CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

022504Orig1s000

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	**November 11, 2010**
From	**Suresh Kaul, MD, MPH**
Subject	**Cross-Discipline Team Leader Review**
NDA#	**22,504**
Applicant	**Acrux Pharma Ltd.**
Date of Submission	**January 25, 2010**
PDUFA Goal Date	**November 25, 2010**
Early Action Date	**November 23, 2010**
Proprietary Name / Established (USAN) names	**Axiron** **Testosterone solution**
Dosage forms / Strength	**60mg (1 pump actuation of 30mg to each axilla) applied topically once daily**
Proposed Indication(s)	**Male Hypogonadism**
Recommended:	***Approval***

Cross Discipline Team Leader Review Template

1. Introduction

I believe that **Axiron** (Testosterone solution for transdermal use) should receive an **approval action** for the indication of “hypogonadism” in adult males. Axiron testosterone solution for transdermal use has demonstrated “substantial evidence” of effectiveness in producing a serum testosterone level within the normal range in hypogonadal men and an acceptable safety profile.

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

Male hypogonadism results from insufficient production of testosterone and is characterized by low serum testosterone concentrations. Symptoms associated with male hypogonadism include decreased sexual desire with or without impotence, fatigue and loss of energy, mood depression, regression of secondary sexual characteristics, and osteoporosis.

The exact prevalence of androgen deficiency in men is not known. Although serum total and free testosterone concentrations decline in men with advancing age, the significance of age-related decline in testosterone concentration is incompletely understood.

2. Background

2.1 Testosterone

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

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

2.2 Product

Axiron is a colorless to pale yellow clear homogeneous solution for topical administration containing 2% testosterone. It is packaged into a multi-dose pump. The drug product is in a low-density (b) (4) /aluminum pouch. The pouch is attached to a white (b) (4) bottle and closed with an airless metered dose pump dispenser. Each bottle is filled with 110 ml of the drug product and able to dispense 90 ml of product. The pump delivers 1.5 ml of product on each actuation.

The Axiron formulation is a single-phase solution containing 2 % w/v testosterone, and a permeation enhancer, octisalate (b) (4), together with povidone (b) (4) (b) (4) ethanol (b) (4) and isopropanol. The product is applied via a metered-dose pump with a nozzle which is designed to deliver a unit volume of the formulation uniformly to an applicator which is then used to apply the product to the skin of the axilla.

(b) (4)

2.3 Regulatory Background

An IND was submitted to the Division of Reproductive and Urologic Products on August 11, 2006 by, Acrux Pharma. Under this IND, their transdermal testosterone metered-dose lotion (Testosterone MD-Lotion®) was evaluated as a therapy for males with conditions associated with a deficiency or absence of endogenous testosterone.

An end-of-phase 2 meeting between Acrux and the Division was held on March 13, 2008. At this meeting, the design of Acrux's planned phase 3 study was discussed, including the dose titration scheme, the primary and secondary endpoints and the safety monitoring for the trial.

Prior to this meeting, Acrux had completed studies evaluating their product and the effect of deodorant use, application site washing, and person to person transfer. These initial studies had been conducted using a 1% formulation of the product rather than the 2% formulation that the Sponsor intends to market. This change in formulation was discussed and the Division indicated that, while it is unlikely that these trials would need to be repeated using the new formulation, a final decision would only be possible after review of the study reports.

A number of Chemistry, Manufacturing and Control issues were also discussed.

On August 31, 2009, a pre-NDA meeting was held between Acrux and the Division. The content and format of the submission was discussed. A number of issues

regarding possible labeling were discussed and the Division indicated that no decision on these issues would be possible until the submission was reviewed. The need for a clinical study evaluating the ability of soap and water to remove the product from the skin was discussed. Several Chemistry, Manufacturing and Control issues were also discussed.

The Sponsor submitted the MTE11 study report, evaluating the ability of soap and water to wash testosterone from the skin. The results of this study are incorporated into this review.

During the review, the review team believed that the absence of a study evaluating person-to-person transfer using the to-be-marketed formulation (2% testosterone) was a significant deficiency. The study that was submitted with the application evaluated a 1% solution. This was discussed with the Sponsor who agreed to perform the necessary study with to be marketed 2% solution. The Sponsor submitted this study report, MTE12, and the results have been incorporated in this review.

3. CMC/Device

Dr. Hitesh Shroff, Chemistry Reviewer from Branch IV, Division of New Drug Quality Assessment II, Office of NDQA has the following recommendation.

Recommendation
Dated: 10.22.2010
This NDA has provided sufficient information to assure identity, strength, purity and quality of the drug product. However, labeling issues are still pending and an overall "Acceptable" recommendation from the Office of Compliance has not been made as of the date of this review. Therefore, from the CMC perspective, this NDA is NOT recommended for approval until labeling issues are resolved as well as an overall "Acceptable" recommendation is made from the Office of Compliance.

Recommendation and Conclusion on Approvability
Dated: 11.19.2010
The CMC Review #1 noted two pending issues: No "Acceptable" recommendation from the Office of Compliance, and labeling issues.
Now, the labels have adequate information as required and an overall "Acceptable" recommendation from the Office of Compliance has been made.
Therefore, from the CMC perspective, this NDA is now recommended for approval.

Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps.
No recommendation at this time.

Basis for Approvability:
Dr. Shroff in his review of this application wrote, the sponsor has provided sufficient information on raw material controls including the drug substance manufacturing

processes and process controls, and adequate specifications for assuring consistent product quality of the drug product. This NDA also provided sufficient stability information on the drug product to assure strength, purity and quality of the drug product during the expiration dating period.

During the process of this review, Dr. Shroff identified two very important issues:

1. Presence of pale red color in three batches BN0514, BN0515 and BN0516 at (b) (4). However, Axiron samples stored up to 12 months at 25°C/60% RH did not exhibit the pale red color. Upon the recommendation of the Division, Acrux methodically investigated the cause of red coloration and attempted to isolate and identify the red impurity. Acrux submitted three reports regarding their investigation and the following conclutions were made:

1. The red color observed at the six month accelerated time point was likely due to the povidone lot used in the manufacture of the registration batches. As it is only present in trace amounts, it is not considered to affect the safety and efficacy of Axiron and therefore is not expected to pose a risk to patients.
2. In all of the povidone lots studied, the results to date indicate that the propensity for lot 03800203503 to form a color is related to the presence of (b) (4) material which is the most likely cause for the formation of red-colored species in the registration batches.
3. The red color species (b) (4) material during manufacture of the povidone. Therefore, the color is unlikely to reoccur due to the added controls (b) (4) for the supply of the povidone raw material (b) (4)
4. The stability test results obtained from 15 month data on the Registration batches and 24 month data on the Phase 3 Clinical batches support a shelf life of 24 months for Axiron when the product is stored at controlled room temperature.

Chemistry Reviewer's Evaluation:
The sponsor has carried out a large number of experiments with the manufacturer of povidone to determine the root cause of red color and to identify/isolate the species causing the red coloration only during the accelerated stability study of Axiron at (b) (4) RH. Based on their experiments it was concluded that (b) (4) povidone is the cause of red color. However, they were unable to isolate and identify the color causing species because they are present in trace amounts. According to the Pharm/Tox review dated 14-Sep-2010, since these impurities are in trace amount, they do not have significant effect on the overall quality of the drug product. Thus, Axiron is deemed safe.

2. Oily droplets
During the stability studies at 25°C/60% RH and 40°C/75% RH over a period of six months, oily droplets were observed during the priming and the life of the product. The sponsor initiated the following 4-part investigation.

- Part 1: Determination of the presence or absence of the oily droplets in registration batches BN0514, BN0515 and BN0516
- Part 2: Determination of the source of the oily droplets
- Part 3: Identification of the oily droplets
- Part 4: Determination of the loading in a pump

Based on the results of this investigation the following conclusions were made regarding the presence of the oily droplets in Axiron:

1. The oily droplets are Dimethicone (b) (4) originating from the (b) (4) pump. Dimethicone is introduced during the assembly of the pumps and the source is documented in (b) (4) DMF (b) (4)
2. Dimethicone has been found in the (b) (4) pump lots used in Acrux Phase 1, 2, 3 clinical trial batches and Orion registration batches.
3. The dimethicone comes into contact with the Axiron formulation during actuation of the pump, however greater than (b) (4) of the dimethicone is removed from the registration batch pumps during the 3 priming actuations.
4. The dimethicone remaining after 3 priming actuations of the pump lot used for registration batches is of a low quantity, averaging (b) (4) expelled per unit from start of life to end of life.
5. The quality of the drug product is not affected by the presence of dimethicone. Following storage at 25°C/60% RH for up to 15 months, all results obtained during testing of the registration batches, including testosterone and octisalate assay and related substances results, complied with the shelf life specifications, all results are within trend when compared with previous time points and stability batches, for example, Phase 3 batches.

Chemistry Reviewer's Evaluation:
The sponsor has successfully identified the cause of oily drops and demonstrated that it is a minute amount of dimethicone (b) (4) oil used in the assembly of the (b) (4) pump. The majority of the oil is expelled during the priming of the pump. The medical grade dimethicone is used in other approved topical drugs. According to the Pharm/Tox review dated 14-Sep-2010 the ubiquitous presence of dimethicone in cosmetics, in the clinical batch, and its known low dermal toxicity represents a low human safety risk in this testosterone 2% solution and therefore, Axiron is recommended for approval as there are no safety concerns regarding the presence of oily drops as dispensed from the pump.

***CTDL Comment**: I fully concur with Chemistry review team's justification towards the resolution of issues involving presence of red coloration in the accelerated stability batches and detection of dimethicone oil from the pump.*

4. Nonclinical Pharmacology/Toxicology

The Pharmacology/Toxicology review team, Jeffrey D. Bray, PhD and Lynnda Reid PhD, made the following recommendations in their final review dated September 22nd, 2010.

Recommendations
Nonclinical data support **Approval** of testosterone 2% solution for topical (axilla) testosterone replacement in hypogonadal men.

Addendum dated 11.19.2010.
Pharm/Tox has reviewed the final submitted labeling and finds it acceptable.

Additional Non Clinical Recommendations
None

Dr. Bray in his review wrote the following:
The sponsor submitted no new nonclinical information, and is relying on published studies of 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. However, the formulation contains an excipient not present in previously approved testosterone products.

Octisalate is a penetration enhancer that is widely used in dermatological products including sunscreens and cosmetics that was found to be safe at concentrations up to 5%.

Two issues arose with characterization of the drug product. A ***red coloration*** noted in the accelerated stability registration batches was investigated by the sponsor and the source was found to be specific to (b) (4) povidone (b) (4). It was not isolated or identified, suggesting that it was present only in trace amounts. Since the red color-causing species is only present at trace levels under accelerated conditions, and a likely source has been identified and can be eliminated through CMC specifications, the impurity's presence in the registration batches does not affect approval of this product from a Pharm/Tox perspective. ***Dimethicone oil*** from the pump was detected in drug product following the first few pump actuations. The ubiquitous presence of dimethicone in cosmetics, in the clinical batch, and its known low dermal toxicity represents a low human safety risk in this testosterone 2% solution. Therefore, dermal exposure of dimethicone in the drug product at the amounts detected appears to be reasonable safe from a pharm/tox perspective.

CTDL Comment*: I fully concur with Pharmacology/Toxicology review team's recommendation and their justification towards the resolution of issues involving presence of red coloration in the accelerated stability batches and detection of dimethicone oil from the pump.*

5. Clinical Pharmacology/Biopharmaceutics

The Clinical Pharmacology Review team, Chongwoo Yu, Ph.D and Myong –Jin Kim, Pharm.D, made the following recommendation in their review signed November 17th, 2010:

The Office of Clinical Pharmacology/Division of Clinical Pharmacology III (OCP/DCP-III) has reviewed NDA 22504 submitted on January 25, 2010, May 12, 2010, May 20, 2010, August 16, 2010, September 24, 2010, and October 14, 2010. A formal consult to the Division of Scientific Investigations (DSI) was made for clinical and bioanalytical study sites inspections (signed off by Dr. E. Dennis Bashaw in DARRTS on March 18, 2010) and ***there are no unresolved issues related to the approvability of Axiron***™. The overall Clinical Pharmacology information submitted to support this NDA is acceptable provided that a satisfactory agreement is reached regarding the labeling language.

OCP's Overall Recommendation on the Product Labeling (November 22, 2010)
The final agreed upon product labeling between the Sponsor and the DRUP was submitted by the Sponsor on November 19, 2010 (Supporting Document Number 17). *There are no outstanding Clinical Pharmacology issues.*

Overall Recommendation (November 22, 2010)
The Division of Clinical Pharmacology 3, OCP finds NDA 022504 acceptable from a Clinical Pharmacology perspective.

POST-MARKETING REQUIREMENTS / COMMITMENTS
None

Dr. Chongwoo Yu in his review wrote the following:
The Sponsor submitted 12 Biopharmaceutical and Clinical Pharmacology studies including multiple-dose pharmacokinetics (PK), evaluation of the effect of antiperspirant/deodorant applications, evaluation of the effect of application site washing, evaluation of application site residual T following washing, and evaluation of interpersonal transferability potential together with the phase 3 clinical study (MTE08) and the extension study (MTE09) to support the approval of Axiron™. Study MTE08 is an open-label titration study to evaluate the safety and efficacy of various doses of Axiron™ in hypogonadal men for 120 days while Study MTE09 is an open-label extension of Study MTE08 to 180 days to evaluate skin safety.

Out of the 12 studies submitted, 7 studies containing relevant information acquired during the Axiron™ product development were reviewed. Studies not reviewed include studies conducted under development programs using different formulation (i.e., T 1% solution) or using different patient populations (e.g., healthy females with low T for single dose studies or healthy men with chemically suppressed T levels to simulate hypogonadism).

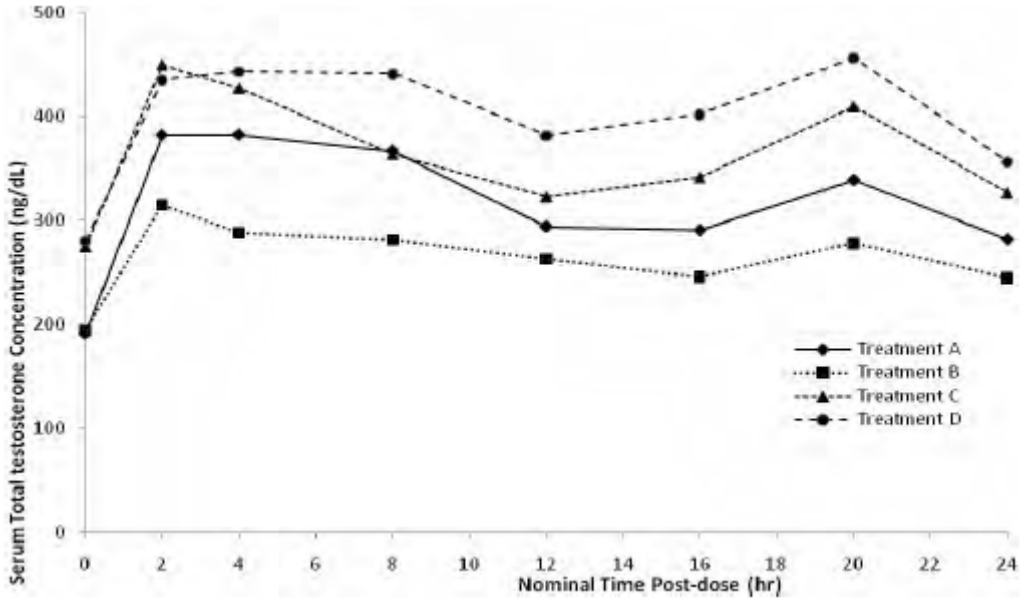
PK parameters of total T and its PK profiles:

The following PK profiles of total T were obtained with a daily dose of 30 mg, 60 mg, or 90 mg Axiron™ applied to the axilla(s) of hypogonadal men for 7 days. PK of the 120 mg dose was not characterized in this study. PK parameters in Table 1 were calculated in the population (i.e., Per Protocol Population) that completed the study without any significant protocol violations or deviations. 3 study participants (i.e., Study participants 0304, 0903, and 0906) that had deviations from the protocol with regard to treatments administered were omitted from the Per Protocol analysis set**.**

Table 1: Arithmetic Mean (SD) PK Parameters of Total T by Treatment (Per Protocol analysis; N=18)

Treatment	C_{ave} (ng/dL)	AUC(0-24) (ng·hr/dL)	C_{max} (ng/dL)	C_{min} (ng/dL)	T_{maxa} (hr)
30 mg Axiron™	267 (100)	6399 (2405)	395 (216)	161 (50)	16.00 (1.95, 23.93)
60 mg Axiron™	368 (131)	8837 (3131)	547 (242)	214 (99)	4.13 (0, 20.00)
90 mg Axiron™	413 (173)	9907 (4145)	588 (223)	239 (123)	12.01 (1.92, 23.97)

Figure 1: **Arithmetic mean total T serum concentrations following 7 days of once-daily administration of 30 mg (Treatment B), 60 mg (Treatment C), or 90 mg (Treatment D) Axiron™ (Study MTE07, N=18)**



As shown in Figure 1 above after an initial plateau of serum total T concentration was observed between 2 and 4 hr post-dose, a second plateau that is comparable or even higher than the first one was observed between approximately 16 and 20 hr post-dose. This might be contributing to the difference of the median Tmax values observed in the 60 mg Axiron™ arm compared to the other dose strengths. While it is hard to conclude whether this observation is due to the contribution of endogenous T,

it should be noted that this trend was observed consistently in the PK profiles of Axiron™. Mean Cavg and AUC(0-24) of total T following daily administration with 30, 60, and 90 mg of Axiron™ for 7 days are not dose proportional but treatment dependent.

With single daily applications of Axiron™ for 120 days and dose titrations on Days 15 and 60 as necessary, the overall average (± SD) daily T concentration produced by Axiron™ applied to the axilla(s) of hypogonadal men of the completer set (N=135) was reported to be 480 ± 177 ng/dL (Study MTE08). The completer set included all subjects who were included in the full analysis set and who completed the Day 120 visit. 135 subjects completed the study with 20 withdrawals, 3 of which were due to AEs. The primary efficacy analysis in the pivotal Phase 3 study, MTE08 was based on the completer set since this analysis set was as close as possible to the full analysis set, but included data obtained at Day 120.

Effects of Deodorant and Antiperspirants

In a single dose, parallel group study (Study MTE10) conducted in healthy premenopausal female subjects (18-45 yr old with BMI of 19-30 kg/m2) to evaluate the impact of antiperspirant/deodorant application on T absorption when applied prior to application of 30 mg Axiron™ (Groups 1, 2, and 3), results show numerically lower concentrations (i.e., up to 32.8% reduction in AUC(0-72)) of total T compared to the control group which only applied 30 mg Axiron™ (Group 4). 2 pre-dose baseline PK blood samples were collected, 1 within 30 min prior to Axiron™ administration and 1 right before Axiron™ administration. Pre-dose baseline total T concentrations ranged between 18.18 and 43.62 ng/dL with the exception of Subject 001035 (Group 3) that had baseline T concentrations of 91.37 and 72.46 ng/dL and were comparable between each group. Demographic and other baseline characteristics (i.e., age, race, height, weight, BMI, smoking habits, and alcohol consumption) among the treatment groups were comparable and no significant differences were observed.

Table 2 : **Summary of Baseline-uncorrected Mean PK Parameters (Study MTE10)**

Parameter	Group 1	Group 2	Group 3	Group 4
AUC(0-72) (ng·hr/dL)	9098.0	8399.8	7380.1	10975.6
C_{max} (ng/nL)	260.4	271.0	238.0	341.9

Group 1: Antiperspirant/deodorant stick applied 2 min prior to Axiron™ application
Group 2: Antiperspirant/deodorant spray applied 2 min prior to Axiron™ application
Group 3: Deodorant spray applied 2 min prior to Axiron™ application
Group 4: Control group - Axiron™ only

This study has used the lowest available Axiron™ dose strength (i.e., 30 mg) that would probably show the maximal impact of antiperspirant/deodorant application on T absorption compared to when using higher dose strengths of Axiron™. While it is hard to conclude the extent of impact of antiperspirant/deodorant application on T absorption (i.e., when applied prior to Axiron™ application) in hypogonadal men, the impact of antiperspirant/deodorant use will be accounted for in the clinical dose titration process. Therefore, despite the existence of impact on T absorption from

antiperspirant/deodorant application, restriction of antiperspirant/deodorant application prior to Axiron™ application appears to be unnecessary.

Effects of Application Site Washing

In a single dose, parallel group study (Study MTE10) conducted in healthy premenopausal female subjects (18-45 yr old with BMI of 19-30 kg/m2) to evaluate the impact of washing the application site on T absorption at 2 hr (Group 5) and 6 hr (Group 6), respectively, following application of Axiron™, results show numerically lower concentrations (i.e., up to 35.3% AUC(0-72) reduction) of total T compared to the control group (Group 4). 2 pre-dose baseline PK blood samples were collected, 1 within 30 min prior to Axiron™ administration and 1 right before Axiron™ administration. Pre-dose baseline total T concentrations ranged between 18.18 and 38.28 ng/dL and were comparable between each group. Demographic and other baseline characteristics (i.e., age, race, height, weight, BMI, smoking habits, and alcohol consumption) among the treatment groups were comparable and no significant differences were noted.

Table 3: **Summary of Baseline-uncorrected Mean PK Parameters (Study MTE10)**

Parameter	Group 4	Group 5	Group 6
AUC(0-72) (ng·hr/dL)	10975.6	7097.9	8108.8
Cmax (ng/nL)	341.9	220.6	279.7

Group 4: Control group - Axiron™ only
Group 5: Application site washed 2 hr post Axiron™ application
Group 6: Application site washed 6 hr post Axiron™ application

A 35.3% reduction in mean AUC(0-72) of total T was observed in the treatment group that washed the application site 2 hr following application of Axiron™ (Group 5). According to the Biostatistic reviewer, Dr. Xin Fang, the difference of AUC (0-72) between Group 4 (control) vs. Group 5 is statistically significant (p-value = 0.005). The treatment group that washed the application site 6 hr following application of Axiron™ (Group 6) still showed a reduction in total T exposure but to a smaller extent. This study has used the lowest available Axiron™ dose strength (i.e., 30 mg) that would probably show the maximal effect of washing compared to when using higher dose strengths of Axiron™. While this assessment was conducted in premenopausal women, Axiron™ users should avoid swimming or washing the application site for 2 hr after Axiron™ application.

Application Site Residual Evaluation following Washing

A clinical study was conducted to evaluate the amount of residual T remaining on the axilla in 10 healthy Caucasian males between ages of 18-70 yr with a mean BMI of 25.1 kg/m2 of who went through a post Axiron™ dose washing procedure. After showering on Day 1, all subjects received 120 mg Axiron™ (equivalent to a 60 mg dose per axilla). Axiron™ was allowed to dry for 5 min and the left axilla was wiped with alcohol towelettes which were assayed for T content. Subjects were required to shower following a predefined procedure with soap and water 30 min after application. The right axilla was then wiped with alcohol towelettes which were assayed for T

content. The study results show that the use of a showering procedure utilizing a commercially available soap and water removes the majority (i.e., approximately 95%) of T applied to the axilla using the highest dose (i.e., 120 mg) of Axiron™ that is recommended for clinical use.

Interpersonal Transfer Potential
A single dose clinical study was conducted to evaluate the potential for interpersonal transfer from healthy male subjects using Axiron™ to healthy female subjects when vigorous contact is made for 15 min at 2 hr post-application of 120 mg Axiron™. 10 males and 10 females between the ages of 18 and 45 yr were enrolled. The application site was covered with a 100% cotton long sleeve T-shirt prior to the transfer procedure. Female subjects underwent intensive PK sampling for a 24 hr period for baseline characterization. Study results show approximately 13% increase in both geometric mean total T AUC(0-24) and Cavg values following the transfer procedure. Although some marginal increases in total T concentrations compared to baseline may occur following the transfer procedure in the presence of clothing covering the application area, covering the application area with clothing highly reduces the transfer of T from Axiron™.

Drug-Drug Interactions
No drug-drug interaction (DDI) studies were conducted with Axiron™.

Bioanalytical Methods
Serum samples were analyzed for total T and dihydrotestosterone (DHT) by validated bioanalytical methods including radioimmunoassays (RIA), liquid chromatography-mass spectrometric (LC-MS), and liquid chromatography-tandem mass spectrometric (LC-MS/MS) methods. The determination of sex hormone binding globulin (SHBG) for the Phase 3 study samples was performed using an enzyme immunoassay. Acceptance criteria and assay performance for each analyte were in compliance with the *Bioanalytical Method Validation*

CTDL Comment:
I concur with Dr. Yu's review and *recommendation.*

6. Clinical Microbiology

The microbiology reviewer, Dr. Robert Mello made the following recommendations:

Recommendations
A. Recommendation on Approvability – Recommend Approval

B. Recommendations on Phase 4 Commitments and/or Agreements, if Approvable – N/A

Summary of Microbiology Assessments

A. Brief Description of the Manufacturing Processes that relate to Product Quality Microbiology – The drug product is an alcoholic solution [redacted] (b) (4)

Ethanol [redacted] (b) (4) and isopropanol [redacted] (b) (4)

B. Brief Description of Microbiology Deficiencies – None

C. Assessment of Risk Due to Microbiology Deficiencies – N/A

CTDL Comment*:*
I concur with Dr. Mello's conclusion and recommendation.

7. Clinical/Statistical- Efficacy

Clinical Program for Efficacy
Study MTE08 was reviewed for the purpose of establishing the efficacy of Axiron.
Study MTE09 was the extension of Study MTE08 to evaluate skin safety.
Study MTE10 was reviewed to evaluate the effect of using deodorant or antiperspirant on the efficacy of Axiron and also to evaluate the effect of washing the application site on efficacy.

7.1 Design, Primary Objective and Efficacy Assessment

Design:
Study MTE08 was a multinational Phase III, open-label, titration trial to evaluate the efficacy and safety of AXIRON in the treatment of hypogonadal men, while Study MTE09 was the extension of Study MTE08 with additional 60-day administration of final titration dose to evaluate the skin safety. Study MTE08/09 was conducted in 26 centers across 6 countries: 4 centers in Australia, 3 centers in Germany, 2 centers in France, 3 centers in UK, 2 centers in Sweden, and 12 centers in USA.

All eligible subjects started with one starting dose of 3 mL (60 mg) and were titrated to a lower dose or a higher dose twice during the study. Subjects with total testosterone levels of < 300 ng/mL and who satisfied other inclusion/exclusion criteria received starting dose of 3 mL (60 mg) at the beginning of the study. Two titrations on Day 45 and on Day 90 were performed after the initial treatment. On Day 15, all subjects were to undergo pharmacokinetic (PK) sampling. On Day 45 if a subject's day-15 testosterone (C_{avg}) was within the normal range (300-1050 ng/dL), the subject continued the starting 60 mg dose, otherwise, he was titrated to either the lower dose (30 mg) or to the higher dose (90 mg) on Day 45. On Day 60, PK samples were

repeated. On Day 90, subjects with their day-60 testosterone (C_{avg}) out of normal range received a final dose titration. All subjects remained in their final titrated dose until Day 120. On Day 120, the final PK samples were obtained.

Immediately after Day 120, about 71 subjects continued their maintained dose for additional 60 days. On Day 150 and Day 180, their vital signs, concomitant medication, adverse events and a Draize score were taken. The follow-up visit for Study MTE08/09 were between Day 7 to Day 10 after the final dose.
The treatment duration was 120 days for Study MTE08 and 60 days for Study MTE09.

The primary objective of the Study MTE08 was to determine the proportion of subjects having C_{avg} total testosterone levels within the normal range (300-1050 ng/dL) on Day 120.

- Safety Set – 155 subjects received at least one dose of study drug.
- Completer Set – 138 subjects completed the study through the day 120 visit plus any subjects that withdrew prior to day 120 for reasons of efficacy or adverse event. This set is the basis for the primary efficacy evaluation.
- Full Analysis Set – 143 subjects received at least one dose of study drug and had on-treatment data for at least one efficacy variable. Analyses based on this set were considered as supportive.
- Per-protocol Set – 123 subjects completed study MTE08 with no protocol violations. Analyses based on the Per-Protocol Set were considered as supportive for the primary efficacy endpoint.

***CTDL Comment*:**
The Study design was adequate to assess the efficacy in hypogonadal men in terms of proportion of patients with normal ranging testosterone C_{avg} on Day 120.

Analysis of Primary Endpoint(s)
Primary Endpoint
The primary efficacy endpoint for MTE08 was to achieve a proportion of subjects with C_{AVG} (0-24 hours) total testosterone in the defined normal range (300-1050 ng/dL) on Day 120. As agreed upon by the Division, the product would be considered to have achieved this endpoint if the observed response rate was ≥75% of subjects, with the lower limit of the 95% confidence interval (CI) >66.8% on day 120.

Results: Table 4 shows the proportion of subjects having C_{AVG} total testosterone within the normal range at three time points (Day 15, 60 and Day 120).

Table 4: Proportion of Subjects with Serum Total Testosterone C_{AVG} in the Range of 300 – 1050 ng/dL (Percent, 95% CI, N)

Data Set	Day 15/16	Day 60/61	Day 120/121
Completer Set (N=138)	76.1% (69.0 – 83.2) 105/138	84.8% (78.8 – 90.8) 117/138	84.1% (78.0 – 90.2) 116/138
Full Analysis Set (N=143)	77.6% 111/143	86.2% 119/138	84.1% 116/138

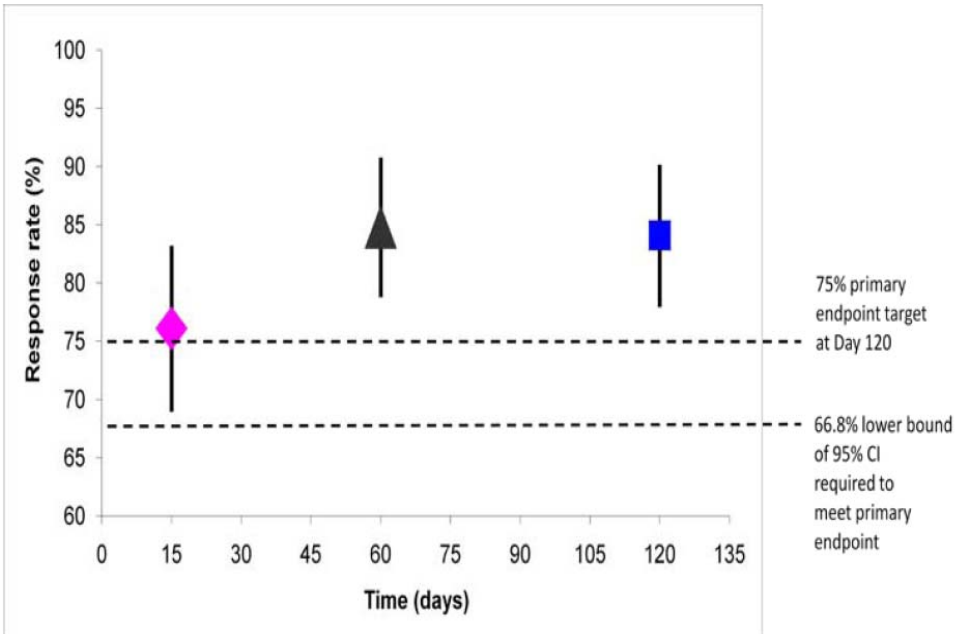
Source: NDA 22504, Module 5.3.5.2, Table 11-1, page 92.

Table 5: Number and percent of subjects with Serum Total testosterone PK levels on Day 120 (N=138, Completers Population)

PK Levels	N (%)	95% CI	
C_{avg} (300-1050) ng/dL	*116 (84.1)*	*(78.0, 90.2)*	
C_{max}:			
<1500 ng/dL	*7 (5.1)*	*(1.4, 8.7)*	
>1800ng/dL and ≤ 2500 ng/dL	*4 (2.9)*	*(0.1, 5.7)*	
>2500ng/dL	*1 (0.7)*	*(0.0, 2.1)*	
C_{min} <300ng/dL	*90 (65.2)*	*(57.3, 73.2)*	

Source: MO analysis

Figure 2: Proportion of Subjects with Serum Total Testosterone C_{AVG} in the Range of 300 – 1050 ng/dL



Source: NDA 22504, Module 5.3.5.2, Figure 11-1

CTDL Comment:
The Sponsor has demonstrated that Axiron is effective in normalizing serum testosterone levels in men who are hypogonadal. They have also demonstrated the pre-specified criteria for efficacy after a single titration, i.e., 15 days following initiation of therapy. The second titration at 60 days did not meaningfully change the proportion of subjects having serum testosterone within the normal range.

Additionally, the dihydrotestosterone levels similarly increased with treatment. Mean DHT concentration at the time of enrollment was 18.7 ng/dL, that increased to 90.5 ng/dL on day 120.

Free testosterone levels were calculated using testosterone, SHBG and albumin levels. As a calculated fraction of total testosterone levels, free testosterone levels (C_{avg}, C_{max} and C_{min}) as well as the t_{max} mirrored those of total testosterone. The geometric mean levels increased from 56.7 pg/ml prior to initiation of drug treatment to 121 pg/ml on day 120.

Secondary Endpoints
The following secondary efficacy endpoints were evaluated.

- The proportion of subjects with total testosterone C_{MAX} <1500 ng/dL. As agreed upon by the Division, the product would be considered to have achieved this endpoint if >85% of subjects had C_{MAX} <1500 ng/dL on day 120.
- The proportion of subjects with total testosterone C_{MAX} between 1800 ng/dL and 2500 ng/dL. As agreed upon by the Division, the product would be considered to have achieved this endpoint if 5% of subjects had C_{MAX} in this range on day 120.
- The proportion of subjects with total testosterone C_{MAX} >2500 ng/dL. As agreed upon by the Division, the product would be considered to have achieved this endpoint if no subjects had C_{MAX} >2500 ng/dL on day 120.
- The proportion of subjects with total testosterone C_{MIN} <300 ng/dL.
- Quality of Life Assessments
    - SF-36 mental and physical components.
    - Psychosexual Social Questionnaire evaluating sexual desire and enjoyment, mood, sexual activity and sexual performance.

Results:
Table 6: shows the data for three secondary endpoints that are based on pharmacokinetic data.

Table 6. Secondary Serum Total Testosterone Pharmacokinetic Endpoints (Completer Set)

Data	Target	Day 15/16	Day 60/61	Day 120/121
C_{MAX} < 1500 ng/dL	> 85%	95.6% 130/136	91.2% 124/136	94.5% 128/135
C_{MAX} > 2500 ng/dL	0	1.5% 2/136	1.5% 2/136	0.7% 1/135
C_{MAX} >1800 and ≤2500 ng/dL	*< 5%*	*2.2%* *3/136*	*4.4%* *6/136*	3.0% 4/135

Source: NDA 22504, Module 5.3.5.2, Table 11-2, page 93

Proportion of subjects with C_{MAX} less than 1500 ng/dL

At each PK sampling period the number of subjects in the Completer Set with Cmax below 1500 ng/dL was always greater than 90% and at Day 120 it was 94.8%. At all time points, the trial target of more than 85% of subjects with their Cmax below 1500 ng/dL was achieved. Across the entire trial 87.5% of subjects had a Cmax<1500 ng/dL.

Proportion of subjects with Serum Total Testosterone C_{MAX} between 1800 ng/dL and 2500 ng/dL

At each of the intensive PK sampling days this target was met and at Day 120 the number of subjects who fell into this category numbered 4 out of 135 or 3.0%. Of the four subjects at Day 120 who fell into this category only one had a reasonably sustained level of testosterone between 1800 and 2500 ng/dL and this was mirrored by increases in DHT as well. However, this subject's testosterone level remained within the normal desired range after a single titration.

Proportion of subjects with Serum Total Testosterone C_{MAX} greater than 2500 ng/dL

During the course of the trial five patients had a C_{MAX} >2500 ng/dL at some point. These patients are shown in Table.

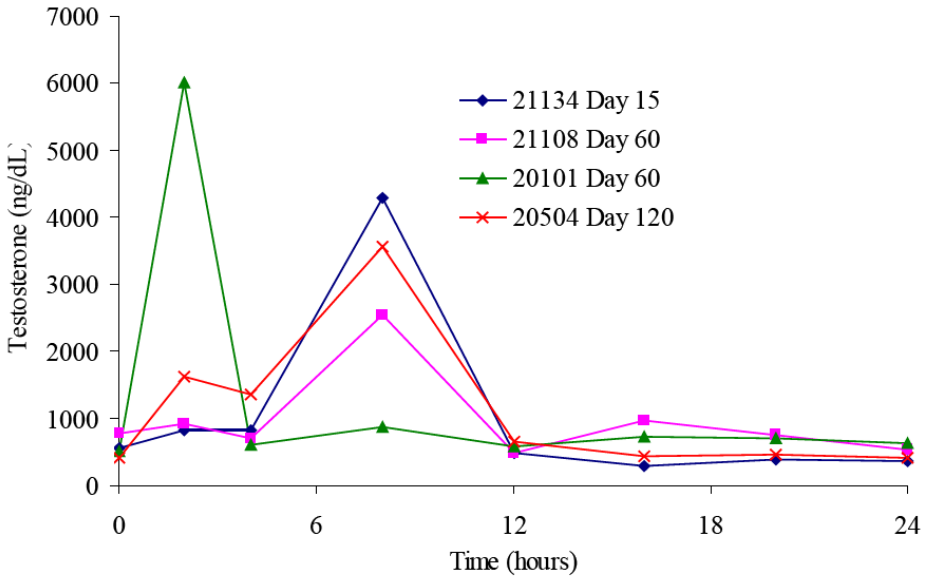
Table 7: Subjects with Serum Total Testosterone C_{MAX} >2500 ng/dL

Subject	C_{MAX} (ng/dL)	T_{MAX} (hours)	pK Sampling Day
21134	4280	8	Day 15
21139	3247	12	Day 15
21108	2554	8	Day 60
20101	5996	2	Day 60
20504	3457	8	Day 120

Source: NDA 22504, Module 5.3.5.2, Table 11-3, page 94

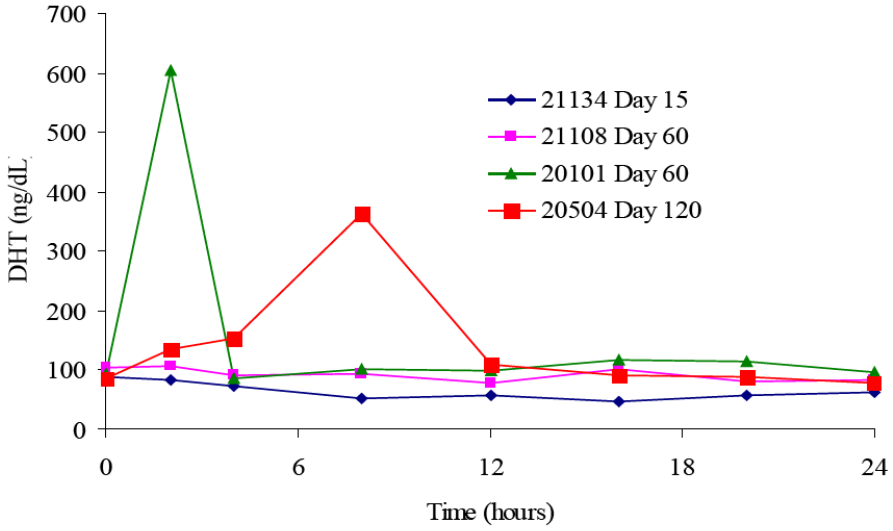
An analysis of the pharmacokinetic data for the five subjects shows that, in four of the five, the elevated value is a single point that appears to be out of line with respect to the data points on either side of it. Figure 3 and Figure 4 show a graphical representation of the testosterone and DHT pK data for these four subjects on the day on which the elevated C_{MAX} was seen.

Figure 3: Serum Total Testosterone pK Profiles for Four Subjects having C_{MAX} >2500 ng/dL



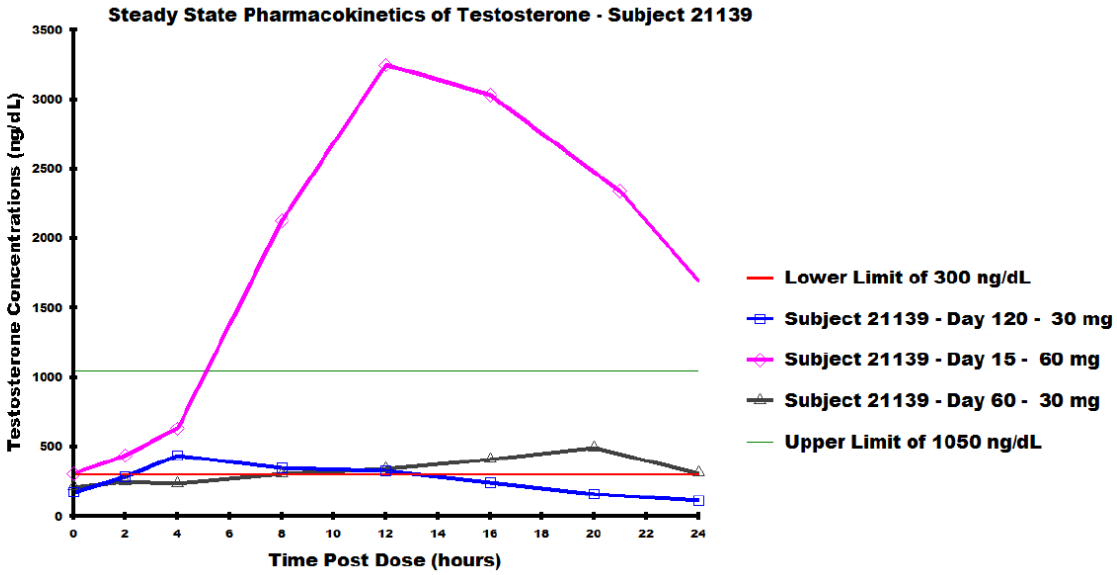
Source Data: Report on Pharmacokinetic Assessment, Appendix 12.0 Individual PK Profiles (Appendix 16.1.9)

Figure 4: Serum DHT pK Profiles for Four Subjects having Testosterone C_{MAX} >2500 ng/dL



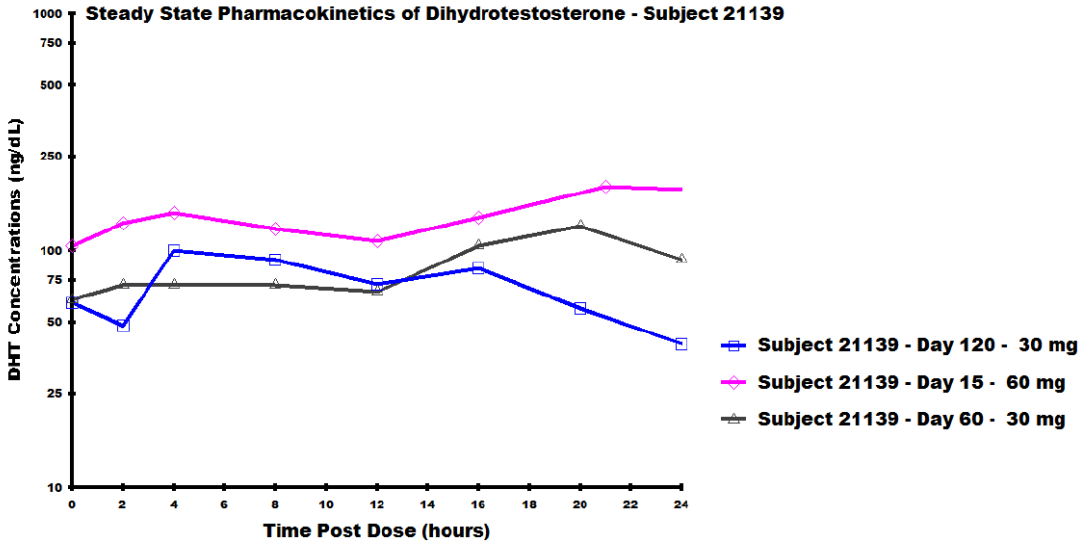
Source Data: Report on Pharmacokinetic Assessment, Appendix 12.0 Individual PK Profiles (Appendix 16.1.9)

Figure 5: Subject 21139 Total Testosterone Concentration



Source: NDA 22504, Module 5.3.5.2.12, page 444

Figure 6: Subject 21139 DHT Concentration



CTDL Comment:
In two of the four subjects, 21134 and 21108, the testosterone elevation was not accompanied by any significant elevation of DHT. Therefore, in my opinion, in these subjects the testosterone elevation is more likely secondary to contamination of the blood sample.

In the other two subjects (20101 and 20504), high levels of testosterone were mimicked by a high level of DHT, suggests systemic exposure to these levels of testosterone for short periods of time (< 4 hours). However, the transient and incongruous nature of this exposure, suggests contamination of the blood draw site with testosterone and subsequent absorption from this contamination. This likely occurred because the testosterone solution after application came in contact with the blood sampling port and is anatomically quite feasible given the relative proximity of the dosing site and blood draw site.

The incident of a Cmax >2500 ng/dL that occurred in Subject 21139 was associated with a pattern of apparently sustained exposure. However, this apparent increase in testosterone was not accompanied by a parallel increase in DHT suggesting that contamination of the sample set for this subject must have occurred after the samples were taken. Indeed, comparison of Figure …4 and Figure …5 indicate a decline in DHT at the time the testosterone levels were rising in Subject 21139.

Other Subpopulations Evaluated:
Pediatric Use
No pediatric studies were conducted. Safety and efficacy of Axiron™ has not been established in males < 18 years of age. This is reflected in the product labeling.

Use in Women
Axiron™ is contraindicated for pregnant or breast feeding women. Precaution should be taken for unintentional secondary exposure. This is reflected on the product labeling.

Geriatric Use
There have not been sufficient numbers of geriatric patients involved in controlled clinical studies utilizing Axiron™ to determine whether efficacy in those over 65 yr of age differs from younger subjects. 21 geriatric patients of over 65 yr of age (out of a total of 155 patients) were enrolled in the pivotal Phase 3 clinical study utilizing Axiron™.

Patients with Renal/Hepatic Impairment
No studies were conducted in patients with renal or hepatic impairment.

Subject Disposition

There were one hundred fifty-five subjects enrolled in study MTE08. Twenty subjects were subsequently withdrawn from the study. Of the 20 subjects who discontinued the study, three did so because of adverse events. The remainder discontinued because of withdrawal of consent, lack of compliance, or being lost to follow-up. The subjects that discontinued due to an adverse event were: superficial thrombophlebitis (not thought to be drug related), malenoma of scalp (from a prior existing scalp mole that progressed to melenoma) and a subject who continued to have emotional changes.

Table 8: Reasons for Withdrawal from Study MTE08

Reason for Withdrawal	Number of Subjects
Withdrew consent	9
Non-compliance with study drug	3
Lost to follow-up	2
Non-compliance with site directives	1
Sponsor request	1
Screening Testosterone level >300 ng/dL	1
AE: Superficial thrombophlebitis	1
AE: Melanoma of scalp	1
AE: Emotional changes	1

Source: NDA 22504 submission, Module 5.3.5.2, Table 10-1

CTDL Comment: There *were only three subjects who withdrew because of an adverse event. As per the primary medical officer's review, the subject who developed* superficial thrombophlebitis was not related to the drug. The second subject had a prior existing mole present on the scalp that progressed to melanoma. The third subject also had prior history of emotional disorder. However, in the opinion of the primary medical reviewer, the study drug might have contributed to the precipitation of his emotional status and I concur with that.

7.4 Statistical Review:

The statistical review team Xin Fang and Mahboob Sobhan from the Division of Biometrics III concluded that the efficacy data from a single study (Study MET08) support the efficacy of AXIRON as testosterone replacement therapy in hypogonadal men. The proportion of subjects with Cavg total serum testosterone within the normal range (300-1050 ng/dL) at day 120 was 84.1%; with the lower bound of the 95% confidence interval for the point estimate was 78%, greater than 66.8% limit set by the Division.

From a statistical perspective, the efficacy has been demonstrated in support of the transdermal 2% testosterone solution (Axiron) as the testosterone replacement therapy for conditions associated with androgen deficiency.

Label:

We agree to include day 15 efficacy data in Table 3 of section 14.1 of the label.

***CTDL Comment**:*
I concur with the assessment of Xing Fang and Mahboob Sobhan from the Division of Biometrics III.

8. Safety

Studies MTE07, MTE08, MTE09, MTE10, MTE11 and MTE12 are the major source of safety information since they were done using the to-be-marketed 2% Testosterone solution. Studies DDS08, DDS15, DDS16, MTE04, MTE05, and MTE06 were considered as supportive since they used formulations that differed from the to-be-marketed formulation.

8.1 Safety Population and Overall Exposure

There were 155 subjects who were exposed to all doses of Testosterone solution, i.e., 30mg, 60mg, 90mg and 120mg. Demographics included an age range of 19-78, with a good representation of all races, mean weight ranging from 59-126kg's and BMI ranging from 18.2-38.9.

Table 9: Exposure to Testosterone Solution – Studies MTE08 and MTE09

	Number of Patients With Exposure to Solution for			
Dose	**≥30 Days**	**≥90 Days**	**≥120 Days**	***≥180 Days***
Any Dose	149	147	134	*51*
30 mg/Day	3	2	0	*0*
60 mg/Day	137	107	97	*40*
90 mg/Day	34	8	5	*0*
120 mg/Day	9	3	0	0

Source: MO Analysis of Module 5.3.5.2.25.3.1, Analysis Dataset ADSL

***CTDL Comment:** Exposure to testosterone solution appears to be adequate as was specified at the End-of-Phase 2 meeting.*

8.2 Demographics

Table 10: Demographics - Study MTE08 and MTE09

	Maintenance Dose of Testosterone Solution				
	All Doses N=155	**30 mg N=3**	**60 mg N=117**	**90 mg N=25**	**120 mg N=10**
Age					
Mean	51.5	57.3	51.3	52.9	48.7
Range	19 – 78	51 – 65	19 – 78	25 – 75	30 – 62
Race					
Asian	1 (0.7%)	0	1 (0.9%)	0	0
Caucasian	122 (84.7%)	2 (66.7%)	94 (86.2%)	19 (86.4%)	7 (70%)
African American	6 (4.2%)	0	2 (1.8%)	3 (13.6%)	1 (10.0%
Hispanic	13 (9.0%)	1 (33.3%)	10 (9.2%)	0	2 (20.0%)
Other	2 (1.4%)	0	2 (1.8%)	0	0
Weight (kg)					
Mean	94.4	83.4	94.5	94.6	95.1
Range	59.1 – 126.1	79.4 – 90.3	59.1 – 126.1	75.5 – 119.7	75.9 – 123.6
BMI (kg/m^2)					
Mean	29.5	28.1	29.6	29.7	29.1
Range	*18.2 – 38.9*	*24.8 –34.4*	*18.2 – 38.9*	*24.6 – 35.0*	23.9 – 34.8

Source: Module 5.3.5.2.3, Table 14.1.2.1

***CDTL Comment**: As per primary reviewer, Dr. McNellis's review, the subjects requiring only a 30 mg/day dose of testosterone are lighter in weight, and with a lower BMI than other subjects. Overall, the demographics of the study population appear to be representative of the target population for this medication.*
I concur with the primary reviewer's observation.

8.3 Adverse Events

The most common adverse events were application site erythema/irritation/edema, increased hematocrit, headache, diarrhea, vomiting, increased PSA and nasopharyngitis.

Table 11: Common Treatment-emergent Adverse Events (>2%) occurring in Study MTE08

Medra SOC Preferred Term	Dose of Testosterone Solution				
	30mg N (%)	60mg N (%)	90mg N (%)	120mg N (%)	Overall N (%)
Subjects with at least one TEAE	3 (75%)	71 (45.8%)	13 (37.1%)	5 (50.0%)	81 (52.3%)
Total number of TEAEs	4	177	31	8	220
General Disorders and Administrative Site Conditions					
Application site erythema	0	8 (5.2%)	0	0	8 (5.2%)
Application site irritation	0	10 (6.5%)	1 (2.9%)	1 (10%)	12 (7.7%)
Infections and Infestations					
Nasopharyngitis	0	5 (3.2%)	1 (2.9%)	0	6 (3.9%)
Investigations					
Hematocrit increased	0	5 (3.2%)	1 (2.9%)	0	6 (3.9%)
PSA Increased	0	2 (2.8%)	1 (5.0%)	0	3 (4.2%)
Nervous System Disorders					
Headache	0	8 (5.2%)	0	0	8 (5.2%)
Gastrointestinal Disorders					
Diarrhea	0	2 (1.3%)	2 (5.7%)	0	4 (2.6%)
Vomiting	0	3 (1.9%)	1 (2.9%)	0	4 (2.6%)

Source: NDA 22504, Module 5.3.5.2.3, Table 12-3.

CTDL Comment: *It is reasonable to say that the application site erythema and irritation, increased hematocrit and PSA change are likely drug related. Skin reactions and increase in hematocrit were mild and did not require any further medical intervention or discontinuation of medication. The highest level for hematocrit increase was 61% seen in a subject at Day 180. The entry cut off for hematocrit was 54% for this study. There were three subjects with an increase in PSA. However, there was only one subject with a rise in PSA that resulted in obtaining a prostate biopsy for confirmation of diagnosis of prostate cancer. In my opinion this subject had an underlying low grade prostate cancer prior to joining this study. Increase in PSA is a recognized feature associated with testosterone therapy. Therefore, with an increase in PSA, that prompted obtaining a biopsy lead to a positive diagnosis that was unrelated to the study drug.*

8.4 Deaths

There were no subject deaths during the clinical studies evaluating this product.

8.6 Events of Special Interest seen with Testosterone products

As expected with all testosterone products, there was an increase in PSA seen in 3 subjects and an increase in hematocrit seen in 7 subjects. These were reported as adverse events during studies MTE08 and MTE09.

Table 12: Elevated PSA and Hematocrit

	Dose of Testosterone Solution				
	30 mg	**60 mg**	**90 mg**	**120 mg**	**Overall**
Elevated PSA (>4 ng/ml)	0	2 (1.7%)	1 (4.0%)	0	3 (1.9%)
Elevated Hematocrit (>54%)	0	6 (5.1%)	1 (4.0%)	0	7 (4.5%)
Elevated Hemaglobin (>18.1)	*0*	*2 (1.7%)*	*0*	*0*	2 (1.3%)

Source: NDA 22504, Module 5.3.5.2.3, Table 12-14.

PSA Increase: In two of the three subjects there was an increase in the PSA from the baseline after treatment with Axiron, which normalized by Day 120 (the primary end point). However, in the third subject, the PSA increased from 1.27 at baseline to 7.28 and 6.36 when repeated. He was withdrawn from the study MTE09. He was refered to a Urologist for further investigation of his elevated PSA. A prostate biopsy was obtained which revealed evidence of prostate cancer.

CDTL Comment:
In my opinion, evidence of cancer from the biopsy can not be likely from four months of testosterone therapy, however, testosterone therapy likely lead to his PSA increase (as is commonly seen with testosterone therapy) which in turn helped in the diagnosis of already existing low grade prostate cancer.

Elevated Hematocrit: Hematocrit entry criteria for MTE08 and MTE09 was <51%. However, at DAY 120, there were seven subjects with Hct. level >54%.

Table 13: Subjects with Hematocrit >54%

Subject	Screening Hct	Maximal Hct	Final Hct	Screening Testosterone	Day 120 C_{AVG}	Maintenance Dose of Testosterone Solution
202-11	48	61	57	271	945	90 mg
203-21	51	57	53	26	697	60 mg
207-02	50	58	54	324	889	60 mg
210-05	48	55	53	256	256	60 mg
210-07	51	58	57	241	362	60 mg
211-26	45	61	61	280	433	60 mg
212-03	45	55	54	301	650	60 mg

Source: MO Analysis

CDTL Comment: *The rise of hematocrit with testosterone therapy is well known. This study excluded the enrollment of subjects with a hematocrit >51%. However, there were seven subjects with a HCT. level of > 54%. In most of these seven subjects the*

Hct. ranged from 53% to 57% at Day 120, with only one subject at 61%.This subject with HCT. 61% was not allowed to continue on to the extension study MTEo9. None of these seven subjects required any further medical intervention or dose adjustment.

Application Site Reactions:
In studies MTE08 and MTE09, the effect of Axiron, topical solution on the application site was evaluated using a categorical (Draize) scale with subsets of erythema and edema. The highest Draize score of 8 was considered as significant.

The site of application was evaluated at every study visit. The majority of subjects did not register a Draize score of greater than zero at any time point.

All Draize scores of greater than zero were reported at the 60 mg dose and all events were transient in nature. In addition to the above objective measurements of skin irritation, AEs related to the sensation of irritation reported by the subjects at each study visit were recorded.

In MTE08, 7/155 subjects (4.5%; six at the 60 mg dose and one at the 120 mg dose) reported Application Site Irritation (transient burning sensation at the site of application).

In the MTE09 study, one subject (on the 90 mg dose) experienced this type of event and the subject withdrew from the study.

***CTDL Comment**: Application site reactions and irritation do not appear to be a significant clinical issue with this product.*

Abnormal Laboratory Findings: There were no significant abnormal laboratory findings i.e, cholesterol, LDL, HDL, triglycerides, AST, ALT, bilirubin, creatinine, WBC and platelet count associated with Axiron treatment during the clinical trials MTE08 and MTE09.

9. Advisory Committee Meeting

No Advisory Committee meeting was held for this new application.

10. Pediatrics

The Applicant requested a full waiver of the requirement to conduct assessments of Testosterone solution in pediatric patients.

We are waiving the pediatric study requirement for this application because the necessary studies would be impossible or highly impractical and there are too few children with the disease/condition to study.

11. Other Relevant Regulatory Issues

Division of Scientific Investigation (DSI)

There were three **clinical sites** selected by Clinical-Pharmacology Review team. Inspections of clinical portions were conducted for study MTE08 and MTE09 at:
Site-l: Regional Urology (Regional), Shreveport, LA
Site-2: Deerfoot Internal Medicine (Deerfoot), Birmingham, AL
Site-3: Northwest Clinical Trials (Northwest), Boise, ID
No Form FDA-483's were issued for Shreveport, LA and Birmingham, AL sites. However, a Form FDA-483 was issued for Boise, ID clinical site. General Health Screen Information and Consent Forms, that were not IRB approved, and were signed by the subjects prior to evaluating them for pre-screening for the study were identified as the only deficiency.

The firm's response was received on August 16, 2010. The response was reviewed by DSI and **found to be acceptable**.

***CTDL Comment**:*
Clinical team concurs with DSI.

The clinical-Pharmacology team also requested DSI to conduct two analytical site Inspections.

1. (b) (4) (study MTE06 for TT, DHT, and SHBG)
2. (b) (4) (studies MTE07, MTE08, MTE09 and MTE10 for TT and DHT).

(b) (4) TT and SHBG runs using incorrect QC concentrations were reviewed. The TT QC results using lot TESM4A remain acceptable. However, SHBG QC errors did not affect acceptance of any runs. (b) (4) response indicates that the observed errors were only in their analytical report, and that the actual run acceptance/rejection decisions used the correct values. The firm indicated that they would require additional review and approval to complete future final reports.
DSI recommends this is acceptable.

(b) (4) the reported frozen stability study was questionable, as results of the stability QC samples were not compared to freshly prepared reference QC samples. During the inspection, DSI noted that the reference QCs were prepared and frozen a day prior to analysis and they considered these samples as fresh.

In their response to Form FDA-483, (b) (4) acknowledged this observation and revised their SOP and now requires using fresh reference QCs.

DSI recommended that (b) (4) should demonstrate stability of TT and DHT by comparing results of the stability QC samples to results of the freshly-prepared reference QC samples or their nominal values in future studies. *The matrix stability studies for TT and DHT audited in the present inspection were found to be acceptable when results of the stability QC samples were compared to the nominal values.*

CTDL Comment:
Response from (b) (4) was acceptable to both DSI and to the Clinical-Pharmacology review team.

Dr. Chonwoo Yu (Clinical Pharmacology Reviewer) wrote the following:
Following a detail examination of the Study MTE06 data, it was found that samples of 2 subjects (i.e., Subjects 19 and 20 of Run 07080981) of Part a (interpersonal transfer study) were part of the runs identified with deficiencies.

However, data from these subjects were not used in making any conclusions of the study or any recommendations on the product labeling. Therefore, it does not affect OCP's final recommendation on the product approval.

As noted in the Clinical Pharmacology Individual Study Review dated November 17, 2010 in DARRTS, SHBG was not the primary analyte of interest and was not reviewed in detail. Therefore, the deficiency of SHBG data does not affect OCP's recommendation on the product approval.

ISR assessment is a good practice that the Agency is recommending to Sponsors since the February 8, 2008 Crystal City meeting (on GLP Bioanalysis) held in Arlington, VA and it provides confidence in the assay reproducibility for analyses of subject samples. However, given that the bioanalytical method validation and bioanalytical study performance of the studies mentioned above had no major deficiencies observed, the lack of ISR assessment data alone should not delay approval. It should be noted that while the Bioanalytical Method Validation Guidance is currently being updated with recommendations of ISR assessments, currently it does not require the submission of the ISR assessment data.

CDTL Comment:
I concur with the Clinical Pharmacology Reviewer's conclusion and assessment of DSI identified deficiencies.

Division of Medication Errors and Prevention (DMEPA)
The DMEPA review team made the following recommendations:

The **Proprietary Name** Risk Assessment findings indicate that the proposed name, Axiron, is not vulnerable to name confusion nor is the name considered promotional. Thus, the Division of Medication Error Prevention and Analysis (DMEPA) has **no objection** to the proprietary name, Axiron, for this product at this time. DMEPA considers this a final review.

DMEPA review team also made recommendations for the label and the carton container. All the recommended changes for the label were incorporated. However, for carton container, after relatively extensive discussions between chemistry review team and the DMEPA review team, final recommendations were incorporated into the carton container i.e.

Revised Retail Container Label (front panel and back panel)

(b) (4)

Revised DMEPA Recommendation, Dated November 19, 2010.
Review of the revised documents show that the Applicant implemented DMEPA's recommendations under OSE review #2010-367. The revised labels and labeling are also reflective of recommendations agreed upon between the Office of New Drug Quality Assessment (ONDQA) and DMEPA. DMEPA has no additional recommendations at this time.

Division of Drug Advertising, Marketing and Communication (DDMAC)
DDMAC reviewer, Janice Maniwang reviewed both the PI and the Medication Guide for AXIRON and provided the input and recommendations. All the recommendations from DDMAC were consistent with Androgel 1% PI and Testim 1% PI. These were incorporated into the label and the medication guide as appropriate.

Division of Risk Management (DRISK)
Shawna Hutchins, Patient Labeling Reviewer (DRISK) made the following recommendations:

Recommendations:
DRISK concurs with the elements of the REMS as proposed by the applicant.

Please note, the timetable for submission of the assessment is required to be approved as part of the REMS, but not the Applicant's proposed information about the details of the REMS evaluation (methodology/instruments). The methodology and instruments do not need to be reviewed or approved prior to approval of the REMS.

DRISK had comments and recommendation about the time lines and goals that were incorporated into the REMS document. The REMS document was accepted by the sponsor.

SEALD
Laurie Burke, OND Associate Director for Labeling had the following Recommendation: **Dated: November19, 2010.**
This memo confirms that all critical prescribing information (PI) deficiencies found in the SEALD Labeling Review filed 17 November 2010 for this application have been addressed.

SEALD agrees with the Division that the PI is ready for approval at this time.

12. Labeling

A substantially complete draft label was sent to the sponsor on –November 1st, 2010. A complete draft label was sent to the sponsor (second round) on November 10th, 2010. A teleconference was held between the sponsor and all involved disciplines on November 15, 2010. Label was finalized between the sponsor and the Division on November 18, 2010.

Proprietary name:

Axiron is the proprietary name that was approved by DMEPA earlier during this review cycle.

Key Safety issues/labeling changes:

Highlights of PI:

Boxed Warning

- The boxed warning that has been adopted by other topical testosterone products was also included in the Axiron label. This boxed warning discusses the potential for interpersonal transfer of testosterone and the consequences of that transfer.

Indication and Usage

- Important Limitations of Use: Safety and Efficacy of Axiron in males <18years old have not been established. This statement was introduced into the Indication and Usage section as per SEALD recommendation.

Dosage and Administration

- The application site and dose of Axiron are not interchangeable with other topical testosterone products. This statement was added to the D and A section.

Dosage Forms and Strengths

- After extensive discussions between Chemistry review team and DMEPA review team, the following language was agreed upon and introduced into the Dosage Forms and Strengths section. Axiron (testosterone) topical solution is supplied as a metered dose pump, capable of dispensing 90 ml of solution in 60 metered doses. 1 pump actuation delivers 30mg of testosterone in 1.5ml of solution.

Warnings and Precautions

- Monitoring of patients for worsening signs and symptoms of BPH was included into the W/P section.
- Monitoring of serum PSA and Hematocrit periodically were also included in the W and P section.

Adverse Reactions

- Adverse Events were revised to Adverse Reactions as per the SEALD guidance.

Clinical Section 14.1

- Day 15, responder rate data was included into Table 3 of Section 14.1 with a foot note that states the following: On Day 15, 72.2% of the 90 subjects in the US population had an average serum testosterone in the range of 300-1050ng/dl.

- Figure showing mean (SD) steady state serum testosterone concentrations on Day 120 (30, 60,90 or 120mg testosterone) in patients who completed 120 Days of Axiron once daily treatment after appropriate titrations, was included into section 14.1 of the label.

CTDL Comment:
Labelling language as discussed above was incorporated into the Highlights section of Axiron label.

Additionally, responder rate for Day 15, 60 and Day 120 was incorporated into the clinical section of the label. The Day 15 responder rate demonstrates the response without any titration. However, Day 60 and Day 120 response rates show the effect on overall response of one or two titrations. This information will be useful to the prescribing physicians and will demonstrate the importance of titrations.

During the labeling negotiation with the sponsor on November 15th, 2010, sponsor proposed to include a figure in the clinical section (14.1) of the label to demonstrate serum testosterone concentrations on Day 15 and Day 120 in patients who completed 120 Days of Axiron once daily treatment. This was discussed with the clinical-pharmacology review team on November 17th, 2010. Clinical-pharmacology review team (Chongwoo Yu and MJ-Kim) agreed with the clinical review team to include this graph in the clinical section 14.1 of the label with ***only Day 120 data****. Sponsor was asked to delete the Day 15 data from the proposed graph, and they agreed to do so before a final label was agreed upon.*

It is my strong belief as the CDTL, that inclusion of this figure (showing Day 120 data) in the clinical section of the label, not only demonstrates accurate, but worthwhile information for the prescribing physicians.

Carton Container:

1 pump actuation delivers 30mg of testosterone in 1.5ml of solution. This verbiage was negotiated and agreed upon by Chemistry review team and DMEPA (OSE) review team for the carton container.

Medication guide was negotiated between the Division, sponsor and DRISK. A substantially complete draft Medication guide was also sent to the sponsor on November 10th, 2010.

13. Recommendations/Risk Benefit Assessment

Recommended Regulatory Action:
In my opinion, the sponsor has provided sufficient evidence for efficacy and safety in support of this NDA (22,504). Therefore, an approval action should be granted for AXIRON 2% topical solution.

Risk Benefit Assessment

A comprehensive review of NDA 22,504 by the clinical review team has provided substantial evidence that the Sponsor's testosterone solution will have the effect claimed in labeling. This claim is that this solution is an effective treatment for men with hypogonadism. This testosterone solution was efficacious in achieving its primary endpoint and two of three secondary efficacy endpoints. No significant safety issues were detected.

The primary objective for MTE08 was to establish that the percentage of subjects with C_{AVG} total testosterone levels within the normal range (300-1050 ng/dL) on Day 120 of the study was greater than 75%. *The study showed that 84.1% of subjects had a normal testosterone on Day 120.*

There were three secondary objectives of the study, all evaluated at Day 120.

- Establish the percentage of subjects with C_{max} > 1500 ng/dL. This should be less than 15% of subjects; *the study result showed this to be 5.2%.*
- Establish the percentage of subjects with C_{max} between 1800 and 2500 ng/dL. This should be less than 5% of subjects; *the study result showed this to be 3.0%.*
- Establish the percentage of subjects with a C_{max} greater than 2500 ng/dL. This should be 0%; *the study result showed this to be 0.7% (1 of 135 subjects).*

Axiron has been shown to be generally safe for its intended use as recommended in the label by all tests reasonably applicable to assessment of safety. The pattern of adverse events is similar to other drugs in its class. The most common adverse events (seen in >4% of subjects) were: application site erythema and irritation, nasopharyngitis, increase in hematocrit and PSA, headache, diarrhea, and vomiting.

The potential for transfer of testosterone to another individual by direct contact was evaluated by the Sponsor. This evaluation showed that direct skin-to-skin contact resulted in significant transfer. However, a clothing barrier (T-Shirt) was shown to be effective in preventing clinically significant transfer.

The ability to wash the product from the skin was also evaluated. This study showed that approximately 5% of the applied testosterone remained on the skin following washing the application site with soap and water.

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

Recommendation for Post marketing Requirement

No post marketing requirement was requested by the primary Medical Officer.

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

/s/

SURESH KAUL
11/23/2010

GEORGE S BENSON
11/23/2010