable in Studies P08-001, P10-002, and P10-003.

Reviewer's Comment*: Based on the results of the three studies that assessed formulation dependent safety, this reviewer concludes that:*

- *Vogelxo has been shown to be safe with respect to skin irritation and sensitization.*
- *Hand washing was an effective method for removing most of the residual testosterone from the hand after application of Vogelxo.*
- *Skin-to-skin transfer of testosterone from a male dosed with Vogelxo to a non-dosed female can be effectively mitigated by wearing a cotton t-shirt or by washing the site of application after the drug is applied.*

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

In addition to the bioequivalence studies (Studies P06-001 and P06-011) described in Section 5.1, three safety studies were conducted to evaluate the formula dependent area of safety. The safety studies are listed in Table 17.

Table 17: Studies Performed to Evaluate Formulation-Dependent Safety

Type of Study	Study Number	Study Objective	Study Design	Test Product	N	Type of Subjects
Skin Irritation and Sensitization	P08-001	To evaluate the cumulative irritation and sensitization produced by Vogelxo compared with Testim on the skin	Randomized, double-blind	Vogelxo Testim 1%	225	Healthy male volunteers
Residual Testosterone after Hand Washing	P10-002	To assess the removal of Vogelxo from hands after washing with soap and water	Randomized, open-label, 3-way crossover study	Vogelxo	36	Healthy male volunteers
Interpersonal Transfer of Testosterone	P10-003	To evaluate the transfer of testosterone from a treated male to an untreated female via skin contact	Randomized, open-label, 3-way crossover study	Vogelxo	48 males 48 female	Healthy volunteers

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

7.2 Adequacy of Safety Assessments

In the opinion of this reviewer, the finding of bioequivalence to the RLD, Testim, the Agency's prior finding of safety for the RLD, and the formulation-dependent safety studies that were submitted provide an adequate evaluation of the safety of Vogelxo.

7.3 Major Safety Results

7.3.1 Deaths

No deaths were reported during the bioequivalence or formulation dependent safety studies submitted with the NDA.

7.3.2 Nonfatal Serious Adverse Events

One subject reported a serous adverse event (SAE) during the skin Irritation and sensitization study (Study P08-001). Subject 070, a 21-year-old male, reported the SAE of ruptured spleen and broken clavicle during Study P08-001. The SAE resulted from a bicycle accident and was assessed by the Sponsor as not being related to treatment.

No other SAEs were reported during the bioequivalence or safety studies.

Reviewer's Comment*: This reviewer agrees with the Sponsor's assessment of the SAE reported in Study P08-001.*

7.4 Supportive Safety Results

7.4.5 Special Safety Studies/Clinical Trials

Three safety studies were conducted for Vogelxo. Study P08-001 evaluated the irritation and sensitization potential of Vogelxo, Study P10-002 evaluated the removal of Vogelxo by hand washing, and Study P10-003 evaluated the potential for transfer of Vogelxo between dosed-males and non-dosed females after skin-to-skin contact. The safety studies are listed in Table 17. The design of each study is presented in section 5.3 Discussion of Individual Studies/Clinical Trials. The results of each study are discussed in this section.

7.4.5.1 A Study to Evaluate the Irritation and Sensitization Potential of Repeat Application of Vogelxo and Testim Gel 1% in Healthy Human Subjects (Study P08-001)

This was a single-site, randomized, double-blind study of healthy adult male subjects. During the induction phase, Vogelxo, Testim, a positive control, and a low irritant control were applied under occlusive conditions to 4 sites on both upper outer arms and evaluated for irritation response for 21 days. Following a rest phase, the subjects were dosed with all four treatments on four sites on the upper back, which were evaluated for sensitization to Vogelxo and Testim.

Study Subjects

Four hundred twenty-six (426) potential subjects, all male, were screened for eligibility for inclusion in the study. Two-hundred fifty five (255) subjects, ages 18 - 63 years, were enrolled into the study. Table 18 summarizes the disposition of the patients.

Table 18: Subject Disposition (Study P08-001)

	n	
Total number of subjects enrolled		255
Total number of premature discontinuations		26
Discontinued by investigator subsequent to adverse event	3	
Subject elected to withdraw due to application site irritation	0	
Subject elected to withdraw	5	
Subjects discontinued due to screening labs out of range	4	
Subjects discontinued due to non-compliance with study schedule	14	
Safety Population Total		255
Evaluable Population (Irritation)		255
Evaluable Population (Sensitization)		229

Source: NDA 204399, Module 5, CSR P08-001, Table 10-1, p. 43.

Three subjects (Subjects 070, 143, and 169) were discontinued due to an adverse event.

Subject 070 reported 2 serious adverse events (SAEs), ruptured spleen and broken clavicle, that were due to a bicycle accident. The relationship of the events to the study drug was considered unlikely or none.

Subject 143 reported the adverse event of chest pain, which was treated with one dose of nitroglycerin and one dose of aspirin. The relationship of the event to the study drug was considered unlikely or none.

Subject 169 reported the adverse event of folliculitis, which was treated with Keflex. The relationship of the event to the study drug was considered unlikely or none.

Reviewer's Comment*: It is unlikely that the study drug was related to the adverse events that resulted in discontinuation of Subjects 070, 143, and 169.*

Study Demographics
The demographics of the study population are summarized in Table 19.

Table 19: Summary of Subject Demographics (Study P08-001)
(N = 255)

Parameter	Statistic	Value
Age (years)	Mean (SD) Range	29.6 (11.3) 18 – 63
Weight (lbs.)	Mean (SD) Range	196.6 (37.1) 119.0 – 297.0
Height (in.)	Mean (SD) Range	70 (2.7) 62.0 – 81.0
BMI	Mean (SD) Range	28.2 (4.8) 18.9 – 39.2
Sex	Male Female	255 (100%) 0 (0%)
Hispanic	American Indian or Alaska Native Asian Black or African American Hawaiian or Other Pacific Islander White Other	3 (1.18%) 0 (0.00%) 0 (0.00%) 0 (0.00%) 8 (3.14%) 0 (0.00%)
Non-Hispanic	American Indian or Alaska Native Asian Black or African American Hawaiian or Other Pacific Islander White Other*	4 (1.57%) 3 (1.18%) 9 (3.53%) 1 (0.39%) 226 (88.63%) 1 (0.39%)

*Other= More than one race
Source: NDA 204399, Module 5.3.3.1.1, CSR P08-001, Table 11-3, page 48; Appendix 16.2.4, page 1162.

***Reviewer's Comment**: Over 88% of the subjects in this study were white. Other racial groups were under represented.*

Study Results
Cumulative Irritation Assessment
The null hypothesis was rejected for the hypothesis test comparing Vogelxo to Testim for the converted cumulative irritation evaluation scores (the upper bound of the one-sided 95% confidence interval is less than or equal to zero). This indicates "the test product (Vogelxo) is non-inferior to the reference product (Testim) in irritation" in the Intent-To-Treat population. The results of the statistical analysis are summarized in Table 20.

Table 20: Summary of Cumulative Irritation Analysis (Study P08-001)
Intent-To-Treat Population (N = 255)

Variable	Hypotheses	Upper Bound of One-Sided 95% CI	Description of Observed Response
Converted Cumulative Irritation Evaluation Scores	H_O: $\mu_T - 1.25\ \mu_R > 0$ H_1: $\mu_T - 1.25\ \mu_R \leq 0$	-7.9230	This suggests the test product is non-inferior to the reference product in irritation.

Source: NDA 204399, Module 5.3.3.1.1, CSR P08-001, Table 11-4, page 49.

Statistical analysis of the data comparing the converted cumulative irritation evaluation scores indicated that the test product (Vogelxo) is no more irritating than the reference product (Testim) when topically applied over a continuous 21-day period.

The total numbers of converted irritation evaluation scores received during the induction phase of the study are summarized by treatment in Table 21.

Table 21: Summary of Total Converted Irritation Evaluation Scores (Study P08-001)
Intent-To-Treat Population (N = 255)

Treatment	Scores, n(%)				
	0	1	2	≥3	Total Sites Scored
A	2642 (49.3%)	2563 (47.9%)	129 (2.4%)	21 (0.4%)	5355
B	1658 (31.0%)	3342 (62.4%)	302 (5.6%)	53 (1.0%)	5355
C	363 (6.8%)	1003 (18.7%)	3627 (67.7%)	362 (6.8%)	5355
D	3310 (61.8%)	1915 (35.8%)	100 (1.9%)	30 (0.6%)	5355

Treatment A: Vogelxo
Treatment B: Testim
Treatment C: Positive Irritant Control (0.05% sodium lauryl sulfate)
Treatment D: Low Irritant Control (0.9% aqueous sodium chloride)
Source: NDA 204399, Module 2.7.4, Summary of Safety Information, Table 23, page 57.

The majority (range: 93.2% to 99.6%) of scores for all treatments were less than 3. The incidence of scores ≥3 during the induction phase in the Vogelxo group (0.4%) was similar to the low irritant control (0.6%), both of which were lower than the incidence observed for the Testim group (1.0%); as expected, the incidence was higher for the positive irritant control (6.8%).

The mean converted irritation scores collected by treatment and score received for all subjects included in the intent-to-treat population (N=255) during the induction phase are summarized in Table 22.

Table 22: Summary of Converted Irritation Evaluation Scores (Study P08-001)
Intent-To-Treat Population (N = 255)

	Treatment A	Treatment B	Treatment C	Treatment D
N	5355	5355	5355	5355
Mean	0.54	0.77	1.74	0.41
Standard Deviation	0.57	0.59	0.68	0.56
Median	1	1	2	0
Minimum	0	0	0	0
Maximum	3	3	3	3

Treatment A: Vogelxo
Treatment B: Testim
Treatment C: Positive Irritant Control (0.05% sodium lauryl sulfate)
Treatment D: Low Irritant Control (0.9% aqueous sodium chloride)
Source: NDA 204399, Module 5.3.3.1.1, CSR P08-001, Table 11-6, page 49.

When comparing the total mean irritation score for each treatment during the induction phase, the positive irritant control had the highest score with a total mean score (± standard deviation) of 1.74 ± 0.68 compared with Vogelxo (0.54 ± 0.57), Testim (0.77 ± 0.59), and the low irritant control (0.41 ± 0.56), which produced similar mean scores. These data indicate that Vogelxo, Testim, and the low irritant control produced very mild irritation.

The number of subjects requiring that an application site be moved due to test article irritation, and the number of days from the initial application to the required change in application site is summarized in Table 23.

Table 23: Application Site Changes Summarized by Treatment (Study P08-001)
Intent-To-Treat Population

Treatment	Subjects requiring application site change (N=255) n(%)	Number of days from initial application to application site change Days (range)
Vogelxo	4 (1.6)	12-20
Testim	6 (2.4)	5-18
Positive Irritant Control (0.05% sodium lauryl sulfate)	37 (14.5)	4-19
Low Irritant Control (0.9% aqueous sodium chloride)	3 (1.2)	7-18

Source: NDA 204399, Module 2.7.4, Summary of Safety Information, Table 24, page 58.

The proportion of subjects requiring an application site change due to irritation in the Vogelxo group (1.6%) was similar to the low irritant control (1.2%), both of which were lower than the Testim group (2.4%); the proportion was highest in the positive irritant control (14.5%), which was expected.

Based on the study data, the Sponsor concluded that the irritation properties of Vogelxo were no more irritating than the reference product, Testim.

***Reviewer's Comment**: This reviewer agrees that the irritation potential of Vogelxo is similar to that of Testim.*

Sensitization Assessment

Results from the sensitization data were collected for all subjects that were qualified to continue to the challenge phase of the study (N=229). In the challenge phase any subject with a converted score of 2 or more at 48 hours post-patch removal was considered to be potentially sensitized and was re-challenged at least 3 to 4 weeks after the conclusion of the challenge phase to confirm the sensitization reaction.

The total numbers of converted sensitization evaluation scores received during the challenge phase of the study are summarized by treatment in Table 24.

Table 24: Total Converted Sensitization Evaluation Scores (Study P08-001) Per-Protocol Population (N = 229)

Treatment	Scores, n(%)					
	0	0.5	1	2	3	Total Sites Scored
A	587 (64.1%)	298 (32.5%)	22 (2.4%)	2 (0.2%)	7* (0.8%)	916
B	557 (60.8%)	317 (34.6%)	31 (3.4%)	7 (0.8%)	4** (0.4%)	916
C	554 (60.5%)	339 (37.0%)	23 (2.5%)	0	0	916
D	649 (70.9%)	255 (24.6%)	12 (1.3%)	0	0	916

Treatment A: Vogelxo
Treatment B: Testim
Treatment C: Positive Irritant Control (0.05% sodium lauryl sulfate)
Treatment D: Low Irritant Control (0.9% aqueous sodium chloride)
*Two subjects reported a score of 3 for Treatment A (Subject 045 and Subject 079).
**Two subjects reported a score of 3 for Treatment B (Subject 045 and Subject 079).
Source: NDA 204399, Module 2.7.4, Summary of Safety Information, Table 25, page 59.

There were no reaction scores greater than 1 for the positive irritant control and the low irritant control at the 48 hour post-patch removal time point during the challenge phase of the study. Following administration of Vogelxo and Testim, three (1.3%) of 229 subjects had reaction scores greater than 1 at the 48 hour post-patch removal time point during the challenge phase of the study. These were identified as being the same three subjects (Subjects 045, 079, and 114) for both products. All three subjects demonstrating a reaction were contacted for a confirmatory re-challenge. One subject (Subject 114) was not eligible to participate in the re-challenge phase as a result of

being enrolled in another study. The other two subjects were re-challenged with Vogelxo and Testim (greater than 14 days after the initial challenge). Following re-challenge both subjects demonstrated reaction scores of 3 at 0.5, 24, and 48 hours post-patch removal, and a reaction score of 2 or greater 72 hours post-patch removal.

Both subjects demonstrated reactions at the challenge and re-challenge study phases, which is suggestive of sensitization to both Vogelxo and Testim. Results from the sensitization data for all subjects indicate that both Vogelxo and Testim demonstrate a low, but equal propensity for inducing sensitization (i.e., allergic contact dermatitis).

***Reviewer's Comment**: Based on the results of the challenge and re-challenge phase of the study, this reviewer agrees that the sensitization potential of Vogelxo is similar to that of Testim.*

Adverse Events

A total of 121 treatment emergent adverse events (TEAEs) were reported by 67 (26.3%) subjects during the study. No deaths or TEAEs leading to discontinuation were reported. One subject reported 2 SAEs (ruptured spleen and broken clavicle due to bicycle accident) during the study that were considered to be not related to treatment. All TEAEs that were assigned a severity grading were mild or moderate in severity. The most commonly reported TEAEs were application site pruritus (7.5%), pharyngolaryngeal pain (4.3%), and headache (3.9%).

Of the 121 TEAEs reported, 36 were judged to be at least possibly related to the study medication. The possibly related TEAEs are summarized in Table 25.

Table 25: Treatment-related Adverse Events (Study P08-001)
Safety Population

	Overall	
	N=255	
Preferred Term	**n (%)**	**Events**
Application site hyperaesthesia	1 (0.4)	1
Application site irritation	2 (0.8)	2
Application site pain	2 (0.8)	2
Application site pruritus	19 (7.5)	22
Fatigue	1 (0.4)	1
Musculoskeletal stiffness	1 (0.4)	1
Myalgia	2 (0.8)	2
Dysgeusia	1 (0.4)	1
Headache	1 (0.4)	1
Paraesthesia	1 (0.4)	2
Mood altered	1 (0.4)	1

Source: NDA 204399, Module 2.7.4, page 37.

***Reviewer's Comment**: The adverse events reported during Study P08-001 were similar to those seen with other testosterone products and do not raise any new safety issues. Most treatment-related adverse events were treatment site related as expected.*

7.4.5.2 A Randomized, Single-Center, Open-Label, Three-Way Crossover Study of the Removal of Upsher-Smith Laboratories, Inc. Testosterone Gel 1% by Hand Washing (Study P10-002)

This was an open-label Phase 1 study to assess the removal of Vogelxo from the hands of healthy male subjects after washing with soap and water. The design of this study is presented in section 5.3.4 Hand Washing Study P10-002.

Study Subjects
Thirty-six (36) male subjects were randomized and dosed in this study. Of the 36 subjects, 35 completed all treatment periods. One subject was withdrawn from the study in Period 2 due to non-compliance with the study protocol. Each of the 36 subjects randomized applied at least one dose of the study medication and is included in the safety population.

Subject Demographics
The baseline characteristics of subjects included in the skin swab data analysis of the study are summarized in Table 26.

Table 26: Summary of Subject Demographics (Study P10-002)

Parameter	Statistic	Value
Age (years)	Mean ± SD Range	44.4 ± 12.36 19 – 64
Weight (kg.)	Mean ± SD Range	78.88 ± 8.953 59.0 – 96.5
Height (cm.)	Mean ± SD Range	173.46 ± 5.733 163.0 – 188.5
BMI (kg/m^2)	Mean ± SD Range	26.18 ± 2.353 19.8 – 30.9
Sex	Male Female	36 0
Ethnicity	Non-Hispanic Hispanic	27 9
Race	White Black or African American Asian American Indian or Alaska Native Hawaiian or Other Pacific Islander	32 4 0 0 0

Source: NDA 204399, Module 5.3.3.1.3, pages 44-45.

Results

This study quantified the amount of Vogelxo remaining on a subject's hand after applying the drug to the application site, both before and after washing the hand with soap and water. Three treatment groups were defined based on drying time after application of the drug and drying method after washing. The treatment groups are summarized in Table 27.

Table 27: Treatment Groups (Study P10-002)

Treatment	A	B	C
Drying time after application of drug (mins.)	3	3	0
Drying method after washing and rinsing hands	Cloth towel	Air dried (9 mins)	Cloth towel

A dry, porous swab was used to measure the testosterone on the surface of the skin. Skin swab samples of the hand used for application were collected prior to dosing, after application of a 5 g tube of Vogelxo, and after hand washing, and then analyzed for testosterone. The hand used for application was divided into four equal areas of 10 cm^2 and each skin swab sample was collected from a different 10 cm^2 area.

Testosterone levels obtained from the skin swab samples at baseline, before washing, and after washing are summarized in Table 28.

Table 28: Testosterone Level (µg) Obtained From Skin Swab Samples

		Treatment A	Treatment B	Treatment C
Baseline	N	36	35	35
	Mean (SD)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)
	Range	0.0 – 0.0	0.0 – 0.0	0.0 – 0.0
Before Washing	N	36	35	35
	Mean (SD)	58.59 (38.74)	60.54 (41.67)	70.29 (43.58)
	Range	11.23 – 141.86	7.57 – 185.74	10.75 – 174.98
After Washing	N	36	35	35
	Mean (SD)	0.65 (1.03)	0.52 (1.24)	0.16 (0.46)
	Range	0.00 – 3.95	0.00 – 6.61	0.00 – 1.64

Source: NDA 204399, Module 5.3.3.1.3, Table 14.2.1 pages 59-60.

The percentages of the 50 mg dose remaining on the hand after application before and after washing, and the percentage of testosterone remaining on the hand removed by washing, are summarized in Table 29.

Table 29: Percentage of Testosterone on the Hand

		Treatment A	Treatment B	Treatment C
% Dose Remaining on Hand Before Washing[1]	N	36	35	35
	Mean (SD) Range	0.47 (0.31) 0.09 – 1.13	0.48 (0.33) 0.06 – 1.49	0.56 (0.35) 0.09 – 1.40
% Dose Remaining on Hand After Washing[1]	N	36	35	35
	Mean (SD) Range	0.01 (0.01) 0.00 – 0.03	0.00 (0.01) 0.00 – 0.05	0.00 (0.00) 0.00 – 0.01
% Testosterone Removed by Washing[2]	N	36	35	35
	Mean (SD) Range	98.65 (2.32) 92.25 – 100.00	99.02 (2.58) 85.70 – 100.00	99.77 (0.70) 96.96 – 100.00

[1] Calculated as 100 x (baseline-corrected level before or after washing x 4 / 1000) divided by 50.
[2] Calculated as 100 x (baseline-corrected level before washing minus baseline-corrected level after washing) divided by baseline-corrected level before washing.
Source: NDA 204399, Module 5.3.3.1.3, Table 14.2.2 page 61.

Discussion

Testosterone levels of the hand used to apply the drug product were obtained from skin swab samples before and after washing. The mean testosterone levels before washing were 58.59, 60.54, and 70.29 µg for Treatments A, B, and C, respectively. The mean testosterone level for Treatment C, which lacked a drying period after gel application, was slightly increased compared to Treatments A and B, which included a 3 minute drying period after gel application.

Mean testosterone levels of the hand after washing were 0.65, 0.52, and 0.16 µg for Treatments A, B, and C, respectively. Therefore, washing reduced the testosterone level remaining on the hand after application of the gel by 98.65%, 99.02%, and 99.77% for Treatments A, B, and C, respectively.

Conclusion

This study showed that washing was effective in removing approximately 99% of the testosterone remaining on the skin of the hand used to apply Vogelxo. This result was consistent regardless of whether or not the gel remaining on the hand after application was allowed to dry, or the method (towel or air dry) used to dry the hands after washing. The study provided information that is necessary to properly label the product.

7.4.5.3 A Randomized, Single-Center, Open-Label, Three-Way, Crossover Study of the Transferability of Upsher-Smith Laboratories, Inc. Testosterone Gel 1% During Skin-to-Skin Contact With Clothing, Without Clothing, and After Washing (Study P10-003)

This was an open-label Phase 1 study to determine the extent of skin-to-skin testosterone transfer from male subjects dosed with Vogelxo to non-dosed female subjects in the presence of clothing, in the absence of clothing, and after the application site had been washed. The design of this study is presented in section 5.3.5 Transferability During Skin-to-Skin Contact Study P10-003.

Study Subjects
Ninety-six (96) subjects (48 dosed males and 48 non-dosed females) were enrolled in the study. Eighty-four (84) subjects (42 dosed males and 42 non-dosed females) completed all treatment periods of the study. Six pairs of subjects did not complete the study (when one subject from a randomized pair was withdrawn from participation, both subjects in the randomized pair were withdrawn).

Disposition of Subjects
Of the 12 subjects (6 pairs) who did not complete the study, 1 female subject (Subject 148) was withdrawn due to an adverse event, 3 male subjects (Subjects 008, 030, and 031) were withdrawn due to a protocol violation, 2 female subjects (Subjects 102 and 125) withdrew consent. Six (6) subjects (Subjects 002, 025, 048, 108, 130, and 131) were withdrawn from the study because when one subject from a randomized pair was withdrawn from participation, both subjects in the randomized pair were withdrawn.

Reviewer's Comment*: Subjects 030 and 031 were withdrawn because their ALT levels were higher than 1.5 times the upper limit of normal range, which was an exclusion criterion for the study. The Study Report states that the reason for discontinuation for both subjects was Protocol Violation. An adverse event of "increased ALT" was reported for each subject at the time of withdrawal from the study. These clinically significant laboratory results are reviewed in detail below.*

Subjects Withdrawn Due to an Adverse Event or Clinically Significant Laboratory Result
Subject 148: This subject was withdrawn from the study due to the adverse event of vomiting on Day 1 of Period 3. The adverse event occurred before the subject had skin contact with her male partner and was assessed as not related to the study drug by the investigator.

Reviewer's Comment*: This reviewer agrees that the adverse event was not drug related.*

Subject 030: This subject presented at check-in of Period 1 (27 March 2011) with an elevated ALT (63 U/L; normal range: 0-41 U/L) that was higher than 1.5 times the upper

limit of normal range. A repeat test was performed on the same day and the result (60 U/L) was judged to be not clinically significant. The subject was then judged "OK to dose" for Period 1 by the on-site investigator. At check-in of Period 3 (26 April 2011), the subject presented again with an ALT (67 U/L) that was out of the accepted range. A repeat test (65 U/L) performed later in the same day was also out of the accepted range and the subject was judged "Not OK to dose" for Period 3. At the End of Study time point (27 April 2011), the subject's ALT was still 65 U/L. At the time of the last study visit (10 May 2011), the subject's ALT had returned to 59 U/L, which was judged to be not clinically significant by the investigator.

Reviewer's Comment*: This subject's ALT was slightly elevated at all time points during the study including screening (54 U/L) and Period 2 check-in (44 U/L). This reviewer does not consider the ALT elevation to be related to the study drug.*

Subject 031: This subject presented at check-in of Period 2 (10 April 2011) with an ALT level (90U/L; normal range: 0-41 U/L) that was higher than 1.5 times the upper limit of normal range. The subject was judged "Not OK to dose" for Period 2 by the on-site investigator. This subject's abnormal test results were judged to be clinically significant, an adverse event was reported and the subject was withdrawn from the study.

At screening (18 March 2011) the subject's ALT was within normal range (39 U/L), but at check-in for Period 1 (27 March 2011) it was slightly elevated (54 U/L). At the End of Study time point (11 April 2011) the ALT was elevated (98 U/L). An additional ALT on 22 April 2011 was 49 U/L, which was considered not clinically significant.

Reviewer's Comment*: The subject's ALT was slightly elevated before exposure to the drug at Period 1 check-in, but was 2.2 times the ULN 13 days after receiving one dose of the study drug. No ALT assessments were done between the time the drug was administered during Period 1 and the Period 2 check-in. This reviewer considers it unlikely that the subject's elevated ALT was drug related, but cannot rule it out because of the limited amount of information available.*

Subjects Withdrawn for Reasons Other than an Adverse Event or Clinically Significant Laboratory Result

Subject 008: This dosed male subject was withdrawn due to a protocol violation. The subject used an excluded OTC medication (acetaminophen) during the washout period between Periods 1 and 2 and was withdrawn from Period 2 (Treatment C), but completed Periods 1 (Treatment A) and 3 (Treatment B).

Subjects 102 and 125: Two (2) non-dosed female subjects withdrew from the trial for no apparent reason. Subject 102 withdrew consent prior to study drug application in Period 2 and did not participate in Periods 2 and 3. Subject 125 did not show up at check-in of Period 3.

Subjects 002, 025, 048, 108, 130, and 131: Three (3) dosed male subjects and three (3) non-dosed female subjects were withdrawn because their partners withdrew or were withdrawn.

The reasons for subject discontinuations are summarized in Table 30.

Table 30: Summary of Discontinuations (Study P10-003)

	Female	Male
Reason for Discontinuation		
Adverse event	1	0
Protocol violation	0	3[1]
Withdrawal of consent	2	0
Withdrawn because partner was withdrawn	3	3
Total Subjects withdrawn	6	6

[1]Includes 2 subjects with clinically significant elevations in ALT
Source: NDA 204399, Module 5.3.3.1.16, Listing 16.2.1.1.

***Reviewer's Comment**: The study discontinuations appear reasonable. The adverse event and clinically significant laboratory results that caused 3 subjects to be withdrawn from the study do not appear to be drug related.*

Subject Demographics
The demographics of the 48 non-dosed female subjects included in the PK analyses are summarized in Table 31.

Table 31: Summary of Subject Demographics (Study P10-003)
Subjects Included in the PK Analyses (N=48)

Parameter	Statistic	Value
Age (years)	Mean (SD) Range	53.8 (8.40) 31 – 64
Weight (kg.)	Mean (SD) Range	65.69 (9.025) 51.6 – 92.5
Height (cm.)	Mean (SD) Range	160.36 (5.113) 151.5 – 173.0
BMI (kg/m^2)	Mean (SD) Range	25.61 (2.994) 20.0 – 30.9
Sex	Male Female	0 48
Ethnicity	Non-Hispanic Hispanic	42 6
Race	White Black or African American Asian American Indian or Alaska Native Hawaiian or Other Pacific Islander	48 0 0 0 0

Source: NDA 204399, Module 5.3.3.1, Table 11.2.1, pages 61-62.

***Reviewer's Comment**: Except for a lack of racial diversity, the 48 non-dosed female subjects included in the PK analyses were, in general, representative of the population of females who might be exposed to testosterone from skin-to-skin contact with males using Vogelxo.*

Results

Tables 32, 33, and 34 summarize the pre-exposure, uncorrected post-exposure, and baseline corrected post-exposure AUC_{0-24} and C_{max} for testosterone, respectively, for the 48 non-dosed female subjects included in the PK population.

Table 32: Pre-exposure Testosterone AUC_{0-24} and C_{max}

Parameter		Treatment A (n=47)	Treatment B (n=47)	Treatment C (n=42)
AUC_{0-24} (hr*pg/mL)	Mean (SD)	3660.0 (2148.4)	3441.8 (1784.8)	3421.0 (1638.7)
	Range	719.7 - 10963.9	725.4 - 10740.2	771.3 - 9713.0
C_{max} (pg/mL)	Mean (SD)	198.2 (96.7)	186.7 (81.9)	191.4 (82.2)
	Range	72 - 532.2	82.7 - 521.3	85.8 - 459.7

Treatment A - with shirt; Treatment B - without shirt or washing; Treatment C - after washing
Source: NDA 204399, Module 5.3.3.1, Table 11.4.1.1, 11.4.1.2, 11.4.1.3 page 68.

***Reviewer's Comment**: The pre-exposure testosterone levels as reflected by the AUC_{0-24} and C_{max} were similar in each of the three treatment groups.*

Table 33: Post-exposure Uncorrected Testosterone AUC_{0-24}, RD_{AUC}, and C_{max}

Parameter		Treatment A (n=47)	Treatment B (n=47)	Treatment C (n=42)
AUC_{0-24} (hr*pg/mL)	Mean (SD)	3762.1 (2115.3)	11273.0 (5866.8)	3597.6 (1697.7)
	Range	676.5 - 11230.1	3692.4 - 37710.1	1116.3 - 10198.7
RD_{AUC} (%)	Mean (SD)	4.0 (11.7)	277.0 (217.4)	8.7 (21.7)
	Range	-33.6 - 30.3	28.2 - 1178.4	-38.7 - 103.1
C_{max} (pg/mL)	Mean (SD)	203.8 (103.3)	793.8 (655.1)	194.8 (83.1)
	Range	76.1 - 530.6	229.2 - 4736.57	94.8-514.1

Treatment A - with shirt; Treatment B - without shirt or washing; Treatment C - after washing
Source: NDA 204399, Module 5.3.3.1, Tables 11.4.1.4, 11.4.1.5, 11.4.1.6 page 69.

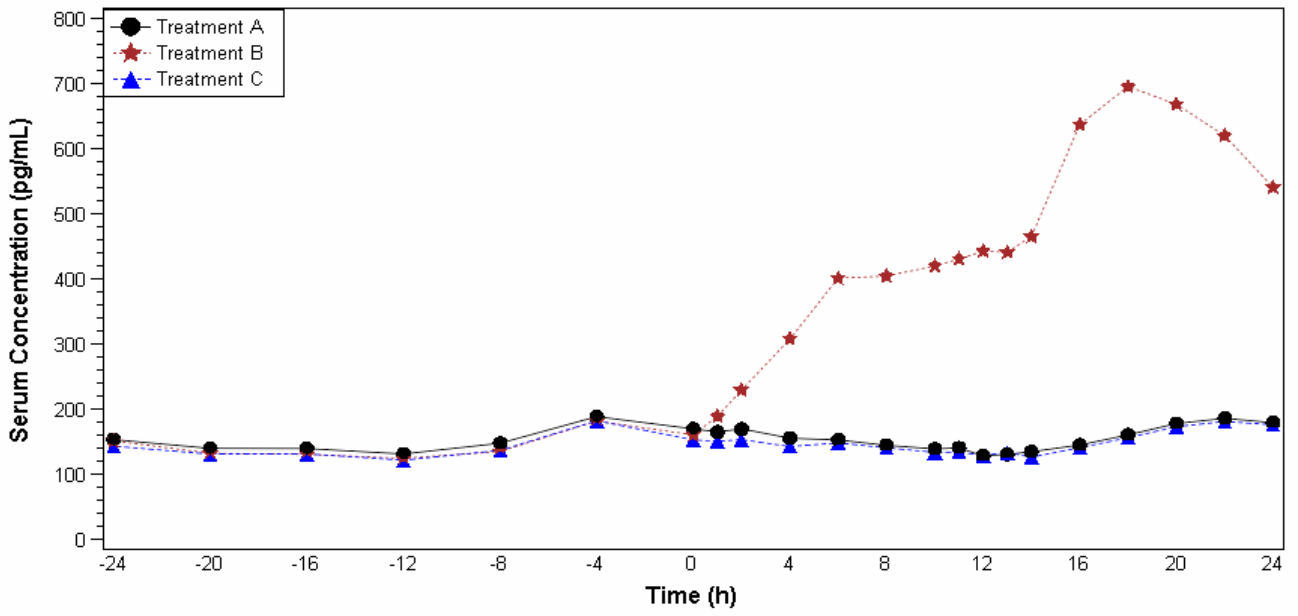
Table 34: Post-exposure Baseline Corrected Testosterone AUC_{0-24} and C_{max}

Parameter		Treatment A (n=47)	Treatment B (n=47)	Treatment C (n=40)
AUC_{0-24} (hr*pg/mL)	Mean (SD)	307.1 (196.0)	7793.6 (5276.5)	364.8 (226.0)
	Range	8.6 - 651.9	913.42 - 33374.0	43.6 - 839.0
C_{max} (pg/mL)	Mean (SD)	50.1 (29.0)	648.6 (640.6)	53.7 (26.7)
	Range	5.3 - 158.1	109.8 - 4555.9	10.7 - 110.2

Treatment A - with shirt; Treatment B - without shirt or washing; Treatment C - after washing
Source: NDA 204399, Module 5.3.3.1, Table 11.4.1.7, 11.4.1.8, 11.4.1.9 page 70-71.

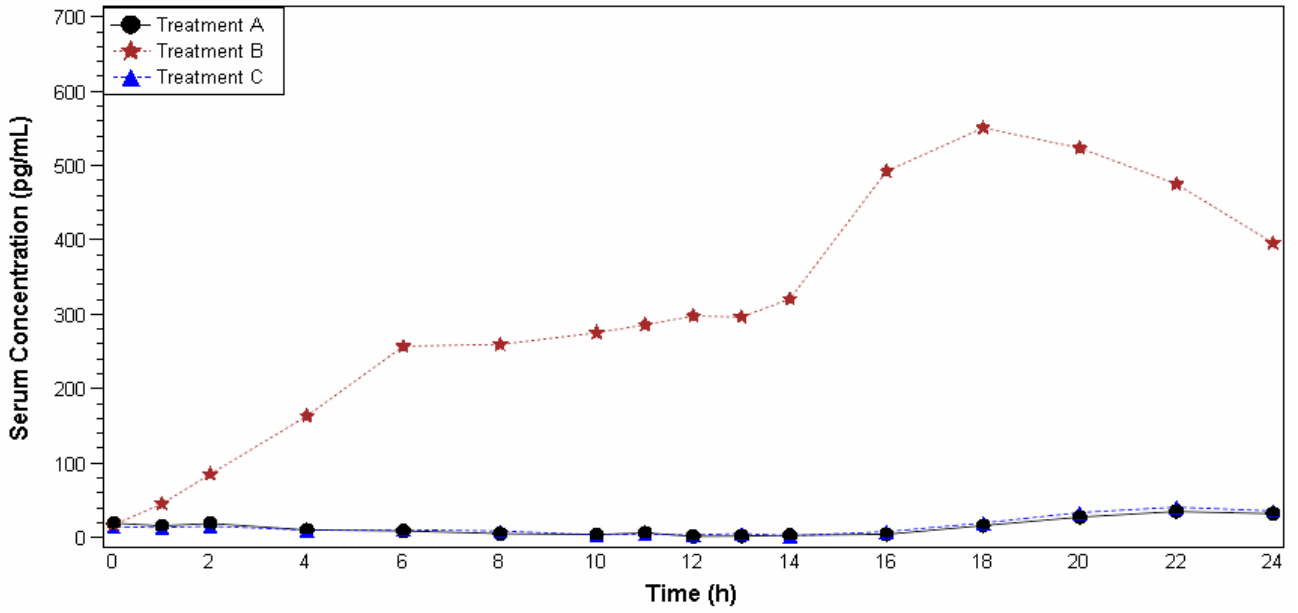
The post-exposure uncorrected and baseline corrected testosterone mean serum concentration-time profiles are displayed graphically in Figures 1 and 2.

Figure 1: Uncorrected Testosterone Mean Serum Concentration -Time Profiles



Treatment A - with shirt; Treatment B - without shirt or washing; Treatment C - after washing
Source: NDA 204399, Module 5.3.3.1, Appendix 16.2.6, Figure 49, page 334.

Figure 2: Baseline-corrected Testosterone Mean Serum Concentration-Time Profiles



Treatment A - with shirt; Treatment B - without shirt or washing; Treatment C - after washing
Source: NDA 204399, Module 5.3.3.1, Appendix 16.2.6, Figure 51, page 336.

The 24-hour post-exposure maximal testosterone concentrations for each subject during each of the three treatments are summarized in Table 35.

Table 35: Maximum Uncorrected Testosterone Concentration 24-Hrs. Post-exposure

Subject	Maximal Testosterone Concentration (pg/mL)		
	Treatment A	Treatment C	Treatment B
101	180.1	184.44	**817.73***
102	312.73		
103	155.18	164.75	**732.02***
104	140.35	123.42	**941.2***
105	308.26	366.03	**1361.96***
106	166.78	176.14	**937.4***
107	221.59	249.03	509.94
108	151.59		**762.46***
109	122.53	184.26	699.03
110	179.78	148.88	390.28
111	205.13	223.71	445.38
112	87.98	150.89	462.8
113	234.23	262.86	608.86
114	96.55	112.78	690.59
115	160.84	147.16	492.8
116	139.4	159.07	526.12
117	245.4	223.94	**1283.15***
118	183.11	171.04	229.17
119	167.89	200.34	555.59
120	76.07	94.82	597.22
121	111.36	124.71	463.86
122	190.58	292.05	349.38
123	163.06	165.49	**789.27***
124	110.19	172.45	**1383.01***
125	513.97		**908.04***
126	127.31	147.45	394.32
127	320.27	289.76	**4736.57***
128	316.84	277.86	**1040.72***
129	190.19	134.69	558.65
130	116.08		354.23
131			630.84
132	134.37	132.84	498.74
133	379.19	375.91	1154.75
134	172.16	162.35	515.49
135	408.35	261.52	**950.99***
136	94.19	107.78	281.67
137	201.3	179.22	**1294.94***

138	290.6	204.68	647.94
139	191.25	221.58	**1102.62***
140	178.62	165.47	689.1
141	158.31	144.01	**709.6***
142	210.38	218.01	544.27
143	315.19	201.14	438.61
144	106.7	113.02	525.27
145	148.06	107.27	664.05
146	113.25	125.86	693.46
147	530.62	514.1	**978.42***
148	248.72		**966.63***

*Values greater than the upper limit of normal range of testosterone for females (700 pg/mL)
Source: Reviewer's analysis, NDA 204399, Module 5.3.3.1, Datasets: PP and DM.

Review's Comment*: When the application site was clothed (Treatment A) or washed (Treatment C) prior to contact, none of the female subjects had a maximal testosterone concentration greater than the upper limit of the normal range of testosterone (700 pg/mL) for healthy females during the 24 hour period following skin-to-skin contact with their dosed male partner. By comparison, when the application site was neither clothed nor washed (Treatment B), 18 (38%) female subjects had a maximal testosterone concentration that was greater than the normal range.*

Reviewer's Discussion
The primary objective of this study was to determine the extent of skin-to-skin testosterone transfer from male subjects dosed with Vogelxo to non-dosed female subjects under the following conditions: (1) in the presence and absence of clothing on the application site (Treatments A and B, respectively) and (2) after the application site had been washed (Treatment C).

When skin-to-skin contact between the dosed male and non-dosed female occurred without the clothing barrier or washing the application site (Treatment B), the mean total exposure to testosterone during the 24 hours following contact (AUC_{0-24}) increased from 3442 to 11273 hr*pg/mL and the mean maximal testosterone concentration (C_{max}) increased from 187 to 794 pg/mL. The mean relative difference between the pre-exposure and post-exposure AUC_{0-24} (RD_{AUC}) was approximately 277%.

In comparison, when skin-to-skin contact occurred while the dosed male was wearing a cloth shirt over the application site (Treatment A), the mean total exposure to testosterone during the 24 hours following contact (AUC_{0-24}) increased from 3660 to 3762 hr*pg/mL and the mean maximal testosterone concentration (C_{max}) increased from 198 to 204 pg/mL. The mean relative difference between the pre-exposure and post-exposure AUC_{0-24} (RD_{AUC}) was approximately 4%.

Similar to the results for Treatment A, when the dosed male washed the application site prior to contact with the non-dosed female (Treatment C), the mean total exposure to testosterone during the 24 hours following contact (AUC_{0-24}) increased from 3421 to 3597 hr*pg/mL and the mean maximal testosterone concentration (C_{max}) increased from 191 to 194 pg/mL. The mean relative difference between the pre-exposure and post-exposure AUC_{0-24} (RD_{AUC}) was approximately 9%.

Additionally, when the application site was either covered with a cloth shirt or washed before skin-to-skin contact, none of the female subjects had a maximal testosterone concentration that exceeded normal testosterone levels for healthy females during the 24-hour period following contact. When the application site was not clothed or washed, the maximal testosterone concentration exceeded normal levels in 18 (38%) of the female subjects.

Conclusions
This study showed that testosterone is transferred from males treated with Vogelxo to non-dosed females through skin-to-skin contact, but covering the application site with clothing or washing the application site before contact could reduce the amount of testosterone transferred. In the absence of clothing or application site washing, a nearly 3-fold increase in testosterone levels was observed in non-dosed females following skin-to-skin contact with dosed males. However, when the application site was clothed or washed, testosterone levels increased by less than 10% after contact.

Based on the data from the study, it is reasonable to conclude that covering the application site with clothing or washing the application site before contact are effective methods for preventing clinically significant testosterone transfer from one person to another. When the application site was clothed or washed before contact, the post-exposure maximum serum testosterone levels of each of the non-dosed female subjects was within the normal range for healthy women.

The labeling for Vogelxo should contain information about the potential for interpersonal transfer of testosterone. It should also explain that wearing clothing after application of the drug product or showering before skin-to-skin contact are effective methods for reducing transfer.

7.4.6 Immunogenicity

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

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

No analyses of dose dependency of adverse events were done.

7.5.2 Time Dependency for Adverse Events

No analyses of time dependency of adverse events were done.

7.5.3 Drug-Demographic Interactions

No analyses of drug-demographic interactions were done.

7.5.4 Drug-Disease Interactions

No analyses of drug-disease interactions were performed.

7.5.5 Drug-Drug Interactions

No drug-drug interaction studies were performed.

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

Testosterone is an endogenous androgenic hormone. At this time, there is no evidence which suggests that the drug is carcinogenic in humans.

Reviewer's Comment*: Because of its effect on preexisting breast and prostate cancer, testosterone is contraindicated in men with carcinoma of the breast or prostate.*

7.6.2 Human Reproduction and Pregnancy Data

Vogelxo is not indicated for females, therefore, no reproduction or pregnancy data were submitted with this application. Because testosterone may cause fetal harm, product labeling should state that pregnant and nursing women should avoid skin contact with Vogelxo.

7.6.3 Pediatrics and Assessment of Effects on Growth

Vogelxo is indicated for adult males and has not been evaluated in males less than 18 years of age. Use of testosterone in children may cause premature epiphyseal closure and adversely affect bone growth.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

There were no reports of overdose during the development program for Vogelxo. The current labeling for Testim includes one report of acute overdosage by injection of testosterone enanthate in which testosterone levels of up to 11,400 ng/dL were implicated in a cerebrovascular accident. Treatment of overdosage would include discontinuation of the drug, washing the application site, and appropriate symptomatic and supportive care.

Testosterone is a Schedule III controlled substance due to its abuse potential as a performance enhancing drug. Inappropriate use of the drug may result in significant adverse events.

No information on withdrawal or rebound was submitted with this application.

7.7 Additional Submissions / Safety Issues

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

8 Postmarket Experience

Vogelxo is a new product, therefore, there is no postmarketing experience with the product.

9 Appendices

9.1 Literature Review/References

None

9.2 Labeling Recommendations

The labeling for Vogelxo should be similar to the labeling for Testim, the reference listed drug. It should include the same Boxed Warning, Contraindications section, and Warnings and Precautions section required in the labeling for other topical testosterone products.

The Boxed Warning should state that virilization has been reported in children secondarily exposed to testosterone gel and explain that children should avoid contact with unwashed or unclothed application sites to reduce the risk of secondary exposure.

Vogelxo should be contraindicated in men with carcinoma of the breast or known or suspected carcinoma of the prostate and in women who are or may become pregnant, or who are breastfeeding.

The Warnings and Precautions section should discuss the following:

- Worsening of benign prostatic hyperplasia (BPH) and potential risk of prostate cancer
- Potential for secondary exposure to testosterone
- Potential for increases in hematocrit
- Venous Thromboembolism
- Use in women
- Potential for adverse effects on spermatogenesis
- Hepatic adverse effects
- Potential for edema
- Potential for gynecomastia
- Potentiation of sleep apnea
- Changes in the serum lipid profile
- Potential for hypocalcaemia in cancer patients
- Decrease concentrations of thyroxin-binding globulins
- Flammability

The Indications and Usage section should be the same as that for Testim, but should include the following Limitation of Use:

- Safety and efficacy of Vogelxo in males less than 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.

The Dosage and Administration section should be similar to Testim, but should add administration instructions for the packet and multi-dose metered pump.

9.3 Advisory Committee Meeting

This product was not discussed at an Advisory Committee meeting.

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/s/

MARTIN E KAUFMAN
08/12/2013

SURESH KAUL
08/12/2013

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/s/

MARTIN E KAUFMAN
06/03/2014

SURESH KAUL
06/03/2014

Summary Review for Regulatory Action

Date	August 15, 2013
From	Christine P. Nguyen, M.D.
Subject	Deputy Director for Safety Summary Review
NDA #	204-399
Applicant Name	Upsher Smith Laboratories, Inc.
Date of Submission	October 18, 2012
PDUFA Goal Date	August 18, 2013
Proprietary Name / Established (USAN) Name	Vogelxo/Testosterone Gel
Dosage Forms / Strength	Gel (50 mg testosterone tube or packet); metered dose pump (12.5 mg testosterone per actuation)
Proposed Indication(s)	Testosterone replacement therapy in males for conditions associated with a deficiency or absence of endogenous testosterone
Action/Recommended Action	Tentative Approval (*see sections 11 and 13*)

Material Reviewed/Consulted OND Action Package, including:	**Names of discipline reviewers**
Clinical Review	Martin Kaufman, DPM, MBA
Statistical Review	Xin Fang, PhD Mahboob Sobhan, PhD
Pharmacology Toxicology Review	Jeffrey Bray, PhD Lynnda Reid, PhD
CMC Review	Bogdan Kurtyka, PhD Moo Jhong Rhee, PhD
ONDQA Biopharmaceutics Review	Tapash Ghosh, PhD Angelica Dorantes, PhD
Clinical Pharmacology Review	Lanyan Fang, PhD Hae-Young Ahn, PhD
Office of Scientific Investigations	Seongeun Julia Cho, PhD Sam Haidar, PhD, RPh
CDTL Review	Suresh Kaul, MD, MPH
OSE/DMEPA	Manizheh Siahpoushan, PharmD Jim Schlick, RPh, MBA
OSE/DRISK	Cynthia LaCivita, PharmD Claudia Manzo, PharmD
Office of Prescription Drug Promotion	Jina Kwak, PharmD
Division of Medical Policy Program	Shawna Hutchins, RN, BSN, MPH Melissa Hulett, RN, BSN, MSBA
Controlled Substance Staff	James Tolliver, PhD Michael Klein, PhD
Project Management Staff	Jeannie Roule Jennifer Mercier

OND=Office of New Drugs
OSE= Office of Surveillance and Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis
DRISK=Division of Risk Management
CMC=Chemistry, Manufacturing, Controls
ONDQA=Office of New Drugs Quality Assessment
CDTL=Cross-Discipline Team Leader

Signatory Authority Review

1. Introduction

Upsher Smith Laboratories, Inc. submitted this 505(b)(2) new drug application (NDA) for testosterone gel 1% (tradename Vogelxo), seeking an indication of testosterone replacement therapy in males for conditions associated with a deficiency or absence of endogenous testosterone. A variety of dosage forms and routes of administration of testosterone, including topical gel and solution, transdermal patch, buccal tablet, oral capsule and tablet, intramuscular injection, and testosterone implant, are approved for this indication. Testosterone gel and solution products have the unique significant safety risk of skin-to-skin transfer of testosterone from patients to others, especially children, and these products carry a boxed warning and a Medication Guide REMS to address this risk.

The Applicant initially sought in 2007 marketing approval of its testosterone gel 1%, hereafter referred to as the tradename Vogelxo, in unit-dose package through the Abbreviated New Drug Application (ANDA) pathway, relying on the approved testosterone gel 1% (Testim) as the reference listed drug. (b) (4)

This 505(b)(2) NDA substantially relies on the Agency's finding of efficacy and safety for Testim, the reference drug. The Applicant submitted bioequivalence data to support therapeutic equivalence of Vogelxo to Testim, and clinical evaluations of skin tolerability and sensitization, hand washing, and secondary skin transfer to address formulation-specific safety concerns of special interest for testosterone gel products.

This memorandum provides the basis for the regulatory action for this application.

2. Background

Testosterone is the predominant circulating androgen in males and is responsible for the development and maintenance of male reproductive functions and secondary sex characteristics. Male hypogonadism, resulting in low serum testosterone concentrations, may be due to primary (testicular failure) or secondary (hypothalamic or pituitary) dysfunctions. Testosterone replacement therapy is used to normalize serum testosterone concentrations in symptomatic hypogonadal men.

Approved under NDA 21453, Testim is currently marketed by Auxilium Pharmaceuticals, Inc. for testosterone replacement therapy in adult males with conditions associated with a deficiency or absence of endogenous testosterone. A single application of Testim to the skin on the shoulders and/or upper arms provides continuous transdermal delivery of testosterone

during the 24-hour dosing period. Daily application of 5 g or 10 g of Testim contains 50 mg and 100 mg testosterone, respectively. Vogelxo contains the same active ingredient (testosterone) and strength (1%), using the same dosage form (topical gel) and the same route of administration (transdermal) as Testim. Therefore, Vogelxo is pharmaceutically equivalent to Testim and is intended for the same conditions of use as Testim.

Relying on Testim as the reference listed drug, the Applicant submitted in August 2007 an ANDA for Vogelxo in individual unit-dose packets (ANDA 79-178). (b) (4)

In response to a citizen petition, the Agency determined in 2009 that testosterone gel products that are not qualitatively and quantitatively identical to reference listed drug would need to provide clinical safety data on formulation-specific transfer of testosterone via person-to-person contact. Subsequently, OGD issued a (b) (4) The need for additional clinical data to address such deficiency precluded the ANDA approval pathway. OGD advised the Applicant to work with the Office of New Drugs.

In a Type C guidance meeting held in September 2009, the Division recommended studies of hand washing and person-to-person transferability for Vogelxo to provide clinical data necessary for a 505(b)(2) application. A pre-NDA teleconference was held in August 2011 to discuss the NDA submission.

3. CMC/Device

Vogelxo (testosterone) gel 1% is a clear, alcohol-based testosterone gel intended for topical application. Three container closure systems for Vogelxo will be available: single-use 5 g tubes and packets, and 88 g multiple dose metered pump.

The Biopharmaceutics reviewer (Tapash Ghosh, PhD) found the proposed in-vitro drug release method and acceptance criteria acceptable for product release and on stability. In the review dated August 9, 2013, the CMC reviewer (Bogdan Kurtyka, PhD) concluded that "from the ONDQA perspective, this NDA is now recommended for Approval."

***Comment**: I concur with the conclusions reached by the chemistry reviewer regarding the acceptability of the manufacturing of the drug product and drug substance. Manufacturing site inspections were acceptable. Stability testing supports an expiry of 36 months for the unit dose tube and packet dosage forms and 24 months for the multiple dose metered pump at controlled room conditions. There are no outstanding chemistry issues.*

4. Nonclinical Pharmacology/Toxicology

No new nonclinical studies were requested or submitted to support this application. In the review dated April 10, 2013, the pharmacology/toxicology reviewer (Jeff Bray, PhD) recommended approval of Vogelxo from a nonclinical pharmacology/toxicology perspective.

Comment: *I concur with the conclusions reached by the pharmacology/toxicology reviewer that there are no outstanding pharm/tox issues that preclude approval.*

5. Clinical Pharmacology/Biopharmaceutics

The Applicant conducted a pivotal bioequivalence (BE) study (P06-011) to establish therapeutic equivalence of Vogelxo to Testim. In addition, two pharmacokinetic (PK) studies were conducted to assess safety regarding skin-to-skin transference (P10-003) and hand and application site washing to remove residual testosterone (P10-002).

Bioequivalence Study (P06-011): This was a single center, open-label, single-dose, open-label, randomized, 2-treatment, 4-way replicate crossover study conducted under fasting conditions comparing equal doses (100 mg testosterone) of the test (Vogelxo) and reference (Testim) products. Treatment phases were separated by a washout period of 7 days. A total of 84 adult males with hypogonadism (an average of two morning total serum testosterone levels ≤ 300 ng/dL [measured on two separate days]) were enrolled. Seventy three (73) subjects completed study, although only 58 subjects contributed to the PK analyses after 15 subjects were excluded for having a mean baseline testosterone serum concentrations > 350 ng/dL during at least one dosing period. The 90% confidence intervals about the ratio of the geometric means of Vogelxo (referred to as USL240 in Table 1) to Testim were within the 80.00% and 125.00% limits for PK parameters C_{max}, $AUC_{0\text{-}24hr}$ and $AUC_{0\text{-}72hr}$ of the ln-transformed baseline-corrected data shown in Table 1.

Table 1: Baseline Corrected BE Analysis (Study P06-011: PK eligible subjects, N=58)

Parameter	USL240 (Test) Mean	Testim® (RLD) Mean	Ratio[1]	90% Geometric CI[2]
C_{max} (pg/mL)	5084.02	4898.21	103.79%	96.90%, 111.18%
$AUC_{0\text{-}24hr}$ (pg*h/mL)	58778.32	53233.56	110.42%	104.55%, 116.61%
$AUC_{0\text{-}72hr}$ (pg*h/mL)	94370.14	85296.16	110.64%	104.19%, 117.49%

CI=confidence interval.
1. Calculated using least-squares means of USL240/Testim®.
2. 90% Geometric Confidence Interval using ln-transformed data.
Source: Primary clinical pharmacology review (7/12/13), Table 1

Comment*: The clinical pharmacology reviewer finds acceptable that the pivotal BE study was conducted using the 100 mg testosterone dose, despite the fact that the starting dose for Testim and Vogelxo is 50 mg. The reviewer concludes that the use of 100 mg dose could minimize the noise from the endogenous testosterone concentrations in assessing BE between Vogelxo and*

Testim. An earlier pilot bioequivalence/bioavailability study evaluating 3 different formulations of the Applicant's testosterone gel 1% demonstrated that one of the formulations (Vogelxo) showed BE to Testim at the tested dose of 50 mg. These findings and those from the pivotal BE study support BE for Vogelxo at the indicated doses of 50 mg and 100 mg.

The pivotal BE study results satisfy the regulatory requirements for demonstration of bioequivalence of Vogelxo to Testim and may be relied upon to bridge efficacy and general safety of Vogelxo to Testim.

Secondary Skin-to-Skin Transfer Study (P10-003): This was a single-center, open-label, randomized, 3-way crossover study to assess the transferability of Vogelxo during skin-to-skin contact with and without clothing coverage of the application site, and after washing of the application site. A total of 96 healthy subjects (48 male and 48 female subjects) were randomized in pairs (a dosed male was matched with a non-dosed female for the duration of the study). Male subjects applied a single dose of 5 gram of Vogelxo (50 mg testosterone) on the upper arm/shoulder/back in each treatment period. Female subjects rubbed the anterior portion of their forearm over the application site of male subjects. Blood samples were taken from the non-dosed female subjects for determination of serum testosterone concentrations.

In the non-dosed females, direct skin contact at the unclothed application site increased systemic testosterone concentrations by approximately 3-fold from baseline (treatment 1), whereas clothing covering (treatment 2) or washing the application site (treatment 3) prior to skin contact resulted in post-exposure serum testosterone concentrations similar to baseline. Table 2 summarizes results of pre- and post-exposure serum testosterone concentrations in non-dosed females.

Table 2: Percent Change Between Mean Pre- and Post-exposure Testosterone AUC_{0-24} and C_{max} in the Non-dosed Female

Parameter	Treatment 1* (n=47)	Treatment 2* (n=47)	Treatment 3* (n=42)
AUC_{0-24} (mean ± SD) (hr*pg/mL)			
Pre-exposure	3441.8 (1784.8)	3660.0 (2148.4)	3421.0 (1638.7)
Post-exposure	11273.0 (5866.8)	3762.1 (2115.3)	3597.6 (1697.7)
% Change	**+277**	**+4**	**+9**
C_{max} (mean ± SD) (pg/mL)			
Pre-exposure	186.7 (81.9)	198.2 (96.7)	191.4 (82.2)
Post-exposure	793.8 (655.1)	203.8 (103.3)	194.8 (83.1)

*Treatment 1 - without shirt or washing; Treatment 2 – with shirt; Treatment 3 - after washing
Source: Primary clinical pharmacology review (7/12/13); adapted from Table 2.

***Comment**: Washing or covering the application site is effective in decreasing the risk of secondary transfer of testosterone. This information will be included in labeling.*

Hand Washing Study (P10-002): This was a single-center, open-label, randomized, 3-way crossover study in 36 healthy male subjects to quantify residual testosterone on the hand after washing procedure. After applying 5 gram Vogelxo (50 mg of testosterone) to the application site, all subjects underwent 3 hand washing procedures in a cross-over manner: hand air dry

for 3 minutes prior to wash and rinse (treatment A), air dry for 3 minutes prior to wash/rinse and then air dry after wash/rinse (treatment B), or washed and rinsed immediately (treatment C). Skin swab samples of the application hand were collected for testosterone within 15 min prior to dosing, after testosterone application, and after washing.

The testosterone level (micrograms) on the hand surface before and after washing and the percentage of testosterone removed from the skin surface by washing were determined from the skin swab data. Results are shown in Table 3. Hand washing removes approximately 99% of testosterone from the hand skin surface.

Table 3: Testosterone Level (micrograms) on Hand Skin Surface Before and After Washing Procedures

Treatment	N	Before wash (µg, mean ± SD)	After wash (µg, mean ± SD)	% Removal by washing (mean)
A (air-dry followed by wash/rinse)	36	58.59 ± 38.74	0.64 ± 1.03	98.7%
B (air-dry followed by wash/rinse and air-dry)	35	60.54 ± 41.67	0.52 ± 1.24	99.0%
C (wash/rinse immediately)	35	70.29 ± 43.58	0.16 ± 0.46	99.8%

Source: Primary clinical pharmacology review (7/12/13), Table 3

***Comment**: Hand washing under the various scenarios tested, which likely mimic actual use conditions, significantly reduces the risk of secondary transfer via direct skin contact with the patient's hand. This information will be included in labeling to mitigate the risk of transfer of testosterone to others via contact with the patient's hand.*

The clinical pharmacology reviewer (Lanyan Fang, PhD) concluded that:

1. Bioequivalence has been demonstrated for Vogelxo with Testim as the reference drug.
2. Washing or covering the application site with clothing was effective in decreasing the known risk of skin to skin transference of testosterone gel products.
3. Hand washing was effective in removing residual testosterone from the hand and is another effective strategy to decrease the risk of transference via contact with the patient's hand surface.

In the review dated July 12, 2013, the clinical pharmacology reviewer (Lanyan Fang, PhD) concluded that "the overall Clinical Pharmacology information submitted to support this NDA is acceptable provided that a satisfactory agreement is reached regarding the labeling language."

***Comment**: Labeling negotiations are now complete. I concur with the conclusions reached by the clinical pharmacology reviewer that there are no outstanding clinical pharmacology issues that preclude approval.*

6. Clinical Microbiology

Non-applicable.

7. Clinical/Statistical-Efficacy

The efficacy of Vogelxo relies on the successful demonstration of bioequivalence of systemic testosterone exposure with the reference drug Testim in hypogonadal male subjects in study P06-011. The efficacy evaluation included the following PK parameters: AUC_{0-t}, $AUC_{0-\infty}$, C_{max}, T_{max}, Kel and $T_{1/2}$ for baseline uncorrected and baseline corrected testosterone. The 90% confidence interval of the ratios of exposure measures (AUC, C_{max}) of Vogelxo compared to Testim were within the BE limit of 80% to 125%, confirming bioequivalence (see Section 5 Clinical Pharmacology/Biopharmaceutics). No other clinical efficacy trials were requested or conducted.

The proposed dosing for Vogelxo is 50 mg testosterone (a single application of one 5-gram gel tube, one 5-gram gel packet, or four metered dose pump actuations [12.5 mg per actuation]) applied once daily to clean, drug intact skin of shoulders and/or upper arms. The daily dose may be increased to 100 mg testosterone (two 5-gram tubes/packets or eight pump actuations), if indicated. Labeling will instruct the use of tube/packet separately from metered dose pump.

The clinical reviewer (Martin Kaufman, DPM, MBA) and CDTL (Suresh Kaul, MD, MPH) concluded that bioequivalence between Vogelxo and Testim has been demonstrated to support the conclusion that Vogelxo is effective as testosterone replacement therapy in the intended population. A statistical review was not necessary for this application.

Efficacy summary: From an efficacy standpoint, the demonstration of bioequivalence between Vogelxo and Testim, together with their known pharmaceutical equivalence, supports a regulatory conclusion of therapeutic equivalence.

8. Safety

The general safety of Vogelxo is supported by a demonstration of bioequivalence to Testim. The overall adverse events reported in the 5 studies conducted with Vogelxo did not raise any new concerns from the known safety profile of testosterone gel products. No deaths or drug-related non-fatal serious adverse events were reported in the development program of Vogelxo.

Formulation-specific safety of Vogelxo was assessed in the skin transference, hand washing, and skin irritation-sensitization studies. Detailed discussions of the skin transference and hand washing studies are found in Section 5 Clinical Pharmacology/Biopharmaceutics. The following section discusses only the skin irritation-sensitization study.

Skin Sensitization and Irritation Study: This was a single-center, within-subject randomized, double-blind study in 255 healthy adult male subjects to evaluate the cumulative irritation and sensitization produced by Vogelxo compared with Testim. Each subject received all 4 test materials (Vogelxo, Testim, positive irritant, low irritant). The study evaluated skin irritation response during the 21-day induction phase using the Berger/Bowman Skin Irritation Scale. The induction phase was followed by a 2-week no-drug rest phase, after which the

subjects were challenged (dosed) and evaluated for sensitization. Subjects with reactions suggestive of sensitization were rechallenged 3 – 4 weeks after resolution of the original reactions. The actual irritation/sensitization score was a combination of a numerical and letter score. Letter scores were converted into numerical equivalents. A converted score was the sum of the numerical score and the numerical equivalent of the letter score. Assay sensitivity was established with the observation of expected skin reactions with a positive irritant control and a low irritant control.

Skin irritation: The total numbers of converted irritation scores by treatment observed during the induction phase are shown in Table 4.

Table 4: Converted Irritation Scores by Treatment (Intent to Treat)

Treatment	Scores, n(%)				
	0	1	2	≥3	Total Sites Scored
Vogelxo	2642 (49)	2563 (48)	129 (2)	21 (<1)	5355
Testim	1658 (31)	3342 (62)	302 (6)	53 (1)	5355
Positive irritant*	363 (7)	1003 (19)	3627 (68)	362 (7)	5355
Low irritant*	3310 (62)	1915 (36)	100 (2)	30 (1)	5355

*Positive Irritant Control (0.05% sodium lauryl sulfate); Low Irritant Control (0.9% aqueous sodium chloride)
Source: Primary clinical review (8/12/13), adapted from Table 21

The converted irritation scores were summed across the 21 days of the induction phase to provide a cumulative converted irritation score for each subject and for each test article. Descriptive statistics included the group mean values of cumulative converted irritation score for the test (Vogelxo, μ_T) and reference (Testim, μ_R) products. The statistical plan prespecified that if the upper bound of a one-sided 95% confidence interval (CI) for the difference between the mean values of the test (Vogelxo, μ_T) and 1.25 times the reference (Testim, μ_R) was less than or equal to zero (i.e. $\mu_T - 1.25\ \mu_R \leq 0$), Vogelxo would be deemed non-inferior in skin irritation to Testim. The upper bound of one-sided 95% CI for the difference between the mean converted cumulative irritation scores of Vogelxo and Testim was -7.9; Vogelxo was non-inferior to Testim in skin irritation.

Skin sensitization: In the challenge phase, any subject with a converted score ≥ 2 at 48 hours post-patch removal was considered to be potentially sensitized. These subjects were to be re-challenged 3 to 4 weeks after the conclusion of the challenge phase to confirm the sensitization reaction. The total numbers of converted sensitization scores by treatment observed during the challenge phase are summarized in Table 5.

Table 5: Converted Sensitization Scores by Treatment (Per Protocol Population)

Treatment	Scores, n(%)					
	0	0.5	1	2	3	Total Sites Scored
Vogelxo	587 (64)	298 (33)	22 (2)	2 (<1)	7 (1)	916
Testim	557 (61)	317 (35)	31 (3)	7 (1)	4 (<1)	916
Positive Irritant*	554 (61)	339 (37)	23 (3)	0	0	916
Low Irritant*	649 (71)	255 (25)	12 (1)	0	0	916

*Positive Irritant Control (0.05% sodium lauryl sulfate; Low Irritant Control (0.9% aqueous sodium chloride)
Source: Primary clinical review (8/12/13), adapted from Table 24

In the per protocol population of 229 subjects, three subjects (045, 079, 014) had converted score of ≥ 2 at 48 hours post removal at both Testim and Vogelxo test sites, suggesting that each of the 3 subjects had skin sensitization to both products. Two of the 3 subjects (045, 079) had positive re-challenge to both Testim and Vogelxo; subject 114 was not eligible as a result of being enrolled in another study by the time the re-challenge was to be administered.

In the review dated August 12, 2013, the clinical reviewer (Martin Kaufman, DPM, MBA) concluded that Vogelxo appears to be reasonably safe with respect to skin irritation and sensitization potential; that hand washing was effective in removing residual testosterone after application of Vogelxo; and secondary skin transference can be effectively mitigated by washing or covering the application site with clothing.

The clinical reviewer and CDTL recommended approval of this NDA based on a favorable benefit-risk balance.

Safety summary: Results from the three formulation-specific studies (interpersonal transference, hand washing, and skin irritation-sensitization) support the safety of the inactive ingredients of Vogelxo that differ from Testim. These findings and the demonstration of bioequivalence of Vogelxo to Testim provide evidence of acceptable safety for Vogelxo.

Labeling will contain information about these safety studies and strategies that have been shown to be effective in mitigating the risk of skin transference. Risk management for Vogelxo will be similar to that of other testosterone gel products, including Testim. This strategy will include labeling with a boxed warning for skin transference and a Medication Guide REMS to mitigate this risk.

9. Advisory Committee Meeting

No Advisory Committee meeting was necessary for this application. To date, the Agency has approved six testosterone gels (Androgel 1%, Androgel 1.62%, and Testim, Fortesta, Teva's testosterone gel, Perrigo's testosterone gel) and one testosterone solution (Axiron) as testosterone replacement therapy in hypogonadal men. A Pediatric Advisory Committee was convened in June 2009 to discuss the safety concern of secondary skin transference of testosterone, especially to children. Based on the Committee's feedback, all currently approved testosterone gel and solution products contain a boxed warning and a Medication

Guide under the REMS to mitigate the transference risk. The same labeling and Medication Guide REMS will apply to Vogelxo.

10. Pediatrics

The Applicant requested a full pediatric waiver. Because it does not involve a new active ingredient, new indication, new dosage form, new dosing regimen, or new route of administration, this application does not trigger PREA requirements.

11. Other Relevant Regulatory Issues

Office of Scientific Investigations (OSI): At the request of the Office of Clinical Pharmacology, OSI inspected the analytical portion of the pivotal BE study (P06-011). OSI concluded "although inconsistent integration in chromatogram processing is objectionable, the inspection did not identify any incidents in which integrity or accuracy of the data was compromised." The final determination was "VAI."

Office of Compliance: Compliance determined that inspections of the drug substance and drug product manufacturing and testing operations are acceptable (December 31, 2012).

Office of Surveillance and Epidemiology

- *Division of Medication Error Prevention and Analysis (DMEPA):* DMEPA found the tradename Vogelxo, and the container and carton labeling acceptable.
- *Division of Risk Management (DRISK):* DRISK found the Risk Evaluation and Mitigation Strategy (REMS) acceptable.

Controlled Substance Staff (CSS): Vogelxo will be a Schedule III controlled substance, as with other testosterone products. CSS found acceptable the labeling under Section 9 (Drug Abuse and Dependence), which was identical to the language recommended by CSS in April 2012 for the Testosterone Gel 1% under NDA 203-098.

Financial Disclosure*:* The Applicant certified that no clinical investigator participating in studies with Vogelxo had disclosable financial interest. The clinical team did not identify any concerns regarding financial disclosures for this NDA.

Litigation: The NDA holder of the reference drug Testim, Auxilium Pharmaceuticals Inc., has initiated a patent infringement suit against the Applicant in the US District Court for the District of Delaware (Auxilium Pharmaceuticals Inc. et al v. Upsher-Smith Laboratories Inc. Docket#: 13-CV-148). Therefore, final approval cannot be granted at this time.

Comment: *The ongoing infringement suit is the only unresolved regulatory issue at this time.*

12. Labeling

Labeling negotiations are completed. Labeling for Vogelxo is now consistent with that of Testim and with other approved testosterone gel products with respect to secondary transfer potential, including a boxed warning and Medication Guide. The labeling for Vogelxo also includes class labeling of known safety concerns of testosterone. The Office of Prescription Drug Promotion (OPDP) recommended revisions the prescribing information, and OPDP and the Division of Medical Policy Programs provided revisions to the Medication Guide. These recommendations were considered and incorporated into the agreed upon labeling. The agreed upon labeling was acceptable to the Study Endpoints and Label Development Team, after minor formatting revisions.

13. Decision/Action/Risk Benefit Assessment

- **Regulatory Action**

I agree with the CDTL and the review teams that Vogelxo should be approved as testosterone replacement therapy in males for conditions associated with a deficiency or absence of endogenous testosterone.

Because of ongoing patent infringement litigation against Vogelxo, however, this NDA will receive a ***tentative approval*** at this time. Final approval is contingent upon the final determination by the US District Court or expiry of the affected patents, and the assurance that there have been no changes to the conditions at the time of tentative approval that could impact final approval.

- **Risk Benefit Assessment**

Vogelxo is pharmaceutically equivalent to Testim in testosterone content and has been shown to be bioequivalent to the reference drug Testim. Therefore, therapeutic equivalence, and general safety, between Vogelxo and Testim has been established. Formulation-specific safety issues were adequately assessed in the studies of skin transference, hand washing, and comparative skin irritation-sensitization with Testim. Findings from the skin transference and hand washing studies show that specific actions effectively mitigated the risk of secondary transfer of testosterone, and these actions will be conveyed in labeling. The skin irritation and sensitization potential of Vogelxo was comparable to that of Testim. Overall, I believe that the benefit of Vogelxo outweighs its risks in the intended population.

- **Recommendation for Postmarketing Risk Evaluation and Mitigation Strategies**

At the time of final NDA approval, a Medication Guide REMS will be required to mitigate the risk of secondary testosterone skin transference to others, especially women and children. This requirement is a class REMS for all currently approved testosterone gel or solution products.

- **Recommendation for other Postmarketing Requirements and Commitments**

None.

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/s/

CHRISTINE P NGUYEN
08/15/2013

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

/s/

MARTIN E KAUFMAN
06/03/2014

SURESH KAUL
06/03/2014

NDA 204,399
Testosterone Gel 1%

Medical Officer's Filing Review Memorandum

Application Letter Date:	October 17, 2012
60-Day Filing Review Date:	December 17, 2012
PDUFA Goal Date:	August 18, 2013
Sponsor:	Upsher-Smith Laboratories, Inc.
Product and Dose:	Testosterone Gel 1%
Indication:	Hypogonadism in males

1. Executive Summary Objective: This review is conducted to fulfill a regulatory requirement of reviewing **NDA 204,399** (testosterone Gel 1%) to determine its suitability for filing under 21 CFR 314.50. This document will also serve as the basis for communicating to the sponsor the review issues identified during the initial filing period.

Recommendation: Following a preliminary review of results from the pivotal bioequivalence study, as well as from the skin irritation, the hand/site washing and the transfer studies, it is the impression of the clinical reviewer that the application is sufficiently complete to permit a substantive clinical review and should be filed.

2. NDA Filing Review
Testosterone is an endogenous androgen that is responsible for normal growth and development of the male sex organs and for maintenance of secondary sex characteristics. Male hypogonadism results from insufficient production of testosterone and is characterized by low serum testosterone concentrations. Symptoms associated with male hypogonadism include decreased sexual desire with or without impotence, fatigue and loss of energy, mood depression, regression of secondary sexual characteristics, and osteoporosis. The Endocrine Society guidelines suggest that the diagnosis of testosterone deficiency in adult men should be based on a comprehensive review of patient symptoms and signs, and measurement of serum testosterone levels by a reliable assay.

Testosterone replacement therapy in men is chronic in nature and designed to improve clinical manifestations of low testosterone and also to place circulating levels of this important hormone into the normal physiological range for healthy men (~300 to ~1050 ng/dL). Male hypogonadism has historically been treated with testosterone replacement therapy via oral or parenteral routes to elevate serum testosterone levels into the normal range.

Currently available treatment options for hypogonadism include intramuscular injections, sub dermal implants, buccal systems, oral formulations, and transdermal patches and gels. The most commonly used formulations are the gels, which are applied with the hands to the shoulders and upper arms and/or abdomen.

This is a 505(b)(2) application and the reference listed drug is Testim. The Sponsor's gel formulation differs from Testim as shown in Table 1. The Sponsor's application includes three dosage forms –5 gm tubes, 5 gm foil packages and a multidose pump. Testim is available in a single dosage form – 5 gm tubes.

Table 1. Composition of USL and Testim Testosterone Gel 1%

Component	Function	Gel Formulation % (w/w)	
		USL	Testim
Testosterone	Drug substance	1.00	1.00
Ethyl Alcohol, Anhydrous			(b) (4)
Glycerin			
Diisopropyl Adipate			
Methyl Laurate			
Oleyl Alcohol			
(b) (4)			
Propylene Glycol			
Polyethylene Glycol (b) (4)			
Purified Water			
Tromethamine			
TOTAL		100.0	100.0

Source: NDA 204399, Module 2, 23-qos-dp, Table 2 page 6 and NDA 21454, Chemistry Filing Review, page 4.

Criteria for Filing: This review is based on the three criteria proposed in the FDA Guidance "New Drug Evaluation Guidance Document: Refusal to File" (July 12, 1993), which represents FDA's interpretation of 21 CFR 314.50. These criteria are:

- Omission of a section of the NDA required under 21 CFR 314.50, or presentation of a section in an incomplete manner
- Failure to include evidence of effectiveness compatible with the statute and regulations

- Omission of critical data, information or analyses needed to evaluate effectiveness and safety or failure to provide adequate directions for use.

Question 1: Does this NDA omit a section required under CFR 314.50 or was a particular section presented in such a manner to render it incomplete for clinical review?

Answer: No

This application is a 505(b)(2) submission. The Sponsor will rely on the Agency's finding of the efficacy and safety of Testim. They have submitted a study evaluating the bioavailability of their Testosterone 1% gel as compared to the bioavailability of Testim. In addition, as requested by the Agency, they have evaluated the skin tolerability of their product, the ability to wash it from the skin, and the potential for transfer to other individuals.

This NDA contains the critical sections in sufficient detail to permit a substantive clinical review. As requested by the Division, the Sponsor has submitted the report of a bioequivalence study evaluating their product in relation to Testim. They have also submitted safety data that is consistent with ICH requirements, labeling, and Safety/Efficacy summaries. This data includes a skin irritation and sensitization study, studies of hand washing effectiveness, and a study of the transfer of testosterone from a treated individual to another by direct contact. The Sponsor has not quantified the amount of testosterone remaining on the skin after washing the application site. However, they have done a post-application-site-washing transfer evaluation.

Question 2: Does the NDA clearly fail to include evidence of effectiveness compatible with the statute and regulations, for example:

- **Lack of any adequate and well-controlled studies, including use of obviously inappropriate or clinically irrelevant study endpoints**
- **Presentation or what appears to be only a single adequate and well-controlled trial without adequate explanation**
- **Use of study design clearly inappropriate**

Answer: No

The Sponsor is relying on the Agency's finding of the effectiveness of Testim. In support of the appropriateness of that reliance, the Sponsor has conducted two bioequivalence studies evaluating the pharmacokinetics of their product as compared to Testim.

In these studies, bioequivalence was to be concluded if the 90% geometric confidence intervals of the ratio (USL240/Testim) of the least-squares means for ln-transformed area under the concentration-time curve from time 0 to the last measured concentration (AUC_{0-t}) and maximum serum concentration (C_{max}) were within the acceptable range of 80.00% to 125.00% for baseline-corrected, dose non-normalized data. In both the pilot (Study P06-001) and pivotal (Study P06-011) studies, the bioequivalence criteria

were met as the 90% confidence intervals were within the acceptance range for AUC_{0-t} and C_{max}. A summary of the data is shown in Table 2.

Table 2. Summary of ln-Transformed Baseline-corrected, Dose Non-normalized Pharmacokinetic Parameters by Study

Study	Parameter	USL240 (Test) Mean	Testim (Reference) Mean	Ratio [1]	90% Geometric CI [2]
P06-001	AUC_{0-t}	40063.98	37390.26	103.41%	87.10, 122.78
	C_{max}	2375.21	2514.33	94.77%	81.45, 110.27
P06-011	AUC_{0-t}	9437.01	8529.62	110.64%	104.19, 117.49
	C_{max}	508.40	489.82	103.79%	96.90, 111.18

CI=confidence interval.

1. Calculated using least-squares means of USL240/Testim®.
2. 90% Geometric Confidence Interval using ln-transformed data.

Data source: Module 5, Study P06-001, Table 1 and Study P06-011, Table 11.2.

Comment: *The data appear to show that the Sponsor's testosterone gel product is bioequivalent to the approved product Testim.*

Question 3: Does the NDA omit critical data, information or analyses needed to evaluate effectiveness and safety or provide adequate directions for use, for example:

- **Total patient exposure at relevant doses that is clearly inadequate to evaluate safety**
- **Clearly inadequate evaluation for safety and/or effectiveness of the population intended to use the drug, including pertinent subsets, such as gender, age and racial subsets**
- **Absence of comprehensive analysis of safety data**
- **Absence of an analysis of data supporting the proposed dose and dose interval**

Answer: No

In addition to the bioequivalence study that is the primary mode of evaluating the efficacy of the product, the Sponsor has provided reports of three studies that were designed to evaluate potential safety issues associated with testosterone gel products. These are: 1) a skin irritation and sensitization study, 2) a study evaluating the ability to wash the gel from the hands, and 3) a study evaluating transfer of testosterone from a patient via interpersonal contact.

Study P08-001: A Study of Skin Sensitization and Irritation

This was a single-center, randomized, double-blind, Phase 1 study in healthy adult male subjects to evaluate the cumulative irritation and sensitization produced by USL240 compared with Testim on intact skin. Two hundred fifty-five (255) subjects had four 3.14 cm2 sites demarcated on the upper outer region of both arms. Each of the 4 treatments

(80 μl [0.3 mg] of USL240, 80 μl [0.3 mg] of Testim, 0.2 mL of the positive irritant control, and 0.2 mL of the low irritant control) was applied for 24 hours under occlusive conditions during the induction phase and was evaluated for irritation response. Subjects received 21 applications of the test articles to the same skin site over a 3-week period to achieve 21 continuous days of skin contact; these sites were evaluated for irritation response each day. Following a rest period of 14 to 17 days, the subjects were dosed with all 4 treatments on four 3.14cm2 sites on the upper back for 48 hours. These sites were evaluated for sensitization at 24, 48, and 72 hours after removal of the test article. Safety variables were also evaluated.

Skin responses to each patch application were examined and scored under light supplied by a 100-watt incandescent blue bulb lamp. Each of the scores represented the presence of a visible or palpable dermal reaction that was localized in the active test system portion of the application area. All skin responses observed with the test articles were reported. If a test site exhibited a strong reaction (numerical score of ≥ 3 or letter grade of F, G, or H), that test site was discontinued from further use. The test sites were evaluated for irritation on study days 1 to 21 at no less than 20 minutes and no more than 30 minutes after test system removal. Irritation evaluation scores by treatment are presented in Table 3. Higher scores reflect stronger reactions.

Table 3. Total Converted Irritation Evaluation Scores Summarized by Treatment (Study P08-001: Intent-To-Treat Population)

Treatment	Scores, n (%)				Total Sites Scored
	0	1	2	≥3	
USL240	2642 (49.3%)	2563 (47.9%)	129 (2.4%)	21 (0.4%)	5355
Testim® 1% (testosterone gel)	1658 (31.0%)	3342 (62.4%)	302 (5.6%)	53 (1.0%)	5355
Positive irritant control (0.05% sodium lauryl sulfate)	363 (6.8%)	1003 (18.7%)	3627 (67.7%)	362 (6.8%)	5355
Low irritant control (0.9% aqueous sodium chloride)	3310 (61.8%)	1915 (35.8%)	100 (1.9%)	30 (0.6%)	5355

Notes:
(1) Percent was calculated as the number (n) of sensitization scores recorded over all time points divided by the total number of sites scored.
(2) A converted score of 3 or greater was carried forward.
(3) Scores for subjects with discontinued patches follow Last Observation Carried Forward imputation method.
Data source: NDA 204399, Module 5, CSR P08-001, Table 11-5.

Comment: *The irritation potential of the Sponsor's testosterone gel appears to be reasonably low and comparable to the reference product.*

Results from the sensitization data were collected for all subjects who were qualified to continue to the challenge phase of the study (N=229), as judged by the criteria outlined in the study protocol. Table 4 summarizes the total number of converted sensitization evaluation scores received per treatment during the challenge phase.

Table 4. Total Converted Sensitization Evaluation Scores Summarized by Treatment (Study P08-001: Per-Protocol Population)

Treatment	Scores, n (%)					Total Sites Scored
	0	0.5	1	2	≥3	
USL240	587 (64.1%)	298 (32.5%)	22 (2.4%)	2 (0.2%)	7 (0.8%)	916
Testim® 1% (testosterone gel)	557 (60.8%)	317 (34.6%)	31 (3.4%)	7 (0.8%)	4 (0.4%)	916
Positive irritant control (0.05% sodium lauryl sulfate)	554 (60.5%)	339 (37.0%)	23 (2.5%)	0	0	916
Low irritant control (0.9% aqueous sodium chloride)	649 (70.9%)	225 (24.6%)	12 (1.3%)	0	0	916

Notes:
(1) Percent was calculated as the number (n) of sensitization scores recorded over all time points divided by the total number of sites scored.
(2) A converted score of 3 or greater was carried forward.
(3) Scores for subjects with discontinued patches follow Last Observation Carried Forward imputation method.

Data source: NDA 204399, Module 5, CSR P08-001, Table 14.2.20a, 14.2.20b, 14.2.20c, 14.2.20d.

Comment:*The sensitization potential of the Sponsor's testosterone gel appears to be low. The number of grade 2 and 3 scores appears to be reasonably similar to the reference product.*

Study P10-002: A Randomized, Single-Center, Open-Label, Three-Way Crossover Study of the Removal of Upsher- Smith Laboratories, Inc. Testosterone Gel 1% by Hand Washing

This was a single-center, randomized, open-label, 3-way crossover, Phase 1 study to assess the removal of USL240 from the hands after being washed with soap and water. Subjects self-applied the entire contents of one 5 g tube (50 mg of testosterone) over a 500 cm^2 area of the upper shoulder/arm that was opposite of the subject's dominant hand. Skin swab samples of the application hand were collected within 15 minutes prior to dosing (0 hour), after testosterone gel application, and after washing (according to the randomization scheme and the treatment procedures defined below), then analyzed for testosterone.

- Treatment A: After application of USL240, hands were allowed to dry for 3 minutes, then washed and rinsed, and dried with a cloth towel;
- Treatment B: After application of USL240, hands were allowed to dry for 3 minutes, then washed and rinsed, and air dried for 9 minutes;
- Treatment C: After application of USL240, hands were not allowed to dry but were washed and rinsed immediately, and dried with a cloth towel.

Subjects reported to the study center on Day -1 and were confined up to the 24 hours post-dose assessment. The treatment phases were separated by washout periods of 7 days. Safety and PK variables were evaluated.

The testosterone levels obtained from skin swab samples before washing were slightly higher for Treatment C (no drying period) compared to Treatments A and B (drying period of 3 minutes for each); the mean levels were 58.6, 60.5, and 70.3 µg for Treatments A, B, and C, respectively. Following hand washing, the mean testosterone levels were comparable for Treatments A and B, but lower for Treatment C; the mean levels were 0.647, 0.523, and 0.163 µg for Treatments A, B, and C, respectively. The diminution of testosterone levels following hand washing was, respectively, 98.7%, 99.0%, and 99.8% for Treatments A, B, and C, indicating that hand washing substantially removes USL240 from the surface of the skin, reducing the risk of cross contamination between individuals. Moreover, hand washing immediately after dose application allows a greater removal of USL240 from the skin.

Comment: *Washing the hands appears to remove testosterone reasonably well. Treatment C is likely to be to most common scenario in clinical practice, and this shows the most effective wash-off of testosterone with 99.8% removed. No comparison to the reference product was done.*

Study P10-003: A Randomized, Single-Center, Open-Label, Three-Way, Crossover Study of the Transferability of Upsher-Smith Laboratories, Inc. Testosterone Gel 1% During Skin-to-Skin Contact With Clothing, Without Clothing, and After Washing

This was a single-center, randomized, open-label, 3-way crossover, Phase 1 study to assess the transferability of USL240 during skin-to-skin contact with and without clothing. A total of 96 healthy subjects (48 male and 48 female subjects) were included in this study. Subjects were randomized in pairs (a dosed male was matched with a non-dosed female for the duration of the study). Male subjects received a single dose of 5 g (50 mg testosterone) of USL240 applied by the study staff on the upper arm/shoulder/back in each study treatment period in accordance with the randomization scheme. Female (non-dosed) subjects rubbed (using side-to-side and up and down motion patterns) the anterior portion of her forearm over the dosed subject's application site for 5 minutes (10 to 15 rubs per minute) and then maintained contact with the same forearm at the application site for another 10 minutes without the rubbing motion. Treatment methods were as follows:

- Treatment A: After application of USL240, the dosed subject clothed the site application with a long-sleeve 100% cotton shirt (clothing barrier);
- Treatment B: After application of USL240, the dosed subject maintained site application unclothed (without clothing barrier);
- Treatment C: After application of USL240, the dosed subject showered the site application (site application washed).

Subjects reported to the study center on Day -1 and were confined from at least 24 hours prior to drug administration up to 30 hours post-dose. The treatment phases were separated by washout periods of at least 14 days. Safety was evaluated in all subjects, and PK variables were evaluated in non-dosed subjects.

Serum testosterone concentrations were measured in non-dosed females before (baseline) and after exposure to dosed males in the three treatment groups. The baseline testosterone levels were similar in non-dosed females, independent of the treatment group with mean AUC0-24h, Cmax, and Cavg respectively ranging from 3421 to 3660 hr*pg/mL, 187 to 198 pg/mL, and 143 to 152 pg/mL.

The post-exposure mean PK parameters calculated on uncorrected data for Treatments A (with clothing), C (application site washed) and B (without clothing) were respectively 3762, 3598, and 11273 hr*pg/mL for AUC0-24, 204, 195, and 794 pg/mL for Cmax and 157, 150, and 470 pg/mL for Cavg. The post-exposure mean PK parameters calculated on baseline corrected data for Treatments A (with clothing), C (application site washed) and B (without clothing) were respectively 307, 365, and 7794 hr*pg/mL for AUC0-24, 50, 54, and 649 pg/mL for Cmax and 13, 15, and 325 pg/mL for Cavg. The mean relative difference between the AUC0-24 post and prior exposure to USL240 (RDAUC) was approximately 277% for Treatment B (without clothing). However, clothing (Treatment A) and washing of the application site (Treatment C) markedly reduced the potential for transfer as evidenced by RDAUC <10% for both treatment groups.

In treatment group B (without clothing), the Cmax (794 pg/mL) for non-dosed females was increased 4-fold from baseline (Cmax = 187 pg/mL). In treatment groups A (with clothing) and C (washing of the application site), the Cmax observed post-exposure was very close to maximum concentration observed at baseline, indicating no noticeable transfer from dosed males to non-dosed females in these treatment groups. The mean Tmax and T½ el were comparable between treatment groups with values respectively ranging from 16 hr to 19 hr and 4 hr to 8 hr.

Comment: *The study appears to show that while there is significant transfer of testosterone with skin-to-skin contact, either a clothing barrier or washing the application site is reasonably effective in reducing the transfer.*

3. Reviewer's Conclusions

A preliminary review of the Sponsor's submission indicates that they appear to have submitted adequate evidence of bioequivalence to the reference drug, Testim. In addition, the Sponsor has submitted data to allow a substantive review of the safety of testosterone 1% gel to be conducted. This safety information includes data from hand washing and interpersonal transfer studies that appear to have been designed and conducted according to the advice provided by the Division.

4. Recommended Regulatory Action

From a clinical perspective, the application is suitable for filing.

Donald McNellis
Medical Officer
Division of Reproductive and Urological Products

CLINICAL FILING CHECKLIST – NDA 204399

NDA/BLA Number: 204399 **Applicant: Upsher Smith Labs** **Stamp Date: October 17, 2012**

Drug Name: Testosterone Gel 1% **NDA/BLA Type: 505(b)(2)**

On initial overview of the NDA/BLA application for filing:

	Content Parameter	Yes	No	NA	Comment
FORMAT/ORGANIZATION/LEGIBILITY					
1.	Identify the general format that has been used for this application, e.g. electronic CTD.	X			
2.	On its face, is the clinical section organized in a manner to allow substantive review to begin?	X			
3.	Is the clinical section indexed (using a table of contents) and paginated in a manner to allow substantive review to begin?	X			
4.	For an electronic submission, is it possible to navigate the application in order to allow a substantive review to begin (*e.g.*, are the bookmarks adequate)?	X			
5.	Are all documents submitted in English or are English translations provided when necessary?	X			
6.	Is the clinical section legible so that substantive review can begin?	X			
LABELING					
7.	Has the applicant submitted the design of the development package and draft labeling in electronic format consistent with current regulation, divisional, and Center policies?	X			
SUMMARIES					
8.	Has the applicant submitted all the required discipline summaries (*i.e.*, Module 2 summaries)?	X			
9.	Has the applicant submitted the integrated summary of safety (ISS)?	X			
10.	Has the applicant submitted the integrated summary of efficacy (ISE)?		X		Not required
11.	Has the applicant submitted a benefit-risk analysis for the product?	X			
12.	Indicate if the Application is a 505(b)(1) or a 505(b)(2). If Application is a 505(b)(2) and if appropriate, what is the reference drug?	X			Reference Drug - Testim
DOSE					
13.	If needed, has the applicant made an appropriate attempt to determine the correct dosage and schedule for this product (*i.e.*, appropriately designed dose-ranging studies)? Study Number: Study Title: Sample Size: Arms: Location in submission:			X	Bioequivalence to Testim implies same dosing

	Content Parameter	Yes	No	NA	Comment
EFFICACY					
14.	Do there appear to be the requisite number of adequate and well-controlled studies in the application? Pivotal Study #1 Indication: Pivotal Study #2 Indication:	X			BE Study, Skin sensitization & irritation studies, Washing & Transfer Studies
15.	Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?	X			
16.	Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints.	X			
17.	Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission?			X	US Data
SAFETY					
18.	Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division?	X			
19.	Has the applicant submitted adequate information to assess the arythmogenic potential of the product (*e.g.*, QT interval studies, if needed)?			X	
20.	Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product?	X			
21.	For chronically administered drugs, have an adequate number of patients (based on ICH guidelines for exposure[1]) been exposed at the dose (or dose range) believed to be efficacious?			X	Product approval will hinge on bioequivalence to Testim , for which there is an extensive safety history
22.	For drugs not chronically administered (intermittent or short course), have the requisite number of patients been			X	

[1] For chronically administered drugs, the ICH guidelines recommend 1500 patients overall, 300-600 patients for six months, and 100 patients for one year. These exposures MUST occur at the dose or dose range believed to be efficacious.

	Content Parameter	Yes	No	NA	Comment
	exposed as requested by the Division?				
23.	Has the applicant submitted the coding dictionary[2] used for mapping investigator verbatim terms to preferred terms?		X		
24.	Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs?	X			
25.	Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)?			X	No deaths or SAEs were encountered in the Sponsor's studies
OTHER STUDIES					
26.	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?	X			Transfer and washing studies
27.	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (*e.g.*, label comprehension, self selection and/or actual use)?			X	
PEDIATRIC USE					
28.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?	X			
ABUSE LIABILITY					
29.	If relevant, has the applicant submitted information to assess the abuse liability of the product?			X	
FOREIGN STUDIES					
30.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?			X	
DATASETS					
31.	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?	X			
32.	Has the applicant submitted datasets in the format agreed to previously by the Division?			X	
33.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?	X			
34.	Are all datasets to support the critical safety analyses available and complete?	X			
35.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?	X			
CASE REPORT FORMS					
36.	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?			X	
37.	Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?			X	

[2] The "coding dictionary" consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

	Content Parameter	Yes	No	NA	Comment
FINANCIAL DISCLOSURE					
38.	Has the applicant submitted the required Financial Disclosure information?	X			
GOOD CLINICAL PRACTICE					
39.	Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?	X			

IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE? _Yes_____

If the Application is not fileable from the clinical perspective, state the reasons and provide comments to be sent to the Applicant.

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

No clinical review issues were identified.

Reviewing Medical Officer Date

Clinical Team Leader Date

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

/s/

DONALD R MCNELLIS
12/11/2012

SURESH KAUL
12/11/2012