CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

204399Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

EXCLUSIVITY SUMMARY

NDA # 204399 SUPPL # HFD #

Trade Name Vogelxo

Generic Name testosterone gel

Applicant Name Upsher-Smith Laboratories

Approval Date, If Known June 4, 2014

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES ☒ NO ☐

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3,SE4, SE5, SE6, SE7, SE8

505(b)(2)

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES ☒ NO ☐

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

N/A

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

N/A

d) Did the applicant request exclusivity?

YES ☒ NO ☐

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

3 years

e) Has pediatric exclusivity been granted for this Active Moiety?

YES ☒ NO ☐

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

No

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES ☐ NO ☒

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES
(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES ☒ NO ☐

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s). ***Please see attachment after the last page of this document**

NDA#

NDA#

NDA#

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES ☐ NO ☐

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered “NO” for original approvals of new molecular entities.)
IF “YES,” GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of

summary for that investigation.

YES ☒ NO ☐

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES ☒ NO ☐

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES ☐ NO ☒

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES ☐ NO ☒

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES ☐ NO ☒

If yes, explain:

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

BE Study #: Study P06-011
Transfer Study #: Study P10-003
Skin irritation study #: Study P08-001
Hand washing study #: Study P10-002

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1	YES ☐	NO ☒
Investigation #2	YES ☐	NO ☒
Investigation #3	YES ☐	NO ☒
Investigation #4	YES ☐	NO ☒

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1	YES ☐	NO ☒
Investigation #2	YES ☐	NO ☒
Investigation #3	YES ☐	NO ☒
Investigation #4	YES ☐	NO ☒

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

BE Study #: Study P06-011
Transfer Study #: Study P10-003
Skin irritation study #: Study P08-001
Hand washing study #: Study P10-002

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1		!
		!
IND # 76654	YES ☒	! NO ☐
		! Explain:

Investigation #2		!
		!
IND # 76654	YES ☒	! NO ☐

		! Explain:
Investigation #3		!
		!
IND # 76654	YES ☒	! NO ☐
		! Explain:
Investigation #4		!
		!
IND # 76654	YES ☒	! NO ☐
		! Explain:

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1	!
	!
YES ☐	! NO ☐
Explain:	! Explain:

Investigation #2	!
	!
YES ☐	! NO ☐
Explain:	! Explain:

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES ☐ NO ☒

If yes, explain:

==========

Name of person completing form: Jeannie Roule

Title: Senior Regulatory Health Project Manager
Date: June 4, 2014
Name of Office/Division Director signing form: Christine Nguyen, M.D.
Title: Deputy Director of Safety

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05; removed hidden data 8/22/12

Appl No	Proprietary Name
A083976	TESTRED
A080767	METHYLTESTOSTERONE
A084310	METHYLTESTOSTERONE
A086450	ANDROID 10
A087147	ANDROID 25
N020489	ANDRODERM
N021015	ANDROGEL 1%
N022309	ANDROGEL 1.62%
N021454	TESTIM
A080911	TESTOPEL
N022504	AXIRON
N202763	TESTOSTERONE GEL
N021463	FORTESTA
N021543	STRIANT
A090387	TESTOSTERONE CYPIONATE
A090387	TESTOSTERONE CYPIONATE
A040530	TESTOSTERONE CYPIONATE
A085635	DEPO-TESTOSTERONE
A085635	DEPO-TESTOSTERONE
A040615	TESTOSTERONE CYPIONATE
A040615	TESTOSTERONE CYPIONATE
A040652	TESTOSTERONE CYPIONATE
A086030	TESTOSTERONE CYPIONATE
N009165	DELATESTRYL
A040575	TESTOSTERONE ENANTHATE
A040647	TESTOSTERONE ENANTHATE
A085598	TESTOSTERONE ENANTHATE

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

/s/

JEANNIE M ROULE
06/04/2014

CHRISTINE P NGUYEN
06/04/2014

MEMORANDUM

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

DATE: November 21, 2012

TO: NDA 204399, testosterone gel

THROUGH: Jeannie Roule

SUBJECT: Information for PREAA

Please see attached Pediatric page. PREAA does not apply to this application.

PEDIATRIC PAGE
(Complete for all filed original applications and efficacy supplements)

NDA/BLA#: 204399 Supplement Number: _____ NDA Supplement Type (e.g. SE5): _____

Division Name:DRUP PDUFA Goal Date: 8/18/13 Stamp Date: 10/18/2012

Proprietary Name: _____

Established/Generic Name: testosterone gel

Dosage Form: gel

Applicant/Sponsor: Upsher-Smith

Indication(s) *previously approved* (please complete this question for supplements and Type 6 NDAs only):
(1) _____
(2) _____
(3) _____
(4) _____

Pediatric use for each pediatric subpopulation must be addressed for each indication covered by current application under review. A Pediatric Page must be completed for each indication.

Number of indications for this pending application(s):1
(Attach a completed Pediatric Page for each indication in current application.)

Indication: Replacement therapy in males for conditions associated with a deficiency or absence of endogenous testosterone

Q1: Is this application in response to a PREA PMR? Yes ☐ Continue
No ☒ Please proceed to Question 2.

If Yes, NDA/BLA#: _____ Supplement #:_____ PMR #:_____

Does the division agree that this is a complete response to the PMR?

☐ Yes. Please proceed to Section D.

☐ No. Please proceed to Question 2 and complete the Pediatric Page, as applicable.

Q2: Does this application provide for (If yes, please check all categories that apply and proceed to the next question): NO

(a) NEW ☐ active ingredient(s) (includes new combination); ☐ indication(s); ☐ dosage form; ☐ dosing regimen; or ☐ route of administration?*

(b) ☒ No. PREA does not apply. **Skip to signature block.**

**** Note for CDER: SE5, SE6, and SE7 submissions may also trigger PREA.***

Q3: Does this indication have orphan designation?

☐ Yes. PREA does not apply. **Skip to signature block.**

☐ No. Please proceed to the next question.

Q4: Is there a full waiver for all pediatric age groups for this indication (check one)?

- ☐ Yes: (Complete Section A.)
- ☐ No: Please check all that apply:
  - ☐ Partial Waiver for selected pediatric subpopulations (Complete Sections B)
  - ☐ Deferred for some or all pediatric subpopulations (Complete Sections C)
  - ☐ Completed for some or all pediatric subpopulations (Complete Sections D)
  - ☐ Appropriately Labeled for some or all pediatric subpopulations (Complete Sections E)
  - ☐ Extrapolation in One or More Pediatric Age Groups (Complete Section F)

  (Please note that Section F may be used alone or in addition to Sections C, D, and/or E.)

Section A: Fully Waived Studies (for all pediatric age groups)

Reason(s) for full waiver: (**check, and attach a brief justification for the reason(s) selected**)

- ☐ Necessary studies would be impossible or highly impracticable because:
  - ☐ Disease/condition does not exist in children
  - ☐ Too few children with disease/condition to study
  - ☐ Other (e.g., patients geographically dispersed): _____
- ☐ Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients AND is not likely to be used in a substantial number of pediatric patients.
- ☐ Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- ☐ Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- ☐ Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)

☐ Justification attached.

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please complete another Pediatric Page for each indication. Otherwise, this Pediatric Page is complete and should be signed.

Section B: Partially Waived Studies (for selected pediatric subpopulations)

Check subpopulation(s) and reason for which studies are being partially waived (fill in applicable criteria below):

Note: If Neonate includes premature infants, list minimum and maximum age in "gestational age" (in weeks).

				Reason (see below for further detail):			
		minimum	maximum	Not feasible#	Not meaningful therapeutic benefit*	Ineffective or unsafe†	Formulation failedΔ
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

Reason(s) for partial waiver (**check reason** corresponding to the category checked above, and **attach a brief justification**):

Not feasible:

☐ Necessary studies would be impossible or highly impracticable because:

- ☐ Disease/condition does not exist in children
- ☐ Too few children with disease/condition to study
- ☐ Other (e.g., patients geographically dispersed): _____

***** Not meaningful therapeutic benefit:

☐ Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients in this/these pediatric subpopulation(s) AND is not likely to be used in a substantial number of pediatric patients in this/these pediatric subpopulation(s).

† Ineffective or unsafe:

☐ Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)

☐ Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)

☐ Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)

Δ Formulation failed:

☐ Applicant can demonstrate that reasonable attempts to produce a pediatric formulation necessary for this/these pediatric subpopulation(s) have failed. (*Note: A partial waiver on this ground may only cover the pediatric subpopulation(s) requiring that formulation. An applicant seeking a partial waiver on this ground must submit documentation detailing why a pediatric formulation cannot be developed. This submission will be posted on FDA's website if waiver is granted.)*

☐ Justification attached.

For those pediatric subpopulations for which studies have not been waived, there must be (1) corresponding study plans that have been deferred (if so, proceed to Sections C and complete the PeRC Pediatric Plan Template); (2) submitted studies that have been completed (if so, proceed to Section D and complete the PeRC Pediatric Assessment form); (3) additional studies in other age groups that are not needed because the drug is appropriately labeled in one or more pediatric subpopulations (if so, proceed to Section E); and/or (4)

additional studies in other age groups that are not needed because efficacy is being extrapolated (if so, proceed to Section F). Note that more than one of these options may apply for this indication to cover all of the pediatric subpopulations.

Section C: Deferred Studies (for selected pediatric subpopulations).

Check pediatric subpopulation(s) for which pediatric studies are being deferred (and fill in applicable reason below):

Deferrals (for each or all age groups):				**Reason for Deferral**			**Applicant Certification †**
Population		minimum	maximum	Ready for Approval in Adults	Need Additional Adult Safety or Efficacy Data	Other Appropriate Reason (specify below)*	Received
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	All Pediatric Populations	0 yr. 0 mo.	16 yr. 11 mo.	☐	☐	☐	☐
	Date studies are due (mm/dd/yy): _____						

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

* Other Reason: _____

† Note: Studies may only be deferred if an applicant submits a certification of grounds for deferring the studies, a description of the planned or ongoing studies, evidence that the studies are being conducted or will be conducted with due diligence and at the earliest possible time, and a timeline for the completion of the studies. If studies are deferred, on an annual basis applicant must submit information detailing the progress made in conducting the studies or, if no progress has been made, evidence and documentation that such studies will be conducted with due diligence and at the earliest possible time. This requirement should be communicated to the applicant in an appropriate manner (e.g., in an approval letter that specifies a required study as a post-marketing commitment.)

If all of the pediatric subpopulations have been covered through partial waivers and deferrals, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section D: Completed Studies (for some or all pediatric subpopulations).

Pediatric subpopulation(s) in which studies have been completed (check below):					
Population		minimum	maximum	PeRC Pediatric Assessment form attached?.	
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	Yes ☐	No ☐

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

Note: If there are no further pediatric subpopulations to cover based on partial waivers, deferrals and/or completed studies, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section E: Drug Appropriately Labeled (for some or all pediatric subpopulations):

Additional pediatric studies are not necessary in the following pediatric subpopulation(s) because product is appropriately labeled for the indication being reviewed:			
Population		minimum	maximum
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

If all pediatric subpopulations have been covered based on partial waivers, deferrals, completed studies, and/or existing appropriate labeling, this Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section F: Extrapolation from Other Adult and/or Pediatric Studies (for deferred and/or completed studies)

Note: Pediatric efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations if (and only if) (1) the course of the disease/condition AND (2) the effects of the product are sufficiently similar between the reference population and the pediatric subpopulation for which information will be extrapolated. Extrapolation of efficacy from studies in adults and/or other children usually requires supplementation with other information obtained from the target pediatric subpopulation, such as

pharmacokinetic and safety studies. Under the statute, safety cannot be extrapolated.

Pediatric studies are not necessary in the following pediatric subpopulation(s) because efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations:					
Population		minimum	maximum	Extrapolated from:	
				Adult Studies?	Other Pediatric Studies?
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	☐	☐

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

Note: If extrapolating data from either adult or pediatric studies, a description of the scientific data supporting the extrapolation must be included in any pertinent reviews for the application.

If there are additional indications, please complete the attachment for each one of those indications. Otherwise, this Pediatric Page is complete and should be signed and entered into DFS or DARRTS as appropriate after clearance by PeRC.

This page was completed by:

{See appended electronic signature page}

Regulatory Project Manager

(Revised: 6/2008)

NOTE: If you have no other indications for this application, you may delete the attachments from this document.

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

/s/

JEANNIE M ROULE
11/21/2012

Upsher-Smith Laboratories, Inc.
Original New Drug Application/NDA 204399
Testosterone Gel 1%

DEBARMENT CERTIFICATION

Upsher-Smith Laboratories, Inc. hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application.

9/7/2012

Nancy VanGieson, MBA
ASQ CQA, CQE, CMoQ/OE, CSQE, CBA
Vice President, Quality and Corporate
Compliance/Chief Compliance Officer

Date

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION[1]

NDA # 204399 BLA #	NDA Supplement # BLA Supplement #	If NDA, Efficacy Supplement Type:
Proprietary Name: Vogelxo Established/Proper Name: testosterone gel Dosage Form: topical gel		Applicant: Upsher-Smith Laboratories Agent for Applicant (if applicable): N/A
RPM: Jeannie Roule		Division: DBRUP

NDAs and NDA Efficacy Supplements:

NDA Application Type: ☐ 505(b)(1) ☒ 505(b)(2)
Efficacy Supplement: ☐ 505(b)(1) ☐ 505(b)(2)

(A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). Consult page 1 of the 505(b)(2) Assessment or the Appendix to this Action Package Checklist.)

505(b)(2) Original NDAs and 505(b)(2) NDA supplements:

Listed drug(s) relied upon for approval (include NDA #(s) and drug name(s)):

NDA 21454, Testim

Provide a brief explanation of how this product is different from the listed drug.

☐ This application does not reply upon a listed drug.
☐ This application relies on literature.
☐ This application relies on a final OTC monograph.
☒ This application relies on (explain) This application relied upon a RLD and literature

For ALL (b)(2) applications, two months prior to EVERY action, review the information in the 505(b)(2) Assessment and submit the draft[2] to CDER OND IO for clearance. Finalize the 505(b)(2) Assessment at the time of the approval action.

On the day of approval, check the Orange Book again for any new patents or pediatric exclusivity.

☐ No changes ☒ Updated Date of check: 06/03/14

If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.

❖ Actions	
• Proposed action • User Fee Goal Date is June 4, 2014	☒ AP ☐ TA ☐ CR
• Previous actions *(specify type and date for each action taken)*	☐ None TA on August 16, 2013

[1] The **Application Information** Section is (only) a checklist. The **Contents of Action Package** Section (beginning on page 5) lists the documents to be included in the Action Package.
[2] For resubmissions, (b)(2) applications must be cleared before the action, but it is not necessary to resubmit the draft 505(b)(2) Assessment to CDER OND IO unless the Assessment has been substantively revised (e.g., nrew listed drug, patent certification revised).

❖ If accelerated approval or approval based on efficacy studies in animals, were promotional materials received? Note: Promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see http://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf). If not submitted, explain _____	☐ Received
❖ Application Characteristics [3]	

Review priority: ☒ Standard ☐ Priority
Chemical classification (new NDAs only):

☐ Fast Track
☐ Rolling Review
☐ Orphan drug designation
☐ Rx-to-OTC full switch
☐ Rx-to-OTC partial switch
☐ Direct-to-OTC

NDAs: Subpart H
- ☐ Accelerated approval (21 CFR 314.510)
- ☐ Restricted distribution (21 CFR 314.520)

Subpart I
- ☐ Approval based on animal studies

BLAs: Subpart E
- ☐ Accelerated approval (21 CFR 601.41)
- ☐ Restricted distribution (21 CFR 601.42)

Subpart H
- ☐ Approval based on animal studies

☐ Submitted in response to a PMR
☐ Submitted in response to a PMC
☐ Submitted in response to a Pediatric Written Request

REMS:
- ☐ MedGuide
- ☐ Communication Plan
- ☐ ETASU
- ☐ MedGuide w/o REMS
- ☐ REMS not required

Comments:

❖ BLAs only: Ensure *RMS-BLA Product Information Sheet for TBP* and *RMS-BLA Facility Information Sheet for TBP* have been completed and forwarded to OPI/OBI/DRM (Vicky Carter)	☐ Yes, dates
❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 *(approvals only)*	☐ Yes ☒ No
❖ Public communications *(approvals only)*	
• Office of Executive Programs (OEP) liaison has been notified of action	☒ Yes ☐ No
• Press Office notified of action (by OEP)	☒ Yes ☐ No
• Indicate what types (if any) of information dissemination are anticipated	☒ None ☐ HHS Press Release ☐ FDA Talk Paper ☐ CDER Q&As ☐ Other

[3] Answer all questions in all sections in relation to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA. For example, if the application is a pending BLA supplement, then a new *RMS-BLA Product Information Sheet for TBP* must be completed.

❖ Exclusivity	
• Is approval of this application blocked by any type of exclusivity?	☒ No ☐ Yes
• NDAs and BLAs: Is there existing orphan drug exclusivity for the "same" drug or biologic for the proposed indication(s)? *Refer to 21 CFR 316.3(b)(13) for the definition of "same drug" for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification.*	☒ No ☐ Yes If, yes, NDA/BLA # and date exclusivity expires:
• (b)(2) NDAs only: Is there remaining 5-year exclusivity that would bar effective approval of a 505(b)(2) application)? *(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)*	☒ No ☐ Yes If yes, NDA # and date exclusivity expires:
• (b)(2) NDAs only: Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? *(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)*	☒ No ☐ Yes If yes, NDA # and date exclusivity expires:
• (b)(2) NDAs only: Is there remaining 6-month pediatric exclusivity that would bar effective approval of a 505(b)(2) application? *(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)*	☒ No ☐ Yes If yes, NDA # and date exclusivity expires:
• NDAs only: Is this a single enantiomer that falls under the 10-year approval limitation of 505(u)? *(Note that, even if the 10-year approval limitation period has not expired, the application may be tentatively approved if it is otherwise ready for approval.)*	☒ No ☐ Yes If yes, NDA # and date 10-year limitation expires:
❖ Patent Information (NDAs only)	
• Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought. If the drug is an old antibiotic, skip the Patent Certification questions.	☒ Verified ☐ Not applicable because drug is an old antibiotic.
• Patent Certification [505(b)(2) applications]: Verify that a certification was submitted for each patent for the listed drug(s) in the Orange Book and identify the type of certification submitted for each patent.	21 CFR 314.50(i)(1)(*i*)(A) ☒ Verified 21 CFR 314.50(i)(1) ☐ (ii) ☐ (iii)
• [505(b)(2) applications] If the application includes a **paragraph III** certification, it cannot be approved until the date that the patent to which the certification pertains expires (but may be tentatively approved if it is otherwise ready for approval).	☐ No paragraph III certification Date patent will expire
• [505(b)(2) applications] For **each paragraph IV** certification, verify that the applicant notified the NDA holder and patent owner(s) of its certification that the patent(s) is invalid, unenforceable, or will not be infringed (review documentation of notification by applicant and documentation of receipt of notice by patent owner and NDA holder). *(If the application does not include any paragraph IV certifications, mark "N/A" and skip to the next section below (*Summary Reviews*)).*	☐ N/A (no paragraph IV certification) ☒ Verified

- [505(b)(2) applications] For **each paragraph IV** certification, based on the questions below, determine whether a 30-month stay of approval is in effect due to patent infringement litigation.

  Answer the following questions for **each** paragraph IV certification:

  (1) Have 45 days passed since the patent owner's receipt of the applicant's notice of certification? ☒ Yes ☐ No

  (Note: The date that the patent owner received the applicant's notice of certification can be determined by checking the application. The applicant is required to amend its 505(b)(2) application to include documentation of this date (e.g., copy of return receipt or letter from recipient acknowledging its receipt of the notice) (see 21 CFR 314.52(e))).

  *If "**Yes**," skip to question (4) below. If "**No**," continue with question (2).*

  (2) Has the patent owner (or NDA holder, if it is an exclusive patent licensee) submitted a written waiver of its right to file a legal action for patent infringement after receiving the applicant's notice of certification, as provided for by 21 CFR 314.107(f)(3)? ☐ Yes ☐ No

  *If "**Yes,**" there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip the rest of the patent questions.*

  *If "**No**," continue with question (3).*

  (3) Has the patent owner, its representative, or the exclusive patent licensee filed a lawsuit for patent infringement against the applicant? ☐ Yes ☐ No

  (Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2))).

  *If "**No**," the patent owner (or NDA holder, if it is an exclusive patent licensee) has until the expiration of the 45-day period described in question (1) to waive its right to bring a patent infringement action or to bring such an action. After the 45-day period expires, continue with question (4) below.*

  (4) Did the patent owner (or NDA holder, if it is an exclusive patent licensee) submit a written waiver of its right to file a legal action for patent infringement within the 45-day period described in question (1), as provided for by 21 CFR 314.107(f)(3)? ☐ Yes ☒ No

  *If "**Yes,**" there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (*Summary Reviews*).*

  *If "**No**," continue with question (5).*

(5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the (b)(2) applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification? (Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced within the 45-day period). *If "**No**," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (*Summary Reviews*).* *If "**Yes**," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the OND ADRA and attach a summary of the response.*	☒ Yes ☐ No

CONTENTS OF ACTION PACKAGE	
❖ Copy of this Action Package Checklist[4]	6/11/14
Officer/Employee List	
❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list *(approvals only)*	☒ Included
Documentation of consent/non-consent by officers/employees	☒ Included
Action Letters	
❖ Copies of all action letters *(including approval letter with final labeling)*	Action(s) and date(s) Approval: 6/4/14 Tentative AP 8/16/13
Labeling	
❖ Package Insert *(write submission/communication date at upper right of first page of PI)*	
• Most recent draft labeling. If it is division-proposed labeling, it should be in track-changes format.	Included
• Original applicant-proposed labeling	Oct 18, 2012
• Example of class labeling, if applicable	Not included

[4] Fill in blanks with dates of reviews, letters, etc.

❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling *(write submission/communication date at upper right of first page of each piece)*	☒ Medication Guide ☐ Patient Package Insert ☐ Instructions for Use ☐ Device Labeling ☐ None
• Most-recent draft labeling. If it is division-proposed labeling, it should be in track-changes format.	Included
• Original applicant-proposed labeling	October 18, 2012
• Example of class labeling, if applicable	Not included
❖ Labels (**full color** carton and immediate-container labels) *(write submission/communication date on upper right of first page of each submission)*	
• Most-recent draft labeling	April 7, 2014
❖ Proprietary Name • Acceptability/non-acceptability letter(s) *(indicate date(s))* • Review(s) *(indicate date(s)* • *Ensure that both the proprietary name(s), if any, and the generic name(s) are listed in the Application Product Names section of DARRTS, and that the proprietary/trade name is checked as the 'preferred' name.*	July 23, May 15 and May 9, 2013 July 11 and May 1, 2013
❖ Labeling reviews *(indicate dates of reviews and meetings)*	☒ RPM August 5, 2013 ☒ DMEPA 4/3/14, 4/22/14 and May 1, 2013 ☒ DMPP/PLT (DRISK) 4/29/14 and July 30, 2013 ☒ ODPD (DDMAC) 4/21/14, 5/8/14 and August 6, 2013 ☒ SEALD August 14, 2013 ☒ CSS July 31, 2013 ☐ Other reviews
Administrative / Regulatory Documents	
❖ Administrative Reviews *(e.g., RPM Filing Review[5]/Memo of Filing Meeting) (indicate date of each review)* ❖ All NDA (b)(2) Actions: Date each action cleared by (b)(2) Clearance Cmte ❖ NDA (b)(2) Approvals Only: 505(b)(2) Assessment *(indicate date)*	RPM Filing February 13, 2013 ☐ Not a (b)(2) ☐ Not a (b)(2) June 4, 2014
❖ NDAs only: Exclusivity Summary *(signed by Division Director)*	☒ Included
❖ Application Integrity Policy (AIP) Status and Related Documents http://www fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm	
• Applicant is on the AIP	☐ Yes ☒ No
• This application is on the AIP o If yes, Center Director's Exception for Review memo *(indicate date)* o If yes, OC clearance for approval *(indicate date of clearance communication)*	☐ Yes ☒ No ☐ Not an AP action
❖ Pediatrics *(approvals only)* • Date reviewed by PeRC _____ If PeRC review not necessary, explain: PREAA does not apply to this application • Pediatric Page/Record *(approvals only, must be reviewed by PERC before*	☒ Included

[5] Filing reviews for scientific disciplines should be filed behind the respective discipline tab.

finalized)	
❖ Debarment certification (original applications only): verified that qualifying language was not used in certification and that certifications from foreign applicants are cosigned by U.S. agent *(include certification)*	☒ Verified, statement is acceptable
❖ Outgoing communications *(letters, including response to FDRR (do not include previous action letters in this tab), emails, faxes, telecons)*	October 22, December 21, 2012, March 18, July 16, 23, 2013 and April 1, 2014
❖ Internal memoranda, telecons, etc.	None
❖ Minutes of Meetings	
• Regulatory Briefing *(indicate date of mtg)*	☒ No mtg
• If not the first review cycle, any end-of-review meeting *(indicate date of mtg)*	☐ N/A or no mtg
• Pre-NDA/BLA meeting *(indicate date of mtg)*	☐ No mtg August 2, 2011
• EOP2 meeting *(indicate date of mtg)*	☒ No mtg
• Other milestone meetings (e.g., EOP2a, CMC pilots) *(indicate dates of mtgs)*	PIND November 8, 2007
❖ Advisory Committee Meeting(s)	☒ No AC meeting
• Date(s) of Meeting(s)	
• 48-hour alert or minutes, if available *(do not include transcript)*	
Decisional and Summary Memos	
❖ Office Director Decisional Memo *(indicate date for each review)*	☒ None
Division Director Summary Review *(indicate date for each review)*	☐ None 6/4/14 and 8/15/13
Cross-Discipline Team Leader Review *(indicate date for each review)*	☐ None 6/3/14 and 8/12/13
PMR/PMC Development Templates *(indicate total number)*	☒ None
Clinical Information[6]	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) *(indicate date for each review)*	
• Clinical review(s) *(indicate date for each review)*	June 3, 2014, August 12, 2013, and 12/11/12
• Social scientist review(s) (if OTC drug) *(indicate date for each review)*	☐ None
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here ☐ and include a review/memo explaining why not *(indicate date of review/memo)*	See Clinical Review, dated August 12, 2013, page 13
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers *(indicate date of each review)*	☒ None
❖ Controlled Substance Staff review(s) and Scheduling Recommendation *(indicate date of each review)*	☐ Not applicable May 1, 2014 and July 31, 2013

[6] Filing reviews should be filed with the discipline reviews.

❖ Risk Management • REMS Documents and Supporting Statement *(indicate date(s) of submission(s))* • REMS Memo(s) and letter(s) *(indicate date(s))* • Risk management review(s) and recommendations (including those by OSE and CSS) *(indicate date of each review and indicate location/date if incorporated into another review)*	6/4/14, 5/12/14, 8/15/13, 7/22/13 and 10/18/12 ☐ None
❖ DSI Clinical Inspection Review Summary(ies) *(include copies of DSI letters to investigators)*	☒ None requested
Clinical Microbiology ☐ None	
❖ Clinical Microbiology Team Leader Review(s) *(indicate date for each review)*	☒ None
Clinical Microbiology Review(s) *(indicate date for each review)*	☒ None
Biostatistics ☐ None	
❖ Statistical Division Director Review(s) *(indicate date for each review)*	☒ None
Statistical Team Leader Review(s) *(indicate date for each review)*	☒ None
Statistical Review(s) *(indicate date for each review)*	☐ None 7/17/13 and 12/13/12
Clinical Pharmacology ☐ None	
❖ Clinical Pharmacology Division Director Review(s) *(indicate date for each review)*	☒ None
Clinical Pharmacology Team Leader Review(s) *(indicate date for each review)*	☒ None
Clinical Pharmacology review(s) *(indicate date for each review)*	☐ None 6/2/14, 7/12/13, and 12/13/12
❖ DSI Clinical Pharmacology Inspection Review Summary *(include copies of DSI letters)*	☐ None 01/09/13
Nonclinical ☐ None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) *(indicate date for each review)*	☒ None
• Supervisory Review(s) *(indicate date for each review)*	☒ None
• Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)*	☐ None 5/28/14, 4/10/13, 12/12/12
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer *(indicate date for each review)*	☒ None
❖ Statistical review(s) of carcinogenicity studies *(indicate date for each review)*	☒ No carc
❖ ECAC/CAC report/memo of meeting	☒ None
❖ DSI Nonclinical Inspection Review Summary *(include copies of DSI letters)*	☒ None requested

Product Quality ☐ None	
❖ Product Quality Discipline Reviews	
• ONDQA/OBP Division Director Review(s) *(indicate date for each review)*	☒ None
• Branch Chief/Team Leader Review(s) *(indicate date for each review)*	☒ None
• Product quality review(s) including ONDQA biopharmaceutics reviews *(indicate date for each review)*	☐ None 5/20/14, 5/1/14, 8/9/13, 6/14/13, 12/10/12
❖ Microbiology Reviews ☐ NDAs: Microbiology reviews (sterility & pyrogenicity) (OPS/NDMS) *(indicate date of each review)* ☐ BLAs: Sterility assurance, microbiology, facilities reviews (OMPQ/MAPCB/BMT) *(indicate date of each review)*	☒ Not needed
❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer *(indicate date of each review)*	☐ None 7/16/13, 12/11/12
❖ Environmental Assessment (check one) (original and supplemental applications)	
☒ Categorical Exclusion *(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)*	See Quality review, dated June 14, 2013, page 71
☐ Review & FONSI *(indicate date of review)*	
☐ Review & Environmental Impact Statement *(indicate date of each review)*	
❖ Facilities Review/Inspection	
☒ NDAs: Facilities inspections (include EER printout) *(date completed must be within **2 years** of action date) (only original NDAs and supplements that include a new facility or a change that affects the manufacturing sites[7])*	Date completed: May 14, 2014 ☒ Acceptable ☐ Withhold recommendation ☐ Not applicable
☐ BLAs: TB-EER *(date of most recent TB-EER must be within **30 days** of action date) (original and supplemental BLAs)*	Date completed: ☐ Acceptable ☐ Withhold recommendation
❖ NDAs: Methods Validation *(check box only, do not include documents)*	☒ Completed ☐ Requested ☐ Not yet requested ☐ Not needed (per review)

[7] I.e., a new facility or a change in the facility, or a change in the manufacturing process in a way that impacts the Quality Management Systems of the facility.

Appendix to Action Package Checklist

An NDA or NDA supplemental application is likely to be a 505(b)(2) application if:

(1) It relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application.
(2) **Or** it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval.
(3) **Or** it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations(see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

(1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies).
(2) **And** no additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application.
(3) **And** all other "criteria" are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

(1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2).
(2) **Or** the applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement.
(3) **Or** the applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your ODE's ADRA.

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/s/

JEANNIE M ROULE
06/11/2014

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

DATE: April 1, 2014

TO: NDA 204399, Vogelxo

THROUGH: Jeannie Roule

SUBJECT: Carton and Container edits

APPLICATION NUMBER: NDA 204399 (testosterone gel)

Comments from the DMEPA and CMC reviewers concerning the cartons and containers were emailed to the Sponsor.

Please see attached email correspondences for all of the details.

From:	Roule, Jeannie
To:	Kristine.Higgins@upsher-smith.com
Subject:	More carton and container comments
Date:	Tuesday, April 01, 2014 11:11:00 AM
Attachments:	Carton and Container comments DMEPA and CMC April 1 2014.doc

Kristine,

Please see attached. I will call you soon.

Regards,

Jeannie

NDA 204399, Vogelxo:

The CMC and DMEPA reviewers have the following recommendations and request that they be implemented prior to approval of your NDA:

A.Container Labels and Carton Labeling for Vogelxo (testosterone gel)

1.Revise the usual dosage statement on the container label for the tube and packet, (b) (4) to read "Usual dosage: See package insert" so that the user is directed to read all pertinent dosage and administration information to safely use this product. This recommendation is also meant to de-clutter the label.

2. Consider modifying the statement (located on the principal display panel [PDP] of the carton labeling for all package configurations) (b) (4) to read "To be applied to the shoulders and upper arms" for clarity and to decrease clutter on the PDP.

3. Increase the prominence of the NDC number to assist the pharmacy in dispensing the correct product. Improving the prominence may be done by improving the color contrast or by removing this information from the color block.

4. Revise the statement "Alcohol based gels are flammable. Avoid fire, flame . . ." from all upper case letters to mixed case letters.

B.Container Labels and Carton Labeling for Authorized Generic for Testosterone Gel

1. See recommendations A1 through A4.

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/s/

JEANNIE M ROULE
04/01/2014

MEMORANDUM

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

DATE: July 23, 2013

TO: NDA 204399

THROUGH: Jeannie Roule

SUBJECT: Carton and Container edits

APPLICATION NUMBER: NDA 204399 (testosterone gel)

Comments from the DMEPA and CMC reviewers concerning the cartons and containers were emailed to the Sponsor.

Please see attached email correspondences for all of the details.

From: Michele.Heintz@upsher-smith.com
To: Roule, Jeannie
Cc: Kristine.Higgins@upsher-smith.com
Subject: RE: NDA 204399 Carton and Container comments
Date: Tuesday, July 23, 2013 3:04:01 PM

Jeannie,

Thank you. I have received the comments and we will provide updated labeling as quickly as possible.

Kind regards,
Michele

From: "Roule, Jeannie" <Jeannie.Roule@fda.hhs.gov>
To: "Michele.Heintz@upsher-smith.com" <Michele.Heintz@upsher-smith.com>
Cc: "Kristine.Higgins@upsher-smith.com" <Kristine.Higgins@upsher-smith.com>
Date: 07/23/2013 02:00 PM
Subject: RE: NDA 204399 Carton and Container comments

Michele and Kristine,

Please see comment/request from DMEPA:

1. In respect to your Pump label and pump carton labeling:

Revise the 'Dosing Table:' section on the side panel of the container label and carton labeling to read:

'Patient: Please refer to the table below to determine the number of full pump actuations
required for the daily dose prescribed by your healthcare provider.
Please see package insert for additional
application instructions. (to the Applicant: you can then place the table below this section)

2. All container labels and carton labeling (except the tube label):

As currently presented, only the tube label displays a place holder for the lot and expiration date. Please ensure a place holder for the lot and expiration appears on all container labels and carton labeling.

Please send me an updated version to all of the above at your earliest convenience.

Regards,
Jeannie

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

/s/

JEANNIE M ROULE
07/23/2013

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

NDA 204399

PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE

Upsher-Smith Laboratories, Inc
6701 Evenstad Drive
Maple Grove, MN 55369

ATTENTION: Kristine Higgins
Senior Specialist, Regulatory Affairs

Dear Ms. Higgins:

Please refer to your New Drug Application (NDA) dated October 17, 2012, and received October 18, 2012, submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Testosterone Gel, 50 mg/5 g, 100 mg/10 g.

We also refer to your correspondence, dated and received May 3, 2013, requesting review of your proposed proprietary name, Vogelxo. We have completed our review of the proposed proprietary name and have concluded that it is acceptable.

The proposed proprietary name, Vogelxo, will be re-reviewed 90 days prior to the approval of the NDA. If we find the name unacceptable following the re-review, we will notify you.

If **any** of the proposed product characteristics as stated in your May 3, 2013, submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Shawnetta Jackson, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-4952. For any other information regarding this application contact Jeannie Roule, Regulatory Project Manager in the Division of Bone, Reproductive and Urologic Products (DBRUP), at (301) 796-3993.

Sincerely,

{See appended electronic signature page}
Carol Holquist, RPh
Director
Division of Medication Error Prevention and Analysis
Office of Medication Error Prevention and Risk Management
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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

/s/

CAROL A HOLQUIST
07/23/2013

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 204399

LABELING DISCUSSION COMMENTS

Upsher-Smith Laboratories, Inc.
Attention: Kristine Higgins
Regulatory Affairs Sr. Specialist
6701 Evenstad Drive
Maple Grove, MN 55369

Dear Ms. Higgins:

Please refer to your October 18, 2012, New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for testosterone gel.

We also refer to our December 21, 2012, letter in which we notified you of our target date of July 18, 2012, for communicating labeling changes and/or postmarketing requirements/commitments in accordance with the "PDUFA REAUTHORIZATION PERFORMANCE GOALS AND PROCEDURES – FISCAL YEARS 2008 THROUGH 2012."

On January 23, 2013, we received your proposed labeling submission to this application, and have proposed revisions that are included as an enclosure.

If you have any questions, call me at (301) 796-3993.

Sincerely,

{See appended electronic signature page}

Jeannie Roule
Regulatory Health Project Manager
Division of Bone, Reproductive, and Urologic Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

ENCLOSURE: Content of Labeling

33 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

JEANNIE M ROULE
07/18/2013

MEMORANDUM

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

DATE: July 15, 2013

TO: NDA 204399

THROUGH: Jeannie Roule

SUBJECT: Carton and Container edits

APPLICATION NUMBER: NDA 204399 (testosterone gel)

Comments from the DMEPA and CMC reviewers concerning the cartons and containers were emailed to the Sponsor.

Please see attached email correspondences for all of the details.

From:	Roule, Jeannie
To:	"Kristine.Higgins@upsher-smith.com"
Subject:	Carton and Container comments
Date:	Monday, July 15, 2013 9:45:00 AM
Attachments:	DMEPA and CMC carton container comments.doc

Kristine,

I have attached a word document that contains the comments for the changes that need to be made to your carton/containers.

Please submit your revised carton/containers at your earliest convenience.

Regards,
Jeannie

Jeannie Roule
Senior Regulatory Project Manager
Division of Bone, Reproductive, and Urologic Products
Center for Drug Evaluation and Research
Food and Drug Administration
Phone: (301) 796-2130 (main)
Direct Line: (301) 796-3993
Fax: (301) 796-9897
Email: jeannie.roule@fda.hhs.gov

COMMENTS TO THE APPLICANT

General Comments for all Container Labels and Carton Labeling

1. The container labels and carton labeling do not clearly state that the exposure level for testosterone may differ for Tradename compared to other topical testosterone products. Please add the following statement to the principal display panels of all carton labeling and, if space permits, all container labels:

   "*Topical testosterone products may have different doses, strengths, or application instructions that may result in different systemic exposure.*"

2. Remove the (b) (4) descriptor that appears in conjunction with the root name, Tradename. This revision will be consistent with other testosterone products that are marketed with (b) (4) (i.e., Axiron and Fortesta).

3. Revise the presentation of the proprietary name from all capital letters (i.e. TRADENAME) to title case (i.e., Tradename) to increase readability.

4. Replace the hyphen with the word "to" in the storage information to provide more clarity. Additionally add "°C" and "°F" to the numbers 20, 68, 15, and 30. The revised storage statement should appear as: "20°C to 25°C (68°F to 77°F); excursions permitted to 15°C to 30°C (59°F to 86°F)."

5. Add the statement "This package is not child resistant." to follow the statement "Keep out of reach of children" on all container labels and carton labeling.

6. Please ensure the lot number and expiration date are stamped on all the container labels and carton labeling If not, revise the container labels and carton labeling to include a lot number and expiration date per 21 CFR 201.17 and 21 CFR 201.18.

7. All container and carton labels should include flammability warning "ALCOHOL BASED GELS ARE FLAMMABLE. AVOID FIRE, FLAME OR SMOKING DURING APPLICATION OF VOGELXO UNTIL THE GEL HAS DRIED"

Tube Label

1. Revise the statement "(b) (4)" to read: "50 mg testosterone per tube". Additionally, ensure this statement appears immediately below the established name and dosage form statement "testosterone gel", in the highlighted area with the same prominence as the established name and the dosage form statement. The presentation would appear as:

   "**Tradename**
   (testosterone) gel
   50 mg testosterone per tube"

2. Relocate (b) (4) to the bottom portion of the label. Change the statement to "Each unit-dose tube contains 5 grams of gel".

3. Relocate the route of administration statement "For topical use only" to appear under the statement of strength after revisions (i.e., 50 mg testosterone per tube).
4. Relocate the bar code to the side panel where the manufacturer's information appears. As currently presented, the bar code crowds the principal display panel.
5. Relocate the manufacturer's logo to the bottom of the principal display panel in the space provided after relocating the barcode. Additionally, reduce the prominence of the logo. As currently presented, this information competes in prominence with that of the proprietary name and established name due to its coloring and size.
6. Revise the statement [redacted] (b) (4) to read "Usual Dosage: Apply complete contents of tube once daily."
7. Delete the statement [redacted] (b) (4) on the side panel. This information is presented on the carton labeling and its presence on the side panel of the container label is not necessary. Additionally, the space provided by removing this statement can be utilized for the placement of the bar code after being relocated from the principal display panel.

Packet Label

1. Revise the statement [redacted] (b) (4) to read: "50 mg testosterone per packet". Additionally, ensure this statement appears immediately below the established name and dosage form statement "testosterone gel", in the highlighted area with the same prominence as the established name and the dosage form statement. The presentation would appear as:

   "**Tradename**
   (testosterone) gel
   50 mg testosterone per packet"

2. Relocate the route of administration statement from the back panel to appear below the statement of strength after revisions (i.e., Each packet contains 5 grams of gel) on the principal display panel.
3. Revise the statement [redacted] (b) (4) to read "Usual Dosage: Apply complete contents of packet once daily."

Pump Label

1. Delete the word "[redacted] (b) (4)" that currently appears under the dosage form "testosterone gel".
2. Revise the statement [redacted] (b) (4) to read:

"12.5 mg of testosterone per pump actuation*"

*Each actuation delivers 1.25 grams of gel

Multi-dose pump capable of dispensing 60 metered pump actuations."

Additionally, the correct placement of these statements will be discussed below.

3. Place the statement "12.5 mg of testosterone per pump actuation*" immediately below the dosage form (testosterone gel) in the highlighted area, as this statement is considered the statement of strength and should appear below the dosage form. The statements "*12.5 mg of testosterone per pump actuation*" and "Multi-dose pump capable of dispensing 60 metered pump actuations" may appear further down in the white space of the principal display panel.
4. You may place a net quantity statement of "88 g" at the bottom of the principal display panel.
5. Relocate the route of administration statement 'For topical use only" to the principal display panel. Following the revisions, the order of information on the principal display panel would appear as:

"**Tradename**
(testosterone) gel
12.5 mg of testosterone
Per pump actuation*

*Each actuation delivers 1.25 grams of gel.
Multi-dose pump capable of dispensing
60 metered pump actuations

For topical use only.

Topical testosterone products may have different doses, strengths, or application instructions that may result in different systemic exposure.

Dispense the accompanying
Medication Guide to each patient.

88 g"

6. Include a dosing table on the side panel of the pump label. This recommendation is consistent with our current recommendations for testosterone pump labels (e.g., Androgel products). The dosing table may appear similar to:

Prescribed Daily Dose	Number of Pump Actuations
50 mg	4
100 mg	8

Tube Carton Labeling

1. Revise the statement "[redacted] (b) (4)" to read: "50 mg testosterone per tube". Additionally, ensure this statement appears immediately below the established name and dosage form statement "testosterone gel", in the highlighted area and with the same prominence as the established name and the dosage form statement. The presentation would appear as:

   "**Tradename**
   (testosterone) gel
   50 mg testosterone per tube"

2. Relocate the route of administration statement "For topical use only" to appear under the statement of strength after revisions (i.e., 50 mg testosterone per tube).

Packet Carton Labeling

1. Revise the statement [redacted] (b) (4) to read: "50 mg testosterone per packet". Additionally, ensure this statement appears immediately below the established name and dosage form statement "testosterone gel", in the highlighted area with the same prominence as the established name and the dosage form statement. The presentation would appear as:

   "**Tradename**
   (testosterone) gel
   50 mg testosterone per packet"

2. Relocate the route of administration statement from the back panel to appear below the statement of strength after revisions (i.e., 50 mg testosterone per packet) on the principal display panel.

Pump Carton Labeling

1. Delete the word [redacted] (b) (4)" that currently appears under the dosage form "testosterone gel".
2. Revisions to the statements [redacted] (b) (4) will be recommended in the steps to follow below.
3. Place the strength statement "12.5 mg of testosterone per pump actuation*" immediately below the established name and dosage form statement (i.e., testosterone gel) in the highlighted area, and with the same prominence as the established name and dosage form statement.
4. Place the statements "*12.5 mg of testosterone per pump actuation*" further down in the white space of the principal display panel followed by the statement "Multi-dose pump capable of dispensing 60 metered pump actuations."
5. You may place a net quantity statement of "2 canisters containing 88 grams each" at the bottom of the principal display panel.

6. Relocate the route of administration statement from the side panel to the principal display panel. Following the revisions, the order of information on the principal display panel would appear as:

"**Tradename**
(testosterone) gel
12.5 mg of testosterone
Per pump actuation*

*Each actuation delivers 1.25 grams of gel.
Multi-dose pump capable of dispensing
60 metered pump actuations

For topical use only.

Topical testosterone products may have different doses, strengths, or application instructions that may result in different systemic exposure.

Dispense the accompanying Medication Guide to each patient

2 canisters containing 88 grams each"

7. Include a dosing table on the side panel of the pump carton labeling that includes the number of days of supply along with the prescribed daily dose and the number of pump actuations. Including the number of days of supply will help assist the dispensing pharmacist to enter the correct number in the computer as well as to dispense the appropriate number of pumps. The dosing table may appear similar to:

Prescribed Daily Dose	Number of Pump Actuations	Days of Supply
50 mg	4	25
100 mg	8	7

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/s/

JEANNIE M ROULE
07/16/2013

MEMORANDUM

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

DATE: July 15, 2013

TO: NDA 204399

THROUGH: Jeannie Roule

SUBJECT: Financial Disclosure

APPLICATION NUMBER: NDA 204399 (testosterone gel)

The Medical Officer requested that the Sponsor clarify some of the information regarding financial disclosures.

Please see attached email correspondences for all of the details.

From:	Kristine.Higgins@upsher-smith.com
To:	Roule, Jeannie
Cc:	Michele.Heintz@upsher-smith.com
Subject:	Re: NDA 204399
Date:	Thursday, July 11, 2013 5:13:18 PM

Hi Jeannie,

Responses to the Clinical questions have been provided below in bold text.

Study P10-002

Please confirm that the following did not participate in Study P10-002:

(b) (4)

They were deleted from the Form 1572 signed by Francois Saint-Maurice, M.D. on October 6, 2010, by an Additional Information Form signed on March 23, 2011. However, they appear in the Form 1572 signed by Richard Larouche, M.D. on July 15, 2011.

USL Response: These two physicians did NOT participate in Study P10-002 and should not have been included in the 1572. The Additional Information Form signed on March 23, 2011 is correct.

Study P10-003

As indicated in the Statement of Investigator (Form 1572) signed by Richard Larouche, M.D. on November 14, 2011, please confirm that the following did not participate in Study P10-003:

(b) (4)

USL Response: The 4 physicians indicated above did not participate in Study P10-003

Please let me know if you need anything additional at this time.

Kind regards,
Kristine

Kristine Higgins
Regulatory Affairs Sr. Specialist
Upsher-Smith Laboratories, Inc.
Ph 763-315-2337

From: "Roule, Jeannie" <Jeannie.Roule@fda.hhs.gov>
To: "Kristine.Higgins@upsher-smith.com"

<Kristine.Higgins@upsher-smith.com>
Date: 07/10/2013 08:18 AM
Subject: NDA 204399

Kristine,

Study P10-002

Please confirm that the following did not participate in Study P10-002:

(b) (4)

They were deleted from the Form 1572 signed by Francois Saint-Maurice, M.D. on October 6, 2010, by an Additional Information Form signed on March 23, 2011. However, they appear in the Form 1572 signed by Richard Larouche, M.D. on July 15, 2011.

A: These two physicians did NOT participate in the study and should not have been included in the 1572. The Additional Information Form signed on March 23, 2011 is correct.

Study P10-003

As indicated in the Statement of Investigator (Form 1572) signed by Richard Larouche, M.D. on November 14, 2011, please confirm that the following did not participate in Study P10-003:

(b) (4)

A: These 4 physicians did not participate in the study.

Regards,
Jeannie Roule
Senior Regulatory Project Manager
Division of Bone, Reproductive, and Urologic Products
Center for Drug Evaluation and Research
Food and Drug Administration
Phone: (301) 796-2130 (main)
Direct Line: (301) 796-3993
Fax: (301) 796-9897
Email: jeannie.roule@fda.hhs.gov

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/s/

JEANNIE M ROULE
07/15/2013

MEMORANDUM of TELECONFERENCE

MEETING DATE: May 2, 2013
TIME: 10:30 am
LOCATION: CDER WO 4322 conf rm Bldg 22
APPLICATION: NDA 204399
DRUG NAME: [redacted] (b) (4) (testosterone) gel, 50 mg of testosterone per 5 gram of gel
TYPE OF MEETING: Tcon with Upsher Smith

MEETING CHAIRS: *DMEPA TL/OSE SRPM*

FDA ATTENDEES:
Shawnetta Jackson, M.S., OSE SRPM
Jim Schlick, RPh, MBA, DMEPA TL
Manizheh Siapoushan, PharmD, DMEPA SE

APPLICANT ATTENDEES:
Kristine Higgins, Sr. Regulatory Affairs CMC Specialist
Michele Heintz, Assoc. Director, Regulatory Affairs, CMC
Greg Wedin, Pharm D., Assoc. Director Pharmacovigilance and Risk Management
Greg Gilmet, M.D., M.P.H. Sr. Director Medical Affairs

BACKGROUND:

Upsher-Smith submitted the proposed proprietary name, [redacted] (b) (4), for NDA 204399 on March 19, 2013. DMEPA found the first proposed proprietary name, [redacted] (b) (4) unacceptable and communicated this decision to the Applicant during the March 11, 2013 teleconference.

DMEPA requested this teleconference to inform Upsher-Smith of preliminary concerns identified during the review of the proposed proprietary name, [redacted] (b) (4)

MEETING OBJECTIVES:

This is a courtesy call to notify Upsher-Smith of DMEPA's preliminary findings and safety concerns with regards to the proposed proprietary name, [redacted] (b) (4) submitted on March 19, 2013.

DMEPA CONCERNS WITH THE PROPOSED NAME

DMEPA's preliminary review has identified that the proposed proprietary name, [redacted] (b) (4), is unacceptable from a look-alike perspective for the following reasons;

1. The proposed proprietary name, [redacted] (b) (4), is orthographically similar to and shares overlapping product characteristics with [redacted] (b) (4)

(b) (4)

(b) (4)

(b) (4)

We note that differences in packaging, dosage form, route of administration, and other differences may minimize the potential of a patient administering the wrong product. However, even if a patient receives the wrong product and does not administer that product, the medication error and name confusion still occurred because the wrong product was dispensed to the patient. Post-marketing reports indicate cases in name confusion that lead patients to be dispensed the wrong drug product containing a different dosage form, route of administration, and packaging and those patients did not question the receipt of such products. Documented cases of confusion with Advicor (a solid oral tablet) and Advair (inhaled powder), Cerebyx (an injectable solution) and Celebrex (a solid oral capsule), and Lunesta (a solid oral tablet) and Neulasta (an injectable solution) exemplify how such confusion may lead to errors despite the differences mentioned above, due to compelling orthographic or phonetic similarities among product names.

We note that our conclusion differs from (b) (4) external name evaluation.

(b) (4)

REGULATORY OPTIONS

1. Wait for DMEPA to complete the review of [redacted] (b) (4) by the OSE PDUFA goal date of July 19, 2013 and issue a formal decision (denying the name).
2. Withdraw the proposed name, [redacted] (b) (4), and submit an alternate name for review.

DISCUSSION

The Applicant agreed to withdraw the proposed name, [redacted] (b) (4) and submit more than one name for review, as recommended by DMEPA. The Applicant withdrew the name, [redacted] (b) (4), on May 2, 2013 and submitted new proprietary names for review on May 3, 2013.

ACTION ITEMS

- *DMEPA will designate final signatory authority for minutes (DMEPA TL or Deputy Director or Director*

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/s/

JAMES H SCHLICK
05/15/2013

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Silver Spring, MD 20993

NDA 204399

PROPRIETARY NAME REQUEST WITHDRAWN

Upsher-Smith Laboratories, Inc
6701 Evenstad Drive
Maple Grove, MN 55369

ATTENTION: Kristine Higgins
Senior Specialist, Regulatory Affairs

Dear Ms. Higgins:

Please refer to your New Drug Application (NDA) dated October 17, 2012, and received October 18, 2012, submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Testosterone Gel 1%, 5 g/50 mg, 10 g/100 mg.

We acknowledge receipt of your May 2, 2013, correspondence, received May 3, 2013, notifying us that you are withdrawing your request for a review of the proposed proprietary name (b) (4) This proposed proprietary name request is considered withdrawn as of May 3, 2013.

We also acknowledge receipt of your May 3, 2013, correspondence requesting review of the proposed proprietary name, Vogelxo.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Shawnetta Jackson, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-4952. For any other information regarding this application contact Jeannie Roule, Regulatory Project Manager in the Office of New Drugs (OND), at (301) 796-3993.

Sincerely,

{See appended electronic signature page}

Carol Holquist, RPh
Director
Division of Medication Error Prevention and Analysis
Office of Medication Error Prevention and Risk Management
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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/s/

CAROL A HOLQUIST
05/09/2013

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 204399 **INFORMATION REQUEST**

Upsher-Smith Laboratories, Inc.
Attention: Kristine Higgins
Senior Specialist, Regulatory Affairs
6701 Evenstad Drive
Maple Grove, MN 55369

Dear Ms. Higgins:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Testosterone Gel 1%.

We are reviewing the Quality section of your submission and have the following comments and information requests. We request a written response by April 5, 2013 in order to continue our evaluation of your NDA.

1. Your approach to develop the *in-vitro* release test (IVRT) as a quality control tool at release as well as during stability is acceptable. We would like to remind you that you need to submit the details of the development and validation of your **IVRT method** (apart from the analytical method development and validation) in the NDA. The SUPAC SS clearly mentions that the in vitro release methodology should be appropriately validated. The IVRT method development and validation report should contain (but not limited to) the following information:

    - Choice of *in-vitro* diffusion apparatus and condition
    - Linearity and Range
    - Accuracy/Precision and Reproducibility
    - Recovery, Mass Balance & Dose Depletion
    - Sensitivity
    - Specificity
    - Selectivity
    - Robustness
    - Membrane Inertness/Binding
    - Receptor Solution Solubility/Stability

2. While your in-vitro release method ((b) (4) -1811-LC) has evaluated some parameters, explanation/validation of some other parameters (e.g., choice of in-vitro diffusion apparatus and condition, membrane inertness/binding, receptor solution solubility/stability) could not be found in the submission. Please include that information

along with the raw data associated with the evaluation of parameters included as Validation Data in Tables 26 and 27 for Method (b) (4)-1811-LC.

3. Also, based on the data submitted in Table 4 (under justification of specifications), we recommend the acceptance criterion for the *in vitro* release test be tightened to (b) (4) µg/(cm^2/$min^{1/2}$).

4. In summary, submit to FDA the report of in-vitro release test with the complete information (raw data and release profiles) for the testing conducted with all the batches (both for development as well as stability batches) to review the appropriateness of the proposed in vitro drug release method and criterion.

If you have any questions, call LT Kerri-Ann Jennings, Regulatory Project Manager, at (301) 796-2919.

Sincerely,

{See appended electronic signature page}

Moo-Jhong Rhee, Ph.D.
Chief, Branch IV
Division of New Drug Quality Assessment II
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

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/s/

MOO JHONG RHEE
03/18/2013
Chief, Branch IV

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 204399

FILING COMMUNICATION

Upsher-Smith Laboratories, Inc.
Attention: Kristine Higgins
Regulatory Affairs Sr. Specialist
6701 Evenstad Drive
Maple Grove, MN 55369

Dear Ms. Higgins:

Please refer to your New Drug Application (NDA) dated and received October 18, 2012, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act, for testosterone gel.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR 314.101(a), this application is considered filed 60 days after the date we received your application. The review classification for this application is **Standard**. Therefore, the user fee goal date is August 18, 2013.

We are reviewing your application according to the processes described in the Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, mid-cycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing commitment requests by July 18, 2013.

At this time, we are notifying you that, we have not identified any potential review issues. Please note that our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review.

We request that you submit the following information:

1. Please submit a copy of the Master Batch Record

During our preliminary review of your submitted labeling, we have identified the following labeling format issues:

1. In the boxed warning located in the highlights section, add the verbatim statement "***See full prescribing information for complete boxed warning***." centered immediately beneath the heading.

2. **Bolded** revision date (i.e., "**Revised: MM/YYYY** or **Month Year**") must be at the end of the Highlights section.

We request that you resubmit labeling that addresses these issues by January 22, 2012, The resubmitted labeling will be used for further labeling discussions.

We acknowledge your request for a waiver of the requirement that the **Highlights** of Prescribing Information be limited to no more than one-half page. We will consider your request during labeling discussions.

Please respond only to the above requests for information. While we anticipate that any response submitted in a timely manner will be reviewed during this review cycle, such review decisions will be made on a case-by-case basis at the time of receipt of the submission.

PROMOTIONAL MATERIAL

You may request advisory comments on proposed introductory advertising and promotional labeling. Please submit, in triplicate, a detailed cover letter requesting advisory comments (list each proposed promotional piece in the cover letter along with the material type and material identification code, if applicable), the proposed promotional materials in draft or mock-up form with annotated references, and the proposed package insert (PI), and Medication Guide. Submit consumer-directed, professional-directed, and television advertisement materials separately and send each submission to:

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion (OPDP)
5901-B Ammendale Road
Beltsville, MD 20705-1266

Do not submit launch materials until you have received our proposed revisions to the package insert (PI), and Medication Guide, and you believe the labeling is close to the final version.

For more information regarding OPDP submissions, please see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm. If you have any questions, call OPDP at 301-796-1200.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Because none of these criteria apply to your application, you are exempt from this requirement.

If you have any questions, call Jeannie Roule, Regulatory Health Project Manager, at (301) 796-3993.

Sincerely,

{See appended electronic signature page}

Audrey Gassman, M.D.
Deputy Director
Division of Reproductive and Urologic Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

AUDREY L GASSMAN
12/21/2012
For DD

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 204399

NDA ACKNOWLEDGMENT

Upsher-Smith Laboratories, Inc.
Attention: Kristine Higgins
Regulatory Affairs Sr. Specialist
6701 Evenstad Drive
Maple Grove, MN 55369

Dear Ms. Higgins:

We have received your New Drug Application (NDA) submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA) for the following:

Name of Drug Product: testosterone gel

Date of Application: October 18, 2012

Date of Receipt: October 18, 2012

Our Reference Number: NDA 204399

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 December 17, 2012, in accordance with 21 CFR 314.101(a).

If you have not already done so, promptly submit the content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Failure to submit the content of labeling in SPL format may result in a refusal-to-file action under 21 CFR 314.101(d)(3). The content of labeling must conform to the content and format requirements of revised 21 CFR 201.56-57.

You are also responsible for complying with the applicable provisions of sections 402(i) and 402(j) of the Public Health Service Act (PHS Act) [42 USC §§ 282 (i) and (j)], which was amended by Title VIII of the Food and Drug Administration Amendments Act of 2007 (FDAAA) (Public Law No, 110-85, 121 Stat. 904).

The NDA number provided above should be cited at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Reproductive and Urologic Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

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If you have any questions, call me at (301) 796-3993.

Sincerely,

{See appended electronic signature page}

Jeannie Roule
Senior Regulatory Health Project Manager
Division of Reproductive and Urologic Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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

/s/

JEANNIE M ROULE
10/22/2012

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 076654

MEETING MINUTES

Upsher-Smith Laboratories, Inc.
Attention: Kristine Higgins
Regulatory Affairs Sr. Specialist
6701 Evenstad Drive
Maple Grove, MN 55369

Dear Ms. Higgins:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for testosterone gel 1%.

We also refer to the teleconference between representatives of your firm and the FDA on August 2, 2011. The purpose of the meeting was to discuss your plans for submitting an NDA to the Division in the spring of 2012.

A copy of the official minutes of the teleconference is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Jeannie Roule, Regulatory Health Project Manager at (301) 796-3993.

Sincerely,

{See appended electronic signature page}

Suresh Kaul, M.D.
Medical Team Leader
Division of Reproduction and Urologic Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

ENCLOSURE:
Meeting Minutes

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MEMORANDUM OF MEETING MINUTES

Meeting Type:	**Type B**
Meeting Category:	**Pre-NDA**
Meeting Date and Time:	**August 2, 2011**
Meeting Location:	**White Oak, Building 22, room 1311**
Application Number:	**IND 076654**
Product Name:	**testosterone gel 1%**
Indication:	**testosterone replacement therapy**
Sponsor/Applicant Name:	**Upsher Smith Laboratories, Inc**
Meeting Chair:	**Suresh Kaul, M.D, MPH**
Meeting Recorder:	**Jeannie Roule**

FDA ATTENDEES

George Benson, M.D.	Deputy Director, Division of Reproductive and Urologic Products (DRUP)
Suresh Kaul, M.D, MPH	Medical Team Leader, DRUP
Donald McNellis, M.D.	Medical Officer, DRUP
Jeffrey Bray, Ph.D.	Pharmacology Reviewer, DRUP
Hyunjin Kim, Pharm.D	Division of Clinical Pharmacology (DCP) III, Office of Clinical Pharmacology (OCP), Office of Translational Sciences (OTS)
Rajiv Agarwal, Ph.D.	Office of Pharmaceutical Sciences (OPS), Office of New Drug Quality Assessment (ONDQA), Division of Pre-Marketing Assessment (DPA) II
Jennifer Mercier	Chief, Project Management Staff (CPMS), DRUP
Jeannie Roule	Regulatory Health Project Manager, DRUP

SPONSOR ATTENDEES

Mark B. Halvorsen, Pharm.D.,	Sr. Director, Clinical Development
Cynthia G. Farner, RAC	Director, Regulatory Affairs
Chris F. Wertz, Ph.D.,	Associate Director, Pharmaceutical Development
Kurt S. Roinestad, Ph.D.,	Associate Director, Chemistry and Analytical Sciences
Ying Verdi	Sr. Chemist, Chemistry and Analytical Sciences
Lindy L. Bancke, Pharm.D.,	Sr. Clinical Research Scientist, Clinical Development
(b) (4)	Pharmaceutical Development Consultant
Kristine R. Higgins, RAC	Sr. Regulatory Affairs Specialist CMC, Regulatory Affairs

(b) (4)

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BACKGROUND

The Sponsor intends to submit an NDA for a metered dose testosterone gel product in the spring of 2012. An ANDA that had been submitted for the same gel product (b) (4) (b) (4) (b) (4) a Citizen's Petition, that testosterone gel products that are not qualitatively and quantitatively identical to a reference listed drug would need to provide clinical data regarding the transfer of testosterone via person-to-person contact. The 505(b)(2) pathway was believed to be the appropriate pathway for this product.

August 2, 2011, a teleconference was held to discuss the Sponsor's plans and questions related to submitting an NDA to the Division.

DISCUSSION

Preliminary responses were provided to the Applicant on July 26, 2011, in response to the questions posed in the Sponsor's meeting package provided to the Division on June 27, 2011. The Sponsor's questions are presented below in **bolded** text, followed by the Division's responses in normal text. Prior to the meeting, the Sponsor prepared responses to the Division's preliminary draft responses and they are included as part of the additional discussion. All additional discussion held during the meeting is summarized below in *italics*.

Question 1 (Nonclinical):
The pharmacology of the active ingredient in USL240, testosterone, is well known. Additionally, the risks and benefits of testosterone replacement therapy are well established and FDA-approved products have been in use for several years. The inactive ingredients in USL240 are commonly used ingredients in pharmaceutical or cosmetic applications. At the November 8, 2007 Pre-IND meeting, the Agency determined that no further evidence of safety, beyond information from the Inactive Ingredient Database (IID) and, in the case of ethyl alcohol and diisopropyl adipate, evaluations of safety based on reviews of the available literature, is required to support the use of the inactive ingredients in USL240. (Refer to Section 10.2.3 for additional information regarding the inactive ingredients and to Appendix 1 for the November 2007 meeting minutes.) Since USL plans to rely on the nonclinical data for the reference product, Testim®, and has conducted no additional nonclinical studies, we propose to omit Module 4 and Sections 2.4 and 2.6 of Module 2 from the NDA.

Does the Agency agree that the nonclinical data for the reference product, Testim®, are sufficient and that no additional nonclinical studies are required for approval of USL240 and, therefore, Module 4 and Sections 2.4 and 2.6 of Module 2 may be omitted from the NDA?

Division Response: The Division concurs that no additional nonclinical studies are necessary, but does not concur with regard to omitting Modules 2.4 and 4. To satisfy the nonclinical requirements for a 505(b)(2) application, you will need to provide an adequate scientific justification for the appropriateness of reliance on Testim® or otherwise address the nonclinical requirements for your proposed testosterone product in Module 2.4. Alternatively or additionally, you can submit published literature references to support the nonclinical sections of the labeling (Sections 8 and 13) in Module 4. Additionally, you will need to submit the evaluations of ethyl alcohol and diisopropyl adipate safety with the appropriate literature references.

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Additional Discussion: The Sponsor proposed that the scientific justification for the appropriateness of reliance on Testim will be presented in Module 2.4. It is based on the therapeutic equivalence of USL240 to Testim with following qualifications:

- *The products are Pharmaceutical Equivalents, i.e., the products are formulated to contain the same amount of active ingredient, in the same dosage form, with the same route of administration, to meet the same compendial or other applicable standards (i.e., strength, quality, purity, and identity), even though they differ slightly in excipients in the topical gel. (Note: USL previously obtained the Division's concurrence to support the safety of the inactive ingredients in USL240 with information from the Inactive Ingredient Database (IID) and, in the case of ethyl alcohol and diisopropyl adipate, evaluations of safety based on reviews of the available literature. As indicated in original Question 5, USL proposed and the Division agreed to this information being provided in the pharmaceutical development section Module 3.2.P.2.)*
- *The products are adequately labeled.*
- *The products are manufactured in compliance with CGMP.*
- *The products are bioequivalent as demonstrated in 3 studies which compared USL240 with Testim:*
    1. *a pilot formulation bioequivalence study in hypogonadal males,*
    2. *a pivotal replicate design bioequivalence study in hypogonadal males,*
    3. *a comparative cumulative skin irritation and sensitization study in healthy male volunteers.*

    The two bioequivalence studies demonstrate that USL240 is bioequivalent to Testim® 1% (testosterone gel) after both a 50 and 100 mg dose. The comparative cumulative skin irritation and sensitization study demonstrates that USL240 is no more irritating or sensitizing to the skin than Testim.

The Sponsor inquired if the Division concurred that this type of justification would provide an adequate scientific rationale for the appropriateness of reliance on Testim to satisfy the nonclinical requirements in Module 2.4.

The Division agreed with the Sponsor's proposal.

QUESTION 2 (CLINICAL)

The 505(b)(2) NDA for USL240 will rely on the Agency's findings of safety and efficacy for Testim® to satisfy certain clinical and nonclinical requirements. In addition, USL plans to submit the results of the following five Phase 1 studies in support of the efficacy (bioequivalence) and safety of USL240:

- P06-001: "Randomized, Open-Label, 4-Way Crossover Pilot Study to Compare the Bioavailability of Three Different Testosterone 1% Topical Gel Formulations by Upsher-Smith Laboratories Versus Testim® (1% Testosterone) in Hypogonadal Male Volunteers"
- P06-011: "Randomized, Open-Label, 2-Treatment, 4-Way Replicate Crossover, Bioequivalence Study of Testosterone 1% Topical Gel Formulation by Upsher-Smith Laboratories Versus Testim® (1% Testosterone)(Reference) in Hypogonadal Male Volunteers"

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- P08-001: "A Study to Evaluate the Irritation and Sensitization Potential of Repeat Applications of Testosterone Topical Gel 1% by Upsher-Smith Laboratories, Inc. and Testim® Gel (Testosterone Topical Gel 1%) in Healthy Human Subjects"
- P10-002: " A Randomized, Single-Center, Open-Label, Three-Way Crossover Study of the Removal of Upsher-Smith Laboratories, Inc. Testosterone Gel 1% by Hand Washing"
- P10-003: "A Randomized, Single-Center, Open-Label, Three-Way, Crossover Study of the Transferability of Upsher-Smith Laboratories, Inc. Testosterone Gel 1% During Skin-to-Skin Contact With Clothing, Without Clothing, and After Washing"

USL does not plan to integrate the PK and safety data from these studies due to the unique design of each study and proposes to submit them as individual study reports. (Summaries of each study are provided in Section 10.1 of this Information Package.)
Does the Agency concur with the proposed strategy of not integrating the study data?

Division Response: We agree that you do not need to prepare an integrated PK analysis. However, an integrated safety analysis should be submitted.

Additional Discussion: The Sponsor would like to have some additional discussion related to the need for an integrated safety analysis. Upsher Smith believes that the uniqueness of each study including the involvement of different populations (healthy volunteers and hypogonadal males), different doses (<1, 50 and 100 mg) and different duration of exposure prevents the integration of safety data from each study.

The Division stated that despite the differences in study population and study design, it believes that an integrated summary of the adverse events seen during the clinical development program is a necessary part of the NDA application. The Division would like see summary of all Adverse Events (AEs) from five different studies with different populations in an integrated tabular form.

The Sponsor stated that they understood and agreed.

QUESTION 3 (CLINICAL)
The two most recent studies, the hand washing study (P10-002) and the transferability study (P10-003), were conducted in support of the NDA. However, the bioequivalence studies (P06-001 and P06-011) and the cumulative skin irritation and sensitization study (P08-001) were conducted in support of ANDA 79-178[1]. All five studies will be submitted in the NDA with PDF bookmarking and hyperlinks for review purposes. The hand washing and transferability studies will be submitted with SDTM-compliant SAS datasets. SAS data transport files will be submitted for the three ANDA studies; however, USL does not plan to rework the raw data or statistics to meet current NDA CDISC standards.

Does the Agency concur with USL's proposal to provide the ANDA studies (P06-001, P06-011 and P08-001) as legacy documents in the NDA for USL240, as summarized in the table below?

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Study	Clinical Study Report	CRF's	Data
P10-002	PDF Bookmarked and Hyperlinked	PDF Bookmarked and Hyperlinked	SDTM Compliant
P10-003	PDF Bookmarked and Hyperlinked	PDF Bookmarked and Hyperlinked	SDTM Compliant
P08-001	PDF Bookmarked and Hyperlinked	PDF	Legacy Format (Irritation/Sensitization data in SAS v5 Compliant .XPT format)
P06-011	PDF Bookmarked and Hyperlinked	PDF	Legacy Format (PK data in SAS v5 Compliant .XPT format)
P06-001	PDF Bookmarked and Hyperlinked	PDF	Legacy Format (PK data in SAS v5 Compliant .XPT format)

Division Response: Yes

Additional Discussion: The Sponsor informed the Division that additional discussion of this response was not necessary.

Question 4 (Clinical)
USL240 has not been approved for marketing in any country. However, other formulations of testosterone gel are currently marketed under various brand names. Based on the fact that the Agency recently evaluated the safety of these products (see FDA News Release May 7, 2009: *"Testosterone Gel Safety Concerns Prompt FDA to Require Label Changes, Medication Guide"*) and that USL240 has not yet been marketed, USL does not plan to conduct a literature search or analysis of the AERS database and
proposes to omit Section 5.3.6 of Module 5 and Section 2.7.4.6 of Module 2.
Does the Agency concur with this proposal?

Division Response: Yes

Additional Discussion: The Sponsor informed the Division that additional discussion of this response was not necessary.

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QUESTION 5 (CMC)
USL previously obtained Agency concurrence to support the safety of the inactive ingredients in USL240 with information from the Inactive Ingredient Database (IID) and, in the case of ethyl alcohol and diisopropyl adipate, evaluations of safety based on reviews of the available literature; refer to Section 10.2.3 of the Information Package for additional information. USL plans to submit the IID information and literature reviews supporting inactive ingredient safety in the pharmaceutical development section (3.2.P.2) of Module 3.
Does the Agency agree with USL's plan for the Module 3 placement of information supporting the safety of the inactive ingredients?

Division Response: Yes

Additional Discussion: The Sponsor informed the Division that additional discussion of this response was not necessary.

QUESTION 6 (CMC)
As part of the formulation development process, USL conducted a human cadaver skin model study, P05-1019, "Evaluation of the Percutaneous Absorption of Testosterone, In Vitro, Using the Human Cadaver Skin Model". The study evaluated various testosterone gel formulations, including the proposed USL240 formulation; refer to Section 10.3.4 of the Information Package for additional information. USL plans to discuss the results of the study in the pharmaceutical development section (3.2.P.2) of Module 3. USL does not propose to include the complete study report in the NDA.

Does the Agency concur with USL's plan to provide only a summary of the results of the human cadaver skin model study in the NDA and its placement in Module 3?

Division Response: We concur.

Additional Discussion: The Sponsor informed the Division that additional discussion of this response was not necessary.

QUESTION 7 (CMC)
A common bulk gel is used to fill the unit dose gel and metered gel dosage forms of USL240 (5 g tube, 5 g packet, 88 g pump). Consequently, the information contained in Module 3.2.P could be presented in either of two ways: 1) the three packaging presentations can be provided as separate container/closure systems in Subsection 3.2.P.7, or 2) each packaging presentation can be in its own Module 3.2.P folder (i.e., 3.2.P - Tube; 3.2.P - Packet; 3.2.P - Pump).

Does the CMC Reviewer have a preference regarding the Module 3 presentation of the drug product information?

Division Response: It would be preferable to have separate sections for unique information and one section for common information, i.e., three separate container/closure systems in Subsection 3.2.P.7. The stability section should also be organized according to packaging configuration.

Additional Discussion: The Sponsor informed the Division that additional discussion of this response was not necessary.

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QUESTION 8 (CMC)
The suitability of the container closure systems will be supported in part by extractable and leachable testing in each configuration (tube, packet and pump). The leachable testing will be conducted on all three packaging configurations using drug product, and not placebo gel, as originally proposed to and agreed by the Agency. USL proposes to provide extractable data and 3 months leachable data at time of NDA submission for the unit dose tube and packet and multi-dose pump and to provide the 6 month leachable data in an amendment to the pending NDA within 5 months of NDA submission.
Does the Agency agree that USL's proposal for providing extractable/leachable data is acceptable?

Division Response: Yes, we agree that 6 months of leachable data can be provided by month 5 of NDA submission. However, you stated in Question 9 that "USL does not intend to repeat the extractable study on the (b) (4) from the new supplier". Clarify what information is available. See the response to Question 9.

Additional Discussion: Upsher Smith stated that their leachable study will be performed on one batch of drug product in each container closure configuration (tube, packet, and metered pump). The Sponsor asked if the Division agrees that performing a leachable study with one batch of drug product in each container closure configuration is acceptable.

The Division agreed and advised the Sponsor to include this information in the NDA submission.

QUESTION 9 (CMC)
After completion of the tube extractable study, (b) (4) Packaging, the manufacturer of the tube container closure system, changed the supplier of the tube (b) (4) (b) (4) has established that the new (b) (4) supplier provides a (b) (4) material that is equivalent to the (b) (4) from the old supplier. (b) (4) has updated their DMF No. (b) (4) with the new container closure information. Additional information on the change is provided in Section 10.2.7.

The leachable study for the tube configuration will be conducted using the tube manufactured with material from the new (b) (4) supplier. For the NDA, USL does not intend to repeat the extractable study on the (b) (4) from the new supplier and does not plan to repeat stability studies with the tube made using the (b) (4) from the new supplier.
Does the Agency agree that the data provided by the tube manufacturer is sufficient and that no additional stability or extractables data are needed to support the tube manufactured using the new (b) (4) supplier?

Division Response: It is unclear from your package if (b) (4) Packaging has performed extractable studies to establish the equivalency of the two (b) (4) If studies have been performed, the acceptance of the comparability extractable study data between the new and old (b) (4) material, generated by (b) (4) is an NDA review issue, and you do not need to repeat the extractable study on the (b) (4) from the new supplier. If these studies have not been performed, they will need to be repeated.

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In addition, we recommend that you perform stability studies and report at least three months of comparative accelerated stability studies and available long term data on one batch of the drug product to qualify the new tube (b) (4)

Additional Discussion: The Sponsor stated that (b) (4) Packaging has performed extractable studies on both (b) (4) as required by 21 CFR 175.300. The Sponsor further stated that in water and (b) (4) alcohol, both (b) (4) were comparable. In heptane, the new (b) (4) exhibited lower quantities of extractables. For all testing conditions, both (b) (4) met USP specification limits of 0.5 mg/inch^2.
The Sponsor asked if the Division concurs that this data is sufficient and that Upsher Smith does not need to perform additional extractable studies to support the (b) (4) change, assuming acceptable leachable data with the new (b) (4) and acceptable 3 month accelerated stability data on one batch of drug product in the new (b) (4)

The Division stated that it agrees.

QUESTION 10 (CMC)
At time of NDA submission, USL plans to provide, at a minimum, stability data on batches of USL240 packaged in the tube, packet and pump as indicated in the following table.

C/C System	Batch	ACC (40°C/75%RH)	CRT (25°C/60%RH)
5 g Tube[a]	42956	3 M[b]	36 M
	46322	3 M[b]	36 M
	50287	6 M	36 M
5 g Packet	42956A	3 M[b]	36 M
	46322A	3 M[b]	36 M
	50287A	6 M	36 M
Metered Pump	60336A	6 M	24 M
	71766B	3 M[c]	3 M[c]
	TBD	3 M[c]	3 M[c]

[a] Tube manufactured using (b) (4) from the original (b) (4) supplier.
[b] Only 3 months data collected because study was conducted in support of ANDA 79-178.
[c] 6 M ACC data and 6 M CRT data will be provided within five months of NDA submission.

Because a significant body of stability data exists for the bulk gel formulation packaged in two container closure systems (tube and packet) comprised of product contact surface materials that are the same or similar to product contact surface materials for the pump (refer to Table 10.2.6-1), expiry for the metered pump container closure system will be further supported by stability data from both unit dose configurations at the time of submission. Additional information is provided in Section 10.2.7.
Does the Agency agree that these data are sufficient and acceptable for NDA filing? Does the Agency agree that providing 6 month accelerated data and 6 month CRT data on two pump batches in an amendment to the pending NDA within five months of NDA submission is acceptable?

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Division Response: With the addition of the studies outlined in Question 9, the data outlined above should be sufficient for filing of the NDA. We accept your proposal to provide 6 month accelerated data and 6 month CRT data on two pump batches in an amendment to the pending NDA within five months of NDA submission. Any additional stability data on other batches can also be provided at that time.

Additional Discussion: The Sponsor asked, does the Division concur that the substantial amount of data available for the product is sufficient to support a proposed shelf-life expiry of 36 months for the tube and packet and 24 months for the metered pump?

The Division stated that the proposed amount of data is sufficient to review the expiration dating period of 36 months for the tube and packet and 24 months for the metered pump.

The Sponsor inquired if it was feasible to request 24 months for the pump since the Sponsor has less data. The Sponsor further stated that the tube and packet data support the 24 month expiration for the pump.

The Division stated that the Sponsor can request this but the final decision will be made after a complete review of the NDA.

QUESTION 11 (REGULATORY)
USL (b) (4) Testim® 1% (Testosterone Gel), (Auxilium Pharmaceuticals, NDA 21-454) for the unit dose configurations of USL240 (i.e., 5 g tube and 5 g packet).

(b) (4)

(b) (4) USL plans to provide draft labeling for USL240 that substantially matches the labeling for Testim®. The approved labeling for Testim® is currently not in the Physician Labeling Rule (PLR) format (refer to Appendix 3 for a copy of the approved labeling for Testim®). Because the pump labeling is essentially equivalent to the tube and packet, with the exception of pump priming instructions, USL proposes to include pump labeling in the tube and packet prescribing information in non-PLR format.

Does the Agency agree that labeling for USL240 in non-PLR format to match the reference listed drug Testim® labeling is acceptable?

Division Response: No. All labeling must be submitted in PLR format.

(b) (4)

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QUESTION 12 (REGULATORY)
The labeling for the reference listed drug Testim® includes a Medication Guide. The Testim® Medication Guide is part of a Risk Evaluation and Mitigation Strategy (REMS) whose only elements are the Medication Guide and a timetable for submission of REMS assessments. (Refer to Appendix 3 for a copy of the approved Medication Guide for Testim® and to Appendix 4 for a copy of the Testim® REMS.) USL plans to match the Testim® Medication Guide. However, consistent with FDA policy articulated in the draft Guidance for Industry: *Medication Guides – Distribution Requirements and Inclusion in Risk Evaluation and Mitigation Strategies (REMS)* (February 2011), USL proposes to provide the Medication Guide for USL240 in the NDA (b) (4) (b) (4)

Does the Agency agree that a Medication Guide for USL240 that follows the Medication Guide of the reference listed drug Testim® is an acceptable approach (b) (4) (b) (4)

Division Response: No. The REMS for topical testosterone products was established because of cases of secondary exposure of children to testosterone apparently due to drug transfer from adult men. After a review of post marketing data from these products, it was determined that cases of secondary exposure continue to be reported, albeit infrequently. Based on these reports of additional cases, we believe that in order to ensure safe use of these topical products that the REMS for these products should be maintained.

Additional Discussion: Upsher-Smith stated that they are pursuing a 505(b)(2) application and substantially relying on the FDA's findings of safety and efficacy for the RLD, Testim. The Sponsor further stated that the REMS approved for the Testim product includes a Medication Guide and timetable for assessments. Upsher-Smith made note that the REMS Draft Guidance indicates that REMS for NDAs must include a timetable for submission of assessments of the REMS and REMS for ANDAs do not include a timetable for submission of assessments; however, no distinction is made between 505(b)(1) NDA and 505(b)(2) NDA approval pathways. In some cases, NDAs approved via the 505(b)(2) route of approval are more similar to ANDAs than 505(b)(1) NDAs.

The Sponsor stated that their 505(b)(2) NDA will provide demonstration of bioequivalence to Testim, with additional supportive Phase 1 studies, for approval. Upsher-Smith will substantially rely on the FDA's findings of safety and efficacy for Testim. In addition, Upsher-Smith plans to use the same Medication Guide as Testim. Testim is already performing a periodic survey of patients' understanding of the serious risks of the drug at 18 months, 3 years and 7 years, extending to September 2016, which will be approximately 3 years after the Upsher-Smith product is approved and on the market. The Sponsor believes that there is no added value for Upsher-Smith to concurrently provide assessments of the same Medication Guide wording to the same patient population. Therefore, considering the Division's preliminary responses indicating a REMS will be required for this product, (b) (4) (b) (4)

The Division stated that the Sponsor's REMS assessment would be unique to their product and it is a requirement that is mandated by FDAAA. The Division further stated that the Sponsor should refer to the response stated in the preliminary comments.

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QUESTION 13 (REGULATORY)
USL previously obtained Agency concurrence to submit a paper NDA in CTD format. USL is currently exploring options to submit either a paper NDA or an electronic submission using CTD format.
If USL chooses not to submit an electronic submission, does the Agency agree that a paper NDA in CTD format with some electronic elements (e.g., labeling in SPL format and raw and calculated pharmacokinetic data in SAS Transport (.XPT) format) is acceptable?

Division Response: An electronic submission is the preferred format and it is strongly encouraged but a paper submission with electronic elements including labeling in SPL format and PK data in SAS transport format is acceptable.

Additional Discussion: The Sponsor informed the Division that additional discussion of this response was not necessary.

Post meeting information for the Sponsor:

PRESCRIBING INFORMATION
Proposed prescribing information (PI) submitted with your application must conform to the content and format regulations found at 21 CFR 201.56 and 201.57.

Summary of the Final Rule on the Requirements for Prescribing Information for Drug and Biological Products, labeling guidances, sample tool illustrating Highlights and Table of Contents, an educational module concerning prescription drug labeling, and fictitious prototypes of prescribing information are available at: http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/LawsActsandRules/ucm084159.htm. We encourage you to review the information at this website and use it as you draft prescribing information for your application.

ABUSE POTENTIAL ASSESSMENT
Drugs that affect the central nervous system, are chemically or pharmacologically similar to other drugs with known abuse potential, or produce psychoactive effects such as mood or cognitive changes (e.g., euphoria, hallucinations) need to be evaluated for their abuse potential and a proposal for scheduling will be required at the time of the NDA submission [21 CFR 314.50(d)(5)(vii)]. For information on the abuse potential evaluation and information required at the time of your NDA submission, see the draft guidance for industry, "Guidance for Industry Assessment of Abuse Potential of Drugs", available at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM198650.pdf.

MANUFACTURING FACILITIES
To facilitate our inspectional process, the Division of Manufacturing and Product Quality in CDER's Office of Compliance requests that you clearly identify *in a single location*, either on the Form FDA 356h, or an attachment to the form, all manufacturing facilities associated with your application. Include the full corporate name of the facility and address where the manufacturing function is performed, with the FEI number, and specific manufacturing responsibilities for each facility.

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Also provide the name and title of an onsite contact person, including their phone number, fax number, and email address. Provide a brief description of the manufacturing operation conducted at each facility, including the type of testing and DMF number (if applicable). Each facility should be ready for GMP inspection at the time of submission.

Consider using a table similar to the one below as an attachment to Form FDA 356h. Indicate under Establishment Information on page 1 of Form FDA 356h that the information is provided in the attachment titled, "Product name, NDA/BLA 012345, Establishment Information for Form 356h."

Site Name	Site Address	Federal Establishment Indicator (FEI) or Registration Number (CFN)	Drug Master File Number (if applicable)	Manufacturing Step(s) or Type of Testing [Establishment function]
1.				
2.				

Corresponding names and titles of onsite contact:

Site Name	Site Address	Onsite Contact (Person, Title)	Phone and Fax number	Email address
1.				
2.				

ISSUES REQUIRING FURTHER DISCUSSION
None

ACTION ITEMS
Meeting minutes will be conveyed to Sponsor within 30 days.

ATTACHMENTS AND HANDOUTS
See attached

Study ID Number of Centers, Date of Conduct	Design, Control Type	Treatment Arm, Formulation, Route & Regimen	Dose	Primary Endpoints	Data Analysis	Duration of Therapy	Duration of Post-Dose Observation (in each period)	Study Subjects Entered		Population of Study Subjects	Application Site
								M	F		
P06-001 **Single Center, 2006**	Single-dose Open-label Randomized 4-Way Crossover	I: USL Formulation A (testosterone 1% gel) = USL240 (to-be-marketed formulation), topical, single dose II: USL Formulation B (testosterone 1% gel), topical, single dose III: USL Formulation C (testosterone 1% gel), topical, single dose IV: Testim®, 50 mg, topical, single dose	50 mg	Comparative bioavailability (PK) of 3 formulations of USL240 vs. Testim®	PK - systemic	1 day x 4 study periods	In-clinic: 48 hrs PK draws until 72 hrs	26	0	Hypogonadal male volunteers	Single upper arm
P06-011 **Single Center, 2007**	Single-dose Open-label Randomized 4-Way Replicate Crossover	I: USL240, topical, single dose II: Testim®, topical, single dose	100 mg	Comparative bioavailability (PK) of USL240 vs. Testim®	PK - systemic	1 day x 4 study periods	In-clinic: 48 hrs PK draws until 72 hrs	84	0	Hypogonadal male volunteers	Both shoulders/upper arms
P08-001 **Single Center, 2008**	Sub-therapeutic dose, Double-blind, Randomized	I: USL240 (80 µl) II: Positive Irritant Control: Sodium Lauryl Sulfate 0.05% (0.2 mL) III: Low Irritant Control: Saline (0.2 mL) IV: Testim® (80 µl)	< 1 mg	Comparative cumulative irritation potential of USL240 vs. Testim®, and Comparative sensitization potential of USL240 vs. Testim®	Skin evaluation	23 days	~1 hr	255	0	Healthy male volunteers	Upper outer arm (irritation)/ upper back (sensitization)
P10-002 **Single Center, 2010**	Single-dose Open-label Randomized 3-Way Crossover	I: USL240, topical, single dose – Gel allowed to dry on hands after self-dosing, hand wash, pat dry hands with cloth towel II: USL240, topical, single dose – Gel allowed to dry on hands after self-dosing, hand wash, hands allowed to air dry III: USL240, topical, single dose – Hand wash immediately after self-dosing, pat dry hands with cloth towel	50 mg	Evaluate if washing the hands following application of USL240 removes testosterone from the skin surface (comparative swab analysis: pre-dose, post-dose, post-wash)	Hand swab	≤ 12 hrs* x 3 study periods	~12 hrs	36	0	Healthy male volunteers	Single shoulder/upper arm
P10-003 **Single Center, 2011**	Single-dose Open-label Randomized 3-Way Crossover	I: USL240, topical, single dose – Skin-to-skin contact with clothed male II: USL240, topical, single dose – Skin-to-skin contact with unclothed male III: USL240, topical, single dose – Skin-to-skin contact with unclothed male after male had showered	50 mg	Baseline-corrected $AUC_{0\text{-}24}$ in non-dosed female subjects after skin-to-skin contact with dosed male subjects, with clothing, without clothing, and after the male has showered.	Male = No PK Female = PK - systemic	≤ 30 hrs* x 3 study periods	~30 hrs	48	48	Healthy male and Healthy female volunteers (in matched pairs)	Male: Single shoulder/upper arm Female: Single forearm

* All subjects were required to thoroughly wash the application site before leaving the clinic

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/s/

SURESH KAUL
08/31/2011

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

PIND 76,654

MEETING MINUTES

Upsher-Smith Laboratories, Inc.
Attention: Carol Subialka
Regulatory Affairs Specialist
6701 Evenstad Drive
Maple Grove, MN 55369

Dear Ms. Subialka:

Please refer to your Pre-Investigational New Drug Application (PIND) file for Testosterone 1% Gel.

We also refer to the meeting between representatives of your firm and the FDA on September 11, 2009. The purpose of the meeting was to obtain guidance that will enable the advancement of your plans for a submission of an NDA.

A copy of the official minutes of the meeting is attached for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Jeannie Roule, Regulatory Project Manager at (301) 796-3993.

Sincerely,

{See appended electronic signature page}

George Benson, M.D.
Deputy Director
Division of Reproductive and Urologic Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosure

MEMORANDUM OF MEETING MINUTES

Meeting Type:	**Type C**
Meeting Category:	**Guidance**
Meeting Date and Time:	**September 11, 2009@ 11 a.m.-12:30 p.m.**
Meeting Location:	**White Oak, Building #22, Room 1313**
Application Number:	**PIND 76,654**
Product Name:	**Testosterone 1% Gel**
Indication:	**Testosterone replacement therapy**
Sponsor/Applicant Name:	**Upsher-Smith laboratories, Inc.**
Meeting Chair:	**Suresh Kaul, M.D.**
Meeting Recorder:	**Jeannie Roule**

FDA ATTENDEES

George Benson, M.D.	Deputy Director, Division of Reproductive and Urologic Products (DRUP)
Suresh Kaul, M.D., MPH	Medical Team Leader, DRUP
Donald McNellis, M.D.	Medical Officer, DRUP
Jeffrey Bray, Ph.D.	Pharmacology Reviewer, DRUP
Myong Jin Kim, Pharm.D.	Clinical Pharmacology Team Leader, Office of Translational Sciences (OTS), Office of Clinical Pharmacology (OCP), Division of Clinical Pharmacology (DCP) III
Doanh Tran, Ph.D.	Clinical Pharmacology Reviewer, DCP III, OCP, OTS
Xin Fang, Ph.D.	Statistical Reviewer, Division of Biometrics III (DBIII), OTS
Donna Christner, Ph.D.	Pharmaceutical Assessment Lead, Office of Pharmaceutical Sciences (OPS), Office of New Drug Quality Assessment (ONDQA), Division of Pre-Marketing Assessment (DPA) II
Michael Jones	Office of Regulatory Policy (ORP), Center for Drug Evaluation and Research (CDER)
Meredith Francis	Regulatory Counsel, ORP, CDER
Jeannie Roule	Regulatory Health Project Manager, DRUP

SPONSOR ATTENDEES

Alan Rauch, M.D.	Vice President and Chief Medical Officer, Medical and Regulatory Affairs
Steve Berge, Ph.D., R.Ph.	Vice President, Pharmaceutical Sciences
Mark Halvorsen, Pharm. D.	Senior Director, Medical Affairs
Cynthia Farner, RAC	Director, Regulatory Affairs
Yan Alsmeyer, Ph.D	Director, Chemistry and Analytical Sciences
Lindy Bancke, Pharm. D.	Clinical Research Scientist, Medical Affairs

Carol Subialka (b) (4) Regulatory Affairs Specialist, Regulatory Affairs
Pharmaceutical Development Consultant

BACKGROUND:
The Sponsor intends to submit an NDA for a metered dose testosterone gel product. An ANDA that had been submitted for the same gel product (b) (4) (b) (4) (b) (4) a Citizen's Petition, that testosterone gel products that are not qualitatively and quantitatively identical to a reference listed drug would need to provide clinical data regarding the transfer of testosterone via person-to-person contact. The 505(b)(2) pathway was believed to be the appropriate pathway for this product.

This September 11, 2009, meeting to discuss the metered dose product, was scheduled prior to OGD's action on the ANDA. The Sponsor's questions and the Division's responses were submitted with reference to the metered dose product.

MEETING OBJECTIVE:
- To obtain guidance related to the format and content of the planned NDA submission.

DISCUSSION POINTS:
The following preliminary draft responses were provided to the sponsor on September 3, 2009, in response to the questions posed in the sponsor's meeting package update provided to the Division on July 30, 2009. The Sponsor's questions are presented below in **bolded** text, followed by the Division's responses in normal text. Additional discussion held during the meeting is summarized below in *italics.*

(Most of the questions below require that you refer to the briefing document dated July 30, 2009, for various graphs and tables)

Clinical Question:

1. **Does the Agency concur that no further clinical studies are necessary?**

Division Response:
No. While your product is said to be bioequivalent to Testim, it is not qualitatively and quantitatively equivalent in formulation. Given this formulation difference, we will require a clinical study evaluating the potential for the product to transfer to another individual via skin-to-skin contact and evaluating the ability of clothing and washing with soap and water to mitigate any such transfer.

We will also require a study evaluating the amount of product remaining on the skin after the application site has been washed with soap and water. You may wish to include the reference listed drug (RLD) as a comparator in this study in order to show comparable wash-off of your product.

A study evaluating the effect of washing the application site on product bioavailability is also recommended in order to provide information needed to properly label your product.

We recommend that you submit any protocols for review prior to initiation of the studies so that further comments can be provided.

Additional Discussion:

- *The Sponsor stated that they had reviewed both the preliminary responses provided by DRUP and the Agency's recently issued response to Auxilium's Citizen's Petition. The Sponsor believed that there were some apparent differences between the responses. The Sponsor stated that the Citizen's Petition response required transfer and hand washing studies for a testosterone gel product containing different ingredients from the reference listed drug. The Sponsor stated that their understanding of the Citizen's Petition response was that a showering study would be required only if results of the hand washing study show significant differences between the test and the reference listed drug (RLD) products.*

- *The Division responded that transfer and hand washing studies would be required. However, if the hand washing studies prove that there are no significant differences in the residual between the test and RLD products after washing, then showering studies would not be required.*

- *The Sponsor inquired whether the Division's reference to a washing study meant a hand washing study and not an application site washing study.*

- *The Division confirmed that a hand washing study would be acceptable for this product. Comments on study design will be provided once the full protocol is submitted.*

- *The Sponsor stated that they are planning to conduct transferability studies and that they would follow a design similar to the AndroGel® and Testim® studies.*

The Sponsor proposed the following study design for a transferability study (submitted as a handout):

USL240 or Testim® will be administered to a 500 cm^2 area of the upper shoulder/arm of healthy males during each period ("dosed male"). Each male will be matched to a healthy female partner ("non-dosed female"). Rubbing will occur between the non-dosed female's anterior forearm and the dosed male's application site for 5 minutes (10-15 rubs/minute). The female will then maintain contact with the same forearm at the application site for another 10 minutes without the rubbing motion.

Study Design	Subjects	Treatment Arms	Endpoints
Randomized, Single-center, 6-way crossover, Transferability study	60 subjects (30 healthy males and 30 healthy females)	I) Treatment: USL240 Rubbing at 1 hour post-dose with unclothed male II) Treatment: USL240 Rubbing at 1 hour post-dose with clothed male III) Treatment: USL240 Rubbing at 4 hours with unclothed male IV) Treatment: USL240 Rubbing at 12 hours with unclothed male V) Treatment: Testim® Rubbing at 1 hour post-dose with unclothed male VI) Treatment: Testim® Rubbing at 12 hours with unclothed male	Primary Endpoint: Comparison of AUC_{0-24} at baseline vs. AUC_{0-24} in each treatment arm, for all non-dosed females Secondary Endpoint: Cmax

- *The Sponsor stated that their plan is to evaluate transfer of their product at four time points: one hour post-dose unclothed, one hour post-dose clothed, four hours post-dose unclothed and 12 hours post-dose unclothed. Testim® would be evaluated at one hour post-dose unclothed and 12 hours post-dose unclothed.*

- *The Division stated that a key question is whether clothing prevents transfer of testosterone following application of USL240. The Clinical Pharmacology team will primarily consider the results of the USL240 clothed treatment arm (i.e., Treatment II in the proposed transferability study) to make this assessment.*

- *The Sponsor inquired as to whether their proposed method of rubbing the forearm of the non-dosed individual to the application site (shoulder/upper arm) of the dosed individual was acceptable.*

- *The Division responded that it was important to maximize the surface area, provide consistent rubbing, maximize time of contact, and include a total contact time of at least 15 minutes. The Division stated that the Sponsor's study design appeared to be reasonable but a complete protocol would need to be submitted before any agreement could be reached.*

- *The Sponsor described their proposal to define a significant difference in the hand washing study as* (b) (4) *% of the absolute value of the RLD. The Sponsor provided a*

brief description of their hand washing study (1.5 minutes washing with soap and water followed by 1.5 minutes rinsing; sample collection by dry swabbing of the palm and base of fingers).

- *The Division noted that the study design appeared reasonable but the protocol would need to be reviewed to address the specifics of trial design (e.g., application to palm of hand only) as well as the rationale for the chosen design. The Division commented that the hand washing study should emulate what may occur at the application site (e.g., the gel may remain on the application site for an extended period of time before the site is washed). The Sponsor proposed to include multiple time points for washing in the hand washing study.*

- *The Sponsor stated that they were prepared to submit the study protocols within the next few weeks and asked if a timeframe for review could be provided.*

- *The Division stated that it would review the protocol and most likely provide a response within 60 days of receipt.*

- *The Sponsor wanted to clarify whether the Division's major concerns centered on safety. The Division responded that safety was the primary concern.*

- *The Sponsor explained that there are two different endpoints that will be addressed in the requested studies. The first endpoint is the product's potential for transfer and whether it is similar to Testim®'s potential for transfer. This endpoint will be addressed in the transferability study. A Testim® arm will be included to provide the basis for comparison. The second endpoint is the ability of the product to be removed from the skin with soap and water. This endpoint will be addressed in the hand washing study.*

- *The Division questioned whether using a dry swab would be able to accurately measure the residual amount of testosterone on the skin. The Division indicated that the Sponsor would need to show that the proposed method can accurately measure the residual testosterone on the skin.*

- *The Sponsor stated that they will evaluate the swab method to ensure that it adequately recovers applied testosterone from the skin. The Division agreed with this proposal.*

Test and Reference Products

- *The Sponsor noted that the test product is packaged in three container closures (tubes, packets and pump), all containing the same formulation. The Sponsor inquired whether the Division had any concerns regarding which is used as the test product in the studies.*

- *The Division responded that the 5 g tube would be best since it is the same as Testim®, but confirmed that any of the three configurations would be acceptable.*

- *The Division attempted to summarize the transfer and washing discussion by stating that it understands that these are not standardized studies. The questions that needs to be answered are not quantitative since there is a potential for high variability in the studies. There are two important questions that the studies need to answer: 1.Does your drug transfer and does clothing prevent the transfer? 2. Can the product be removed from the skin with washing? The Division stated that it is not looking for specific confidence intervals drawn around the data.*

- *The Sponsor asked whether there was an opportunity to get an update from the Division once the results from the hand washing study become available.*

- *The Division agreed that the results could be submitted prior to filing the NDA and, if submitted, the Division would provide an assessment regarding whether the differences observed between test and reference products are significant enough to warrant a showering study.*

- *At the conclusion of the meeting, the Division asked the Sponsor about their plans for their unit-dose and metered dose submissions. The Sponsor responded that in light of the very recent action by OGD, they had made no decisions regarding their unit-dose submission.*

CHEMISTRY, MANUFACTURING AND CONTROLS QUESTIONS:

2. Does the Agency concur that the proposed qualification studies and acceptance criteria are sufficient to support the metered gel dose form (metered pump system)?

Division Response:
The metered gel pump qualification program appears to be adequate at this time, with the following additions:

a. Extractable/leachable testing should be performed with the drug product.

Below is a response and further questions submitted to the Division after the preliminary responses were received by the Sponsor but prior to the meeting on September 11, 2009.

USL intends to perform extractable testing on any components that will contact drug product using solvents under rigorous extraction conditions as described in the CCS guidance as a one time study and to perform one-time leachable testing on the placebo metered dose pump product after 6 months accelerated stability.

Additional Discussion:

1. *Does the Agency concur that the placebo will represent the drug product?*

   The Division agreed

2. *Does the proposed plan address the Agency's concerns regarding extractable and leachable for the pump system?*

   The Division stated that this appears to be adequate.

3. *Does the Agency concur that, because the product contact surfaces of the packets and tubes are substantially similar to those in the pump, leachable testing from the pump system represents the worst case scenario and, hypothetically, if USL were to include all three container closure systems in one NDA, leachable testing performed with the pump would be sufficient and testing would not need to be repeated with the unit-dose packets and tubes?*

- *The Sponsor addressed their extractable/leachable testing proposal (one-time extractable testing on any components that will contact drug product using solvents and one-time leachable testing on the placebo metered dose pump product after 6 months accelerated stability).They inquired whether using placebo for the leachable study was acceptable and whether the overall proposal was acceptable. The Division concurred that placebo could represent the drug product since the leachable profile would probably not change with the addition of testosterone and that the proposed plan appeared adequate.*

- *The Sponsor explained that the product contact surfaces of the packets and tubes are substantially similar to those in the pump. The Sponsor remarked that since leachable testing with the pump system represents the worst case scenario, if they were to include the unit-dose tubes and packets in the NDA, would the Division concur that leachable testing would not need to be repeated with tubes and packets. The Division stated that it did not necessarily agree that the pump represents the worst case scenario. The Division further stated that the leachables might be more dilute in the pump due to surface area difference. The Division recommended providing a justification in the NDA that includes a side-by side comparison of the container/closure systems and the surface area ratios to gel, as well as 21 CFR references.*

3. Does the Agency concur that the proposed release and stability tests are appropriate and that demonstration of Delivered-Dose Uniformity, as specified in USP <601> for Topical Aerosols, is applicable to a "bag-in-bottle" metered pump system?

Division Response:
From the information provided in the package, the tests appear to be acceptable with the following additions:

a. Delivered dose uniformity should be performed on stability to ensure pump performance over the shelf-life of the product.
b. Develop an in-vitro release test for release and stability testing.

Below is a response and further question submitted to the Division after the preliminary responses were received by the Sponsor but prior to the meeting on September 11, 2009.

Delivered-dose uniformity at release will establish between-unit reproducibility. To establish pump performance on stability, USL proposes to test 1 unit collecting the first dose after priming, the 2nd dose in the middle of the container, and the last dose of the container (actuations 57, 58, 59, 60 after priming). The requirements for dose uniformity are met if each value is between 75 to 125% of the label claimed dose. If one dose collected is outside 75 to 125% of the label claimed dose but not outside 65 to 135%, 2 more pumps would be tested in the same manner. No more than 1 of 9 values can fall outside 75 to 125% and none outside 65 to 135% of the label claimed dose.

Additional Discussion:

1. *Does the Agency concur that this testing on stability will address the Agency's requirements?*

   The Division agreed.

Based on the FDA's request for in-vitro release testing, USL proposes to test the product at release and annually through the product shelf life at controlled room temperature (CRT).

2. *Does the Agency concur that this testing on stability will address the Agency's requirements?*

   - *The Sponsor summarized their proposal for performing delivered dose uniformity on stability (1st stage: 1 unit, 3 doses (beginning, middle and end of container); 2nd stage: two additional units, three doses (beginning, middle and end of container) and inquired if the Division felt these were acceptable. The Division responded that testing one unit was acceptable but the Division would require a minimum of 9-10 doses evenly distributed through the container.*

   - *The Sponsor inquired whether two units were acceptable for the second tier testing. The Division agreed that two additional units similarly tested to the first set would be acceptable for the second tier testing.*

   - *The Sponsor inquired whether shot weight could replace assay if a correlation between assay and shot weight were established. The Division stated that shot weight would be acceptable but only if a justification were provided.*

   - *The Sponsor asked whether the Division concurred with the Sponsor's proposal to perform in vitro release testing at release and annually through product shelf life at CRT. The Division responded that for primary stability batches, in vitro release testing should be performed at all time points both CRT and accelerated in order to establish a specification. The Division further stated that the first three commercial batches should also include testing at each time point for CRT. The Sponsor confirmed that the primary stability batches will be at commercial scale. The Division added that it may be possible to perform annual testing at CRT after reviewing the data on the primary stability batches.*

   - *The Sponsor remarked that in vitro release is a QC test and not stability-indicating. The Division responded that for systemically absorbed transdermal*

products it feels it is important to have a release test similar to dissolution testing for tablets. The Division further stated that in vitro release testing should be performed on all three container closure systems.

- *The Sponsor explained that the unit dose tube and packet batches are at or approaching expiry. The Division stated that there would be no expectation to go back for the in vitro testing but it should be done moving forward and any gaps in data should be clearly explained in the NDA*

4. Does the Agency concur that the proposed accelerated and CRT stability data are sufficient and acceptable for receipt and review of the NDA?

Division Response:
No. We do not agree that the proposed stability data package will be adequate. We have the following comments:

a. Your stability studies in your new container closure system should be performed on three lots of the drug product.

Below is a response and further question submitted to the Division after the preliminary responses were received by the Sponsor but prior to the meeting on September 11, 2009.

Based on the Agency's request, USL plans to conduct stability on 3 batches in the pump container closure system stored in an upright position and provide as much stability data as are available at the time of NDA submission as outlined in the table below. Because a significant body of data exists for this formulation with two container closure systems with the same or similar product contact surfaces, these data will be supported by stability data from the tubes and packets (3 batches of each with at least 24 M CRT) at the time of submission.

Pump Batch	CRT (25°C/60%RH)	ACC (40°C/75%RH)
1	9 M	6 M
2	6 M	6 M
3	3 M	3 M

Additional Discussion:

1. Does the Agency concur that these data are sufficient and acceptable for receipt and review of the NDA?

- *The Sponsor inquired as to whether the revised proposed stability package (three batches in the pump configuration with 6-months accelerated data on two batches and 3-months data on one batch and CRT data of 9-months, 6-months, and 3-months with supportive data from the unit-dose tubes and packets) was acceptable to the Division. The Division responded that it prefers 6 months*

accelerated stability on all three batches but the proposal was acceptable for NDA filing purposes. The Division further remarked that the six month data would need to be submitted during NDA review. The Division also stated data from the unit-dose configurations could be supportive for expiration dating purposes for the metered-dose pump since the three container/closure systems contain the same gel formulation.

- *The Sponsor inquired as to whether the Division concurred with their proposal to perform stability on pumps stored in an upright position. The Sponsor explained that due to the pump's mechanical design, product contact was the same regardless of orientation. The Division responded that one orientation should be adequate; however, a justification based on pump design should be included in the NDA. The Division further noted that it was not familiar with the design of the pump but that there was not a concern with pump functionality. There may be a concern with leakage depending on orientation.*

Regulatory questions:

5. **Upsher-Smith intends to substantially rely on the Agency's previous findings of safety and efficacy for Testim 1% (Testosterone Gel), (Auxilium Pharmaceuticals, NDA 21-454) in support of its 505(b)(2) NDA for a metered gel dosage form of Testosterone Gel 1%.**
   Does the Agency concur that Testim® is the appropriate reference listed drug?

Division Response:
It appears that a 505(b)(2) application using Testim as the reference listed drug would be a reasonable approach at this time based on the information provided. The Division recommends that sponsors considering the submission of an application through the 505(b)(2) pathway consult the Agency's regulations at 21 CFR 314.54, and the October 1999 Draft Guidance for Industry "Applications Covered by Section 505(b)(2)" available at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm.

In addition, FDA has explained the background and applicability of section 505(b)(2) in its October 14, 2003, response to a number of citizen petitions challenging the Agency's interpretation of this statutory provision (see Docket FDA-2003-P-0274-0015, available at http://www.regulations.gov).

If you intend to submit a 505(b)(2) application that relies for approval on FDA's finding of safety and/or effectiveness for one or more listed drugs, you must establish that such reliance is scientifically appropriate, and must submit data necessary to support any aspects of the proposed drug product that represent modifications to the listed drug(s). You should establish a "bridge" (e.g., via comparative bioavailability data) between your proposed drug product and each listed drug upon which you propose to rely to demonstrate that such reliance is scientifically justified. If you intend to rely on literature or other studies for which

you have no right of reference but that are necessary for approval, you also must establish that reliance on the studies described in the literature is scientifically appropriate.

6. **Upsher-Smith plans to submit the 505(b)(2) NDA in the third quarter of 2010. Does the Agency concur that a paper NDA in CTD format is acceptable?**

Division Response:
While a paper submission is acceptable, an electronic submission in eCTD format is the preferred format. We request that you provide the raw and calculated pharmacokinetic data in SAS Transport (.XPT) format.

7. **Upsher-Smith plans to request a full waiver of the requirement to submit pediatric assessments because the drug product is indicated for testosterone replacement therapy in adult males only.**
Does the Agency concur that a request for full pediatric waiver prepared in accordance with the Agency's draft Guidance for Industry, "How to Comply with the Pediatric Research Equity Act" (September 2005), is appropriate for Testosterone Gel 1%?

Division Response:
Yes, we agree with your proposal to request a pediatric waiver. Decisions concerning pediatric waiver requests are made by the Pediatric Review Committee after the NDA has been submitted.

8. (b) (4)

Division Response:
(b) (4)

DECISIONS (AGREEMENTS REACHED):
The Sponsor will prepare protocols for transfer and washing studies and submit them to the Division for comments.

UNRESOLVED ISSUES OR ISSUES REQUIRING FURTHER DISCUSSION:
None

ACTION ITEMS:
Meeting minutes will be provided to the Sponsor within 30 days.

ATTACHMENTS/HANDOUTS:
There was a handout and it is included in the additional discussion under question #1.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
IND-76654	GI-1	UPSHER SMITH	TESTOSTERONE 1%GEL

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

/s/

GEORGE S BENSON
10/09/2009

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville, MD 20857

PIND 76,654

MEETING MINUTES

Upsher-Smith Laboratories, Inc.
Attention: Cynthia G. Farner
Director, Regulatory Affairs
6701 Evenstad Drive
Maple Grove, MN 55369-6026

Dear Ms. Farner:

Please refer to your Pre-Investigational New Drug Application (PIND) file for Testosterone 1% Gel.

We also refer to the meeting between representatives of your firm and the FDA on November 8, 2007. The purpose of the meeting was to discuss the submission of a New Drug Application for testosterone 1% gel pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act.

A copy of the official minutes of the meeting is attached for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call John Kim, R.Ph., J.D., Regulatory Health Project Manager, at (301) 796-0932.

Sincerely,

{See appended electronic signature page}

Mark Hirsch, M.D.
Medical Team Leader
Division of Reproductive and Urologic Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosure - Meeting Minutes

MEMORANDUM OF MEETING MINUTES

MEETING DATE: November 8, 2007 **TIME:** 10 am – 11:30 am

LOCATION: Food and Drug Administration
White Oak Building 22, Conference Room 1419
10903 New Hampshire Avenue
Silver Spring, MD 20993

APPLICATION: PIND 76,654

DRUG NAME: Testosterone 1% Gel

TYPE OF MEETING: Type B, Pre-IND

MEETING CHAIR: Mark Hirsch, M.D.

MEETING RECORDER: John Kim, R.Ph., J.D.

FDA ATTENDEES:
Mark Hirsch, M.D. – Medical Team Leader, Division of Reproductive and Urologic Products (DRUP)
Chong Kim, M.D., Ph.D. – Medical Officer, DRUP
Roger Wiederhorn, M.D. – Medical Officer, DRUP
Eric Andreasen, Ph.D. – Pharmacologist, DRUP
Donna Christner, Ph.D. – Pharmaceutical Assessment Lead, Pre-Marketing Assessment Division II, Office of New Drug Quality Assessment
Myong-Jin Kim, Pharm.D. – Clinical Pharmacology Team Leader, Office of Clinical Pharmacology (OCP)
Doanh Tran, R.Ph., Ph.D. – Clinical Pharmacology Reviewer, OCP
Donald Hare, R.Ph. – Special Assistant to the Director, Office of Generic Drugs (OGD)
Dena R. Hixon, M.D. – Associate Director for Medical Affairs, OGD
Dale Conner, Pharm.D. – Director, Division of Bioequivalence, OGD
Martin H. Shimer, R.Ph. – Branch Chief, Regulatory Support Branch, OGD (*via teleconference*)
John Kim, R.Ph., J.D. – Regulatory Health Project Manager, DRUP

UPSHER-SMITH ATTENDEES:
Mark B. Halvorsen, Pharm.D. – Senior Director, Medical Affairs, Upsher-Smith
Kelly A. Harris, Pharm.D., BCPS – Senior Clinical Research Scientist, Upsher-Smith
Gloria A. Rood, Ph.D. –Senior Scientist I, Pharmaceutical Development, Upsher-Smith
Robert J. Overman III – Manager, Stability, Upsher-Smith
Lisa A. Ward – Associate Manager, Stability, Upsher-Smith
Nancy Cameron, ASQ CQA –Senior Chemist II, Analytical Development, Upsher-Smith
Tanya L. Carone, RAC – Associate Manager, New Product Regulatory Affairs, Upsher-Smith
Cynthia G. Farner – Director, Regulatory Affairs, Upsher-Smith
Carol A. Subialka – Regulatory Affairs Specialist, Upsher-Smith
(b) (4) – Toxicology Consultant

BACKGROUND:
The Sponsor has developed a formulation of testosterone 1% gel for testosterone replacement therapy in hypogonadal males. The Sponsor seeks to file an Abbreviated New Drug Application (ANDA) to the Reference List Drug, Testim® (testosterone 1% gel) through the Office of Generic Drugs (OGD). However, the Sponsor is preclude from filing an ANDA (b) (4) (b) (4) (b) (4) the Sponsor requested this meeting to seek guidance as to the suitability of submitting a 505(b)(2) application to DRUP for its testosterone product. (b) (4) (b) (4)

DISCUSSION POINTS:
The Sponsor presented a slide presentation attached to these minutes. The discussions that follow are generated from the Sponsor's specific questions and preliminary draft responses that were conveyed to the Sponsor on November 6, 2007.

NONCLINICAL

8.1 *Ethyl Alcohol: Upsher-Smith proposes to support the safety of ethyl alcohol at the level in USL's product* (b) (4) *with the following information: 1) the IID levels of* (b) (4) *in a topical gel and* (b) (4) *in a transdermal gel: and 2) the enclosed (see Attachment 2) evaluation of safety based on a review of the available literature.* ***Does the Agency concur with this proposal and that no further evidence of safety is required to support the use of this inactive ingredient?***

FDA Response: Yes, we concur.

8.2 *Diisopropyl Adipate: Upsher-Smith proposes to support the safety of diisopropyl adipate at the level in USL's product* (b) (4) *with the following information: 1) the IID listing of 20% in a topical lotion; and 2) the enclosed (see Attachment 3) evaluation of safety based on a review of the available literature.* ***Does the Agency concur with this proposal and that no further evidence of safety is required to support the use of this inactive ingredient?***

FDA Response: Yes, we concur.

Additional Nonclinical Comment: Submit a copy of the correspondence from the Office of Generic Drugs indicating that IID will be updated for transdermal application of polyethylene glycol (b) (4) and oleyl alcohol based on USL's formulation (Controlled correspondence reference No 07-0862).

Additional Discussion: (b) (4) clarified that these non-clinical responses would be sufficient to satisfy the concerns about the two inactive ingredients that do not meet the limits of the IID. However, the inactive ingredients in this proposed formulation are (b) (4) different than those in the RLD, and review of the Sponsor's pre-IND meeting package revealed more reports of application site rash and application site reaction associated with

the Sponsor's product than with the reference listed drug (RLD) in a single application study. (b) (4) (b) (4)

The Sponsor was also advised that nonclinical studies are generally not required for testosterone products submitted as an NDA unless there is cause for concern, for instance due to the route of administration, formulation, purity or novel clinical concerns arise.

CLINICAL

8.3 *Does the Agency concur that the* (b) (4) (b) (4)

FDA Response: No. (b) (4) (b) (4) (b) (4) More detailed information from the assessment of application site irritation in Study P06-011 (e.g., line listings) should be submitted for further review. (b) (4) (b) (4)

If this concern cannot be resolved with the available information, we would then recommend further testing of the product in clinical trials. For your information, the usual development program for a novel testosterone formulation for testosterone replacement therapy generally includes:

- A single, open-label, Phase 3 study
- Approximately 150 hypogonadal subjects
- Use of a dose-titration paradigm
- At least 50 subjects exposed to the product for at least 6 months for assessment of skin safety.
- Assessment of skin safety using a well recognized and detailed scoring system.

Clinical Pharmacology comments:

The bioavailability of testosterone following repeated administration of your formulation of testosterone gel 1% is not known. If an ANDA is not a viable route and additional clinical trials are necessary, pharmacokinetic information should be obtained at steady state in a Phase 3 trial. In addition, we recommend studies to examine 1) the effect of washing on testosterone bioavailability and 2) the person-to-person transferability of your formulation of testosterone gel 1%.

Additional Discussion:

The Sponsor acknowledged that Table 9.2.6 shows a numerical difference in the incidence of application site adverse events. However, the Sponsor purported that this table does not demonstrate clinically meaningful differences in application site tolerability between the test and reference product. Prior to the meeting, the Sponsor provided a response to FDA's

draft comments that included data from application site evaluations in Protocol P06-011. The Sponsor believes that these data demonstrate that its product was no more irritating than the RLD. It was requested that this information be submitted for further review by DRUP and that comments would be provided.

Regarding the submission of cumulative skin irritation and sensitization studies to OGD, it was recommended that the Sponsor submit a protocol for review by OGD. These investigations should be designed to include 200 subjects receiving both test and reference products over a 21-day induction period, followed by a 2-week rest period and a 48-hour challenge phase. OGD informed the Sponsor that there is a considerable backlog of controlled correspondence and protocol reviews. However, the Sponsor may request to prioritize the review of a skin irritation and sensitization protocol through the OGD Director.

The Sponsor was also given the option of reformulating its drug product to be Q1 and Q2 to the RLD and therefore avoid having to do the application site reaction/rash studies for the proposed drug product.

8.4 *Upsher-Smith plans to rely on the safety and efficacy data contained in NDA 21-454 in support of a 505(b)(2) application for Testosterone Gel 1 % and will not conduct additional studies.* ***Does the Agency concur with this approach?***

FDA Response: No. See response to question 8.3.

Additional Comments:
Should new clinical trials be required to establish the safety and efficacy of your testosterone gel 1%, be aware that the nonclinical information relating to testosterone is considered general knowledge, and the 505(b)(2) pathway would not be appropriate for this application.

CHEMISTRY, MANUFACTURING, AND CONTROLS

8.5 *Upsher-Smith's Testosterone Gel 1% will be packaged in two container closure systems: a unit dose* (b) (4) *tube and a unit dose* (b) (4) *foil packet. (Additional information regarding Testosterone Gel 1 % chemistry, manufacturing and controls, including stability, is provided in Part 11 of the Information Package.) The stability data Upsher-Smith proposes to submit in an NDA to support product in the container closure systems is as follows:*

- Three (3) months accelerated stability data from three commercial scale batches packaged into both tubes and packets.
- Eighteen (18) months controlled room temperature (CRT) stability data on one commercial scale batch (tubes and packets); twelve (12) months CRT data on a second commercial scale batch (tubes and packets); and six (6) months CRT data on a third commercial scale batch (tubes and packets).

Does the Agency concur that the proposed accelerated and CRT stability data is sufficient and acceptable for receipt and review of the NDA?

FDA Response: No. Six months of accelerated stability data should be provided upon submission of the NDA. The amount of CRT stability data is sufficient for receipt and review of the NDA. Expiry will be granted based on review of the submitted stability data.

Additional Discussion: The representative from Office of New Drug Quality Assessment (ONDQA) clarified that six months of accelerated stability data from only one batch would a review issue and therefore, three batches are recommended. Any additional stability data must be submitted prior to month 5 from the date of an NDA submission.

REGULATORY

8.6. *Does the Agency concur that the proposed bioequivalence study will support an* (b) (4) *for Upsher-Smith's Testosterone Gel 1% to Testim® 1% (testosterone gel), (Auxilium Pharmaceuticals, NDA 21-454) in the FDA Approved Drug Products with Therapeutic Equivalence Evaluations (Orange Book)?*

FDA Response: No. (b) (4)

(b) (4)

Additional Discussion: FDA clarified that both 505(b)1 or 505(b)2 applications can be designated (b) (4)

(b) (4)

ACTION ITEMS:

- The Project Manager will provide meeting minutes within 30 days of the meeting date.

ATTACHMENTS: Slide presentation

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Attachment - Slide Presentation
Page 1

Testosterone Protocol P06-011: Brief Summary

November 8, 2007

Upsher-Smith P06-011 Study

- Replicate design, bioequivalence study between Testim and USL Testosterone Gel, 1%
  - 84 subjects enrolled, 73 completed all 4 periods
- Pharmacokinetic assessment of bioequivalence
- Safety Assessment
  - Adverse Events
  - Application site assessment

Table 9.2.6 Incidence of Most Commonly Reported AEs (≥ 3%) in P06-011 Study

Body System / Adverse Event[1]	Reported Incidence by Treatment Groups	
	Test N=81[2]	Reference N=83[2]
	n (%)[3]	n (%)[3]
General disorders and administration site conditions		
Application site erythema	14 (17.3%)	11 (13.3%)
Application site rash	7 (8.6%)	2 (2.4%)
Application site reaction	14 (17.3%)	7 (8.4%)
Catheter site erythema	7 (8.6%)	3 (3.6%)
Catheter site pain	4 (4.9%)	8 (9.6%)
Investigations		
Blood pressure increased	10 (12.3%)	8 (9.6%)

P06-011 AEs Coded to MedDRA Preferred Term: Application Site Reaction

TEST			REFERENCE		
AE verbatim term	Severity	Relationship	AE verbatim term	Severity	Relationship
Application site skin reaction	Mild	Probable	Skin reaction dosing site	Mild	Probable
Skin reaction dosing site	Mild	Possible			
Skin reaction left shoulder upper arm dosing site	Mild	Possible			
Skin reaction right shoulder, dosing site	Mild	Unlikely	Skin reaction left dosing site	Mild	Unlikely
Skin reaction right dosing site	Mild	Unlikely			
Pimple administration site	Mild	Possible			
Pimple dosing site	Mild	Unlikely	Pimples right side	Mild	Unlikely
Pimple both dosing sites	Mild	Unlikely	2 pimples application site	Mild	Unlikely
Pimple administration site	Mild	Unlikely	Pimple at upper left back dosing site	Mild	Unlikely
Pimple both dosing sites	Mild	Unlikely	Pimple located on the upper right shoulder at administration site	Mild	Unlikely
Pimple both dosing sites	Mild	Unlikely			
Three pimples application site	Mild	Unlikely			
1 acne-like lesion dosing site	Mild	Unlikely			
Pimple dosing site	Mild	Not related			
Scratches (dosing site)	Mild	Unlikely	Skin abrasion dosing site	Mild	Not related

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Attachment - Slide Presentation
Page 3

Application Site Assessment

- Each Application Site was evaluated at pre-dose, 0.5, 24, 48, 60, 72 hr post-gel application (5 post-dose evaluations)
- Evaluation completed by trained, blinded study staff
- Each arm was evaluated separately
- Total of 3140 post-dose application site assessments (314 exposures x 5 assessments x 2 arms)
- Seven point scale from FDA Guidance For Industry: Skin Irritation and Sensitization Testing of Generic Transdermal Drug Products (December 1999)

Application Site Assessment Scale

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

Number of Subjects with a Post-dose Non-zero Application Site Evaluation Score

Product	Non-Zero Observations		
	1st exposure	2nd exposure	Both exposures
Test	10	7	3
Reference	8	8	5

Number of Post-dose Non-zero Application Site Evaluation Scores

Product	Total	Score of 1	Score of 2	Score of 3
Test	56	49	7	0
Reference	55	45	8	2

Summary

- Adverse Event data is not the appropriate data set for evaluating application site reactions.
- Application site assessment was conducted using a recognized scoring system.
  - Blinded, independent, trained observer
- Results show no difference in application site reactions between Test & Reference.

Subject Disposition

Study Periods Complete	Number of Subjects	Number of Treatments		
		Test	Reference	Total
Four	73	146	146	292
Three	4	5	7	12
Two	3	3	3	6
One	4	1	3	4
Total	84	155	159	314

Linked Applications	Sponsor Name	Drug Name
IND 76654	UPSHER SMITH	TESTOSTERONE 1%GEL

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/s/

MARK S HIRSCH
12/07/2007