

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*  
**022504Orig1s000**

**CHEMISTRY REVIEW(S)**

**NDA 22-504****Axiron (testosterone) topical solution****30mg of testosterone  
per pump actuation****Acrux Pharma Pty Ltd.****Hitesh Shroff, Ph.D.**  
Review Chemist**Branch IV  
Division of New Drug Quality Assessment II  
Office of New Drug Quality Assessment****CMC Review of NDA 22-504  
For the Division of Reproductive and Urologic Drug  
Products (HFD-580)**

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# Chemistry Review Data Sheet

1. NDA 22-504
2. REVIEW #: 2
3. REVIEW DATE: 19-Nov-2010
4. REVIEWER: Hitesh Shroff, Ph.D.
5. PREVIOUS DOCUMENTS: N/A

<u>Submission(s) Reviewed</u>	<u>Document Date</u>
Original	25-Jan-2010
Amendment – Quality Information	12-May-2010
Amendment – Quality/Stability Information	18-Jun-2010
Amendment – Labeling Information	16-Aug-2010
Amendment – Quality/Stability Information	03-Sep-2010
Amendment – Labeling Information	01-Oct-2010

6. SUBMISSION(S) BEING REVIEWED:

<u>Submission(s) Reviewed</u>	<u>Document Date</u>
Amendment-Labeling	19-Nov-2010

7. NAME & ADDRESS OF APPLICANT:

Name: Acrux Pharma Pty Ltd  
Address: 103-113 Stanley Street  
West Melbourne, Victoria 3003  
Lisa Jenkins, Associate Director, Kendle  
Representative: International, 441 Vine Street, Suite 500,  
Cincinnati, OH 45202  
Telephone: (513) 444-4062

## Chemistry Review Data Sheet

## 8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: AXIRON  
b) Non-Proprietary Name (USAN): testosterone  
c) Code Name/# (ONDQA only): None  
d) Chem. Type/Submission Priority (ONDQA only):  
• Chem. Type: 5  
• Submission Priority: S

## 9. LEGAL BASIS FOR SUBMISSION: 505(b)(2)

## 10. PHARMACOL. CATEGORY: Androgen

## 11. DOSAGE FORM: Topical solution

## 12. STRENGTH/POTENCY: 30 mg testosterone per pump actuation. Each pump actuation delivers 1.5 ml solution.

## 13. ROUTE OF ADMINISTRATION: Topical

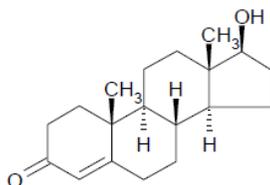
14. Rx/OTC DISPENSED:  Rx  OTC

## 15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

SPOTS product – Form Completed

Not a SPOTS product

## 16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:



## Chemistry Review Data Sheet

Testosterone

Chemical Name: 17 $\beta$ -Hydroxy-androst-4-en-3-one

Molecular Formula: C<sub>19</sub>H<sub>28</sub>O<sub>2</sub>

Molecular Weight: 288.43

### 17. RELATED/SUPPORTING DOCUMENTS:

#### C. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE <sup>1</sup>	STATUS <sup>2</sup>	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	II		(b) (4)	3	Adequate	26-JAN-2010	Last reviewed for NDA 21-015
	III		4	N/A			
	III		3	Adequate	16-May-2007	Last reviewed for NDA 21-015. (b) (4)	
	III		4	N/A		(b) (4)	
	III		4	N/A			
	III		4	N/A			
	III		4	N/A			
	III		4	N/A			

<sup>1</sup> Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 – Type 1 DMF

3 – Reviewed previously and no revision since last review

4 – Sufficient information in application

5 – Authority to reference not granted

6 – DMF not available

7 – Other (explain under "Comments")

<sup>2</sup> Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

Chemistry Review Data Sheet

**B. Other Documents:**

18. STATUS:

**ONDQA:**

<b>CONSULTS/ CMC RELATED REVIEWS</b>	<b>RECOMMENDATION</b>	<b>DATE</b>	<b>REVIEWER</b>
Biometrics	N/A		
EES	Acceptable	04-Nov-2010	E. Johnson
Pharm/Tox	Acceptable	04-Sep-2010	Jeffrey Bray
Biopharm	N/A		
LNC	N/A		
Methods Validation	N/A		
DMEPA	Tradename: Acceptable	22-Sep-2010	Irene Chan
	Dosage Form: Topical Solution	25-Oct-2010	
	Strength: 30 mg testosterone per pump actuation	15-Nov-2010	
EA	Categorical exclusion granted (see review)	10-Oct-2010	Hitesh Shroff
Microbiology	Approval	06-Oct-2010	Mello, Robert J.

# The Chemistry Review for NDA 22-504

## The Executive Summary

### I. Recommendations

#### A. Recommendation and Conclusion on Approvability

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.

#### B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

No recommendation at this time.

### II. Summary of Chemistry Assessments

#### A. Description of the Drug Product(s) and Drug Substance(s)

##### (1) Drug Substance

Testosterone is a white to practically white crystalline powder. It is manufactured by (b) (4). The CMC information is provided in DMF (b) (4) which was reviewed on Jan 26, 2010 and found to be adequate. Since then there have been no changes in the manufacturing process and control testosterone. The NDA applicant provided LOA to reference the DMF for CMC information. The proposed specification including identification, assay, related substances, melting point and particle sizes is deemed adequate to assure the identity, strength, purity and quality of the drug substance.

##### (2) Drug Product

Axiron (testosterone) topical solution is indicated for replacement therapy in males for conditions associated with a deficiency or absence of endogenous testosterone. The drug product is a non-sterile, colorless to pale yellow, transparent 2% (w/v) testosterone solution. Axiron is available as a metered dose pump, which dispenses 90 mL solution in 60 pump actuations. Each pump actuation delivers 30 mg of testosterone in 1.5 mL solution. It is manufactured by (b) (4). The manufacturing process is well controlled by respective operating ranges which are well justified by developmental studies.

## Chemistry Assessment Section

The ingredients in Axiron are testosterone, ethanol, isopropyl alcohol, octisalate and povidone. All ingredients are USP/NF grade and there are no novel excipients used in the formulation. (b) (4)

The release specification of Axiron includes appearance, identification, viscosity, related substances, dose uniformity, microbial tests and assays for testosterone and octisalate. The proposed acceptance criteria for the tests are deemed satisfactory based on their developmental studies and the analytical methods for the tests are adequately validated. Stability data based on three registration batches and Phase III clinical trial batches support their proposed 24-month expiration dating period. Environmental assessment was done and found no significant impact is expected.

**B. Description of How the Drug Product is Intended to be Used**

Axiron is recommended to adult male patients as single daily dose starting at 1.5 mL solution equivalent to 30 mg testosterone. The maximum dose is 6 mL equivalent to 120 mg testosterone. The Axiron topical solution is applied once daily to both arm pits.

**C. Basis for Approvability or Not-Approval Recommendation**

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.

All facilities have "Acceptable" site recommendations. All labels have the required information.

**III. Administrative****A. Reviewer's Signature**

Hitesh Shroff, Ph.D./ November 19, 2010

**B. Endorsement Block**

Moo-Jhong Rhee, Ph.D. Chief, Branch IV, Division II/ONDQA

**CC Block**

Donna Christner, Ph.D.  
Jeannie Roule

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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DONNA F CHRISTNER  
11/19/2010  
Acting on behalf of Hitesh Shroff

MOO JHONG RHEE  
11/19/2010  
Chief, Branch IV

**NDA 22-504****Axiron (testosterone) topical solution  
2%****Acrux Pharma Pty Ltd.****Hitesh Shroff, Ph.D.**

Review Chemist

**Office of New Drug Quality Assessment  
Division of New Drug Quality Assessment II  
Branch IV****CMC Review of NDA 22-504  
For the Division of Reproductive and Urologic Drug  
Products (HFD-580)**

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# Chemistry Review Data Sheet

1. NDA 22-504
2. REVIEW #: 1
3. REVIEW DATE: 10-Oct-2010
4. REVIEWER: Hitesh Shroff, Ph.D.
5. PREVIOUS DOCUMENTS: N/A
6. SUBMISSION(S) BEING REVIEWED:

<u>Submission(s) Reviewed</u>	<u>Document Date</u>
Original	25-Jan-2010
Amendment – Quality Information	12-May-2010
Amendment – Quality/Stability Information	18-Jun-2010
Amendment – Labeling Information	16-Aug-2010
Amendment – Quality/Stability Information	03-Sep-2010
Amendment – Labeling Information	01-Oct-2010

7. NAME & ADDRESS OF APPLICANT:

Name: Acrux Pharma Pty Ltd  
Address: 103-113 Stanley Street  
West Melbourne, Victoria 3003  
Lisa Jenkins, Associate Director, Kendle  
Representative: International, 441 Vine Street, Suite 500,  
Cincinnati, OH 45202  
Telephone: (513) 444-4062

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: AXIRON  
b) Non-Proprietary Name (USAN): testosterone

## Chemistry Review Data Sheet

- c) Code Name/# (ONDQA only): None  
d) Chem. Type/Submission Priority (ONDQA only):
- Chem. Type: 5
  - Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: 505(b)(2)

10. PHARMACOL. CATEGORY: Androgen

11. DOSAGE FORM: Topical solution

12. STRENGTH/POTENCY: 2.0% w/v

13. ROUTE OF ADMINISTRATION: Topical

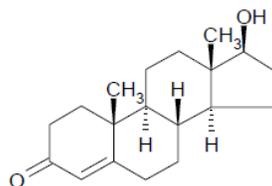
14. Rx/OTC DISPENSED:  Rx  OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

SPOTS product – Form Completed

Not a SPOTS product

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



Testosterone

Chemistry Review Data Sheet

Chemical Name: 17β-Hydroxy-androst-4-en-3-one  
 Molecular Formula: C<sub>19</sub>H<sub>28</sub>O<sub>2</sub>  
 Molecular Weight: 288.43

17. RELATED/SUPPORTING DOCUMENTS:

**C. DMFs:**

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE <sup>1</sup>	STATUS <sup>2</sup>	DATE REVIEW COMPLETED	COMMENTS
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	III		4	N/A			
	III		3	Adequate	16-May-2007	Last reviewed for NDA 21-015. (b) (4)	
	III		4	N/A		(b) (4)	
	III		4	N/A			
	III		4	N/A			
	III		4	N/A			
	III		4	N/A			

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7 – Other (explain under "Comments")

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Chemistry Review Data Sheet

**B. Other Documents:**

18. STATUS:

**ONDQA:**

<b>CONSULTS/ CMC RELATED REVIEWS</b>	<b>RECOMMENDATION</b>	<b>DATE</b>	<b>REVIEWER</b>
Biometrics	N/A		
EES	Pending		
Pharm/Tox	Acceptable	04-Sep-2010	Jeffrey Bray
Biopharm	N/A		
LNC	N/A		
Methods Validation	N/A		
DMEPA	N/A		
EA	Categorical exclusion granted (see review)	10-Oct-2010	Hitesh Shroff
Microbiology	Approval	06-Oct-2010	Mello, Robert J.

# The Chemistry Review for NDA 22-504

## The Executive Summary

### I. Recommendations

#### A. Recommendation and Conclusion on Approvability

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.

#### B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

No recommendation at this time.

### II. Summary of Chemistry Assessments

#### A. Description of the Drug Product(s) and Drug Substance(s)

##### (1) Drug Substance

Testosterone is a white to practically white crystalline powder. It is manufactured by (b) (4). The CMC information is provided in DMF (b) (4) which was reviewed on Jan 26, 2010 and found to be adequate. Since then there have been no changes in the manufacturing process and control testosterone. The NDA applicant provided LOA to reference the DMF for CMC information. The proposed specification including identification, assay, related substances, melting point and particle sizes is deemed adequate to assure the identity, strength, purity and quality of the drug substance.

##### (2) Drug Product

Axiron (testosterone) topical solution 2% is indicated for replacement therapy in males for conditions associated with a deficiency or absence of endogenous testosterone. The drug product is a non-sterile, colorless to pale yellow, transparent 2% (w/v) testosterone solution. Axiron is available as a metered dose pump, which dispenses 90 mL solution in 60 pump actuations. Each pump actuation delivers 30 mg of testosterone in 1.5 mL solution. It is manufactured by (b) (4). The manufacturing process

## Chemistry Assessment Section

is well controlled by respective operating ranges which are well justified by developmental studies.

The ingredients in Axiron are testosterone, ethanol, isopropyl alcohol, octisalate and povidone. All ingredients are USP/NF grade and there are no novel excipients used in the formulation. (b) (4)



The release specification of Axiron includes appearance, identification, viscosity, related substances, dose uniformity, microbial tests and assays for testosterone and octisalate. The proposed acceptance criteria for the tests are deemed satisfactory based on their developmental studies and the analytical methods for the tests are adequately validated. Stability data based on three registration batches and Phase III clinical trial batches support their proposed 24-month expiration dating period. Environmental assessment was done and found no significant impact is expected.

## B. Description of How the Drug Product is Intended to be Used

Axiron is recommended to adult male patients as single daily dose starting at (b) (4) mL solution equivalent to 30 mg testosterone. The maximum dose is 6 mL equivalent to 120 mg testosterone. The Axiron solution is applied once daily to both arm pits.

## C. Basis for Approvability or Not-Approval Recommendation

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.

However, the label/labeling issues are still pending and an overall "Acceptable" recommendation from the Office of Compliance has not been made.

## III. Administrative

### A. Reviewer's Signature

Hitesh Shroff/ October 10, 2010

### B. Endorsement Block

Moo-Jhong Rhee, Branch Chief, Branch 4, Division 2

## Chemistry Assessment Section

**C. CC Block**

Donna Christner

Jeannie Roule

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/s/

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HITESH N SHROFF  
10/22/2010

MOO JHONG RHEE  
10/22/2010  
Chief, Branch IV

Initial Quality Assessment  
Branch III  
Pre-Marketing Assessment Division II

**OND Division:** Division of Reproductive and Urologic Products  
**NDA:** 22-504  
**Applicant:** ACRUX Pharma  
**Stamp Date:** 25-Jan-2010  
**PDUFA Date:** 25-Nov-2010  
**Trademark:** Axiron  
**Established Name:** Testosterone  
**Dosage Form:** Testosterone solution, 2%  
**Route of Administration:** Topical  
**Indication:** Treatment of hypogonadism

**PAL:** Donna F. Christner, Ph.D.

	YES	NO
<b>ONDQA Fileability:</b>	x	<input type="checkbox"/>
<b>Comments for 74-Day Letter</b>	x	<input type="checkbox"/>

**Summary and Critical Issues:**

**A. Summary**

Axiron (testosterone solution) 2% is a non-sterile solution for transdermal administration to the axilla (underarm). It is packaged (b) (4) with a (b) (4) metered dose pump. It is applied on the skin surface with an applicator. The applicator has no moving parts (b) (4)

Each bottle is filled with 110 ml of solution and is able to dispense 90 ml of product. Each depression of the pump delivers 1.5 ml of product, which is equivalent to 30 mg testosterone. The starting dose is 3.0 ml, equivalent to 60 mg of testosterone, dosed once daily.

**B. Critical issues for review**

**Drug Substance:**

*The primary reviewer should check the DMF to see what Amendments have been submitted since the last review. Depending on what has been submitted, a DMF review may be warranted.*

*For drug substance specifications, Impurities and Related Substances should not be solely listed using the Eur.Ph. abbreviations, but should also be listed on the specification sheet with the names, e.g., **Impurity** (b) (4)*

## Drug Product:

1. *The sponsor has identified two changes seen on stability for **the registration batches manufactured at the proposed commercial Orion facility** (See Stability section of this document). The first change is the appearance of a pale red color. The second change is the appearance of oily droplets in the delivered dose.*

- *On accelerated stability studies at 6 months, a pale red color was seen in the transfer/registration stability batches manufactured at the proposed commercial manufacturing site. During development, the acceptance criteria for the color specification was **NMT Reference Standard** (b) (4). It appears that it was changed to **NMT Reference Standards** (b) (4) in response to the pale red color change. The sponsor states that a full laboratory investigation is being conducted to investigate the possible root cause of the pale red coloration. Until full information is provided on the cause of the color change and it has been shown that this does not affect the safety or efficacy of the product, it appears that this change in the acceptance criteria should be carefully evaluated.*
- *The sponsor has observed droplets of oil apparent in the delivered dose during storage at room temperature and accelerated stability conditions in the transfer /registration stability batches manufactured at the proposed commercial manufacturing site. Sponsor states that the oily droplets were observed to decrease with continuous actuation of the pump until they disappeared at around 20-30 actuations. **These 20-30 actuations are to be delivered to the patient and are not the priming actuations.***

*The sponsor has identified the oil as dimethicone used by the pump manufacturer to allow the pump parts to be fitted together during manufacture of the pump. The sponsor states that approximately (b) (4) of dimethicone oil comes into contact with the product and that (b) (4) is expelled in the priming shots, while the remaining (b) (4) is progressively expelled in subsequent pump actuations (See Section 2.3.P.2.4). They state that the oil poses no safety risk to the patient because it is medical grade oil widely used in pharmaceutical products. While the sponsor's justification concerning the oily droplets may hold true when reviewed as it pertains to safety, there is also a question on dosing reproducibility and its effect on efficacy. There is also the issue that contamination of the dosage form with oil would give an adulterated product. The sponsor should provide the following information:*

- *The report of the investigation concluding that the oil is dimethicone and that the source is the pump components.*
- *Information on whether the oil droplets were observed in the clinical trial batches. Since stability testing was performed at different sites with different personnel, the Phase 3 clinical supply samples remaining on stability should also be evaluated to determine if the oil was there and if it was missed during stability testing.*
- *Data on the amount of oil dispensed per actuation and address the effect on dose delivery and therefore efficacy.*
- *Information on whether the same lot of (b) (4) pumps were used for the clinical trial batches and the three registration batches, and if this phenomenon was seen only with the registration batches.*

- Clarify how many actuations are performed for priming.

The following points need to be considered during review of the NDA in regard to the red coloration and the oily droplets:

- Careful evaluation is needed to determine if the proposed commercial manufacturing site, Orion in Turku Finland, is able to reproducibly manufacture the drug product.
  - The evaluation of the red color and oily droplets observed in the registration stability samples will have a direct impact on the expiration dating period since the supporting stability data gathered on the Phase 3 clinical supplies may not be able to be used to set the expiration dating period if the quality of the drug product manufactured at the proposed commercial facility cannot be assured. For the issue with the red color, an expiry of only 6 months may be appropriate. For the oil droplets, the product may not be able to be given any expiry.
  - If it is determined that the oil is seen only with the lot of pumps used for the registration batches, this may mitigate the expiry question, but it may be necessary to add strict acceptance criteria for the pumps prior to their use in the commercial product.
  - It may be valuable to inform the sponsor of our concerns and request that they evaluate whether the manufacturing site used to manufacture the clinical supplies could be used for commercialization and to request inspection of the clinical trial material site in the event that the final recommendation after review of the NDA is that the quality of the drug product manufactured at the Orion site cannot be assured.
2. The Total impurity specifications for testosterone and octisalate on stability appear to be wide. It is a review issue on whether they are adequately set.
  3. The sponsor has requested to delete the tests for pH, microscopic observation, and in-vitro release testing. As requested in meetings with the sponsor, full justification has been provided in the NDA for evaluation. This is a review issue. The question on deletion of the in-vitro release test will be determined by the assigned ONDQA BioPharm reviewer, Dr. Angelica Dorantes.

4.  (b) (4)

### C. Comments for 74-Day Letter

For drug substance specifications, Impurities and Related Substances should not be solely listed using the Eur.Ph. abbreviations, but should also be listed on the specification sheet with the names, e.g., **Impurity** (b) (4)

We acknowledge your statement that the oily drops in the dosage form are dimethicone and your justification on why this is not a safety concern, However, while the justification concerning the oily droplets may hold true when reviewed as it pertains to safety, there is also a question on dosing reproducibility and it's effect on efficacy. Provide the following information for our review:

- The report of the investigation concluding that the oil is dimethicone and that the source is the pump components.
- Information on whether the oil droplets were observed in the clinical trial batches. Since stability testing was performed at different sites with different personnel, the Phase 3 clinical supply samples remaining on stability should also be evaluated to determine if the oil was there and if it was missed during stability testing.
- Data on the amount of oil dispensed per actuation and address the effect on dose delivery and therefore efficacy.
- Information on whether the same lot of (b) (4) pumps were used for the clinical trial batches and the three registration batches, and if this phenomenon was seen only with the registration batches.
- Clarify how many actuations are performed for priming.

We acknowledge that the cause of the pale red coloration is currently under investigation. Please submit the results of that investigation as soon as possible for our review. Address the impact on safety and efficacy of this color change. We do not agree that the Appearance acceptance criteria should be changed to include the pale red color until the reason for the color change is determined.

Please be aware that our evaluation of the red color and oily droplets observed in your registration stability samples will have a direct impact on the expiration dating period. Supporting stability data gathered on the Phase 3 clinical supplies may not be able to be used to set the expiration dating period if the quality of the drug product manufactured at the proposed commercial facility cannot be assured.

### D. Recommendation:

This NDA is fileable from a CMC perspective. It has several issues (outlined above) which need to be critically evaluated during the review. There are 5 comments which should be included in the 74-day letter. Hitesh Shroff, Ph.D., has been assigned as the primary CMC reviewer.

---

Donna F. Christner, Ph.D.

NDA Number: 22-504 Type: 3S

Established/Proper Name:  
testosterone

Applicant: Acrux  
Pharma

Letter Date: 25-Jan-2010

Stamp Date: 25-Jan-2010

The following parameters are necessary in order to initiate a full review, i.e., complete enough to review but may have deficiencies. On **initial** overview of the NDA application for filing:

A. GENERAL				
	Parameter	Yes	No	Comment
1.	Is the CMC section organized adequately?	X		
2.	Is the CMC section indexed and paginated (including all PDF files) adequately?	X		
3.	Are all the pages in the CMC section legible?	X		
4.	Has all information requested during the IND phase, and at the pre-NDA meetings been included?	X		Sponsor has provided a comprehensive table of all FDA requests with links to the appropriate NDA sections in Section 1.6.3

B. FACILITIES*				
	Parameter	Yes	No	Comment
5.	Is a single, comprehensive list of all involved facilities available in one location in the application?	X		
6.	For a naturally-derived API only, are the facilities responsible for critical intermediate or crude API manufacturing, or performing upstream steps, specified in the application? If not, has a justification been provided for this omission? <b>This question is not applicable for synthesized API.</b>		X	

7.	<p>Are drug substance manufacturing sites identified on FDA Form 356h or associated continuation sheet? For each site, does the application list:</p> <ul style="list-style-type: none"> <li>• Name of facility,</li> <li>• Full address of facility including street, city, state, country</li> <li>• FEI number for facility (if previously registered with FDA)</li> <li>• Full name and title, telephone, fax number and email for on-site contact person.</li> <li>• Is the manufacturing responsibility and function identified for each facility?, and</li> <li>• DMF number (if applicable)</li> </ul>	X		
8.	<p>Are drug product manufacturing sites identified on FDA Form 356h or associated continuation sheet. For each site, does the application list:</p> <ul style="list-style-type: none"> <li>• Name of facility,</li> <li>• Full address of facility including street, city, state, country</li> <li>• FEI number for facility (if previously registered with FDA)</li> <li>• Full name and title, telephone, fax number and email for on-site contact person.</li> <li>• Is the manufacturing responsibility and function identified for each facility?, and</li> <li>• DMF number (if applicable)</li> </ul>	X		

9.	<p>Are additional manufacturing, packaging and control/testing laboratory sites are identified on FDA Form 356h or associated continuation sheet. For each site, does the application list:</p> <ul style="list-style-type: none"> <li>• Name of facility,</li> <li>• Full address of facility including street, city, state, country</li> <li>• FEI number for facility (if previously registered with FDA)</li> <li>• Full name and title, telephone, fax number and email for on-site contact person.</li> <li>• Is the manufacturing responsibility and function identified for each facility?, and</li> <li>• DMF number (if applicable)</li> </ul>	X		
10.	Is a statement provided that all facilities are ready for GMP inspection at the time of submission?	X		

\* If any information regarding the facilities is omitted, this should be addressed ASAP with the applicant and can be a *potential* filing issue or a *potential* review issue.

<b>C. ENVIRONMENTAL ASSESMENT</b>				
	<b>Parameter</b>	<b>Yes</b>	<b>No</b>	<b>Comment</b>
11.	Has an environmental assessment report or categorical exclusion been provided?	X		Request for categorical exclusion as per 21 CFR 25.31(b)

<b>D. DRUG SUBSTANCE/ACTIVE PHARMACEUTICAL INGREDIENT (DS/API)</b>				
	<b>Parameter</b>	<b>Yes</b>	<b>No</b>	<b>Comment</b>
12.	Does the section contain a description of the DS manufacturing process?	X		Cross-reference to DMF (b) (4)
13.	Does the section contain identification and controls of critical steps and intermediates of the DS?	X		Cross-reference to DMF (b) (4)
14.	Does the section contain information regarding the characterization of the DS?	X		Cross-reference to DMF (b) (4)
15.	Does the section contain controls for the DS?	X		Cross-reference to DMF (b) (4)
16.	Has stability data and analysis been provided for the drug substance?	X		Cross-reference to DMF (b) (4)
17.	Does the application contain Quality by Design (QbD) information regarding the DS?		X	Not a filing issue
18.	Does the application contain Process Analytical Technology (PAT) information regarding the DS?		X	Not a filing issue

<b>E. DRUG PRODUCT (DP)</b>				
	<b>Parameter</b>	<b>Yes</b>	<b>No</b>	<b>Comment</b>
19.	Is there a description of manufacturing process and methods for DP production through finishing, including formulation, filling, labeling and packaging?	X		
20.	Does the section contain identification and controls of critical steps and intermediates of the DP, including analytical procedures and method validation reports for assay and related substances if applicable?	X		
21.	Is there a batch production record and a proposed master batch record?	X		
22.	Has an investigational formulations section been provided? Is there adequate linkage between the investigational product and the proposed marketed product?	X		
23.	Have any biowaivers been requested?		X	
24.	Does the section contain description of to-be-marketed container/closure system and presentations)?	X		
25.	Does the section contain controls of the final drug product?	X		
26.	Has stability data and analysis been provided to support the requested expiration date?	X		24 month expiry requested based on 6 month data on registration batches, 18 month data on Phase III Clinical batches and 24 month data on Phase II clinical batch.
27.	Does the application contain Quality by Design (QbD) information regarding the DP?		X	Not a filing issue
28.	Does the application contain Process Analytical Technology (PAT) information regarding the DP?		X	Not a filing issue

F. METHODS VALIDATION (MV)				
	Parameter	Yes	No	Comment
29.	Is there a methods validation package?	x		

G. MICROBIOLOGY				
	Parameter	Yes	No	Comment
30.	If appropriate, is a separate microbiological section included assuring sterility of the drug product?	X		Consult request for evaluation by CMC Micro sent on 09-Feb-2010.

H. MASTER FILES (DMF/MAF)				
	Parameter	Yes	No	Comment
31.	Is information for critical DMF references (i.e., for drug substance and important packaging components for non-solid-oral drug products) complete?	X		Reviewer should determine if sufficient information is provided in NDA application to make review of some DMFs unnecessary

DMF	TYPE	HOLDER	ITEM REFERENCED	LOA DATE	COMMENTS
(b) (4)	II		(b) (4)	29-May-2009	ADEQUATE on 29-Nov-2007 for NDAs (b) (4) and (b) (4). Updates since last review. <b>May require review.</b>
	III			30-Jul-2007	No review found. <b>May require review.</b>
	III			18-Aug-2009	(b) (4) <b>May require review.</b>
	III			04-Aug-2009	No review found. <b>May require review.</b>
	III			27-Sep-2007	No review found. <b>May require review.</b>
	III			12-Nov-2007	ADEQUATE on 08-Mar-2004 for NDA 21-592. Updates since last review. <b>May require review.</b>
	III			23-Oct-2009	No review found. <b>May require review.</b>

(b) (4)

I. LABELING				
	Parameter	Yes	No	Comment
32.	Has the draft package insert been provided?	X		SPL with DLDE table provided in Section 1.14.1.3
33.	Have the immediate container and carton labels been provided?	X		

J. FILING CONCLUSION				
	Parameter	Yes	No	Comment
34.	<b>IS THE PRODUCT QUALITY SECTION OF THE APPLICATION FILEABLE?</b>	X		
35.	If the NDA is not fileable from the product quality perspective, state the reasons and provide <b>filing</b> comments to be sent to the Applicant.			
36.	Are there any <b>potential review</b> issues to be forwarded to the Applicant for the 74-day letter?	X		See Section C above.

*{See appended electronic signature page}*

Donna F. Christner, Ph.D.  
 Pharmaceutical Assessment Lead  
 Division of Pre-Marketing Assessment # 2  
 Office of New Drug Quality Assessment

Date

*{See appended electronic signature page}*

Moo-Jhong Rhee, Ph.D.  
 Branch Chief  
 Division of Pre-Marketing Assessment # 2  
 Office of New Drug Quality Assessment

Date

## REVIEW NOTES

Clinical studies were performed under IND 70,516. The following CMC-related guidance was provided to the sponsor throughout the development of the product:

### **Pre-IND meeting held 05-Nov-2004**

During the preIND meeting, Sponsor asked if the addition of an applicator (as opposed to direct application to the skin) would cause any concerns. The Division responded that addition of an applicator would be acceptable, provided the suitability of the applicator was supported by data. The “Container Closure” guidance was cited. Sponsor was also advised on minimal drug product specifications which included an in-vitro release test. Advice was provided on leachable and extractable testing, and stability data needed to support the clinical study. A comment was included concerning a possible collaborative review with CDRH concerning the applicator.

### **Original IND submission**

Comments were conveyed to the sponsor concerning the addition of a viscosity test during stability, in-vitro release testing, microscopic observation (b) (4), and a reminder concerning leachable/extractable testing and a possible collaborative review with CDRH.

### **EOP2 meeting held 13-Mar-2008**

Sponsor submitted questions concerning testing performed to determine the efficacy of dose transfer and residual product on the applicator, a washing study for the applicator. Sponsor was given input on types of testing that should be performed. Sponsor also asked if the leachable testing performed to date was adequate and was advised that this testing should be performed using the drug product. The Division also provided input on the Sponsor’s proposed testing protocol for dose reproducibility. The Sponsor also asked if the supporting documents for materials for the container closure system were adequate and was advised that they should submit a LOA for the packaging DMF, which would be reviewed during the NDA review cycle. The sponsor asked if preservative efficacy testing was not required and was advised that it should be continued and submitted in the NDA for review. The Microbiologist also recommended that they consider filtering their product during the manufacturing process to lower the bioburden and limit spores. They also requested removal of the pH, microscopic evaluation, and in-vitro release tests and were advised to continue the tests during development. Additional advice was also provided that stability data would need to be generated on at least three batches of the to-be-marketed formulation. Reference was also given to the Topical Drug Classification article by L. Bushe, et.al. since the sponsor used “solution” and “lotion” interchangeably in the package and the dosage form should be classified.

### **preNDA meeting held 31-Aug-2009**

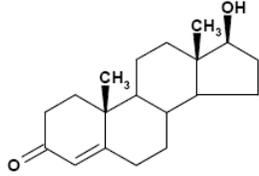
Sponsor began the meeting with a short video demonstrating the proper technique for applying the product. They also stated that the dosage form is a solution since it is a clear, homogeneous, single-phase dosage form (solution) and not an emulsion (lotion). The submitted questions included a strategy for submission of proposed Master Batch Records and executed batch records. The Division stated that the strategy appeared adequate and that a statement should be included in the application that the English translation was a true translation from the Finnish. The sponsor also asked if tests for pH and microscopic observation could be deleted and were advised that the

request should be made in the NDA with full justification and the decision would be made during the NDA review cycle. The sponsor asked if the specification for overall drug delivery and applicator washing were adequate and were advised that they appeared to be adequate, but the final determination was an NDA review issue. The sponsor included a question on product filtering (made in response to a comment from Microbiology during the EOP2 meeting) and agreement was reached that product filtering was not required, but additional information was requested in the NDA submission. The sponsor also requested deletion of in-vitro release testing and testing of ethanol and isopropanol. The sponsor was advised that the proposal appeared adequate, but the final decision would be made during the NDA review. The sponsor was also advised that the iv-vitro release test would be required to support the change in manufacturing site from the clinical site in Australia to the commercial site in Finland, and they responded that the transfer had been successfully accomplished and stability studies initiated on 3 batches of drug product manufactured in Finland. General advice was provided on container/carton labels and on information needed for the NDA submission. The sponsor was reminded to provide full justification for deletion of tests in the NDA.

***Comment:*** *The reviewer should refer to Section 1.6.3 Correspondence Regarding Meetings in the NDA for a comprehensive table of all FDA requests with links to the appropriate NDA section. The meeting minutes, except for the preIND minutes, are also provided in this section. PreIND meeting minutes are available in DARRTS.*

## DRUG SUBSTANCE

The drug substance is testosterone. The majority of the information is cross-referenced to DMF (b) (4). The following information has been provided in the NDA application.



Testosterone

Chemical name: 17-beta-Hydroxyandrost-4-en-3-one, or, Androst-4-en-3-one, 17-beta-hydroxy

CAS registry number: 58-22-0

IUPAC name: 17-hydroxy-10,13-dimethyl-1,2,6,7,8,9,11,12,14,15,16,17-dodecahydrocyclopenta[a]phenanthren-3-one.

## MANUFACTURING

The following facilities have been identified with the responsibility of manufacture, QC testing, labeling, packaging, release and stability testing for the drug substance.

(b) (4)

Testosterone may also be manufactured at a secondary manufacturing site:

(b) (4)

*Comment: EES was submitted on 11-Mar-2010 by Jeannie David.*

SPECIFICATION

The drug substance quality is controlled by the following specification performed by the drug substance manufacturer:

**Table 2.3.S.4.1-1 Testosterone Drug Substance Specifications** (b) (4)

(b) (4)



The drug product manufacturer accepts the drug substance with the following specification:

**Table 2.3.S.4.1-2 Testosterone Drug Substance Specifications (Orion Corporation)**

(b) (4)

The sponsor has provided a side-by-side comparison of release data for three lots of drug substance.

(b) (4)

**STABILITY**

The sponsor states that the drug substance has a 5 year shelf-life.

**Comment:** *Information is adequate for review. Depending on the status of submissions since the last review, the DMF may require review.*

**DRUG PRODUCT**

Axiron (testosterone solution) 2% is a non-sterile solution for transdermal administration to the axilla (underarm). It is packaged (b) (4) with a (b) (4) metered dose pump. It is applied on the skin surface with an applicator. The applicator has no moving parts (b) (4)

Each bottle is filled with 110 ml of solution and is able to dispense 90 ml of product. Each depression of the pump delivers 1.5 ml of product, which is equivalent to 30 mg testosterone. The starting dose is 3.0 ml, equivalent to 60 mg of testosterone, dosed once daily.

The composition is as follows:

**Table 3.2.P.1-1 Batch Formulation**

Component	Function	Formulation by volume	Formulation by weight
Testosterone, USP/EP	Active	2% w/v	2.44% w/w
Octisalate USP	(b) (4)		
Povidone USP/EP			
Isopropyl alcohol USP/EP			
Alcohol USP (b) (4) Ethanol Ph.Eur.)			

Excipients are controlled by adherence to compendial specification.

*Comment: Information is adequate to allow review.*

**PHARMACEUTICAL DEVELOPMENT**

The sponsor has provided an extensive Pharmaceutical Development Section. The following table outlines the different formulations used throughout development:

**Table 2.3.P.2.2.1-2 Summary of lead formulations used in clinical studies**

Study Description	Formulations					
	Human single dose PK study	Human single dose PK study	Human Multidose steady state PK study Comparator (8% OSAL)	Phase 2 Multidose steady state PK study	Phase 2 1% and 2% formulation comparability study.	Pivotal Phase 3 (08) and Safety extension (09)
Study No.	DDS08	DDS16	MTE04	MTE05	MTE07	MTE08/09
<b>Ingredients</b>						
Testosterone	1% w/v	1% w/v	1% w/v	1% w/v	2%w/v	2%w/v
Octisalate	(b) (4)					
Povidone						
Isopropyl Alcohol (IPA)						
Ethanol (b) (4)						
Ethanol (b) (4)						
#	(b) (4)					

## MANUFACTURE

The sponsor has identified the following facilities for responsibilities for commercial manufacture of the product:

Axiron commercial drug product is manufactured, assembled, labeled, packaged and tested for QC release by:

**Orion Corporation**

**FDA Drug Establishment number 3003743938**

**DUNS Number: 537940319**

Orion Pharma Turku site

Tengströminkatu 8

FI-20360 Turku,

Finland.

Microbiological testing for QC release is performed at a secondary site:

**Orion Corporation**

**FDA Drug Establishment number 3003234955**

**DUNS Number: 539763727**

Orion Pharma Espoo site

Orionintie 1

FI-02200 Espoo,

Finland.

Quality Assurance batch release is performed by Orion Corporation by EU Qualified Persons (QPs) at either of the two sites nominated above.

Stability testing may be performed at either of the two Orion Corporation sites nominated above.

***Comment:*** *The Orion site is the site for commercial manufacture. Registration stability samples have been manufactured at this site. The clinical trial materials were manufactured at a facility in Australia.*

*The Orion sites were submitted on 11-Mar-2010 by Jeannie David*

The sponsor has provided the following flow chart for manufacture of the product. They have also provided a narrative.

18 Pages have been Withheld in Full as b4 (CCI/TS) immediately following this page.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22504	ORIG-1	ACRUX PHARMA PTY LTD	TESTOSTERONE

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

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/s/

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DONNA F CHRISTNER  
03/23/2010

MOO JHONG RHEE  
03/23/2010  
Chief, Branch III