Statistics

- reviewer plans to write a short review or memo, although the review is not yet written
- reviewer agrees that —→ are not supported for labeling

Chemistry

- site inspection is completed and is found acceptable
- microbiology consult is completed and it is satisfactory
- CMC deficiencies have been conveyed to the sponsor via regulatory letter; teleconference was held today with the sponsor and deficiencies appear "fixable"
- tradename review should be done in two weeks
- the sponsor requested — expiry; sponsor committed to sending stability data by the end of this month
- reviewer has started working on the label and there will be some edits

Pharmacology and Toxicology

- review is almost completed
- Project Manager and Medical Officer follow up with the reviewer on the status of his review of the carcinogenicity potential for the lactone —

Clinical Pharmacology and Biopharmaceutics

- Cmin, Cmax and Cave are comparable to Androgel
- Clinical Pharmacology reviewer describes his review as "not far yet"
- the reviewer is comfortable with data he's seen to date
- there were three additional studies conducted in addition to the large Phase 3 trial; two transfer studies (one is confirmatory) and data was provided for one showering study which looks no different from Androgel

Action Items:

- labeling needs to be posted on the N drive

(Please see attached electronic signature page)

Signature, minutes preparer

Concurrence, Chair

APPEARS THIS WAY
ON ORIGINAL

cc:
NDA Arch:
HFD-580/Division File
HFD-580/
Concurrences:Davis,Chatterjee,Rhee,Agarwal,Hirsch101502

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/s/

Mark S. Hirsch
10/25/02 01:24:45 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-454

DISCIPLINE REVIEW LETTER

Auxilium A^2
Attention: Diane Myers
Director, Regulatory Affairs
Norriton Office Center
160 W. Germantown Pike, Suite D-5
Norristown, PA 19401

Dear Ms. Myers:

Please refer to your December 31, 2001 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Testim (testosterone 1% gel).

We also refer to your submissions dated January 24, 2002, February 12, 2002, March 28, 2002, May 15, 2002, June 6, 2002, July 7 and 30, 2002.

Our review of the Chemistry, Manufacturing and Controls section of your submission is complete, and we have identified the following deficiencies:

1. Please provide complete addresses of — manufacturers.

2. Please make a commitment that the — is the only supplier of the — to manufacture oxacyclohexadecan-2-one and that if there is a change in the manufacturing process at — or a new supplier is introduced, applicant will notify the FDA via a supplement.

3. Please provide the acceptance specifications of the — used in the synthesis at — If the acceptance testing is not performed at — , you must commit to perform the testings with proposed acceptance specifications.

4. Please provide information on the —

5. Please identify that how many gel tubes are produced from — of bulk drug product gel.

6. Please provide the model # and manufacturers name of each equipment used in the manufacturing.

7. Please provide the total time of operation to ensure the consistent uniformity of the —

8. Results of acceptance testing of oxacyclohexadecan-2-one at — should be provided.

9. The — should be included in the — test for testosterone assay and testosterone assay in in-vitro release by HPLC.

10. Please provide the LOQ, LOD and evaluation of robustness for ethanol assay and the HPLC method used in in-vitro release assay.

11. Please comment on why — degradation product is not detected in — batches but detected in other batches in rather high amounts?

12. Please implement in-process specification to assure —

13. Please revise the acceptance criterion of viscosity from — to —.

14. Please revise the drug product specification sheet for testosterone and oxacyclohexadec-2-ne related impurities as follows:

Attributes	Proposed acceptance criteria by Auxillium	Proposed acceptance criteria by FDA
B. —		
C. Aggregate specified related impurities occurring at a level of —(Non A, B)		
D. Testosterone Impurities Unspecified (Non A, B, C)		
TOTAL TESTOSTERONE IMPURITIES		
Oxacyclohexadecan-2-one Unspecified substances		
Total oxacyclohexadecan-2-one Specified and Unspecified substances		

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ON ORIGINAL

15. Please provide the individual release rates at each time point obtained from the test for in-vitro release rate.

16. Please provide a brief description of the manufacturing, characterization, purity and analytical procedures, COA, storage conditions (container and storage temperature) for the reference standards of oxacyclohexadecan-2-ene

17. Please provide the batch size and date of manufacture of the oxacyclohexadecan-2-one batches produced at . Certificate of analysis of the batches (1200990010 and 1210260010) should contain the results of tests specified in oxacyclohexadecan-2-one product specifications.

18. The following should be included in the post approval stability commitment:
- The post approval commitment should clearly state that "An extension of the expiration dating period will be based on full long term stability data from three production lots in accordance with the stability protocol approved in the NDA".
- The post approval commitment should clearly state that "In accordance with 21 CFR 314.81 (b)(1)(ii), any change or deterioration in the drug product will be reported to FDA".

19. Please also provide the information on manufacturing process and the yield range (weight and percent) of the product.

20. Please include the following information in Executed batch record:

- In process tests and acceptance criteria should be included in each batch record to ensure the quality of the product.
- Information pertaining to Packaging operation should be included in the batch record.
- Information on the tube batch size should be provided for each drug product gel batch.
- Name and addresses of sources of noncompendial excipient, and container closure system should be included.
- Results of any test performed on the components should be provided. This should include the COA from the component manufacturer and test results (ID) for the same batch from the drug product manufacturer.

21. Please provide three updated copies of method validation package.

22. Based on the real time data, only of expiry can be granted.

We are providing these comments to you before we complete our review of the entire application to give you preliminary notice of issues that we have identified. In conformance with the prescription drug user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and subject to change as we finalize our review of your application. In addition, we may identify other information that must be provided before we can approve this application. If you respond to these issues during this review cycle, depending on the timing of your response,

and in conformance with the user fee reauthorization agreements, we may not be able to consider your response before we take an action on your application during this review cycle.

If you have any questions, please call Eufrecina DeGuia, Regulatory Project Manager, at (301) 827-4260.

Sincerely,

Moo-Jhong Rhee, Ph.D.
Chemistry Team Leader, for the
Division of Reproductive and Urologic Drug Products, HFD-580
DNDC II, Office of New Drug Chemistry
Center for Drug Evaluation and Research

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/s/

Amit K. Mitra
8/12/02 10:59:12 AM
Signed as an Acting Team Leader

Screening of New NDA for Statistical Filing
Division of Biometrics II

NDA #: 21-454

Applicant: Auxilium

Trade/Generic Name: Testim 1% testosterone gel

Indication: Testosterone replacement therapy in adult males

Date of Submission: Dec 31, 2001

Filing Date: Feb, 14, 2002

User Fee Goal Date: Oct 31, 2002

Project Manager: Deguia

APPEARS THIS WAY
ON ORIGINAL

Medical Reviewer: Davis

Comments: This NDA is fileable from a statistical perspective. A single principal study (AUX-TG-202) supports efficacy. Section 16 (Appendices) to this study report is missing from Vol 79 (see page 40) However, the MO has these appendices. This study is a blinded, randomized, active control study with Androderm as the comparator. A brief statistical review will be required.

Checklist for Fileability	Check (NA if not applicable)
Index sufficient to locate study reports, analyses, protocols, ISE, ISS, etc.	OK, except as noted above
Original protocols & subsequent amendments submitted	OK
Study designs utilized appropriate for the indications requested	OK
Endpoints and methods of analysis spelled out in the protocols	OK
Interim analyses (if present) planned in the protocol and appropriate adjustments in significance level made	NA
Appropriate references included for novel statistical methodology (if present)	NA
Data and reports from primary studies submitted to EDR according to Guidances	Access to EDR data OK
Safety and efficacy for gender, racial, geriatric, and/or other necessary subgroups investigated	OK

Reviewer: M. Welch

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/s/

Mike Welch
8/9/02 01:01:51 PM
BIOMETRICS

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ON ORIGINAL

Meeting Minutes

Date: July 15, 2002 **Time**: 8:30 – 9:30 AM **Location:** PKLN; Room 17B-43

NDA 21-454 **Drug Name:** Testim (testosterone) 1% gel

Indication: testosterone replacemen'

Sponsor: Auxilium A^2

Type of Meeting: Status Meeting (7-month)

Meeting Chair: Dr. Mark Hirsch

Meeting Recorder: Ms. Eufrecina DeGuia

FDA Attendees:
Mark Hirsch, M.D. – Urology Team Leader, Division of Reproductive and Urologic Drug Products DRUDP (HFD-580)
Daniel Davis, M.D. – Medical Officer, DRUDP (HFD-580)
Eufrecina De Guia - Regulatory Project Manager, DRUDP (HFD-580)
Rajiv Agarwal, Ph.D. – Chemistry Reviewer, DNDC II @ DRUDP (HFD-580)
Moo Jhong Rhee, Chemistry Team Leader, DNDC II @ DRUDP (HFD-580)
Dhruba Chatterjee, Ph.D. – Biopharmaceutics Reviewer, OCPB @ DRUDP (HFD-580)
Margaret Kober, R.Ph. – Chief, Project Management Staff, DRUDP (HFD-580)
Mike Welch, Ph.D. – Team Leader, Division of Biometrics II (DBII) @ DRUDP (HFD-580)

Meeting Objectives: To discuss the status of the review of this pending application.

Background: This NDA for Testim 1% testosterone gel was submitted on December 31, 2001 for the indication of testosterone replacement therapy in adult male

The User Fee Goal Date is October 31, 2002.

Decisions Reached:

- the following dates were agreed upon by the team as tentative goal dates for completion of final reviews:
  October 10, 2002 – the action package should be given to the Medical Team Leader (reviews already concurred by the other discipline team leaders by this time); reviewers for each discipline should set up own timelines with their respective team leaders
  October 24, 2002 – action package should be given to the Director

Clinical

- has just begun review
- there seem to be no major issues in the ISS and ISE

- Dr. Hirsch noted that as soon as Biopharm reviewer says the drug works then the team should start working on the label;

[redacted]

- average blood levels appear acceptable; Medical Officer will check on the outliers
- safety data from the two extension trials was received on July 5, 2002; cut-off date for data was March 15, 2002

Statistics

- no statistical review is planned unless there are concerns, however, a memo will be written since there
- the Medical Team Leader requested that a memo be written and the statistician agreed
- statistician to assist in labeling

Chemistry

- manufacturing and testing sites are acceptable
- microbiology consult still pending
- reviewer is working on the list of deficiencies that will be conveyed to the sponsor in a few weeks
- awaiting data for stability to extend expiry
- the reviewer stated that he will check comparability of lactone from different suppliers (clinical trial versus to-be-marketed)

Pharmacology and Toxicology

- review is ongoing per email from Dr. Raheja

Clinical Pharmacology and Biopharmaceutics

- review not yet started; the reviewer is fully aware of the PDUFA goal date

Action Items:

- follow up on Chemistry comments that need to be conveyed to the sponsor via regulatory letter
- the next Status meeting is scheduled for August 19, 2002
- Medical Officer will do review of financial disclosure information
- follow up on tradename review by DMETS
- Project Manager to send label to DDMAC for review
- Project Manager to send PPI to ODS for review
- Medical Officer to follow up on how to handle Pediatric requirements; will discuss with Dr. Brenda Gierhart based on her experience with Pediatrics.

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/s/

Mark S. Hirsch
10/25/02 01:21:44 PM

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ON ORIGINAL

CONSULTATION RESPONSE
Division of Medication Errors and Technical Support
Office of Drug Safety
(DMETS; HFD-420)

DATE RECEIVED: July 2, 2002	**DUE DATE:** August 16, 2002	**ODS CONSULT #:** 02-0134

TO: Daniel Shames, MD
Director, Division of Reproductive and Urologic Drug Products
HFD-580

THROUGH: Eufrecina DeGuia
Regulatory Project Manager
HFD-580

PRODUCT NAME: Testim 1% (testosterone gel) **NDA #** 21-454	**NDA SPONSOR:** Auxilim A^2, Inc.

SAFETY EVALUATOR: Scott Dallas, R.Ph.

SUMMARY: In response to a consult from the Division of Reproductive and Urologic Drug Products (HFD-580), the Division of Medication Errors and Technical Support (DMETS) conducted a review of the proposed proprietary name, "Testim", to determine the potential for confusion with approved proprietary and established names as well as pending names.

DMETS RECOMMENDATION: DMETS has no objection to the use of the proprietary name, "Testim". This name must be re-evaluated approximately 90 days prior to the expected approval of the NDA. A re-review of the name prior to NDA approval will rule out any objections based upon approvals of other proprietary or established names from the signature date of this document. In addition, DMETS recommends implementation of the labeling revisions outlined in section III of this review to minimize potential errors with the use of this product.

APPEARS THIS WAY
ON ORIGINAL

Carol Holquist, RPh
Deputy Director
Division of Medication Errors and Technical Support
Office of Drug Safety
Phone: (301) 827-3224 Fax (301) 443-5161

Jerry Phillips, RPh
Associate Director
Office of Drug Safety
Center for Drug Evaluation and Research
Food and Drug Administration

APPEARS THIS WAY
ON ORIGINAL

Division of Medication Errors and Technical Support
Office of Drug Safety
HFD-420; Parklawn Building Room 15B32
Center for Drug Evaluation and Research

PROPRIETARY NAME REVIEW

DATE OF REVIEW: August 16, 2002

NDA NUMBER: 21-454

NAME OF DRUG: Testim 1%
(testosterone gel)

APPEARS THIS WAY
ON ORIGINAL

NDA SPONSOR: Auxilim A^2, Inc.

I. INTRODUCTION:

This consult was written in response to a request from the Division of Reproductive and Urologic Drug Products (HFD-580) for an assessment of the proposed proprietary name, Testim. This proposed trademark was submitted with NDA 21-454. The container labels, carton and insert labeling were reviewed for possible interventions in minimizing medication errors.

PRODUCT INFORMATION
"Testim" contains the active ingredient testosterone. This product is seeking approval for testosterone replacement therapy in adult males

The — starting dose is one tube (50 mg) applied once daily (preferably in the morning) to clean, dry intact skin of the shoulders and/or upper arms.

II. RISK ASSESSMENT:

The medication error staff of DMETS conducted a search of several standard published drug product reference texts[1, 2] as well as several FDA databases[3] for existing drug names which sound alike or look alike to "Testim" to a degree where potential confusion between drug names could occur under the usual clinical practice settings. A search of the electronic online version of the U.S. Patent and Trademark Office's trademark electronic search system (TESS) was conducted[4]. The Saegis[5] Pharma-In-Use database was

[1] MICROMEDEX Healthcare Intranet Series, 2002, MICROMEDEX, Inc., 6200 South Syracuse Way, Suite 300, Englewood, Colorado 80111-4740, which includes the following published texts: DrugDex, Poisindex, Martindale (Parfitt K (Ed), Martindale: The Complete Drug Reference. London: Pharmaceutical Press. Electronic version.), Index Nominum, and PDR/Physician's Desk Reference (Medical Economics Company Inc, 2002).
[2] Facts and Comparisons, 2002, Facts and Comparisons, St. Louis, MO.
[3] The Drug Product Reference File [DPR], Established Evaluation System [EES], the DMETS database of proprietary name consultation requests, New Drug Approvals 98-02, and the electronic online version of the FDA Orange Book.
[4] WWW location http://tess.uspto.gov/bin/gate.exe?f=tess&state=k0n826.1.1
[5] Data provided by Thomson & Thomson's SAEGIS(tm) Online Service, available at www.thomson-thomson.com.

searched for drug names with potential for confusion. An expert panel discussion was conducted to review all findings from the searches. In addition, DMETS conducted prescription analysis studies, involving health care practitioners within FDA. This exercise was conducted to simulate the prescription ordering process in order to evaluate potential errors in handwriting and verbal communication of the name.

A. EXPERT PANEL DISCUSSION

An Expert Panel discussion was held by DMETS to gather professional opinions on the safety of the proprietary name "Testim". Potential concerns regarding drug marketing and promotion related to the proposed names were also discussed. This group is composed of DMETS Medication Errors Prevention Staff and representation from the Division of Drug Marketing, Advertising, and Communications (DDMAC). The group relies on their clinical and other professional experiences and a number of standard references when making a decision on the acceptability of a proprietary name.

The Expert Panel identified two proprietary names that were thought to have the potential for confusion with "Testim". These products are listed in Table 1, along with the dosage forms available and usual dosage.

DDMAC did not have any concerns with the promotional aspects of the name "Testim".

TABLE 1

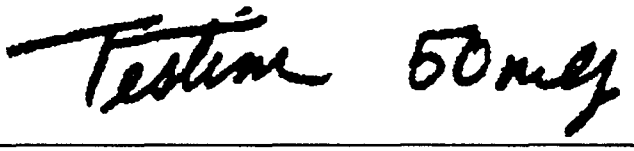
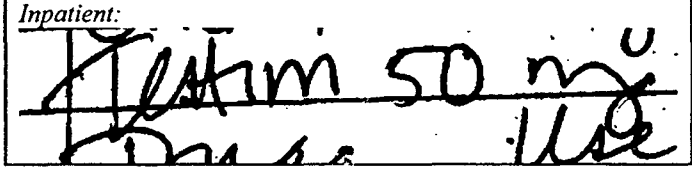
Product Name	Generic name, Dosage form(s), Strength	Usual adult dose*	Other**
Testim	testosterone, gel, 1% or 50 mg/5 grams	Treatment of testoterone replacement therapy: Apply the contents of one tube once daily to clean, dry intact skin of the shoulders and/or upper arms.	
Tequin	Gatifloxacin, Tablets, 200 mg and 400 mg Injection concentrate, 200 mg/20 mL and 400 mg/40 mL Injection premix, 200 mg/100 mL and 400 mg/200 mL	Treatment of infections of susceptible strains of microorganisms: Take one tablet orally daily.	S/A per DMETS
Testred	Methyltestosterone, Capsules, 10 mg	Treatment of testosterone replacement therapy: Take one to five capsules orally once a day.	S/A per DMETS

*Frequently used, not all-inclusive.
**L/A (look-alike), S/A (sound-alike)

B. PRESCRIPTION ANALYSIS STUDIES

1. Methodology

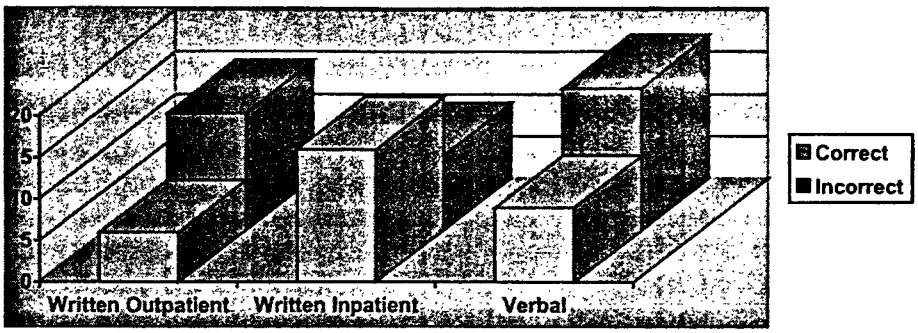
Three separate studies were conducted within FDA for the proposed proprietary name to determine the degree of confusion of Testim with other U.S. drug names due to similarity in visual appearance with handwritten prescriptions or verbal pronunciation of the drug name. These studies employed a total of 107 health care professionals (nurses, pharmacists, and physicians). This exercise was conducted in an attempt to simulate the prescription ordering process. A DMETS staff member wrote an inpatient order and outpatient prescriptions, each consisting of a combination of marketed and unapproved drug products and prescriptions for Testim. These written prescriptions were optically scanned and one prescription was delivered via email to each study participant. In addition, one DMETS staff member recorded a verbal outpatient prescription that was then delivered to a group of study participants via telephone voicemail. Each reviewer was then requested to provide an interpretation of the prescription via email.

HANDWRITTEN PRESCRIPTIONS	VERBAL PRESCRIPTION
Outpatient: 	*Outpatient:* Testim 50 mg Apply as directed every day Dispense number 1
Inpatient: 	

2. Results

Results of the Testim exercises are summarized below:

Study	No. of participants	# of responses (%)	"Testim" response	Other response
Written: Outpatient	32	20 (63%)	6 (30%)	14 (70%)
Inpatient	36	25 (69%)	16 (64%)	9 (36%)
Verbal: Outpatient	39	26 (67%)	9 (35%)	17 (65%)
Total:	107	71 (66%)	31 (44%)	40 (56%)



Among participants in the written outpatient prescription study, 6 of 20 respondents (30%) interpreted the name correctly. Incorrect interpretations included Testine (5), Testin (3), Testime (2), Testem (1), Testina (1), Teatim (1), and Testins (1).

Among participants in the written inpatient prescription study, 16 of 25 respondents (64%) interpreted the name correctly. Incorrect interpretations included Testum (4), Testin (2), Testun (1), Teston (1), and Testine (1).

Among participants in the verbal outpatient prescription study, 9 of 26 respondents (35%) interpreted the name correctly. Incorrect interpretations included Testin (10), Testum (2), Testem (2), Teftin (1), Tesum (1), and Tetenum (1).

None of the misinterpreted names is a currently marketed drug product.

C. SAFETY EVALUATOR RISK ASSESSMENT

In reviewing the proprietary name, "Testim", the primary concerns raised by the DMETS expert panel was related to sound alike names that already exist in the US marketplace. The products considered having the greatest potential for confusion with "Testim" were Tequin and Testred.

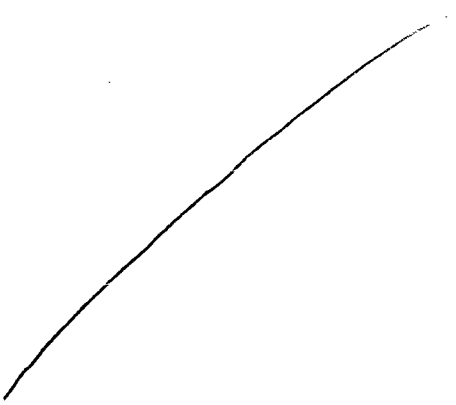
Tequin is the proprietary name for gatifloxacin. Tequin is indicated to treat infections caused by susceptible strains of microorganisms. Tequin is available in dosage formulations of tablets, injection concentrate and premixed bags for intravenous injection. For many infections the usual daily dose taken orally or as injection is 400 mg once a day. When spoken Tequin and Testim have the potential to sound similar. If the names were pronounced as "Te-quin" and "Te-stim", then this would cause a similar rhyming quality. The names would begin with the same "Te" sound and end with a similar "in" or "im" sound. Tequin and Testim have different product strengths (200 mg or 400 mg vs. 1%), package configurations (bottles or premixed intravenous bags vs. tubes), prescription classification (legend vs. schedule CIII), indications for use (infection vs. replacement therapy), route of administration (orally or intravenously vs. topically) and dosage form (tablet or injection vs. gel). Tequin and Testim would probably not be stored in close proximity to each other on a pharmacy shelf. Tequin tablets would probably be stored with the solid dosage formulations, while Testim would probably be stored either in a vault, because it is a controlled substance, or with topical products. Although it is possible for the names to initially sound similar, the risk of dispensing the wrong medication is low based on the differences between the medications.

Testred is the proprietary name for methyltestosterone. Testred is indicated for replacement therapy of testosterone for primary hypogonadism and hypogonadotropic hypogonadism. Testred is also indicated for delayed puberty and metastatic mammary cancer in females. Testred is available as a 10 mg capsule. The recommended dose for replacement therapy can be from one to five capsules daily. When spoken Testred and Testim have the potential to sound similar. If the names were pronounced as "Test-red" and "Test-im", then this would cause the names to have exactly the same first syllable. If pronounced in the above manner, then only the sound of the second syllable could differentiate the two names. Testred and Testim have different product strengths (10 mg vs. 1%), package configuration (bottle vs. tube), dosage form (capsule vs. gel), and route of administration (oral vs. topical). These medications could be stored near each other if stocked in a vault, since both medications are classified as a schedule CIII controlled drug. However, it is common practice to disseminate schedule III medications among non-schedule medications. Therefore, Testred capsules could be stored with the solid dosage formulations, while Testim could be stored in a general area containing ointments, creams and miscellaneous items. Both products can have an overlapping digit (1) in the product strength (10 vs. 1). However, the units of strength (mg vs. percent) should help differentiate the medications. The directions for use are different, since one medication is to be applied to the skin and the other taken orally. Although it is possible for the names to sound similar, the risk of dispensing the wrong medication is low based on the differences between the medications. The most important differences are the sound of the last syllable (red vs. im) and the expression of the product strength (mg vs. percent).

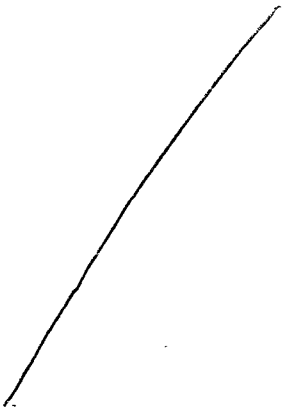
III. LABELING, PACKAGING, AND SAFETY RELATED ISSUES:

DMETS has reviewed the container label, carton labeling, and package insert labeling in an attempt to focus on safety issues to prevent possible medication errors. We have identified areas of improvement, in the interest of minimizing potential user error and patient safety.

A. Container Label (5 gram tube)



B. Carton Labeling (30 unit dose tubes)



C. Package Insert Labeling

1. The presentation of the proprietary and established names is not consistent with the container label and carton labeling. The names should appear as Testim™ 1% (testosterone gel).

2. The "How Supplied" section does not state if
   Include the appropriate information refer to comment B2.

D. Patient Package Insert (Patient Information and Instructions)

1. See comment C1.

2. The presentation of the inactive ingredients and temperature requirements is inconsistent with the container label, carton labeling, and package insert labeling. Please revise accordingly.

APPEARS THIS WAY
ON ORIGINAL

IV. RECOMMENDATIONS:

1. DMETS has no objections to the use of the proprietary name, "Testim".

2. DMETS recommends the above labeling revisions to encourage the safest possible use of the product.

DMETS would appreciate feedback of the final outcome of this consult. We are willing to meet with the Division for further discussion as well. If you have any questions concerning this review, please contact Sammie Beam at 301-827-3242.

Scott Dallas, R.Ph.
Safety Evaluator
Office of Drug Safety (DMETS)

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ON ORIGINAL

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/s/

Scott Dallas
8/29/02 07:47:00 AM
PHARMACIST

Carol Holquist
8/29/02 09:09:19 AM
PHARMACIST

Jerry Phillips
8/29/02 10:52:45 AM
DIRECTOR

APPEARS THIS WAY
ON ORIGINAL

TELECON Meeting Minutes

DATE: 25 June, 2002

APPLICATION NUMBER: NDA 21-454, Testim (testosterone 1%) gel

BETWEEN:

Name:	Diane Myers, Director, Regulatory Affairs
Name:	Roland Catherall, Vice President, Regulatory Affairs
Phone:	610-239-8850
Representing:	Auxilium, A^2 Inc.

AND

Name:	Leslie Stephens, MSN, RN, Project Manager Rajiv Agarwal, Ph.D, Chemistry Reviewer Division of Reproductive and Urologic Drug Products, HFD-580

SUBJECT: Request for Data on excipient

Auxilium A^2 Inc. submitted NDA 21-454 dated December 31, 2001. This telecon was requested by Dr. Agarwal to discuss the characterization of their Novel excipient (CPD).

The sponsor was asked to provide the following information:

1. The IR and NMR of oxacyclohexadecan-2-one (CPD) produced at — are somewhat different from the CPD manufactured at — Please clarify.

2. The batch analyses (test results) on the CPD batches produced to date.

3. The batch size and date of manufacture of the CPD batches produced to date.

4. The NMR of CPD reference standard.

5. A detailed description (e.g. — .) of the manufacturing process carried out at the —

6. Please comment on the — specification.

The sponsor agreed to provide the above information to the Division by July 12, 2002.

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

TO *(Division/Office)*: **DMETS**
ntion: Jerry Phillips

FROM: Leslie Stephens, RN, MSN
Regulatory Health Project Manager
DRUDP; HFD-580

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT:	DATE OF DOCUMENT:
June 10, 2002		21-454	N-000	12.31.2002

NAME OF DRUG:	PRIORITY CONSIDERATION:	CLASSIFICATION OF DRUG:	DESIRED COMPLETION DATE:
Testim 1% (testosterone) Gel	No	3S	August 1, 2002

NAME OF FIRM: Auxilim A^2, Inc.

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE/ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE–NDA MEETING
- ☐ END OF PHASE II MEETING
- ☐ RESUBMISSION
- ☒ SAFETY/EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☐ OTHER *(SPECIFY BELOW)*:

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
YPE A OR B NDA REVIEW END OF PHASE II MEETING ☐ CONTROLLED STUDIES ☐ PROTOCOL REVIEW ☐ OTHER (SPECIFY BELOW):	☐ CHEMISTRY REVIEW ☐ PHARMACOLOGY ☐ BIOPHARMACEUTICS ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE IV STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL-BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG EXPERIENCE

- ☐ PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- ☒ CLINICAL
- ☐ PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS:

APPEARS THIS WAY ON ORIGINAL

SIGNATURE OF REQUESTER	METHOD OF DELIVERY (Check one) ☒ MAIL ☐ HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

TO *(Division/Office)*:
Peter Cooney, PhD (HFD-805)
Microbiology Team Leader
Attention: David Hussong
Parklawn, Room 18B-08

FROM: Leslie Stephens, RN, MSN
Regulatory Health Project Manager
DRUDP; HFD-580

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT:	DATE OF DOCUMENT:
May 2, 2002		21-454	N-000	**Amendment Date: 28-March-2002**

NAME OF DRUG:	PRIORITY CONSIDERATION:	CLASSIFICATION OF DRUG:	DESIRED COMPLETION DATE:
Testim 1% (testosterone) Gel	No	3S	**31-Jul-2002**

NAME OF FIRM: Auxilim A^2, Inc.

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE/ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE-NDA MEETING
- ☐ END OF PHASE II MEETING
- ☐ RESUBMISSION
- ☒ SAFETY/EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☐ OTHER *(SPECIFY BELOW)*:

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
☐ TYPE A OR B NDA REVIEW ☐ END OF PHASE II MEETING ☐ CONTROLLED STUDIES ☐ PROTOCOL REVIEW ☐ OTHER (SPECIFY BELOW):	☐ CHEMISTRY REVIEW ☐ PHARMACOLOGY ☐ BIOPHARMACEUTICS ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE IV STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL-BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

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- ☐ PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS:

Please review this submission to determine if the microbiology limit testing, specifications, and AET are satisfactory.

For Questions, call Leslie Stephens, x7-4259 or Rajiv Agarwal, x7290

NATURE OF REQUESTER	METHOD OF DELIVERY (Check one)
Leslie Stephens, MSN, RN DRUDP, HFD-580 PKLN, Rm 17B-30	☐ MAIL ☒ELECTRONIC (DFS) ☒ HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

Diane P. Myers
Director, Regulatory Affairs
Auxilium A^2, Inc.
160 W. Germantown Pike
Sujte D-5
Norristown, PA 19401

MAR 20 2002

RE: Auxilium A^2, Small Business Waiver Request 2002.007 for Testim (testosterone topical gel)

Dear Ms. Myers:

This responds to your November 19, 2001, letter requesting a waiver of the human drug application fee for the new drug application (NDA) 21-454 for Testim (testosterone topical gel) under the small business waiver provision of section 736(d)(1)(E)[1] of the Federal Food, Drug, and Cosmetic Act (the Act) (Waiver Request 2002.007). For the reasons described below, the Food and Drug Administration (FDA) grants the request from *Auxilium A^2, Inc. (Auxilium)* for a small business waiver of the application fee.

According to your waiver request, Auxilium is a small business with , including its affiliates. You state Auxilium anticipated submitting its first new drug application by December 31, 2001.

Under the Act, a waiver of the application fee shall be granted to a small business for the first human drug application that a small business or its affiliate[2] submits to the FDA for review. The small business waiver provision entitles a qualified small business to a waiver when the business meets the following criteria: (1) a business must employ fewer than 500 persons, including employees of its affiliates, and (2) the marketing application must be the first human drug application, within the meaning of the Act, that a company or its affiliate submits to FDA.

FDA's decision to grant a small business waiver to Auxilium is based on the following findings. First, the Small Business Administration (SBA) determined and stated in its letter dated January 30, 2002, that Auxilium has fewer than 500 employees, including those of its affiliates, Auxilium UK, Ltd., and Auxilium Holdings, Inc. Second, according to FDA records, the marketing application for Testim will be the first human drug application, within the meaning of the Act, to be submitted to FDA by Auxilium or its affiliates. Consequently, your request for a small business waiver of the application fee for Testim (testosterone topical gel) is granted.

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[1] 21 U.S.C. 379h(d)(1)(E).

[2] "The term 'affiliate' means a business entity that has a relationship with a second business entity if, directly or indirectly - (A) one business entity controls, or has the power to control, the other business entity; or (B) a third party controls, or has the power to control, both of the business entities" (21 U.S.C. 379g(9)).

FDA records show that Auxilium's NDA 21-454 was submitted on December 31, 2001, and FDA was notified on December 19, 2001, of payment of $258,451 towards the FY 2002 application fee. If FDA refuses to file the application or Auxilium withdraws the application before it is filed by FDA, a reevaluation of the waiver may be required should the company resubmit its marketing application. If this situation occurs, Auxilium should contact this office approximately 90 days before it expects to resubmit its marketing application to determine whether it continues to qualify for a waiver.

We have asked the Office of Financial Management (OFM) to issue a refund of the $258,451 that you submitted for the review of the application. If you do not receive a check within 30 days of the date of this letter, please contact Donna Simms, OFM, at 301-827-5088.

FDA plans to disclose to the public information about its actions granting or denying waivers and reductions. This disclosure will be consistent with the laws and regulations governing the disclosure of confidential commercial or financial information.

If any billing questions arise concerning the marketing application or if you have any questions about this small business waiver, please contact Beverly Friedman or Michael Jones at 301-594-2041.

Sincerely,

/S/

Jane A. Axelrad
Associate Director for Policy
Center for Drug Evaluation and Research

APPEARS THIS WAY
ON ORIGINAL

BCC:
HFD-5 M. Jones
HFD-5 B. Friedman
HFD-5 Chronological File
HFD-5 Auxilium A^2, Inc. waiver file
HFD-580 L. Stephens, project manager
HFM-110 C. Vincent/K. Zemann
HFA-103 S. Farran (RECORD ON PAYMENT AND ARREARS LIST)
HFA-120 D. Simms (REFUND)
HF-20 F. Claunts

Drafted: B. Friedman 12/31/01, 2/20/2002
Review: M. Jones 2/20/2002
Edited: O. Pritzlaff 2/21/2002
Revised: B. Friedman 2/21/2002
Reviewed: J. Axelrad

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APPEARS THIS WAY
ON ORIGINAL

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation ODE III

FACSIMILE TRANSMITTAL SHEET

DATE: 02.14.02

To: Diane Myers Director, Regulatory Affairs	**From:** Leslie Stephens, MSN, RN Regulatory Project Manager
Company: Auxilium, Inc.	Division of Reproductive and Urologic Drug Products
Fax number: 610-239-8853	**Fax number:** 301-827-4267
Phone number: 610-239-8850	**Phone number:** 301-827-4260

Subject: Requests for information

Total no. of pages including cover:

Comments: Request for informtation

We are providing these comments to you before we complete our review of the entire application to give you preliminary notice of issues that we have identified. In conformance with the prescription drug user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and subject to change as we finalize our review of your application. In addition, we may identify other information that must be provided before we can approve this application. If you respond to these issues during this review cycle, depending on the timing of your response, and in conformance with the user fee reauthorization agreements, we may not be able to consider your response before we take an action on your application during this review cycle.

Document to be mailed: ☐ YES ■ NO

2 Page(s) Withheld

DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service

Division of Reproductive & Urologic Drug Products
Food and Drug Administration
Rockville, MD 20857

MEMORANDUM OF TELEPHONE FACSIMILE CORRESPONDENCE

dfs 2/14/02

Date: February 14, 2002

To: Diane Myers
Director, Regulatory Affairs
Auxilium, Inc.

From: Leslie Stephens, RN, MSN, DRUDP; eso-02.14.02

Through: Dan Davis, MD, Medical Reviewer, DRUDP; eso-02.12.02
Mike Welch, PhD, Biometrics Team Leader, DBII; eso-02.12.02
Dhruba Chatterjee, PhD, Clinical Pharmacology Reviewer, DPE II; eso-02.12.02
Krishan Raheja, DVM, PhD, Pharmacologist, DRUDP; eso-02.12.02

NDA: 21-454

Subject: **Request for information**

The following comments/requests are being conveyed on behalf of the review team and are with reference to NDA 21-454 submitted on December 31, 2001:

1. Please clarify the exact purpose of the pentadecalactone exipient. Does this exipient act — ?

2. Is the "to-be-marketed" formulation the same as the clinical study formulation?

3. Page 79-040, "Table of Contents" for the principal study report refers to Section 16, Appendices. Section 16 (which is supposed to begin at page 782, Vol 81) is missing. This section was to include all protocols and protocol changes to the study. It should also include all versions of the Statistical Analysis Plan. Please provide a completed Section 16.

4. For the Clinical Pharmacology reviewer, please provide a desk copy of all relevant volumes that contain pharmacokinetic data & summaries for the phase 3 clinical study (AUX –202.01R).

We are providing the above information via telephone facsimile for your convenience. **THIS MATERIAL SHOULD BE VIEWED AS UNOFFICIAL CORRESPONDENCE.** Please feel free to contact me if you have any questions regarding the contents of this transmission.

NDA: 21-454 Testim™ [1% testosterone gel]

45 Day Filing Meeting Checklist
CLINICAL

ITEM	YES	NO	COMMENT
1) Is the clinical section of the NDA clearly organized?	X		
2) Is the clinical section of the NDA adequately indexed and paginated?	X		
3) Is the clinical section of the NDA legible?	X		
4) Is there an adequate rationale for selection of dose and dosing schedule?	X		Start at 50 mg dose (1 tube) and may increase to 2 tubes/day in [redacted] 14 days if serum T levels are not in the prescribed normal range.
5) Is the requisite number of adequate and well controlled studies submitted in the application?	X		
6) Are the pivotal efficacy studies of appropriate design and duration to assess approvability of this product for its proposed indication?	X		
7) Are electronic data sets (with adequate documentation for their use) provided for pivotal efficacy studies?	X		
8) Has the applicant submitted line listings in a format to allow review of individual patient data?	X		
9) Has the applicant submitted a rationale for assuming the applicability of foreign trial results to the U.S. population?	N.A.		
10) Has the applicant submitted all required case report forms (i.e., deaths, drop-outs due to ADEs and any other CRFs previously requested by the Division)?	X		30 are submitted as required.
11) If appropriate, have stratified analyses of primary safety and efficacy parameters been conducted for age, gender and race?	N.A.		

ITEM	YES	NO	COMMENT
12) Has the applicant presented the safety data in a manner previously agreed to by the Division?	X		
13) If approved in other countries, have a summary and assessment of foreign post-marketing experience been provided?	N.A.		
14) Has draft labeling been submitted?	X		
15) Have all special studies/data requested by the Division during pre-submission discussions with the sponsor been submitted?	X		Two transfer studies and one washing effect study were completed and submitted.
16) From a clinical perspective, is this NDA fileable? If "no", please state in item #17 below why it is not.	X		
17) Reasons for refusal to file:			

Daniel Davis, MD 2-12-02
Reviewing Medical Officer / Date

APPEARS THIS WAY
ON ORIGINAL

Supervisory Medical Officer/Date

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

/s/

Daniel Davis
2/13/02 10:09:06 AM
MEDICAL OFFICER

Mark S. Hirsch
2/14/02 01:24:51 PM
MEDICAL OFFICER

APPEARS THIS WAY
ON ORIGINAL

NDA FILEABILITY CHECKLIST

NDA Number: 21-454

Applicant: **Auxilium A2. Inc.**
160 W. Germantown Pike
Suite D-5
Norristown, PA 19401

Stamp Date: December 31, 2001
Drug Name: Testim 1% (Transdermal gel)
Container closure: Blind end and capped Alumium tube (5 g per tube)
Strength: 50 mg/g tube, single application

IS THE CMC SECTION OF THE APPLICATION FILEABLE? (Yes ___No ____)

The following parameters are necessary in order to initiate a full review, i.e., complete enough to review but may have deficiencies.

	Parameter	Yes	No	Comment
1	On its face, is the section organized adequately?	x		
2	Is the section indexed and paginated adequately?	x		
3	On its face, is the section legible?	x		
4	Are ALL of the facilities (including contract facilities and test laboratories) identified with full street addresses and CFNs?	x		
5	Is a statement provided that all facilities are ready for GMP inspection?	x		
6	Has an environmental assessment report or categorical exclusion been provided?	x		
7	Does the section contain controls for the drug substance?	x		
8	Does the section contain controls for the drug product?	x		
9	Has stability data and analysis been provided to support the requested expiration date?	x		
10	Has all information requested during the IND phase, and at the pre-NDA meetings been included?		x	In vitro release rate and — — test and acceptance criteria are not included. See comment. Review Issue.
11	Have draft container labels been provided?	x		
12	Has the draft package insert been provided?	x		

13	Has an investigational formulations section been provided?	x		*Sponsor will provide this information. See comment.
14	Is there a Methods Validation package?	x		*Called the sponsor on 1-18-02 and asked for the three copies of Method validation package. Reference to the guidance stating the requirements are also conveyed. See comment.
15	Is a separate microbiological section included?	x		*Sponsor is asked to pooled all the information on microbial testing and provide a separate microbial section.

* = Applicant has agreed to provide this information by the end of March 2002.

This application **meets the filing requirement** from the CMC point of view. This application is adequate to review from the CMC stand point.

Review Chemist: Rajiv Agarwal, Ph.D date: 02-12-02

Team Leader: Moo-Jhong Rhee, Ph.D date: 02-12-01

cc:
Original NDA 21-454
HFD-580/ NDA 21-454/Division File
HFD-580/Chem/RAgarwal/MRhee
HFD-580/PM//StephensL

APPEARS THIS WAY
ON ORIGINAL

Have all DMF References been Identified? YES

DMF Number	Holder	Description	LOA	Status
[redacted]	[redacted]	[redacted]	Included	
[redacted]	[redacted]	[redacted]	Included	
[redacted]	[redacted]	[redacted]	Included	

APPEARS THIS WAY
ON ORIGINAL

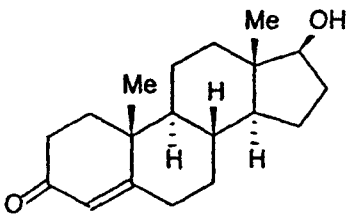
SUMMARY

DRUG SUBSTANCE:

The active ingredient in the "Testim 1%", is Testosterone. Two sites located in [redacted] manufacture the drug substance. Detailed information regarding the synthesis and characterization of Testosterone is provided in their representative Drug Master Files [redacted] A letter from each manufacturer authorizing Auxilium to cross-reference the DMF's is supplied in the submission.

Following information on the drug substance is also provided in the NDA submission.

CAS # 58-22-0
Molecular weight: $C_{19}H_{28}NO_2$
Structural formula:



Testosterone

APPEARS THIS WAY
ON ORIGINAL

Chemical name: 17β -Hydroxyandrost-4-en-3-one

DRUG PRODUCT

Dosage form:	Transdermal gel
Strength:	50 mg/g tube, single application
Route of Administration:	Transdermal

APPEARS THIS WAY
ON ORIGINAL

Components and composition:

Component	Amounts (in g)	% w/w	Function	Reference to standard
Testosterone (micronized)	0.05	1.00	Active	USP
Oxacyclohexadecan-2-one				Validated GC assay; internal Standard
Carbopol				NF
				NF
Propylene Glycol				USP
Glycerin				USP
Polyethylne Glycol				NF
Alcohol				USP
Tromethamine				USP
Purified water				USP

Note: Batch formula is not provided and should be provided (Review issue).

APPEARS THIS WAY
ON ORIGINAL

Manufacturers:

Drug Substance:

APPEARS THIS WAY
ON ORIGINAL

Drug Product:

Manufacturing, stability, and packaging site of the finished product.
Release testing of active and excipients except Oxacyclohexadecan-2-one.

Analytical testing site: Release testing of the testosterone, Oxacyclohexadecan-2-one. QC testing of other excipients, drug product and packaging components for supportive stability studies. Stability QC testing of testosterone and related substances and Oxacyclohexadecan-2-one and related substances.

APPEARS THIS WAY
ON ORIGINAL

Stability:

Primary stability data is provided in the submission and ***a*** ***expiration*** date is requested, which is based on the stability data or **batches** manufactured to date (

scale lots (PCLF, PCLG, RDIK, REBM- *each*) primary stability data:

[**Tests**: description, pH, viscosity, microbial limit, ethanol, testosterone (assay-by , testosterone (assay by , Testosterone impurities , Specified related impurities,

—— , testosterone impurities unspecified, total testosterone impurities.

Additional tests will be submitted on these tests during updates:

Oxacyclohexadecan-2-one specified related substances —

Oxacyclohexadecan-2-one unspecified related substances —

Total Oxacyclohexadecan-2-one specified and unspecified substances —

[For PCLF, PCLG lots]

- **25^{0}C/60% RH:**
- **30^{0}C/60% RH:**
- **40^{0}C/75% RH:**

[For RDIK and REBM lots]

- **25^{0}C/60% RH:**
- **30^{0}C/60% RH:**
- **40^{0}C/75% RH:**

commercial scale lot (RIAB— — — primary stability data:

[For RIAB commercial lot]

- **25^{0}C/60% RH:**
- **30^{0}C/60% RH:**
- **40^{0}C/75% RH:**

Cycling stability studies:

Sponsor states " that drug product can not be frozen at –20^{0}C. As a result no further work on freeze thaw was warranted".

Comment: Sponsor is contacted on 1-23-02 and asked to provide the Viscosity testing at the initial and final cycling points. Information on number of batches used will also be provided. **It is a review issue.**

The sponsor has proposed an expiration date of —— At the current time long term and accelerated stability data is available for only — , on — scale lots and — , on commercial batch. Sponsor has indicated to provide ongoing stability updates. Sponsor did not specify the expiration date in the submission. Sponsor indicated in a t-con dated 1-23-02 that —— of expiry date is requested.

Comment:

According to the pre NDA meeting minutes dated 10-4-01, sponsor was asked to provide the following information in the submission.

1. In vitro release rate and — test and acceptance criteria (see pre NDA minutes dated 10-4-01).
2. Information on the batches used in **Cycling stability studies** (see pre NDA minutes dated 10-4-01). See comment under stability.

Sponsor (Ms. Diane P. Myers) called on 1-22-02 at 10.15 AM and 1-23-02 at 10 AM and committed to provide the followings:

- **In vitro release rate:** Test and acceptance criterion for this attribute will be submitted in around March 2002. This will also include the stability testing addressing this attribute. Certificate of Analysis of the drug product will be provided in March 2002, which will show the result of this testing.
- **Comprehensive Method Validation package** will be provided in March 2002, containing the In- vitro release rate test.
- **Investigational formulation** section will be provided.
- — **test:** This is provided as a part of the "Description" attribute.
- Sponsor clarified the role of **Auxilium A2. Inc.** Sponsor states that this site does the **"Review of Quality Control testing of the finished product performed at** —
- **Cycling stability studies** (Viscosity studies will be provided).
- **Oxacyclohexadecan**-2-one: Drug product specifications for Oxacyclohexadecan-2-one specified related substances — Oxacyclohexadecan-2-one unspecified related substances — , and Total Oxacyclohexadecan-2-one specified and unspecified substances — **will be provided in March 2002.**

APPEARS THIS WAY
ON ORIGINAL

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

/s/

Rajiv Agarwal
2/12/02 03:06:18 PM
CHEMIST
NDA filability (CMC)

Moo-Jhong Rhee
2/12/02 06:01:09 PM
CHEMIST
I concur

Memo to the file

2-12-2002

Subject: NDA 21-454 filing meeting

Auxilium A [2] Inc. NDA 21-454 for Testim (1% testosterone gel) is filable from the P/T prospective.

Krishan L. Raheja
P/T reviewer

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

/s/

Krishan L. Raheja
2/12/02 02:50:10 PM
PHARMACOLOGIST

APPEARS THIS WAY
ON ORIGINAL

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Division of Antiviral Drug Products
Food and drug Administration
Rockville MD 20857

Memorandum of 45 day Filing Meeting

Date: February 12, 2002

Drug: Testim™ (testosterone) Gel 1%

NDA: 21-454

Sponsor: Auxilium A^2, Inc.

FDA Participants: Mark Hirsch, Dan Davis, Rajiv Agarwal, Moo Jhong Rhee, Krishan Raheja, D.J. Chatterjee, Mike Welch, Ashok Batra, Roy Blay Leslie Stephens

Background: The purpose of this meeting is to discuss filability of NDA 21-454, Testim™ (testosterone) Gel 1%, indicated for testosterone replacement therapy in adult males

. This application has been given a Standard review with a 10-month review date. **PDUFA date is October 31, 2002.**

Discussions:

1. **Pharmacology/Toxicology**: Dr. Raheja concluded that the NDA is **filable**. There were no pharmacotoxicologic issues.

2. **Clinical Pharmacology/Biopharmaceutics:** Dr. Chatterjee determined that this NDA is **filable.** The sponsor will be asked to confirm whether the clinical trial formulation is the same as the to-be-marketed formulation

3. **Chemistry:** Dr. Agarwal concluded that the NDA is **filable**. In the minutes of the October 4, 2002 pre-NDA meeting, the sponsor committed to provide in vitro release rate and Phase separation test and acceptance criteria. The sponsor also agreed to provide information on the batches used in Cycling stability studies.

4. **Statistical:** Dr. Welch concluded that the NDA is **filable**.

5. **Clinical:** Dr. Davis concluded that the NDA is **filable.**

6. **DSI:** Roy Blay stated that under the new guidelines, there is no need for a DSI inspection unless concerns arise during the review cycle, therefore there will be no consult requested at this time.

7. **OPDRA:** A request for review of the tradename Testim™ Gel 1% will be sent with a deadline of August 1, 2002 requested.

8. **Pediatric exclusivity:** On January 17, 2002, the sponsor requested a full waiver of the requirements for studying the use of this drug in the pediatric population. This waiver will be considered during the review cycle and the sponsor will be notified of the decision in the action letter.

Conclusion:
The review team concluded that NDA 21-454 is filable. The sponsor will be notified of our decision to file this NDA.

Action Items:

The following requests will be communicated to the sponsor:

1. Please confirm whether or not the clinical trial formulation is the same as the to-be-marketed formulation.

2. Provide in vitro release rate and Phase separation test and acceptance criteria.

3. Provide information on the batches used in Cycling stability studies.

MEMORANDUM OF TELECON

DATE: 23-Jan-2002

APPLICATION NUMBER: NDA 21-454, Testim (testosterone 1%) gel

BETWEEN:

Name:	Diane Myers, Director, Regulatory Affairs
Name:	Roland Catherall, Vice President, Regulatory Affairs
Phone:	610-239-8850
Representing:	Auxilium, A^2 Inc.

AND

Name:	Leslie Stephens, MSN, RN, Project Manager, eso: 4/4/02
	Rajiv Agarwal, Ph.D, Chemistry Reviewer, eso: 4/4/02
	Division of Reproductive and Urologic Drug Products, HFD-580

SUBJECT: Chemistry issues related to NDA filability

Auxilium A^2 Inc. submitted NDA 21-454 dated December 31, 2001. This telecon was requested by Dr. Agarwal to discuss chemistry data needed to determine filability of this NDA.

According to the pre NDA meeting (dated 10-4-01), the sponsor agreed to submit the following data in the NDA package:

1. in-vitro release rate and phase separation tests and their acceptance criteria
   - To be submitted 90 days after filing date as agreed upon in the pre NDA meeting.
2. Viscosity of gel during the freeze and thaw cycles (could be a review issue if data is not provided)
   - Study was terminated because the gel did not freeze

In addition the following information was requested from the sponsor:

- Investigational Formulation (batch numbers used in clinical trials)
- Provide three copies of methods validation within 90 days of original NDA submission.
- Please submit an amendment requesting expiry date
- Please provide micobiology testing data in a summary table

The sponsor agreed to the following action items:

1. Volume and page # of the Investigational Formulation data
2. Microbiology testing package
3. 3 copies of the methods validation package within 90 days of original NDA submission (March 31, 2002)

4. Cycling stability data (with reference to viscosity)
5. Provide a request for expiry date in writing.
6. Provide in writing, the role of Auxilium site.
7. Test and acceptance criteria for "in-vitro release rate" will be submitted in March 2002. This will also include the stability testing addressing this attribute. A Certificate of Analysis of the drug product will be provided in March 2002, which will show the result of this testing.
8. — . test will be provided as a part of the "Description" attribute.
9. Drug product specification for oxa-cyclohexadecan-2-one related substances will be provided in March 2002.

Leslie Stephens, MSN, RN
Regulatory Health Project Manager

APPEARS THIS WAY
ON ORIGINAL

MEMORANDUM

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

Date: January 15, 2002

From: Jeanine Best, M.S.N., R.N.
Senior Regulatory Associate
Division of Reproductive and Urologic Drug Products (HFD-580)

Subject: Review of Financial Disclosure documents

To: NDA 21-454

I have reviewed the financial disclosure information submitted by Auxillium A2, Inc. in support of their NDA 21-454 for Testim™ 1% (testosterone gel).

Two pivotal studies were conducted to assess the safety and efficacy of Testim™ 1% (testosterone gel) indicated for testosterone replacement therapy in adult males — The study numbers and the results of the review of financial disclosure documents are summarized below:

Study Number/Title	Study Status	Financial Disclosure Review
Study AUX-TG-201/ "Evaluation of the Pharmacokinetic Profiles After a Single Dose of a new Testosterone Topical Gel Formulation Compared to a Commercial Topical Testosterone Gel Preparation"	Study Start: 17-JAN-2001 Study Complete: 24-MAR-2001	Appropriate documentation received, no financial disclosure submitted.
Study AUX-TG-202 / "Evaluation of the Use of a Unique Testosterone Topical Gel Formulation and a Transdermal Testosterone Patch (Androderm®) in Males with a Testosterone Level ≤ 300 ng/dL"	Study Start: 13-MAR-2001 Study Complete: 20-NOV-2001	Appropriate documentation received, no financial disclosure submitted.

Documents Reviewed:

- FDA Form 3454, *Certification: Financial Interests and Arrangements of Clinical Investigators*
- Financial Disclosure section of NDA, Volume 1.1 (submitted December 31, 2001)
- Clinical Study Reports submitted in NDA

Study AUX-TG-201

There was one investigator at one site in this trial, enrolling 29 patients. Financial disclosure information was received from the investigator, who reported no disclosable financial information.

Study AUX-TG-202
There were 43 investigators at 43 sites in this trial, enrolling 407 patients. Financial disclosure information was received from all investigators and none reported any disclosable financial information.

Conclusion:
Adequate documentation was submitted to comply with 21 CFR 54. There was no disclosure of financial interests that could bias the outcome of the trials.

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

/s/

Jeanine Best
1/15/02 08:37:09 AM
CSO

APPEARS THIS WAY
ON ORIGINAL

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration

Form Approved: OMB No. 0910-0396
Expiration Date: 3/31/02

CERTIFICATION: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS

TO BE COMPLETED BY APPLICANT

With respect to all covered clinical studies (or specific clinical studies listed below (if appropriate)) submitted in support of this application, I certify to one of the statements below as appropriate. I understand that this certification is made in compliance with 21 CFR part 54 and that for the purposes of this statement, a clinical investigator includes the spouse and each dependent child of the investigator as defined in 21 CFR 54.2(d).

Please mark the applicable checkbox.

☐ (1) As the sponsor of the submitted studies, I certify that I have not entered into any financial arrangement with the listed clinical investigators (enter names of clinical investigators below or attach list of names to this form) whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a). I also certify that each listed clinical investigator required to disclose to the sponsor whether the investigator had a proprietary interest in this product or a significant equity in the sponsor as defined in 21 CFR 54.2(b) did not disclose any such interests. I further certify that no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f).

Clinical Investigators		
	See attached investigator list.	

(2) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that based on information obtained from the sponsor or from participating clinical investigators, the listed clinical investigators (attach list of names to this form) did not participate in any financial arrangement with the sponsor of a covered study whereby the value of compensation to the investigator for conducting the study could be affected by the outcome of the study (as defined in 21 CFR 54.2(a)); had no proprietary interest in this product or significant equity interest in the sponsor of the covered study (as defined in 21 CFR 54.2(b)); and was not the recipient of significant payments of other sorts (as defined in 21 CFR 54.2(f)).

☐ (3) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that I have acted with due diligence to obtain from the listed clinical investigators (attach list of names) or from the sponsor the information required under 54.4 and it was not possible to do so. The reason why this information could not be obtained is attached.

NAME	TITLE
Mike Choi	Chief Financial Officer, Treasurer
FIRM/ORGANIZATION: Auxilium A2, Inc. 160 W. Germantown Pike, Suite D-5, Norristown, PA 19401	
SIGNATURE: Mike Choi	DATE: 12/22/01

Paperwork Reduction Act Statement

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number. Public reporting burden for this collection of information is estimated to average 1 hour per response, including time for reviewing instructions, searching existing data sources, gathering and maintaining the necessary data, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information to the address to the right:

Department of Health and Human Services
Food and Drug Administration
5600 Fishers Lane, Room 14C-03
Rockville, MD 20857

2 Page(s) Withheld

COVER SHEET

See Instructions on Reverse Side Before Completing This Form

A completed form must be signed and accompany each new drug or biologic product application and each new supplement. See exceptions on the reverse side. If payment is sent by U.S. mail or courier, please include a copy of this completed form with payment. Payment instructions and fee rates can be found on CDER's website: http://www.fda.gov/cder/pdufa/default.htm

1. APPLICANT'S NAME AND ADDRESS

Auxilium A^2, Inc.
160 W. Germantown Pike
Suite D-5
Norristown, PA 19401

2. TELEPHONE NUMBER *(Include Area Code)*

(610) 239-8850

3. PRODUCT NAME

Testim ™ (1% testosterone gel)

4. BLA SUBMISSION TRACKING NUMBER (STN) / NDA NUMBER

N021454

5. DOES THIS APPLICATION REQUIRE CLINICAL DATA FOR APPROVAL?

☒ YES ☐ NO

IF YOUR RESPONSE IS "NO" AND THIS IS FOR A SUPPLEMENT, STOP HERE AND SIGN THIS FORM.

IF RESPONSE IS 'YES', CHECK THE APPROPRIATE RESPONSE BELOW:

☐ THE REQUIRED CLINICAL DATA ARE CONTAINED IN THE APPLICATION.

☒ THE REQUIRED CLINICAL DATA ARE SUBMITTED BY REFERENCE TO:

21-454

(APPLICATION NO. CONTAINING THE DATA).

6. USER FEE I.D. NUMBER

4254

7. IS THIS APPLICATION COVERED BY ANY OF THE FOLLOWING USER FEE EXCLUSIONS? IF SO, CHECK THE APPLICABLE EXCLUSION.

☐ A LARGE VOLUME PARENTERAL DRUG PRODUCT APPROVED UNDER SECTION 505 OF THE FEDERAL FOOD, DRUG, AND COSMETIC ACT BEFORE 9/1/92
(Self Explanatory)

☐ A 505(b)(2) APPLICATION THAT DOES NOT REQUIRE A FEE
(See item 7, reverse side before checking box.)

☐ THE APPLICATION QUALIFIES FOR THE ORPHAN EXCEPTION UNDER SECTION 736(a)(1)(E) of the Federal Food, Drug, and Cosmetic Act
(See item 7, reverse side before checking box.)

☐ THE APPLICATION IS A PEDIATRIC SUPPLEMENT THAT QUALIFIES FOR THE EXCEPTION UNDER SECTION 736(a)(1)(F) of the Federal Food, Drug, and Cosmetic Act
(See item 7, reverse side before checking box.)

☐ THE APPLICATION IS SUBMITTED BY A STATE OR FEDERAL GOVERNMENT ENTITY FOR A DRUG THAT IS NOT DISTRIBUTED COMMERCIALLY
(Self Explanatory)

8. HAS A WAIVER OF AN APPLICATION FEE BEEN GRANTED FOR THIS APPLICATION?

☐ YES ☒ NO (applied for)

(See Item 8, reverse side if answered YES)

Public reporting burden for this collection of information is estimated to average 30 minutes per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Department of Health and Human Services
Food and Drug Administration
CBER, HFM-99
1401 Rockville Pike
Rockville, MD 20852-1448

and

Food and Drug Administration
CDER, HFD-94
12420 Parklawn Drive, Room 3046
Rockville, MD 20852

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

SIGNATURE OF AUTHORIZED COMPANY REPRESENTATIVE	TITLE	DATE
Diane F. Thyers	Director, Regulatory Affairs	17 December 2010

FORM FDA 3397 (4/01)

Created by: PSC Media Arts (301) 443-2454 EF

1 Page(s) Withheld

Office of Clinical Pharmacology and Biopharmaceutics
New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA Number	21-454	*Brand Name*	TESTIM™
OCPB Division (I, II, III)	DPE II (HFD 870)	*Generic Name*	Testosterone 1% gel
Medical Division	DRUDP (HFD 580)	*Drug Class*	Testosterone replacement
OCPB Reviewer	Dhruba J. Chatterjee, Ph.D.	*Indication(s)*	T replacement in
OCPB Team Leader	Ameeta Parekh, Ph.D.	*Dosage Form*	Transdermal Gel
Date of Submission	12/31/2001	*Dosing Regimen*	Once daily
Estimated Due Date of OCPB Review	10/1/2001	*Route of Administration*	Transdermal
PDUFA Due Date	10/31/2001	*Sponsor*	Auxilium A² Inc.
Division Due Date	10/24/2001	*Priority Classification*	3S

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	X	4		
Tabular Listing of All Human Studies	X			
HPK Summary	X			
Labeling	X			
Reference Bioanalytical and Analytical Methods	X			
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:				
multiple dose:				
Patients-				
single dose:	X			
multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
body wt.				

renal impairment:				
hepatic impairment:				
PD:				
Phase 2:				
Phase 3:				
PK/PD:				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability:				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies:				
Dissolution:				
(IVIVC):				
Bio-wavier request based on BCS				
BCS class				
III. Other CPB Studies				
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies	**4**			

Filability and QBR comments		
	"X" if yes	**Comments**
Application filable?	**X**	
Comments sent to firm?		
QBR questions (key issues to be considered)		
Other comments or information not included above	**Sponsor confirmed by Fax dated 2/12/2002 that the clinical trial formulation was the same as the to-be-marketed formulation.**	
Primary reviewer Signature and Date		
Secondary reviewer Signature and Date		

CC: NDA XX-XXX, HFD-850(Electronic Entry or Lee), HFD-XXX(CSO), HFD-8XX(TL, DD, DDD), CDR (B. Murphy)

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-454

Auxilium A^2, Inc.
Attention: Dianne P. Myers
Director, Regulatory Affairs
160 Germantown Pike
Norristown, PA 19401

APPEARS THIS WAY
ON ORIGINAL

Dear Ms. Myers:

We have received your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: Testim™ (testosterone) 1% gel

Review Priority Classification: Standard (S)

Date of Application: December 31, 2001

APPEARS THIS WAY
ON ORIGINAL

Date of Receipt: December 31, 2001

Our Reference Number: NDA 21-454

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on March 1, 2002 in accordance with 21 CFR 314.101(a). If the application is filed, the user fee goal date will be October 31, 2002.

Please cite the NDA number listed above at the top of the first page of any communications concerning this application. Address all communications concerning this NDA as follows:

U.S. Postal Service:
Center for Drug Evaluation and Research
Division of Reproductive and Urologic Drug Products
Attention: Division Document Room, 17B-20
5600 Fishers Lane
Rockville, Maryland 20857

APPEARS THIS WAY
ON ORIGINAL

Courier/Overnight Mail:
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Reproductive and Urologic Drug Products, HFD-580
Attention: Document Room 17B-20
5600 Fishers Lane
Rockville, Maryland 20857

If you have any questions, call Leslie Stephens, Regulatory Project Manager, at (301) 827- 4269.

Sincerely,

{See appended electronic signature page}

Terri Rumble
Chief Regulatory Project Manager
Division of Reproductive and Urologic Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

APPEARS THIS WAY ON ORIGINAL