CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22309Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

EXCLUSIVITY SUMMARY

NDA # 022309 SUPPL # HFD # 580

Trade Name AndroGel 1.62%

Generic Name testosterone gel

Applicant Name Abbott Products, Inc.

Approval Date, If Known April 29, 2011

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).

NDA# *Please see attachment after the last page of this document

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:

Study # S176.3.104

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 ☐

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 ☐

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"):

Study # S176.3.104

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 # 50377	YES ☒	! NO ☐
		! Explain:

Investigation #2		!
		!
IND #	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: Regulatory Health Project Manager
Date: April 29, 2011

Name of Office/Division Director signing form: George Benson, M.D.
Title: Deputy Director

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05

Appl No	Proprietary Name
	(b) (4)

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
04/29/2011

GEORGE S BENSON
04/29/2011

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

NDA/BLA#: 022309 | Supplement Number: _____ | NDA Supplement Type (e.g. SE5): _____

Division Name: Division of Reproductive and Urologic Drug Products | PDUFA Goal Date: April 29, 2011 | Stamp Date: 10/29/10

Proprietary Name: AndroGel 1.62%

Established/Generic Name: testosterone gel

Dosage Form: topical gel

Applicant/Sponsor: Abbott Products, Inc.

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 adult 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):

(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.

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

diatric studies are not necessary in the following pediatric subpopulation(s) because efficacy can be trapolated 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. herwise, this Pediatric Page is complete and should be signed and entered into DFS or DARRTS as propriate after clearance by PeRC.

is page was completed by:

{See appended electronic signature page}
Jeannie Roule
Regulatory Project Manager

(Revised: 6/2008)

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

Abbott
901 Sawyer Road
Marietta, GA 30062
t 770 578 9000

Division of Reproductive and Urologic Products
Office of Drug Evaluation III
Food and Drug Administration
Central Document Room
5901-B Ammendale Road
Beltsville, MD 20705-1266

RE: Debarment Certification
NDA 22-309
AndroGel 1.62%

Dear Sir/Madam:

In accordance with Section 306(k) of the Federal Food, Drug, and Cosmetic Act (the Act), as amended by the Generic Drug Enforcement Act of 1992, Abbott Products, Inc. hereby certifies that did not and will not use in any capacity the services of any person debarred under Section 306 of the Act in connection with the above-referenced application. Further, we hereby certify that applicant and/or affiliated persons responsible for the development and submission of this application have not been convicted und the Federal Food, Drug, and Cosmetic Act as amended.

5 Oct 2010

Gregg A. Pratt, Ph.D. Date
Director, Global Regulatory Affairs

Abbott
A Promise for Life

505(b)(2) ASSESSMENT

Application Information		
NDA # 022309	NDA Supplement #: S-	Efficacy Supplement Type SE-
Proprietary Name: AndroGel Established/Proper Name: testosterone gel Dosage Form: gel Strengths: 1.62%		
Applicant: Abbott Products, Inc.		
Date of Receipt: October 29, 2010		
PDUFA Goal Date: April 29, 2011	Action Goal Date (if different):	
Proposed Indication(s): Replacement therapy in males for conditions associated with a deficiency or absence of endogenous testosterone:		

GENERAL INFORMATION

1) Is this application for a recombinant or biologically-derived product and/or protein or peptide product *OR* is the applicant relying on a recombinant or biologically-derived product and/or protein or peptide product to support approval of the proposed product?

YES ☐ NO ☒

*If "**YES** "contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*

INFORMATION PROVIDED VIA RELIANCE (LISTED DRUG OR LITERATURE)

2) List the information essential to the approval of the proposed drug that is provided by reliance on our previous finding of safety and efficacy for a listed drug or by reliance on published literature. *(If not clearly identified by the applicant, this information can usually be derived from annotated labeling.)*

Source of information* (e.g., published literature, name of referenced product)	Information provided (e.g., pharmacokinetic data, or specific sections of labeling)
Published Literature	Non-Clinical labeling

*each source of information should be listed on separate rows

3) Reliance on information regarding another product (whether a previously approved product or from published literature) must be scientifically appropriate. An applicant needs to provide a scientific "bridge" to demonstrate the relationship of the referenced and proposed products. Describe how the applicant bridged the proposed product to the referenced product(s). (Example: BA/BE studies)

The applicant is relying upon the labeling from Androgel 1% that describes the potential toxicities of testosterone in nonclinical species and provided references that support the current language in Sections 8.1 and 13.1 of testosterone labels. The testosterone in this drug product is equivalent to the testosterone in the submitted references, and was evaluated at or above the proposed human doses.

RELIANCE ON PUBLISHED LITERATURE

4) (a) Regardless of whether the applicant has explicitly stated a reliance on published literature to support their application, is reliance on published literature necessary to support the approval of the proposed drug product (i.e., the application *cannot* be approved without the published literature)?

YES ☒ NO ☐

*If "**NO**," proceed to question #5.*

(b) Does any of the published literature necessary to support approval identify a specific (e.g., brand name) *listed* drug product?

YES ☐ NO ☒

*If "**NO**", proceed to question #5.*

*If "**YES**", list the listed drug(s) identified by name and answer question #4(c).*

(c) Are the drug product(s) listed in (b) identified by the applicant as the listed drug(s)?

YES ☐ NO ☐

RELIANCE ON LISTED DRUG(S)

Reliance on published literature which identifies a specific approved (listed) drug constitutes reliance on that listed drug. Please answer questions #5-9 accordingly.

5) Regardless of whether the applicant has explicitly referenced the listed drug(s), does the application **rely** on the finding of safety and effectiveness for one or more listed drugs (approved drugs) to support the approval of the proposed drug product (i.e., the application cannot be approved without this reliance)?

YES ☒ NO ☐

*If "**NO**," proceed to question #10.*

6) Name of listed drug(s) relied upon, and the NDA/ANDA #(s). Please indicate if the applicant explicitly identified the product as being relied upon (see note below):

Name of Drug	NDA/ANDA #	Did applicant specify reliance on the product? (Y/N)

Applicants should specify reliance on the 356h, in the cover letter, and/or with their patent certification/statement. If you believe there is reliance on a listed product that has not been explicitly identified as such by the applicant, please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

7) If this is a (b)(2) supplement to an original (b)(2) application, does the supplement rely upon the same listed drug(s) as the original (b)(2) application?

N/A ☒ YES ☐ NO ☐

*If this application is a (b)(2) supplement to an original (b)(1) application or not a supplemental application, answer **"N/A"**.*

*If "**NO**", please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*

8) Were any of the listed drug(s) relied upon for this application:

a) Approved in a 505(b)(2) application?

YES ☐ NO ☒

*If "**YES**", please list which drug(s).*

Name of drug(s) approved in a 505(b)(2) application:

b) Approved by the DESI process?

YES ☐ NO ☒

*If "**YES**", please list which drug(s).*

Name of drug(s) approved via the DESI process:

c) Described in a monograph?

YES ☐ NO ☒

*If "**YES**", please list which drug(s).*

Name of drug(s) described in a monograph:

d) Discontinued from marketing?

YES ☐ NO ☒

*If "**YES**", please list which drug(s) and answer question d) i. below.*
*If "**NO**", proceed to question #9.*

Name of drug(s) discontinued from marketing:

i) Were the products discontinued for reasons related to safety or effectiveness?

YES ☐ NO ☐

(Information regarding whether a drug has been discontinued from marketing for reasons of safety or effectiveness may be available in the Orange Book. Refer to section 1.11 for an explanation, and section 6.1 for the list of discontinued drugs. If a determination of the reason for discontinuation has not been published in the Federal Register (and noted in the Orange Book), you will need to research the archive file and/or consult with the review team. Do not rely solely on any statements made by the sponsor.)

9) Describe the change from the listed drug(s) relied upon to support this (b)(2) application (for example, "This application provides for a new indication, otitis media" or "This application provides for a change in dosage form, from capsule to solution").

This drug provides for a change in testosterone concentration and different application sites.

The purpose of the following two questions is to determine if there is an approved drug product that is equivalent or very similar to the product proposed for approval that should be referenced as a listed drug in the pending application.

*The assessment of pharmaceutical equivalence for a recombinant or biologically-derived product and/or protein or peptide product is complex. If you answered **YES to question #1**, proceed to question #12; if you answered **NO to question #1**, proceed to question #10 below.*

10) (a) Is there a pharmaceutical equivalent(s) to the product proposed in the 505(b)(2) application that is already approved (via an NDA or ANDA)?

*(**Pharmaceutical equivalents** are drug products in identical dosage forms that: **(1)** contain identical amounts of the identical active drug ingredient, i.e., the same salt or ester of the same therapeutic moiety, or, in the case of modified release dosage forms that require a reservoir or overage or such forms as prefilled syringes where residual volume may vary, that deliver identical amounts of the active drug ingredient over the identical dosing period; **(2)** do not necessarily contain the same inactive ingredients; **and** **(3)** meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates. (21 CFR 320.1(c)).*

***Note** that for proposed combinations of one or more previously approved drugs, a pharmaceutical equivalent must also be a combination of the same drugs.*

YES ☐ NO ☒

*If "**NO**" to (a) proceed to question #11.*

*If "**YES**" to (a), answer (b) and (c) then proceed to question #12.*

(b) Is the pharmaceutical equivalent approved for the same indication for which the 505(b)(2) application is seeking approval?

YES ☐ NO ☐

(c) Is the listed drug(s) referenced by the application a pharmaceutical equivalent?

YES ☐ NO ☐

*If "**YES**" to (c) and there are no additional pharmaceutical equivalents listed, proceed to question #12.*
*If "**NO**" or if there are additional pharmaceutical equivalents that are not referenced by the application, list the NDA pharmaceutical equivalent(s); you do not have to individually list all of the products approved as ANDAs, but please note below if approved approved generics are listed in the Orange Book. Please also contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*

Pharmaceutical equivalent(s):

11) (a) Is there a pharmaceutical alternative(s) already approved (via an NDA or ANDA)?

*(**Pharmaceutical alternatives** are drug products that contain the identical therapeutic moiety, or its precursor, but not necessarily in the same amount or dosage form or as the same salt or ester. Each such drug product individually meets either the identical or its own respective compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times and/or dissolution rates. (21 CFR 320.1(d)) Different dosage forms and strengths within a product line by a single manufacturer are thus pharmaceutical alternatives, as are extended-release products when compared with immediate- or standard-release formulations of the same active ingredient.)*

***Note** that for proposed combinations of one or more previously approved drugs, a pharmaceutical alternative must also be a combination of the same drugs.*

YES ☒ NO ☐

*If "**NO**", proceed to question #12.*

(b) Is the pharmaceutical alternative approved for the same indication for which the 505(b)(2) application is seeking approval?

YES ☒ NO ☐

(c) Is the approved pharmaceutical alternative(s) referenced as the listed drug(s)?

YES ☐ NO ☒

*If "**YES**" and there are no additional pharmaceutical alternatives listed, proceed to question #12.*
*If "**NO**" or if there are additional pharmaceutical alternatives that are not referenced by the application, list the NDA pharmaceutical alternative(s); you do not have to individually list all of the products approved as ANDAs, but please note below if approved generics are listed in the Orange Book. Please also contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*

Pharmaceutical alternative(s):
N020489 ANDRODERM (TESTOSTERONE FILM, EXTENDED RELEASE; TRANSDERMAL);
N021015 ANDROGEL (TESTOSTERONE GEL, METERED; TRANSDERMAL);
N021454 TESTIM (TESTOSTERONE GEL; TRANSDERMAL);
N021543 STRIANT (TESTOSTERONE TABLET, EXTENDED RELEASE; BUCCAL), and a generic pellet (implantation);
N022504 AXIRON (TESTOSTERONE SOLUTION, metered transdermal)
N021463 FORTESTA (TESTOSTERONE GEL, metered transdermal)

PATENT CERTIFICATION/STATEMENTS

12) List the patent numbers of all unexpired patents listed in the Orange Book for the listed drug(s) for which our finding of safety and effectiveness is relied upon to support approval of the (b)(2) product.

Listed drug/Patent number(s):

No patents listed ☐ *proceed to question #14*

13) Did the applicant address (with an appropriate certification or statement) all of the unexpired patents listed in the Orange Book for the listed drug(s) relied upon to support approval of the (b)(2) product?

YES ☒ NO ☐

*If "**NO**", list which patents (and which listed drugs) were not addressed by the applicant.*

Listed drug/Patent number(s):

14) Which of the following patent certifications does the application contain? *(Check all that apply and identify the patents to which each type of certification was made, as appropriate.)*

☐ No patent certifications are required (e.g., because application is based solely on published literature that does not cite a specific innovator product)

☐ 21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA. (Paragraph I certification)

☐ 21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired. (Paragraph II certification)

Patent number(s):

☐ 21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire. (Paragraph III certification)

Patent number(s): 6503894 Expiry date(s): August 30, 2020

☐ 21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be

infringed by the manufacture, use, or sale of the drug product for which the application is submitted. (Paragraph IV certification). *If Paragraph IV certification was submitted, proceed to question #15.*

☐ 21 CFR 314.50(i)(3): Statement that applicant has a licensing agreement with the NDA holder/patent owner (must also submit certification under 21 CFR 314.50(i)(1)(i)(A)(4) above). *If the applicant has a licensing agreement with the NDA holder/patent owner, proceed to question #15.*

☐ 21 CFR 314.50(i)(1)(ii): No relevant patents.

☐ 21 CFR 314.50(i)(1)(iii): The patent on the listed drug is a method of use patent and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent as described in the corresponding use code in the Orange Book. Applicant must provide a statement that the method of use patent does not claim any of the proposed indications. (Section viii statement)

Patent number(s):
Method(s) of Use/Code(s):

15) Complete the following checklist ***ONLY*** for applications containing Paragraph IV certification and/or applications in which the applicant and patent holder have a licensing agreement:

(a) Patent number(s):
(b) Did the applicant submit a signed certification stating that the NDA holder and patent owner(s) were notified that this b(2) application was filed [21 CFR 314.52(b)]?

YES ☐ NO ☐

*If "**NO**", please contact the applicant and request the signed certification.*

(c) Did the applicant submit documentation showing that the NDA holder and patent owner(s) received the notification [21 CFR 314.52(e)]? This is generally provided in the form of a registered mail receipt.

YES ☐ NO ☐

*If "**NO**", please contact the applicant and request the documentation.*

(d) What is/are the date(s) on the registered mail receipt(s) (i.e., the date(s) the NDA holder and patent owner(s) received notification):

Date(s):

(e) Has the applicant been sued for patent infringement within 45-days of receipt of the notification listed above?

***Note** that you may need to call the applicant (after 45 days of receipt of the notification) to verify this information **UNLESS** the applicant provided a written statement from the notified patent owner(s) that it consents to an immediate effective date of approval.*

YES ☐ NO ☐ Patent owner(s) consent(s) to an immediate effective date of approval ☐

APPEARS THIS WAY ON ORIGINAL

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

/s/

JEANNIE M ROULE
04/29/2011

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION[1]

NDA # 022309 BLA #	NDA Supplement # BLA STN #	If NDA, Efficacy Supplement Type:
Proprietary Name: Androgel Established/Proper Name: testosterone gel 1.62% Dosage Form: topical gel		Applicant: Abbott Products, Inc Agent for Applicant (if applicable):
RPM: Jeannie Roule		Division: Division of Reproductive and Urologic Products

NDAs:
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)):

Androgel 1% and literature

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

New formulation with a (b) (4), reduced volume of application and (b) (4).

If no listed drug, explain.
- ☒ This application relies on literature.
- ☐ This application relies on a final OTC monograph.
- ☐ Other (explain)

Two months prior to each action, review the information in the 505(b)(2) Assessment and submit the draft 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: April 29, 2011

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 April 29, 2011	☒ AP ☐ TA ☐ CR
• Previous actions *(specify type and date for each action taken)*	☐ None CR letter issued March 12, 2010

[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.

❖ 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 [2]	

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
☐ 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

[2] 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[3]	April 29, 2011
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) CR: March 12, 2010 AP: April 29, 2011
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.	April 29, 2011
• Original applicant-proposed labeling	February 24, 2011
• Example of class labeling, if applicable	N/A

[3] 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.	April 29, 2011
• Original applicant-proposed labeling	February 24, 2011
• Example of class labeling, if applicable	N/A
❖ 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 22, 2011
❖ Proprietary Name • Acceptability/non-acceptability letter(s) *(indicate date(s))* • Review(s) *(indicate date(s))*	N/A
❖ Labeling reviews *(indicate dates of reviews and meetings)*	☐ RPM None ☒ DMEPA 3/12/2010 and 3/2/11 and 4/27/11 ☒ DRISK 11/10/09 and 4/11/11 ☒ DDMAC 10/6/09 and 4/14/11 ☒ CSS 8/19/09 and 4/04/11 ☒ Other reviews SEALD 4/26/11 and 4/28/11
Administrative / Regulatory Documents	
❖ Administrative Reviews *(e.g., RPM Filing Review[4]/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)*	Filing review: 3/10/10 (from last cycle) ☐ Not a (b)(2) 3/29/11 ☐ Not a (b)(2) 4/29/11
❖ 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 N/A If PeRC review not necessary, explain: PREAA does not apply to this product • Pediatric Page/Record *(approvals only, must be reviewed by PERC before finalized)*	☐ Included

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

❖ 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 (except action letters), emails, faxes, telecons)*	2/20/09, 4/22/09, 8/28/09 (2), 12/10/09, 3/23/10, 5/03/10, 6/18/10, 7/12/10, 9/22/10, 11/10/10, 12/16/10
❖ 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 01/22/08
• EOP2 meeting *(indicate date of mtg)*	☐ No mtg 10/18/06
• Other milestone meetings (e.g., EOP2a, CMC pilots) *(indicate dates of mtgs)*	Tcon with Sponsor: 9/25/09 and 10/01/09 and 12/02/09 Post-Action Meeting: 4/29/10
❖ 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 3/11/10 and 4/29/11
Cross-Discipline Team Leader Review *(indicate date for each review)*	☐ None 3/09/10 and 4/28/11
PMR/PMC Development Templates *(indicate total number)*	☐ None One PMR
Clinical Information[5]	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) *(indicate date for each review)*	
• Clinical review(s) *(indicate date for each review)*	11/02/09, 3/08/10, 12/07/10, 4/20/11 and 4/28/11
• 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 April 20, 2011, pages 17-18
❖ 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 8/19/09 and 4/04/11

[5] 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)*	10/18/2010 4/13/11 and 3/09/10 ☐ None 4/11/11
❖ 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 11/04/09 and 04/26/11
Statistical Review(s) *(indicate date for each review)*	☐ None
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 4/08/09, 04/25/11 and 4/28/11
❖ DSI Clinical Pharmacology Inspection Review Summary *(include copies of DSI letters)*	☐ None 11/09/09
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 3/31/09, 8/06/09, 2/01/11 and 4/28/11
❖ 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 Included in P/T review, page
❖ 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 4/09/09, 10/21/09, 1/04/10, 4/20/11 and 4/27/11
❖ Microbiology Reviews ☒ NDAs: Microbiology reviews (sterility & pyrogenicity) (OPS/NDMS) *(indicate date of each review)* ☐ BLAs: Sterility assurance, microbiology, facilities reviews (DMPQ/MAPCB/BMT) *(indicate date of each review)*	☐ Not needed 10/29/09 and 11/18/10
❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer *(indicate date of each review)*	☒ None
❖ 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)*	10/21/09
☐ 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[6])*	Date completed: 12/09/09 ☒ 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)

[6] 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.

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
04/29/2011

MEMORANDUM

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

DATE: April 13, 2011

TO: NDA 22309, Androgel 1.62% with Abbott Products, Inc

THROUGH: Jeannie Roule

SUBJECT: REMS Memorandum written on March 9, 2010

On March 9, 2010, a REMS memorandum was entered into DARRTS and signed by George Benson. This application then received a Complete Response letter on March 12, 2010. The Application was resubmitted on October 29, 2010.

During the initial review cycle, the application was owned by Unimed Pharmaceuticals, LLC. The resubmission noted a change of ownership and the application was transferred to Abbott Products, Inc. All of the necessary paper work was submitted for that change to be acknowledged.

The REMS memorandum written on March 9, 2010, is sufficient for the review cycle with a PDUFA date of April 29, 2011.

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
04/13/2011

MEMORANDUM

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

DATE: March 21-24, 2011

TO: NDA 22309 (Gregg Pratt)

THROUGH: Jeannie Roule

SUBJECT: The Clinical Pharmacology reviewer requested some information from the Applicant.
In addition, the Applicant responded to a DMEPA recommendation previously sent to the Applicant (see memorandum in DARRTS dated March 17, 2011).

APPLICATION NUMBER: NDA 22309 (Androgel 1.62%)

The following questions were sent to the Sponsor.
Please see attached email correspondence.

Roule, Jeannie

From: Roule, Jeannie
Sent: Monday, March 21, 2011 4:02 PM
To: 'Pratt, Gregg'
Subject: Need some more information

Attachments: IR request from Hyunjin March 21 2011.doc

Gregg,

Please see attached and return as soon as possible.

Thanks,
Jeannie

IR request from
Hyunjin March ...

Jeannie Roule
Regulatory Project Manager
Division of 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

Reference is made to your submission for NDA 022309.

We are continuing our review of your proposed labeling for AndroGel (testosterone gel) 1.62% (specifically the Dosage and Administration section). In order to complete our review, we are requesting some additional information. Please complete the table below and return it as soon as possible.

1. Fill out the table 1 with the number of subjects at <u>each adjusted dose</u> at titration days in study S176.3.104

Table 1 Number of subjects at each dose following titration days in two groups (Formerly Placebo vs. Continuing Active Androgel); S176.3.104

	Formerly Placebo				Continuing Active Androgel			
Dose adjustment at the following titration days	Dose 20.25 mg	 40.5 mg	 60.75 mg	 81 mg	Dose 20.25 mg	 40.5 mg	 60.75 mg	 81 mg
Day 14					Total: Was on 20.25 mg Decreased from 40.5:	Total: Was on 40.5 mg: Increased from 20.25 mg: Decreased from 60.75 mg:	Total: Was on 60.75 mg: Increased from 40.5 mg: Decreased from 81 mg:	Total: Was on 60.75 mg Increased from 60.75 mg:
Day 28					Total: Was on 20.25 mg Decreased from 40.5:	Total: Was on 40.5 mg: Increased from 20.25 mg: Decreased from 60.75 mg:	Total: Was on 60.75 mg: Increased from 40.5 mg: Decreased from 81 mg:	Total: Was on 60.75 mg Increased from 60.75 mg:
Day 42					Total: Was on 20.25 mg Decreased from 40.5:	Total: Was on 40.5 mg: Increased from 20.25 mg: Decreased from 60.75 mg:	Total: Was on 60.75 mg: Increased from 40.5 mg: Decreased from 81 mg:	Total: Was on 60.75 mg Increased from 60.75 mg:
Day 182	Total: Was on 20.25 mg Decreased from 40.5:	Total: Was on 40.5 mg: Increased from 20.25 mg: Decreased from 60.75 mg:	Total: Was on 60.75 mg: Increased from 40.5 mg: Decreased from 81 mg:	Total: Was on 60.75 mg Increased from 60.75 mg:	Total: Was on 20.25 mg Decreased from 40.5:	Total: Was on 40.5 mg: Increased from 20.25 mg: Decreased from 60.75 mg:	Total: Was on 60.75 mg: Increased from 40.5 mg: Decreased from 81 mg:	Total: Was on 60.75 mg Increased from 60.75 mg:
Day 196	Total: Was on 20.25 mg Decreased from 40.5:	Total: Was on 40.5 mg: Increased from 20.25 mg: Decreased from 60.75 mg:	Total: Was on 60.75 mg: Increased from 40.5 mg: Decreased from 81 mg:	Total: Was on 60.75 mg Increased from 60.75 mg:	Total: Was on 20.25 mg Decreased from 40.5:	Total: Was on 40.5 mg: Increased from 20.25 mg: Decreased from 60.75 mg:	Total: Was on 60.75 mg: Increased from 40.5 mg: Decreased from 81 mg:	Total: Was on 60.75 mg Increased from 60.75 mg:
Day 210	Total: Was on 20.25 mg Decreased from 40.5:	Total: Was on 40.5 mg: Increased from 20.25 mg: Decreased from 60.75 mg:	Total: Was on 60.75 mg: Increased from 40.5 mg: Decreased from 81 mg:	Total: Was on 60.75 mg Increased from 60.75 mg:	Total: Was on 20.25 mg Decreased from 40.5:	Total: Was on 40.5 mg: Increased from 20.25 mg: Decreased from 60.75 mg:	Total: Was on 60.75 mg: Increased from 40.5 mg: Decreased from 81 mg:	Total: Was on 60.75 mg Increased from 60.75 mg:
Day 224	Total: Was on 20.25 mg Decreased from 40.5:	Total: Was on 40.5 mg: Increased from 20.25 mg: Decreased from 60.75 mg:	Total: Was on 60.75 mg: Increased from 40.5 mg: Decreased from 81 mg:	Total: Was on 60.75 mg Increased from 60.75 mg:	Total: Was on 20.25 mg Decreased from 40.5:	Total: Was on 40.5 mg: Increased from 20.25 mg: Decreased from 60.75 mg:	Total: Was on 60.75 mg: Increased from 40.5 mg: Decreased from 81 mg:	Total: Was on 60.75 mg Increased from 60.75 mg:
Day 266	Total: Was on 20.25 mg Decreased from 40.5:	Total: Was on 40.5 mg: Increased from 20.25 mg: Decreased from 60.75 mg:	Total: Was on 60.75 mg: Increased from 40.5 mg: Decreased from 81 mg:	Total: Was on 60.75 mg Increased from 60.75 mg:	Total: Was on 20.25 mg Decreased from 40.5:	Total: Was on 40.5 mg: Increased from 20.25 mg: Decreased from 60.75 mg:	Total: Was on 60.75 mg: Increased from 40.5 mg: Decreased from 81 mg:	Total: Was on 60.75 mg Increased from 60.75 mg:

2. Provide the menstrual status of female subjects in the following studies: S176.1.003, S176.1.008, S176.1.009, S176.1.011

Roule, Jeannie

From: Pratt, Gregg [gregg.pratt@abbott.com]
Sent: Thursday, March 24, 2011 9:20 AM
To: Roule, Jeannie
Subject: Carton and Container Label Revisions
Attachments: AndroGel_Logo.pdf

Hi Jeannie,

Marketing has developed a new logo (see below). The general directive of DMEPA was to "shrink and move" the swoosh, which we have done. Other changes have been made to make the products visually distinctive, including color scheme, placement of the CIII). Should we present this to DMEPA for a quick read, or should we wait for revised proofs of all carton/container labels (should be later today or tomorrow I hope). Thanks.

Gregg

All,

Based off of feedback from DMEPA, we engaged the ad agency to revisit our logo. We have evaluated several options and have netted on the attached recommendation. We believe we have addressed DMEPA's comments. See below for transition from 1% to 1.62%. The marketing team is aligned. What is the plan to submit to DMEPA?

1% Logo

(b) (4)

Revised Proposed 1.62% Logo

From: Roule, Jeannie [mailto:Jeannie.Roule@fda.hhs.gov]
Sent: Wednesday, March 16, 2011 3:47 PM
To: Pratt, Gregg

Subject: RE: Carton and Container Label Revisions

Gregg,

Below is a response that I have received from DMEPA.

DMEPA's recommendation to delete the white and green "swoosh" graphic located to the left of the proprietary name, AndroGel, was also due to our concern that the graphic increases the similarity between the Androgel 1 % and 1.62 % products. Our goal is to ensure the two strengths are adequately differentiated so as to minimize product selection errors that may occur. Since the AndroGel 1% product is currently marketed with a green "swoosh", the addition of a similar "swoosh" in a similar location on the AndroGel 1.62% product would negate these efforts.

As an alternative, we recommend that the graphic be minimized and relocated away from the proprietary name.

Let me know if you have anymore questions.

Regards,
Jeannie

From: Pratt, Gregg [mailto:gregg.pratt@abbott.com]
Sent: Wednesday, March 09, 2011 7:13 AM
To: Roule, Jeannie
Subject: Carton and Container Label Revisions

Hi Jeannie,

We are working on incorporating the comments. Marketing though is having some difficulty with DMEPA general comment 3:

3. Delete the white and green "swoosh' graphics located to the left of the proprietary name. As currently presented the graphic distracts from the presentation of the proprietary and established name presentation.

The "swoosh" I am told is an integral part of the branding for this product, as well as for the 1% product. The version for 1% is in all of the print media and DTC ads. The comment though says "As currently presented...". Does that mean they would consider presentations? How could we come to an understanding of what they find objectionable so that we could develop an acceptable alternative?

For this issue and the other comments, if we would present revised labels how long would it take for DMEPA and Chemistry to take another look and provide guidance or approval? Thanks, Jeannie.

Best Regards,

Gregg

Gregg A. Pratt, Ph.D.
Director
Global Regulatory Affairs
GPRA

Abbott Products, Inc.
901 Sawyer Road
Marietta, GA 30062
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Tel:+1 770 578 5829
Mobile/Cell: +1 678 559 9726
Fax: +1 770 578 5864
gregg.pratt@abbott.com

AndroGel®
(testosterone gel) 1.62% CIII

AndroGel®
(testosterone gel) 1.62% CIII

Sponsor Response to 18 March 2011 FDA Information Request
NDA 22309
AndroGel (testosterone gel) 1.62%

On 18 March 2011 the Sponsor received an Information Request from the Division relating to the review of NDA 22-309. Below please find the original text in the Agency inquiry in normal font. Sponsor responses are provided in **bold** font.

Agency Inquiry:
We are in the process of reviewing the proposed product labeling for AndroGel (testosterone gel) 1.62%. In order to complete our review, we have the following requests for additional information regarding the specific application sites used in clinical study S176.3.104.

In the Treatments to Be Administered section (7.1) of the S176.3.104 Clinical Study protocol, we note the recommendation (b) (4)

We further note that during visit days, the application scheme was presented as follows:

- (b) (4)

(b) (4)

Sponsor Response:

(b) (4)

If so, clarify whether this included both the front and the back of the upper arm

Sponsor Response:

(b) (4)

[redacted]

If printed instructional documents regarding specific application sites and specific application methods were provided to patients in the S176.3.104 Clinical Study, submit those documents as soon as possible. These documents may be useful in helping us to complete our review of the proposed product labeling.

Sponsor Response:

Please reference the attached Procedural Guidance document that Solvay/Abbott distributed to clinical sites that enrolled subjects into study S176.3.104. The agency will note that the procedural reference instructed the study personnel to go over the proper application technique with study participants. The Procedural Guidance contains specific instructions for gel application Clinic Visits (PK days) and Outpatient Days. Specifically, Panel 1 outlines the application technique for all doses (actuations), including the highest dose (5 g daily, requiring (4) 1.25 g applications) on Clinic Visit days. The instructions for the 5 g dose list four different application sites similar to what is outlined in the protocol. However, the application sites in the Procedural Guidance vary somewhat from the protocol in that the application sites identified are (1) the right and left shoulder and (2) the right and left upper arms limited to the outer portions of the shoulders (i.e. not to include areas at the level of the bicep or lower). Figure 2 in the Procedural Guidance document illustrates the application sites for Clinic Visits, with a text box to supplement the Figure. The Division will recall that the protocol language (quoted earlier) specified that the front and back of the upper arms could be used in addition to the shoulders. The reason the two instructions differ subtly is that the Sponsor wanted to ensure that the venipuncture site remained free of applied testosterone gel. It is understood that the risk of venipuncture site contamination increases as the gel is applied further down the arm. Accordingly, the presentation of the application methods within the Procedural Guidance document biased application away from areas on the bicep and lower in order to minimize the risk of site contamination.

In summary, both the protocol and the Procedural Guidance document instructed site study personnel to go over the proper application technique with study participants. Both of the previously mentioned documents reinforced the importance of maximizing the surface area of the shoulder and upper arms. Also, both documents outlined the right and left shoulders as the application sites that would accommodate the first and second 1.25 g doses (i.e. starting dose of 2.5 g would be limited to the shoulders only per protocol). The protocol and Procedural Guidance document vary slightly in that the Procedural Guidance document biased the application away from sites in close proximity to the antecubital area from

where blood samples would be drawn. The protocol advised that the front and back of the right and left arms could be used to apply the third and fourth doses of 1.25 g testosterone gel 1.62%.

MEMORANDUM

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

DATE: March 16, 2011

TO: NDA 022309 (Gregg Pratt)

THROUGH: Jeannie Roule

SUBJECT: DMEPA response to the Applicant's question about their carton/container

APPLICATION NUMBER: NDA 022309, Adrogel 1.62%

The DMEPA requested that the following response be sent to the Applicant.
Please see attached email correspondences.

Roule, Jeannie

From: Roule, Jeannie
Sent: Wednesday, March 16, 2011 3:47 PM
To: 'Pratt, Gregg'
Subject: RE: Carton and Container Label Revisions

Gregg,

Below is a response that I have received from DMEPA.

DMEPA's recommendation to delete the white and green "swoosh" graphic located to the left of the proprietary name, AndroGel, was also due to our concern that the graphic increases the similarity between the Androgel 1 % and 1.62 % products. Our goal is to ensure the two strengths are adequately differentiated so as to minimize product selection errors that may occur. Since the AndroGel 1% product is currently marketed with a green "swoosh", the addition of a similar "swoosh" in a similar location on the AndroGel 1.62% product would negate these efforts.

As an alternative, we recommend that the graphic be minimized and relocated away from the proprietary name.

Let me know if you have anymore questions.

Regards,
Jeannie

From: Pratt, Gregg [mailto:gregg.pratt@abbott.com]
Sent: Wednesday, March 09, 2011 7:13 AM
To: Roule, Jeannie
Subject: Carton and Container Label Revisions

Hi Jeannie,

We are working on incorporating the comments. Marketing though is having some difficulty with DMEPA general comment 3:

3. Delete the white and green "swoosh' graphics located to the left of the proprietary name. As currently presented the graphic distracts from the presentation of the proprietary and established name presentation.

The "swoosh" I am told is an integral part of the branding for this product, as well as for the 1% product. The version for 1% is in all of the print media and DTC ads. The comment though says "As currently presented...". Does that mean they would consider presentations? How could we come to an understanding of what they find objectionable so that we could develop an acceptable alternative?

For this issue and the other comments, if we would present revised labels how long would it take for DMEPA and Chemistry to take another look and provide guidance or approval? Thanks, Jeannie.

Best Regards,

Gregg

Gregg A. Pratt, Ph.D.
Director
Global Regulatory Affairs
GPRA

Abbott Products, Inc.
901 Sawyer Road
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Tel:+1 770 578 5829
Mobile/Cell: +1 678 559 9726
Fax: +1 770 578 5864
gregg.pratt@abbott.com

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/s/

JEANNIE M ROULE
03/17/2011

MEMORANDUM

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

DATE: March 17, 2011

TO: NDA 022309 (Gregg Pratt)

THROUGH: Jeannie Roule

SUBJECT: Requests for additional information regarding the specific application sites used in clinical study S176.3.104.

APPLICATION NUMBER: NDA 022309, Androgel 1.62%

The DMEPA and Clinical reviewers had the following requests for information from the Applicant.

Please see attached email correspondences.

Request to Sponsor
NDA 22309
AndroGel (testosterone gel) 1.62%

We are in the process of reviewing the proposed product labeling for AndroGel (testosterone gel) 1.62%. In order to complete our review, we have the following requests for additional information regarding the specific application sites used in clinical study S176.3.104.

In the Treatments to Be Administered section (7.1) of the S176.3.104 Clinical Study protocol, we note the recommendation for the outpatient use of study medication was as follows: (b) (4)

(b) (4)

(b) (4)

Clarify whether the first and second bullets above also included the upper arm. If so, clarify whether this included both the front and the back of the upper arm

If printed instructional documents regarding specific application sites and specific application methods were provided to patients in the S176.3.104 Clinical Study, submit those documents as soon as possible. These documents may be useful in helping us to complete our review of the proposed product labeling.

Roule, Jeannie

From: Pratt, Gregg [gregg.pratt@abbott.com]
Sent: Thursday, March 17, 2011 1:37 PM
To: Roule, Jeannie
Subject: RE: Request for Information

Hello Jeannie,

Receipt is confirmed. Thanks.

Gregg

From: Roule, Jeannie [mailto:Jeannie.Roule@fda.hhs.gov]
Sent: Thursday, March 17, 2011 1:29 PM
To: Pratt, Gregg
Subject: Request for Information

Gregg,

Please see attached word document that contains a request for information. A prompt response is greatly appreciated as it will help expedite the review of your label.
Please confirm receipt of this email.

Regards,
Jeannie

Jeannie Roule
Regulatory Project Manager
Division of 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
03/17/2011
IR for labeleling issues

MEMORANDUM

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

DATE: March 7, 2011

TO: Abbott Products (Gregg Pratt)

THROUGH : Jeannie Roule

SUBJECT: Comments from the Division of Medication Errors Prevention and Analysis (DMEPA)

APPLICATION NUMBER: NDA 022309, Androgel 1.62%

DMEPA requested that the following comments be sent to the Applicant.

Roule, Jeannie

From: Roule, Jeannie
Sent: Monday, March 07, 2011 12:40 PM
To: 'Pratt, Gregg'
Subject: DMEPA comments

Attachments: DMEPA comments March 2011.doc

Greg,

Sorry that this took so long. Please confirm receipt and let me know if you have any questions.

Thanks,
Jeannie

DMEPA
ents March 2011.

Jeannie Roule
Regulatory Project Manager
Division of 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

NDA 22309, AndroGel (testosterone gel) 1.62%

The Division of Medication Errors Prevention and Analysis (DMEPA) is reviewing the labeling section of your submission, and have the following comments:

A. General Comments (All Labels and Labeling)

1. As discussed during the teleconference held February 3, 2011, modify the proprietary and established name, descriptor and strength presentation as follows:

AndroGel
(testosterone gel) 1.62 %
20.25 mg of testosterone per pump actuation*
*Each actuation delivers 1.25 g of gel

2. The blue text color over the gray shaded background is difficult to read. Lighten the color hue of the shaded background to increase the contrast with the blue text.

3. Delete the white and green "swoosh' graphics located to the left of the proprietary name. As currently presented the graphic distracts from the presentation of the proprietary and established name presentation.

4. Remove the white-color block highlighting the descriptor, 1.62 %. Instead, use the white-color block to highlight the strength presentation, "20.25 mg of testosterone per pump actuation."

5. We recognize the bottle is unit-of-use for this product, and we are concerned that children may inadvertently access these bottles. We recommend the bottle utilizes a child-resistant closure to prevent accidental exposure.

B. Pump Container Label-Front (Trade/Sample)

1. Delete the dosing table to minimize crowding of the principal display panel.

2. Modify the statement, [redacted] (b) (4), to read, "Usual Dosage: See Package Insert for compete prescribing information. Additionally, delete the statement, [redacted] (b) (4) located above this statement.

3. A placeholder for the lot number, expiration date and barcode are not indicated on the labels, include the lot number, expiration date and barcode on the labels.

4. Modify the statement, "Multi-dose pump capable of....1.25 g doses" to read, "Multi-dose pump capable of dispensing 60 metered pump actuations." In addition, relocate this statement to the bottom portion of the principal display panel.

5. The physician sample packaging configuration is not intended for commercial sale; therefore it should not be associated with an NDC number. Delete the NDC number located on the principal display panel.

6. Minimize the prominence of the "RX Only" statement.

C. Pump Container Label-Back (Trade/Sample)
1. Relocate the statement, "For Topical Use Only" to the front container label below the strength presentation.

D. Pump Carton Labeling (Trade/Sample)
1. See comment B.2, B.4, B.5, and C above.

2. Delete the (b) (4) on the side panel. In addition, delete the statement, (b) (4) (b) (4)

3. Modify the statement, (b) (4)" to read, "Multi-dose pump capable of dispensing 60 metered pump actuations"

4. Minimize the graphic of the bottle with affixed container label to allow for prominent displaying of the proprietary and established name, descriptor and strength presentation. Additionally, the graphic should reflect the final approved container label.

5. Remove the space indicated for the prescription label. As currently presented, instructions to label the carton labeling in addition to the pump are present, however DMEPA believes this statement will encourage pharmacist to label only the carton and not the pump, as often times only one prescription label is printed for each drug dispensed.

Roule, Jeannie

From: Pratt, Gregg [gregg.pratt@abbott.com]
Sent: Monday, March 07, 2011 1:06 PM
To: Roule, Jeannie
Subject: RE: DMEPA comments

Got 'em, Jeannie - thanks.

How is the label coming? (b) (4)

Best Regards,

Gregg

From: Roule, Jeannie [mailto:Jeannie.Roule@fda.hhs.gov]
Sent: Monday, March 07, 2011 12:40 PM
To: Pratt, Gregg
Subject: DMEPA comments

Greg,

Sorry that this took so long. Please confirm receipt and let me know if you have any questions.

Thanks,
Jeannie

Jeannie Roule
Regulatory Project Manager
Division of 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
03/07/2011

MEMORANDUM

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

DATE: February 15, 2011

TO: NDA 022309

THROUGH : Jeannie Roule

SUBJECT: CMC comments for the carton/container

APPLICATION NUMBER: NDA 022309, Adrogel 1.62%

The CMC reviewer equested that the following comments be sent to the Applicant.

Roule, Jeannie

From: Roule, Jeannie
Sent: Tuesday, February 15, 2011 1:33 PM
To: 'Pratt, Gregg'
Subject: Carton and container

Attachments: Carton container comments Feb 15 2011.doc

Gregg,

Attached is a word doc containing **some** of the comments concerning your carton and container. DMEPA hopes to have theirs ready for you on Friday or early next week.
Do not start to print any cartons yet as there might be additional comments (we do not need anything formally submitted either).

I will need you to confirm receipt of this email.

Regards,
Jeannie

Carton container comments Feb ...

Jeannie Roule
Regulatory Project Manager
Division of 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

NDA 22309, AndroGel (testosterone gel) 1.62%

While the Division of Medication Errors Prevention and Assessment (DMEPA) is reviewing the immediate container/carton label section of your submission, we have the following comments from the Office of New Drug Quality Assessment (ONDA).

The following ONDQA comments apply to the carton and immediate container labels. Revise all occurrences on the labels.

1. Remove [redacted] (b) (4) ' shown below the drug product name.

2. Substitute [redacted] (b) (4) with 'Multi-dose pump capable of dispensing 60 metered pump actuations'

3. As discussed during the teleconference on February 3, 2011, add the multi-dose pump statement below the drug product name.

   AndroGel
   (testosterone gel) 1.62%

   20.25 mg of testosterone per pump actuation*

   *Each actuation delivers 1.25 g of gel

4. Remove [redacted] (b) (4) " adjacent to ethyl alcohol.

The following ONDQA comments apply to the immediate container labels only.

1. Print expiration date per 21 CFR 201.17 and lot number per 21 CFR 201.18

2. Print bar code on immediate container label per 21 CFR 201.25

Please note that additional labeling comments from DMEPA will follow soon.

Roule, Jeannie

From: Pratt, Gregg [gregg.pratt@abbott.com]
Sent: Tuesday, February 15, 2011 1:41 PM
To: Roule, Jeannie
Subject: RE: Carton and container

Thanks, Jeannie. It is understood that these are only part of the comments. I will only forward to labeling so that others outside Regulatory will not be tempted to get ahead of themselves.

Best,

Gregg

From: Roule, Jeannie [mailto:Jeannie.Roule@fda.hhs.gov]
Sent: Tuesday, February 15, 2011 1:33 PM
To: Pratt, Gregg
Subject: Carton and container

Gregg,

Attached is a word doc containing **some** of the comments concerning your carton and container. DMEPA hopes to have theirs ready for you on Friday or early next week.
Do not start to print any cartons yet as there might be additional comments (we do not need anything formally submitted either).

I will need you to confirm receipt of this email.

Regards,
Jeannie

Jeannie Roule
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/s/

JEANNIE M ROULE
02/16/2011

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 022309 **INFORMATION REQUEST**

Abbott Products, Inc.
Attention: Gregg Pratt, Ph.D.
Director, Global Regulatory Affairs Liaison
901 Sawyer Road
Marietta, GA 30062

Dear Dr. Pratt:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for AndroGel®(testosterone gel)1.62 %.

We are reviewing the clinical section of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

1. Table 1 in the proposed draft labeling indicates that the primary method of administration (b) (4) (b) (4)

2. Seven subjects in the relative bioavailability study S176.1.010 (all in the rotating regimen) exhibited at least one testosterone level greater than 2500 ng/dL. This is a review issue.

3. There may be a few more patients in the arms/shoulders transfer study S176.1011 compared to the 4-site transfer study S176.1.009 in whom the T concentrations increased very modestly from baseline despite a T-shirt. This is a review issue. Please provide a comparative analysis of data from these two transfer studies, including your impression of whether the 4-site T-shirt method is more preventative of secondary exposure compared to the arms/shoulders T-shirt method.

4. Based on the efficacy results from study S176.3.104, (b) (4) (b) (4) has been requested. This is a review issue.

5. The complete study report for study S176.3.104 does not highlight changes made to the previous report. If not already provided, please submit a version that highlights the changes from the previous report.

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

Sincerely,

{See appended electronic signature page}

Jennifer Mercier
Chief, Project Management Staff
Division of Reproductive and Urologic Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

JENNIFER L MERCIER
12/16/2010

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADM NISTRATION

REQUEST FOR CONSULTATION

TO *(Division/Office)*:
Mail: OSE-DRISK and DMEPA

FROM: Jeannie Roule, Project Manager, Division of Reproductive and Urologic Products (DRUP)
301-796-3993

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
11/16/10		022309	NDA	10/29/10 (in edr)

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
AndroGel 1.62% Topical Gel	Priority (6 month clock)	Androgen	03/29/11

NAME OF FIRM: Abbott Products

REASON FOR REQUEST

I. GENERAL

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

II. BIOMETRICS

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

III. BIOPHARMACEUTICS

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

IV. DRUG EXPERIENCE

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

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS: Please review the Label, REMS, Medguide and any other pertinent documents. This is an electronic submission. You can view the labeling by going to http://edr.fda.gov, entering the NDA 22-309 and launching global submit.

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

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/s/

JEANNIE M ROULE
11/16/2010

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADM NISTRATION

REQUEST FOR DDMAC LABELING REVIEW CONSULTATION

Please send immediately following the Filing/Planning meeting

TO:

CDER-DDMAC-RPM

FROM: (Name/Title, Office/Division/Phone number of requestor)

Jeannie Roule, Project Manager, Division of Reproductive and Urologic

Drug Products, HFD-580 301-796-3993

REQUEST DATE	IND NO.	NDA/BLA NO.	TYPE OF DOCUMENTS (PLEASE CHECK OFF BELOW)
11/16/10		022309	EDR

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE (Generally 1 week before the wrap-up meeting)
AndgroGel 1.62% Testosterone gel	Priority (6 month clock)	Androgen	03/09/11

NAME OF FIRM:
Abbot Products

PDUFA Date: April 29, 2011

TYPE OF LABEL TO REVIEW

TYPE OF LABELING:
(Check all that apply)
- ✓ PACKAGE INSERT (PI)
- ☐ PATIENT PACKAGE INSERT (PPI)
- ✓CARTON/CONTAINER LABELING
- ✓MEDICATION GUIDE
- ☐ INSTRUCTIONS FOR USE(IFU)

TYPE OF APPLICATION/SUBMISSION
- ☐ ORIGINAL NDA/BLA
- ☐ IND
- ☐ EFFICACY SUPPLEMENT
- ☐ SAFETY SUPPLEMENT
- ☐ LABELING SUPPLEMENT
- ☐ PLR CONVERSION

REASON FOR LABELING CONSULT
- ✓INITIAL PROPOSED LABELING
- ☐ LABELING REVISION

EDR link to submission:

his is an electronic submission. You can view the labeling by going to http://edr.fda.gov, entering the NDA 22-309 and either launching global submit or viewing the labeling directly in EDR.

Once you have received a substantially completed label please review the PI

Please Note: There is no need to send labeling at this time. DDMAC reviews substantially complete labeling, which has already been marked up by the CDER Review Team. The DDMAC reviewer will contact you at a later date to obtain the substantially complete labeling for review.

COMMENTS/SPECIAL INSTRUCTIONS:
Mid-Cycle Meeting: [Insert Date] January 20, 2011
Labeling Meetings: [Insert Dates] March 14 and 17, 2011
Wrap-Up Meeting: [Insert Date] March 16, 2011

SIGNATURE OF REQUESTER Jeannie Roule

SIGNATURE OF RECEIVER	METHOD OF DELIVERY (Check one) ☐ eMAIL ☐ HAND

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/s/

JEANNIE M ROULE
11/16/2010

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

REQUEST FOR CONSULTATION

TO *(Office/Division)*: Controlled Substance Staff
Corinne Moody

FROM (*Name, Office/Division, and Phone Number of Requestor)*:
Jeannie Roule, Regulatory Project Manager
Division of Reproductive and Urologic Products
(301) 796-3993

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
11/16/10		22-309	Electronic	10/29/10 in edr

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
AndroGel 1.62%	Priority PDUFA is 4/29/11	Androgen	2/10/11

NAME OF FIRM: Abbott Products

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE / ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE-NDA MEETING
- ☐ END-OF-PHASE 2a MEETING
- ☐ END-OF-PHASE 2 MEETING
- ☐ RESUBMISSION
- ☐ SAFETY / EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☐ OTHER *(SPECIFY BELOW)*:

II. BIOMETRICS

- ☐ PRIORITY P NDA REVIEW
- ☐ END-OF-PHASE 2 MEETING
- ☐ CONTROLLED STUDIES
- ☐ PROTOCOL REVIEW
- ☐ OTHER (SPECIFY BELOW):
- ☐ CHEMISTRY REVIEW
- ☐ PHARMACOLOGY
- ☐ BIOPHARMACEUTICS
- ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE 4 STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL - BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG SAFETY

- ☐ PHASE 4 SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE, e.g., POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ NONCLINICAL

COMMENTS / SPECIAL INSTRUCTIONS: All of the documents for this NDA are available via edr. AndroGel 1.0% was approved in 2000. This NDA is for AndroGel 1.62% which is considered a Class III controlled substance. Your input and comments are greatly appreciated

SIGNATURE OF REQUESTOR
Jeannie Roule

METHOD OF DELIVERY (Check one)
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PRINTED NAME AND SIGNATURE OF RECEIVER

PRINTED NAME AND SIGNATURE OF DELIVERER

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JEANNIE M ROULE
11/16/2010

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADM NISTRATION

REQUEST FOR DDMAC LABELING REVIEW CONSULTATION

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TO:

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FROM: (Name/Title, Office/Division/Phone number of requestor)

Jeannie Roule, Project Manager, Division of Reproductive and Urologic

Drug Products, HFD-580 301-796-3993

REQUEST DATE	IND NO.	NDA/BLA NO.	TYPE OF DOCUMENTS (PLEASE CHECK OFF BELOW)
11/16/10		022309	EDR

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
AndgroGel 1.62% Testosterone gel	Priority (6 month clock)	Androgen	(Generally 1 week before the wrap-up meeting) 03/09/11

NAME OF FIRM:
Abbot Products

PDUFA Date: April 29, 2011

TYPE OF LABEL TO REVIEW

TYPE OF LABELING:
(Check all that apply)
- ✓ PACKAGE INSERT (PI)
- ☐ PATIENT PACKAGE INSERT (PPI)
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TYPE OF APPLICATION/SUBMISSION
- ☐ ORIGINAL NDA/BLA
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- ☐ SAFETY SUPPLEMENT
- ☐ LABELING SUPPLEMENT
- ☐ PLR CONVERSION

REASON FOR LABELING CONSULT
- ✓INITIAL PROPOSED LABELING
- ☐ LABELING REVISION

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COMMENTS/SPECIAL INSTRUCTIONS:
Mid-Cycle Meeting: [Insert Date] January 20, 2011
Labeling Meetings: [Insert Dates] March 14 and 17, 2011
Wrap-Up Meeting: [Insert Date] March 16, 2011

SIGNATURE OF REQUESTER Jeannie Roule

SIGNATURE OF RECEIVER	METHOD OF DELIVERY (Check one) ☐ eMAIL ☐ HAND

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/s/

JEANNIE M ROULE
11/16/2010

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 022309

ACKNOWLEDGE – CLASS 2 RESPONSE

Abbott Products, Inc.
Attention: Gregg Pratt, Ph.D.
Director, Global Regulatory Affairs Liaison
901 Sawyer Road
Marietta, GA 30062

Dear Dr. Pratt:

We acknowledge receipt on October 29, 2010, of your October 25, 2010, resubmission of your new drug application submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for AndroGel®(testosterone gel)1.62 %.

We consider this a complete, class 2 response to our March 12, 2010, action letter. Therefore, the user fee goal date is April 29, 2011.

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 Reproductive and Urologic Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

JEANNIE M ROULE
11/10/2010

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 021015
NDA 022309

ACKNOWLEDGE TRANSFER NDA OWNERSHIP

Abbott Products, Inc.
Attention: Gregg Pratt, Ph.D.
Director, Global Regulatory Affairs Liaison
901 Sawyer Road
Marietta, GA 30062

Dear Dr. Pratt:

We acknowledge receipt of your correspondences notifying the Food and Drug Administration of the change of ownership of the following new drug applications (NDA):

NDA Number	Drug Name	Letter Date	Receipt Date
021015	AndroGel® (testosterone gel) 1%	August 16, 2010	August 17, 2010
022309	AndroGel® (testosterone gel)1.62 %	August 16, 2010	August 16, 2010

Name of New Applicant: Abbott Products, Inc

Name of Previous Applicant: Unimed Pharmaceuticals, LLC (formally Unimed Pharmacueticals, Inc.) and Solvay Pharmaceuticals, Inc.

Your correspondences provided the information necessary to effect this change, and we have revised our records to indicate Abbott Products, Inc. as the applicant of record for these applications.

All changes in the NDA(s) from those described by the original owner, such as manufacturing facilities and controls, must be reported to us prior to implementation except that changes in the drug product's label or labeling to change the product's brand or the name of its manufacturer, packer, or distributor may be reported in the next annual report. Refer to the *Guidance for Industry: Changes to an Approved NDA or ANDA* for information on reporting requirements. We request that you notify your suppliers and contractors who have DMFs referenced by your applications of the change in ownership so that they can submit a new letter of authorization (LOA) to their Drug Master File(s).

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81. In addition, you are responsible for any correspondence outstanding as of the effective date of the transfer.

Please cite the NDA numbers listed above at the top of the first page of all submissions to these applications. 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

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 Reproductive and Urologic Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

cc: Unimed Pharmaceuticals, LLC
901 Sawyer Road
Marietta, GA 30062

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/s/

JEANNIE M ROULE
09/22/2010

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 022309

GENERAL ADVICE

Abbott Products, Inc.
Attention: Gregg A. Pratt, Ph.D.
Director, Global Regulatory Affairs
901 Sawyer Road
Marietta, GA 30062

Dear Dr. Pratt:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for AndroGel® (testosterone gel) 1.62%.

We also refer to your May 27, 2010, submission, containing (1) your proposed approach to approval for AndroGel 1.62%, and (2) a rationale for the success criteria and sample size in the ongoing S176.1.010 comparative bioavailability study.

We further refer to the General Advice Letter that you received from the Division on June 18, 2010, and your follow-up questions that we received from you on June 21, 2010.

We have completed our review of your questions and have the following responses:

1. **Is the indication that the S176.1.011 transfer study could be the primary pathway for approval based on a high-level evaluation of the headline results of this study that we provided?**

   We indicated that the S176.1.011 transfer study could serve as the primary pathway to approval based upon the proposition that a method of application exists (arms/shoulders only) which fulfills the efficacy requirement and also might allow for use of a t-shirt barrier to prevent transfer. Our comment was not based on a review of the headline results.

2. **Does the Agency agree that the study data demonstrate prevention of transfer?**

   No. Whether the study data demonstrate prevention of transfer is a review issue.

3. **The Agency indicates that they do not agree with the proposed success criteria for the S176.1.010 BA study. However, we cannot tell from the response what might be objectionable. Is it the proposed % difference and/or statistical power that the Agency objects to, or is it that we have placed a greater emphasis on Cavg over Cmax?**

Rather than agreeing to any "success criteria", we prefer to review the entirety of the data from S176.1.010 upon submission of the study report in the Complete Response (CR). The focus of our review will be the ratio of the geometric mean AUC and Cmax for the two treatment regimens, and the 90% confidence intervals for that ratio. Our major concern regarding your specific success criteria is that the proposed % difference allows for a substantive difference between the two treatment regimens for mean exposure (AUC and Cmax), which could result in very high, potentially unsafe, upper confidence limits.

4. **Further relating to Response 2, in the event that the Agency agrees that the S176.1.011 study demonstrates prevention of transfer, does the S176.1.010 BA study become more of a safety study (as is suggested in the last part of Response 2)? If so, does it need to be part of the CR, or could it be submitted post-approval?**

   Whether the Agency agrees that S176.1.011 demonstrates potential for transfer is a review issue. We consider it a reasonable approach for you to provide the report for study S176.1.011 in the CR as the primary pathway for approval, and the report for study S176.1.010 in the CR as a pathway forward in the event that S176.1.011, after our review, is believed to demonstrate transfer.

   If you decide to respond to the CR using S176.1.011 as the only pathway forward, then you must still submit safety results from S176.1.010 as part of the CR. The safety results from S176.1.010 should include adverse events, skin irritation results (if any), and all serum testosterone levels above the upper limit of normal.

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

Sincerely,

{See appended electronic signature page}

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

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22309	GI-1	UNIMED PHARMACEUTICALS INC	ANDROGEL

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/s/

GEORGE S BENSON
07/12/2010

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 022309 **INFORMATION REQUEST**

Abbott Products, Inc.
Attention: Gregg A. Pratt, Ph.D.
Director, Global Regulatory Affairs
901 Sawyer Road
Marietta, GA 30062

Dear Dr. Pratt:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for AndroGel® (testosterone gel) 1.62%.

We also refer to your May 27, 2010, submission, containing (1) your proposed approach to approval for AndroGel 1.62%, and (2) a rationale for the success criteria and sample size in the ongoing S176.1.010 comparative bioavailability study.

We have completed our review of your submission and have the following comments:

1. You conclude that the S176.1.011 transfer study could constitute a complete response (CR) to the March 12, 2010, NDA action. We agree. Nonetheless, you are currently conducting the S176.1.010 comparative bioavailability study, and plan to submit it as part of the CR. It appears that your submission strategy is to provide the S176.1.011 transfer study as the primary pathway to approval, and the S176.1.010 comparative bioavailability study as a pathway forward in the event that the S176.1.011 study, after our review, is believed to demonstrate transfer. If this is your submission strategy, we consider it to be a reasonable approach.

2. The protocol for the S176.1.010 comparative bioavailability study is considered reasonable. However, we do not concur with the proposed success criteria. Upon submission of the results from this study, the comparative bioavailability of the two methods of drug application will be reviewed with emphasis on those patients showing excessively high T concentrations.

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

Sincerely,

{See appended electronic signature page}

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

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22309	GI-1	UNIMED PHARMACEUTICALS INC	ANDROGEL

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/s/

GEORGE S BENSON
06/18/2010

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 022309

MEETING MINUTES

Abbott Products, Inc.
Attention: Kathryn Penhale-Unz
Director, Regulatory Affairs
901 Sawyer Road
Marietta, GA 30062

Dear Ms. Penhale-Unz:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for AndroGel® (testosterone gel) 1.62%.

We also refer to the teleconference between representatives of your firm and the FDA on April 29, 2010. The purpose of the meeting was to discuss the information that was conveyed to you in the Complete Response letter that you received from the Division on March 12, 2010, and to discuss your path forward.

A copy of the official minutes of the teleconference 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 Health Project Manager at (301-796-3993).

Sincerely,

{See appended electronic signature page}

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

Enclosure

MEMORANDUM OF MEETING MINUTES

Meeting Type:	**Type A**
Meeting Category:	**Post-Action**
Meeting Date and Time:	**April 29, 2010 @ 11:00 a.m.-12:00 p.m.**
Meeting Location:	**White Oak Conference Room 5313**
Application Number:	**NDA 022309**
Product Name:	**AndroGel® (testosterone gel) 1.62%**
Indication:	**Testosterone replacement therapy**
Applicant Name:	**Abbott Products, Inc.**
Meeting Chair:	**Mark Hirsch, M.D.**
Meeting Recorder:	**Jeannie Roule**

FDA ATTENDEES

George Benson, M.D.	Deputy Director, Division of Reproductive and Urologic Products (DRUP)
Mark Hirsch, M.D.	Medical Team Leader, DRUP
Roger Wiederhorn, M.D.	Medical Officer, 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
Sandhya Apparaju, Ph.D.	Clinical Pharmacology Reviewer, OCP, OTS, DCP III
Sonia Castillo, Ph.D.	Statistical Reviewer, OTS, Office of Biometrics (OB), Division of Biometrics (DB) III
Jennifer Mercier	Chief, Project Management Staff, DRUP
Jeannie Roule	Regulatory Health Project Manager, DRUP

APPLICANT ATTENDEES

Mike Miller, PharmD	Director, Men's Health Clinical Development
Troy ZumBrunnen, PharmD	Director, Clinical Pharmacology
Jim Hannasch, MD	Associate Director, Global Pharmacovigilance and Risk Management
Cecelia McWhirter	Sr. Project Statistician
Steven Wojtanowski, MPH	Vice President, Global Regulatory Affairs
Greg Pratt, PhD	Director, Global Regulatory Affairs
Kathryn Penhale-Unz	Director, Global Regulatory Affairs
Janet Benesh	Vice President, Project Leadership
H. Peter Bacher	Global Pharma Research/Development - Abbott

BACKGROUND

A Complete Response (CR) letter was issued for NDA 022309 (AndroGel 1.62%) on March 12, 2010. On March 16, 2010, the Applicant requested a Type A, Post-Action meeting. The purpose of this meeting is to discuss the content of the Complete Response letter with special attention to the additional study requested by the Division. An additional meeting objective is to agree upon the content and format of a Complete Response.

DISCUSSION

Preliminary responses were provided to the Applicant on April 27, 2010, in response to the questions posed in the Applicant's meeting package provided to the Division on March 16, 2010. The Applicant'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.*

1. Comparative Bioavailability study (Protocol Study S176.1.010):

a. Solvay will provide a descriptive characterization of the pharmacokinetic parameters of AUC and Cmax for total observed testosterone at steady-state for the two dosing regimens as outlined in the Agency's complete response letter. Solvay proposes to summarize the key parameters by providing the ratios of test (application to 4 anatomic sites) to reference (application rotating between abdomen and upper arms/shoulders) with the associated 90% confidence intervals. Is this acceptable to the Agency?

Response: Yes. In addition, we request that treatment mean ratios for PK parameters and associated 90 % confidence intervals be presented for both baseline-corrected and uncorrected total testosterone. We also recommend that you obtain a separate baseline for each of the treatment periods.

Additional Discussion: The Applicant agreed to present the treatment mean ratios of PK parameters and associated 90 % CI for both baseline-corrected and uncorrected total testosterone. The Applicant also agreed to obtain a separate 24-hour baseline for each of the treatment periods.

b. (b) (4)

(b) (4)

Response: (b) (4)

. An acceptable difference between regimens and an appropriate sample size for S176.1.010 requires further discussion. In determining a final sample size, the number of subjects should reflect study *completers*.

Additional Discussion: The Division stated that concurrence is still being sought within the FDA with regard to what is an acceptable proposed difference between application regimens.

(b) (4)

.

The Division requested that the Applicant submit a focused proposal, including rationale for sample size, for a relative biovailability study where the differences in Cmax and AUC between test method and reference method was less than 50%.

c. We plan to assess skin irritation using the same scale as utilized in the pivotal study S176.3.104. Skin irritation will be assessed for the duration of the study only (approximately 21 days, consisting of seven days of gel application, a one week washout, and another seven days of gel application in a crossover fashion). Does the Agency agree this will be sufficient evaluation and assessment?

Response: Yes.

Additional Discussion: The Applicant stated that they have no further questions or comments regarding this question or response.

d. The pivotal Phase III Study S176.3.104 dosing instructions stated the following, *"Over any 7 day period, study gel can be rotated between the upper arms/shoulders or abdomen (e.g. 4 days upper arms/shoulders; 3 days abdomen) so long as the correct application occurs during pharmacokinetic visits."* Therefore, for the rotation treatment arm of the proposed comparative bioavailability study (Study S176.1.010), we intend to apply 5.0 g Testosterone Gel 1.62% to the abdomen for 3 days, followed by application to the upper arms/shoulders for 4 days. Application would be once daily in the morning for a total of 7 days. Pharmacokinetic sampling will occur on day 7 of the treatment period when gel is applied to the upper arms/shoulders. Does the Agency agree this dosing method is representative of how gel was applied in the previous Phase 3 study and is a suitable rotation schedule for evaluation in Study S176.1.010?

Response: Yes.

Additional Discussion: The Applicant stated that they have no further questions or comments regarding this question or response.

2. Regarding format for the Amendment to the NDA:

a. Study S176.3.104 was designed to include a 6-month double blind period, followed by a 6-month open-label period. Complete safety data from the open-label portion was submitted as part of the 120-Day Safety Update to the NDA. It is not our intention to integrate these data into the eCTD as part of the complete response. We will submit the complete study report for this open-label portion of the phase III study to the NDA as a sNDA post-approval. Does the Agency agree with this approach? If the Agency agrees with this approach, additional tabulations, and tables, including comparing frequencies of adverse events as described under numbers 2, 3, and 5 under the section SAFETY UPDATE, will not be provided. Is the Agency in agreement with this approach as the safety experience to date with the compound remains unchanged?

Response: No. We do not agree with this approach. We request that a final report for Study S176.3.104 (including the open-label period) be submitted in the Complete Response. A final study report would suffice for safety reporting for this study.

Additional Discussion: The Applicant agreed to submit the final study report for Study S176.3.104 in the CR. The Applicant inquired if efficacy data from PK assessments on Days 266 and 364 could be included in the label. The Division agreed, as long as those data were supportive.

b. We anticipate Study S176.1.010 having a sample size of 36 hypogonadal male subjects. The ISS already contains N = 147 hypogonadal subjects enrolled in previous Phase I studies exposed to AndroGel 1.62%, along with N = 234 hypogonadal subjects exposed to AndroGel 1.62% in the Phase III study. We propose that no update of the ISS is necessary as the small number of subjects would not significantly impact the conclusions of the original ISS in the NDA. Does the Agency agree?

Response: Yes. However, we request that a final report for Study S.176.3.104 be submitted in the Complete Response.

Additional Discussion: The Applicant agreed to submit the final study report for Study S176.3.104 in the CR.

c. Solvay intends to address point #7 from the complete response letter under the section SAFETY UPDATE by submitting the Periodic Safety Update Report covering the worldwide experience with testosterone gel (1.0%) to the NDA. This information will not be incorporated into the NDA (eCTD format)

application per se, but will be submitted to the NDA via normal submission standards. Does the Agency agree?

Response: No. The PSUR covering the worldwide experience on the safety of AndroGel 1% should be included in the Complete Response. If AndroGel 1.62% is marketed outside the U.S., then the worldwide experience for that product should also be included in the Complete Response.

Additional Discussion: The Applicant stated that they will include all of this information in the CR and confirmed that Androgel 1.62% is currently not marketed anywhere inside or outside of the United States.

3. Additional Questions not associated with the Complete Response Letter:

a. Solvay intends to perform two studies; One, the Comparative Bioavailability study (S176.1.010) as discussed above and; Two, Study S176.1.011 (please see attached study synopsis) Transfer Study in separate phase I studies. This next transfer study will evaluate the transfer potential for the gel when healthy males apply 2.5 grams to each upper arm/shoulder area (total dose 5 grams) and the cover with a t-shirt. At two hours postdose, 15 minutes of supervised skin contact will occur with a non-dosed female. Assuming no transfer of testosterone is observed in this study; would FDA accept this final study report in the NDA as a complete response to the deficiency listed in the Complete Response Letter dated 12 March 2010?

Response: Yes.

Additional Discussion: The Applicant inquired if it were acceptable to submit the report for Study S176.1.011at 2 – 3 months following submission of the Complete Response. The Division stated that this was a problematic submission strategy for good review management. The Division stated that the Applicant's response to the Division's CR letter should be complete upon submission. It was not acceptable to plan submission of a critical study report for 2- 3 months after the response was submitted.

The Division noted that there appeared to be two different pathways that the Applicant was proposing to resolve the CR deficiency: i. e. resolving the CR with the results from either Study S176.1.010 or Study S176.1.011. The Division recommended that the Applicant decide which pathway to take prior to submission of the CR. The Division further recommended that the Applicant should submit an explanation as to how they are going to pursue resolution of the CR (i.e., using results from Study S176.1.010, from Study S176.1.011, or from both studies). The Division agreed to review the submission promptly, and to convey a response via regulatory letter within one month of receiving that submission.

b. If this is acceptable to the Agency (assuming positive outcome) the data from this study which would include healthy female subjects would not be included in the ISS, inline with the way safety information from previous transfer studies were managed within the application.

Response: This is acceptable.

Additional Discussion: The Applicant stated that they have no further questions or comments regarding this question or response.

ISSUES REQUIRING FURTHER DISCUSSION
None

ACTION ITEMS
The Division will provide meeting minutes to the Applicant within 30 days of the date of the meeting.

ATTACHMENTS AND HANDOUTS
None

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22309	GI-1	UNIMED PHARMACEUTICALS INC	ANDROGEL

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/s/

MARK S HIRSCH
05/27/2010

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 021015
NDA 022309

ACKNOWLEDGE TRANSFER NDA OWNERSHIP

Abbott Products, Inc.
Attention: Kathryn Penhale-Unz
Director, Regulatory Affairs
901 Sawyer Road
Marietta, GA 30062

Dear Ms. Penhale-Unz:

We acknowledge receipt of your correspondences notifying the Food and Drug Administration of the change of ownership of the following new drug applications (NDA):

NDA Number	Drug Name	Letter Date	Receipt Date
021015	AndroGel® (testosterone gel) 1%	March 30, 2010	March 31, 2010
022309	AndroGel® (testosterone gel)1.62 %	March 31, 2010	March 31, 2010

Name of New Applicant: Abbott Products, Inc

Name of Previous Applicant: Unimed Pharmaceuticals, LLC (formally Unimed Pharmacueticals, Inc.) and Solvay Pharmaceuticals, Inc.

Your correspondences provided the information necessary to effect this change, and we have revised our records to indicate Abbott Products, Inc. as the applicant of record for these applications.

All changes in the NDA(s) from those described by the original owner, such as manufacturing facilities and controls, must be reported to us prior to implementation except that changes in the drug product's label or labeling to change the product's brand or the name of its manufacturer, packer, or distributor may be reported in the next annual report. Refer to the *Guidance for Industry: Changes to an Approved NDA or ANDA* for information on reporting requirements. We request that you notify your suppliers and contractors who have DMFs referenced by your applications of the change in ownership so that they can submit a new letter of authorization (LOA) to their Drug Master File(s).

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81. In addition, you are responsible for any correspondence outstanding as of the effective date of the transfer.

Please cite the NDA numbers listed above at the top of the first page of all submissions to these applications. 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

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

Sincerely,

{See appended electronic signature page}
Jennifer Mercier
Chief, Project Management Staff
Division of Reproductive and Urologic Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

cc: Unimed Pharmaceuticals, LLC
901 Sawyer Road
Marietta, GA 30062

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22309	GI-1	UNIMED PHARMACEUTICALS INC	ANDROGEL
NDA-21015	GI-1	UNIMED PHARMACEUTICALS INC	ANDROGEL(TESTOSTERONE GEL) 25MG/50MG

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/s/

JENNIFER L MERCIER
05/03/2010

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 022309 **MEETING REQUEST GRANTED**

Unimed Pharmaceuticals, LLC
Attention: Kathryn Penhale-Unz
Director, Regulatory Affairs
901 Sawyer Road
Marietta, GA 30062

Dear Ms. Penhale-Unz:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for AndroGel® (testosterone gel) 1.62%.

We also refer to your March 17, 2010, correspondence requesting a post-action meeting to discuss the information that was conveyed to you in the Complete Response letter that you received from the Division on March 12, 2010. Based on the statement of purpose, objectives, and proposed agenda, we consider the meeting a type A meeting.

The teleconference is scheduled as follows:

Date: April 29, 2010
Time: 11:00 a.m. -12:00 p.m.
Phone Arrangements: Unimed Pharmaceuticals will call the Division at: (b) (4)

The following participants are invited to the meeting:

George Benson, M.D.	Deputy Director, Division of Reproductive and Urologic Products (DRUP)
Mark Hirsch, M.D.	Medical Team Leader, DRUP
Roger Wiederhorn, M.D.	Medical Officer, 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
Sandyha Apparaju, Ph.D.	Clinical Pharmacology Reviewer, OCP, OTS, DCP III
Jennifer Mercier	Chief, Project Management Staff, DRUP
Jeannie Roule	Regulatory Health Project Manager, DRUP

You had previously provided background information, dated March 17, 2010. As per your request, we will be using that same briefing package for your meeting with our Division.

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

Sincerely,

{See appended electronic signature page}

Jennifer Mercier
Chief, Project Management Staff
Division of Reproductive and Urologic Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22309	GI-1	UNIMED PHARMACEUTICALS INC	ANDROGEL

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/s/

JENNIFER L MERCIER
03/23/2010

NDA/BLA REGULATORY FILING REVIEW

(Including Memo of Filing Meeting)

Application Information		
NDA # 22-309 BLA#	NDA Supplement #:S- BLA STN #	Efficacy Supplement Type SE-
Proprietary Name: AndroGel Established/Proper Name: testosterone gel Dosage Form: gel Strengths: 1.62%		
Applicant: Unimed Pharmaceuticals, LLC Agent for Applicant (if applicable): Solvay Pharmaceuticals, Inc.		
Date of Application: February 11, 2009 Date of Receipt: February 12, 2009 Date clock started after UN:		
PDUFA Goal Date: December 12, 2009 (Saturday)	Action Goal Date (if different): December 11, 2009	
Filing Date: April 13, 2009 Date of Filing Meeting: March 31, 2009		
Chemical Classification: (1,2,3 etc.) (original NDAs only) 3		
Proposed Indication(s): Replacement therapy in males for conditions associated with deficiency or absence of endogenous testosterone.		
Type of Original NDA: AND (if applicable) Type of NDA Supplement: ***Refer to Appendix A for further information.***	☒ 505(b)(1) ☐ 505(b)(2) ☐ 505(b)(1) ☐ 505(b)(2)	
Review Classification: ***If the application includes a complete response to pediatric WR, review classification is Priority.*** ***If a tropical disease Priority review voucher was submitted, review classification defaults to Priority.***	☒ Standard ☐ Priority ☐ Tropical disease Priority review voucher submitted	
Resubmission after withdrawal? ☐ N/A Resubmission after refuse to file? ☐ N/A		
Part 3 Combination Product? ☐	☒ Drug/Biologic ☐ Drug/Device ☐ Biologic/Device	
☐ Fast Track ☐ Rolling Review ☐ Orphan Designation ☐ Rx-to-OTC switch, Full ☐ Rx-to-OTC switch, Partial ☐ Direct-to-OTC Other:	☐ PMC response ☐ PMR response: ☐ FDAAA [505(o)] ☐ PREA deferred pediatric studies [21 CFR 314.55(b)/21 CFR 601.27(b)] ☐ Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) ☐ Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR	

	601.42)
Collaborative Review Division (*if OTC product*):	
List referenced IND Number(s): IND 50,377	
PDUFA and Action Goal dates correct in tracking system? ***If not, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.***	☒ YES ☐ NO
Are the proprietary, established/proper, and applicant names correct in tracking system? ***If not, ask the document room staff to make the corrections. Also, ask the document room staff to add the established name to the supporting IND(s) if not already entered into tracking system.***	☒ YES ☐ NO
Are all classification codes/flags (e.g. orphan, OTC drug, pediatric data) entered into tracking system? ***If not, ask the document room staff to make the appropriate entries.***	☒ YES ☐ NO
Application Integrity Policy	
Is the application affected by the Application Integrity Policy (AIP)? ***Check the AIP list at:*** ***http://www.fda.gov/ora/compliance_ref/aiplist.html*** **If yes**, explain: **If yes**, has OC/DMPQ been notified of the submission? **Comments**:	☐ YES ☒ NO ☐ YES ☐ NO
User Fees	
Form 3397 (User Fee Cover Sheet) submitted	☒ YES ☐ NO
User Fee Status **Comments:**	☒ Paid ☐ Exempt (orphan, government) ☐ Waived (e.g., small business, public health) ☐ Not required
Note: *505(b)(2) applications are no longer exempt from user fees pursuant to the passage of FDAAA. It is expected that all 505(b) applications, whether 505(b)(1) or 505(b)(2), will require user fees unless otherwise waived or exempted (e.g., business waiver, orphan exemption).*	
Exclusivity	

Does another product have orphan exclusivity for the same indication? ***Check the Electronic Orange Book at: http://www.fda.gov/cder/ob/default.htm*** **If yes**, is the product considered to be the same product according to the orphan drug definition of sameness [21 CFR 316.3(b)(13)]? ***If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007)*** **Comments**:	☐ YES ☒ NO ☐ YES ☐ NO
Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? ***(NDAs/NDA efficacy supplements only)*** ***Note:*** *An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.* **Comments**:	☒ YES # years requested: 3 ☐ NO
If the proposed product is a single enantiomer of a racemic drug previously approved for a different therapeutic use (***NDAs only***): Did the applicant (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b) request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)? ***If yes, contact Mary Ann Holovac, Director of Drug Information, OGD/DLPS/LRB.***	☒ Not applicable ☐ YES ☐ NO
505(b)(2) (NDAs/NDA Efficacy Supplements only)	
	☒ **Not applicable**
1. Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?	☐ YES ☐ NO
2. Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action less than that of the reference listed drug (RLD)? (see 21 CFR 314.54(b)(1)).	☐ YES ☐ NO
3. Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug (see 21 CFR 314.54(b)(2))?	☐ YES ☐ NO

Note: *If you answered yes to any of the above questions, the application may be refused for filing under 21 CFR 314.101(d)(9).*	

4. Is there unexpired exclusivity on the active moiety (e.g., 5-year, 3-year, orphan or pediatric exclusivity)? ***Check the Electronic Orange Book at: http://www.fda.gov/cder/ob/default.htm*** **If yes**, please list below:	☐ YES ☐ NO N/A

Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration

If there is unexpired, 5-year exclusivity remaining on the active moiety for the proposed drug product, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 108(b)(2). Unexpired, 3-year exclusivity will only block the approval, not the submission of a 505(b)(2) application.

Format and Content

Do not check mixed submission if the only electronic component is the content of labeling (COL). **Comments**:	☐ All paper (except for COL) ☒ All electronic ☐ Mixed (paper/electronic) ☒ CTD ☐ Non-CTD ☐ Mixed (CTD/non-CTD)
If mixed (paper/electronic) submission, which parts of the application are submitted in electronic format?	
If electronic submission: paper forms and certifications signed (non-CTD) or electronic forms and certifications signed (scanned or digital signature)(CTD)? ***Forms*** *include: 356h, patent information (3542a), financial disclosure (3454/3455), user fee cover sheet (3542a), and clinical trials (3674);* ***Certifications*** *include: debarment certification, patent certification(s), field copy certification, and pediatric certification.* **Comments**:	☒ YES ☐ NO
If electronic submission, does it follow the eCTD guidance? (*http://www.fda.gov/cder/guidance/7087rev.pdf*) **If not,** explain (e.g., waiver granted):	☒ YES ☐ NO

Form 356h: Is a signed form 356h included? ***If foreign applicant, <u>both</u> the applicant and the U.S. agent must sign the form.*** Are all establishments and their registration numbers listed on the form? **Comments**:	☒ YES ☐ NO ☒ YES ☐ NO
Index: Does the submission contain an accurate comprehensive index? **Comments**:	☒ YES ☐ NO
Is the submission complete as required under 21 CFR 314.50 (*NDAs/NDA efficacy supplements*) or under 21 CFR 601.2 (*BLAs/BLA efficacy supplements*) including: ☒ legible ☒ English (or translated into English) ☒ pagination ☒ navigable hyperlinks (electronic submissions only) **If no**, explain:	☒ YES ☐ NO
Controlled substance/Product with abuse potential: Abuse Liability Assessment, including a proposal for scheduling, submitted? Consult sent to the Controlled Substance Staff? **Comments**:	☐ Not Applicable ☐ YES ☐ NO ☒ YES ☐ NO
BLAs/BLA efficacy supplements only: Companion application received if a shared or divided manufacturing arrangement? **If yes**, BLA #	N/A ☐ YES ☐ NO
Patent Information (NDAs/NDA efficacy supplements only)	
Patent information submitted on form FDA 3542a? **Comments**:	☒ YES ☐ NO
Debarment Certification	
Correctly worded Debarment Certification with authorized signature? ***If foreign applicant, <u>both</u> the applicant and the U.S. Agent must***	☒ YES ☐ NO

sign the certification. ***Note:*** *Debarment Certification should use wording in FD&C Act section 306(k)(l) i.e.,"[Name of applicant] 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." Applicant may not use wording such as, "To the best of my knowledge…"* **Comments**:	
Field Copy Certification (NDAs/NDA efficacy supplements only)	
Field Copy Certification: that it is a true copy of the CMC technical section (***applies to paper submissions only***) ***If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.***	☒ Not Applicable (*electronic submission or no CMC technical section*) ☐ YES ☐ NO
Financial Disclosure	
Financial Disclosure forms included with authorized signature? ***Forms 3454 and/or 3455 must be included and must be signed by the APPLICANT, not an Agent.*** ***Note:*** *Financial disclosure is required for bioequivalence studies that are the basis for approval.* **Comments**:	☒ YES ☐ NO
Pediatrics	
PREA ***Note****: NDAs/BLAs/efficacy supplements for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver & deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.* Are the required pediatric assessment studies or a full waiver of pediatric studies included? **If no,** is a request for full waiver of pediatric studies OR a request for partial waiver/deferral and a pediatric plan included? • ***If no, request in 74-day letter.*** • **If yes**, does the application contain the certification(s) required under 21 CFR 314.55(b)(1), (c)(2), (c)(3)/21 CFR 601.27(b)(1), (c)(2), (c)(3) **Comments**:	☐ Not Applicable ☒ YES ☐ NO ☐ YES ☐ NO ☐ YES ☐ NO

<u>BPCA</u> (NDAs/NDA efficacy supplements only): Is this submission a complete response to a pediatric Written Request? ***If yes, contact PMHS (pediatric exclusivity determination by the Pediatric Exclusivity Board is needed).*** **Comments**:	☐ YES ☒ NO
Prescription Labeling	
Check all types of labeling submitted. **Comments**:	☐ **Not applicable** ☒ Package Insert (PI) ☐ Patient Package Insert (PPI) ☐ Instructions for Use ☐ MedGuide ☒ Carton labels ☒ Immediate container labels ☐ Diluent ☐ Other (specify)
Is electronic Content of Labeling submitted in SPL format? ***If no, request in 74-day letter.*** **Comments**:	☒ YES ☐ NO
Package insert (PI) submitted in PLR format? **If no**, was a waiver or deferral requested before the application was received or in the submission? **If before**, what is the status of the request? ***If no, request in 74-day letter.*** **Comments**:	☒ YES ☐ NO ☐ YES ☐ NO
All labeling (PI, PPI, MedGuide, carton and immediate container labels) consulted to DDMAC? **Comments**:	☒ YES ☐ NO
MedGuide or PPI (plus PI) consulted to OSE/DRISK? (*send WORD version if available*) **Comments**: Consult sent for PI review	☐ Not Applicable ☒ YES ☐ NO
REMS consulted to OSE/DRISK? **Comments**:	☒ Not Applicable ☐ YES ☐ NO
Carton and immediate container labels, PI, PPI, and proprietary name (if any) sent to OSE/DMEDP? **Comments**:	☐ Not Applicable ☒ YES ☐ NO

OTC Labeling	
Check all types of labeling submitted. **Comments**:	☒ **Not Applicable** ☐ Outer carton label ☐ Immediate container label ☐ Blister card ☐ Blister backing label ☐ Consumer Information Leaflet (CIL) ☐ Physician sample ☐ Consumer sample ☐ Other (specify)
Is electronic content of labeling submitted? ***If no, request in 74-day letter.*** **Comments**:	☐ YES ☐ NO
Are annotated specifications submitted for all stock keeping units (SKUs)? ***If no, request in 74-day letter.*** **Comments**:	☐ YES ☐ NO
If representative labeling is submitted, are all represented SKUs defined? ***If no, request in 74-day letter.*** **Comments**:	☐ YES ☐ NO
Proprietary name, all labeling/packaging, and current approved Rx PI (if switch) sent to OSE/DMEDP? **Comments**:	☐ YES ☐ NO
Meeting Minutes/SPA Agreements	
End-of Phase 2 meeting(s)? ***If yes, distribute minutes before filing meeting.*** **Comments**:	☒ YES Date(s): October 18, 2006 ☐ NO
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? ***If yes, distribute minutes before filing meeting.*** **Comments**:	☒ YES Date(s): January 22, 2008 and August 13, 2008 ☐ NO
Any Special Protocol Assessment (SPA) agreements? ***If yes, distribute letter and/or relevant minutes before filing meeting.*** **Comments**:	☐ YES Date(s): ☒ NO

ATTACHMENT

MEMO OF FILING MEETING

DATE: March 31, 2009

NDA/BLA #: NDA 22-309

PROPRIETARY/ESTABLISHED NAMES: AndroGel 1.62%

APPLICANT: Unimed Pharmaceuticals, LLC

BACKGROUND: This application contains new clinical data evaluating the efficacy and safety of a new formulation in the target population. This new formulation has (b) (4), reduced volume of application and (b) (4) compared to the currently marketed testosterone gel, AndroGel 1%.

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Jeannie Roule	Y
	CPMS/TL:	Jennifer Mercier	N
Cross-Discipline Team Leader (CDTL)	George Benson		Y
Clinical	Reviewer:	Roger Wiederhorn	Y
	TL:	Mark Hirsch	Y
Social Scientist Review (*for OTC products*)	Reviewer:	N/A	
	TL:		
Labeling Review (*for OTC products*)	Reviewer:	N/A	
	TL:		
OSE	Reviewer:	Lori Cantin	Y
	TL:	Kristina Arnwine	Y
Clinical Microbiology (*for antimicrobial products*)	Reviewer:	N/A	
	TL:		

Clinical Pharmacology	Reviewer:	Sandhya Apparaju	Y
	TL:	Myong-Jin Kim	Y
Biostatistics	Reviewer:	Mahboob Sobhan	Y
	TL:	Mahboob Sobhan	
Nonclinical (Pharmacology/Toxicology)	Reviewer:	Jeffrey Bray and Eric Andreasen	Y Y
	TL:	Lynnda Reid	N
Statistics, carcinogenicity	Reviewer:	N/A	
	TL:		
Product Quality (CMC)	Reviewer:	Hitesh Shroff	Y
	TL:	Donna Christner	Y
Facility (*for BLAs/BLA supplements*)	Reviewer:	N/A	
	TL:		
Microbiology, sterility (*for NDAs/NDA efficacy supplements*)	Reviewer:	N/A	
	TL:		
Bioresearch Monitoring (DSI)	Reviewer:	Roy Blay	Y
	TL:		
Other reviewers	DDMAC: Janice Maniwang CCS: James Tolliver		N N

OTHER ATTENDEES:

505(b)(2) filing issues? **If yes,** list issues:	☒ Not Applicable ☐ YES ☐ NO
Per reviewers, are all parts in English or English translation? **If no**, explain:	☒ YES ☐ NO

Electronic Submission comments **List comments**:	☒ Not Applicable
CLINICAL **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☒ Review issues for 74-day letter
• Clinical study site(s) inspections(s) needed? **If no,** explain: Sites have been previously inspected and there were no concerns.	☒ YES ☐ NO
• Advisory Committee Meeting needed? **Comments**: ***If no, for an original NME or BLA application, include the reason. For example:*** o ***this drug/biologic is not the first in its class*** o ***the clinical study design was acceptable*** o ***the application did not raise significant safety or efficacy issues*** o ***the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease***	☐ YES Date if known: ☒ NO ☐ To be determined Reason:
• If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? **Comments**:	☒ Not Applicable ☐ YES ☐ NO
CLINICAL MICROBIOLOGY **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
CLINICAL PHARMACOLOGY	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE

Comments:	☒ Review issues for 74-day letter
• Clinical pharmacology study site(s) inspections(s) needed?	☒ YES ☐ NO
BIOSTATISTICS **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
NONCLINICAL (PHARMACOLOGY/TOXICOLOGY) **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
PRODUCT QUALITY (CMC) **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• Categorical exclusion for environmental assessment (EA) requested? **If no**, was a complete EA submitted? **If EA submitted**, consulted to EA officer (OPS)? **Comments**:	☐ Not Applicable ☒ YES ☐ NO ☐ YES ☐ NO ☐ YES ☐ NO
• Establishment(s) ready for inspection? ▪ Establishment Evaluation Request (EER/TBP-EER) submitted to DMPQ? **Comments**:	☐ Not Applicable ☒ YES ☐ NO ☐ Not Applicable ☐ YES ☐ NO
• Sterile product?	☐ YES ☒ NO

If yes, was Microbiology Team consulted for validation of sterilization? (**NDAs/NDA supplements only**)	☐ YES ☐ NO
FACILITY (BLAs only) **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter

REGULATORY PROJECT MANAGEMENT

Signatory Authority: George Benson

GRMP Timeline Milestones: Mid-cycle meeting: 07/15/09
6 month review: 08/10/09
PeRC meeting: 08/12/09
7 month review: 09/15/09
8 month review: 10/14/09 (Wrap-up)
Label meeting #1: 08/25/09
Label meeting #2: To be scheduled
All discipline reviews should be in DFS by October 31
Mark Hirsch's final review will be given to George Benson by November 11, 2009

Comments:

REGULATORY CONCLUSIONS/DEFICIENCIES

☐	The application is unsuitable for filing. Explain why:
☒	The application, on its face, appears to be suitable for filing. ☐ No review issues have been identified for the 74-day letter. ☒ Review issues have been identified for the 74-day letter. List (optional): ☒ Standard Review ☐ Priority Review

ACTIONS ITEMS

☒**	Ensure that the review and chemical classification codes, as well as any other pertinent classification codes (e.g., orphan, OTC) are correctly entered into tracking system. **Class 3 (New formulation)
N/A ☐	If RTF action, notify everybody who already received a consult request, OSE PM., and Product Quality PM. Cancel EER/TBP-EER.

N/A ☐	If filed and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
N/A ☐	If BLA or priority reviews NDA, send 60-day letter.
☒	Send review issues/no review issues by day 74

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22309	ORIG-1	UNIMED PHARMACEUTICALS INC	ANDROGEL

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/s/

JEANNIE M ROULE
03/10/2010

MEMORANDUM OF TELECONFERENCE MINUTES

MEETING DATE:	December 2, 2009
TIME:	11-11:30 a.m.
LOCATION:	Room 5394
APPLICATION:	NDA 22-309
DRUG NAME:	Androgel 1.62%
TYPE OF MEETING:	Teleconference

MEETING CHAIR: George Benson, M.D.

MEETING RECORDER: Jeannie Roule

FDA ATTENDEES:

George Benson, M.D	Deputy Director, Division of Reproductive and Urologic Products (DRUP)
Jeannie Roule	Regulatory Health Project Manager, DRUP

EXTERNAL CONSTITUENT ATTENDEES:

Troy ZumBrunnen	Clinical Pharmacology
Jodi Miller	Clinical Pharmacology
Michael Miller	Clinical Development
Barbara Parker	Clinical Development
Cecilia McWhirter	Biostatistics
Sherahe Fitzpatrick	Drug Safety
Janet Benesh	Project Management
Therese Takas	Project Management
Steven Wojtanowski	Regulatory Affairs
Kathryn Penhale-Unz	Regulatory Affairs

DISCUSSION:

- The purpose of the call was to discuss the Applicant's submission of their final Clinical Study Report (CSR) for the recently completed transfer study entitled "*An Open-Label, Parallel Group Study of Serum Testosterone Levels in Non-dosed Females after Secondary Exposure to Testosterone Gel 1.62% (protocol S.176.1.009).*"

- The Division informed the Applicant that a decision concerning the action to be taken on this NDA has not yet been made.

- The Division asked when the Applicant is planning to submit the final CSR. This information is needed to determine whether or not a 90 day clock extension can be considered.

- The Division informed the Applicant that a 90 day clock extension does not guarantee approval.

- The Applicant stated that the raw data sets would be available before December 25, 2009, and the remaining data should arrive by January 15, 2010. The Applicant will provide within the next several days a specific timeline stating when each portion of the following information will be submitted:
    1. Testosterone concentration and PK listing and summary tables (final, QA)
    2. Raw SAS datasets for testosterone
    3. Bioanalytical report for testosterone and DHT (final, QA)
    4. DHT and estradiol concentration listings and summary tables (final, QA)
    5. All safety listings and summary tables (final, QA)
    6. Datasets for all PK and safety data
    7. Bioanalytical report for estradiol (final, QA)
    8. Final clinical study report

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22309	ORIG-1	UNIMED PHARMACEUTICALS INC	ANDROGEL

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/s/

JEANNIE M ROULE
01/04/2010

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 022309

PDUFA GOAL DATE EXTENSION

Unimed Pharmaceuticals, LLC
Attention: Kathryn Penhale-Unz
Director, Regulatory Affairs
901 Sawyer Road
Marietta, GA 30062

Dear Ms. Penhale-Unz:

Please refer to your February 12, 2009, new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for AndroGel® (testosterone gel) 1.62%.

On November 9 and December 8, 2009, we received your November 6 and 24, 2009, major amendments to this application, containing additional clinical and clinical pharmacology safety information.

The receipt date is within three months of the user fee goal date. Therefore, we are extending the goal date by three months to provide time for a full review of the submission. The extended user fee goal date is March 12, 2009.

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

Sincerely yours,

{See appended electronic signature page}

Jennifer Mercier
Chief, Project Management Staff
Division of Reproductive and Urologic Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22309	ORIG-1	UNIMED PHARMACEUTICALS INC	ANDROGEL

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/s/

JENNIFER L MERCIER
12/10/2009

MEMORANDUM OF TELECONFERENCE MINUTES

MEETING DATE:	October 1, 2009
TIME:	3:00-4:00 p.m.
LOCATION:	Room 5394
APPLICATION:	NDA 22-309
DRUG NAME:	Androgel 1.62%
TYPE OF MEETING:	Teleconference

MEETING CHAIR: Mark Hirsch, M.D.

MEETING RECORDER: Jeannie Roule

FDA ATTENDEES:

George Benson, M.D.	Deputy Division Director, Division of Reproductive and Urologic Products (DRUP)
Mark Hirsch, M.D.	Medical Team Leader, DRUP
Roger Wiederhorn, M.D.	Medical Officer, DRUP
Sandhya Apparaju, Ph.D.	Clinical Pharmacology Reviewer, Division of Clinical Pharmacology (DCP) III, Office of Clinical Pharmacology (OCP), Office of Translational Sciences (OTS)
Jeannie Roule	Regulatory Health Project Manager, DRUP

EXTERNAL CONSTITUENT ATTENDEES:

Troy ZumBrunnen	Clinical Pharmacology
Jodi Miller	Clinical Pharmacology
Michael Miller	Clinical Development
Cecilia McWhirter	Biostatistics
Sherahe Fitzpatrick	Drug Safety
Janet Benesh	Project Management
Therese Takas	Project Management
Steven Wojtanowski	Regulatory Affairs

DISCUSSION:

- The Division requested to speak with Sponsor to convey an unresolved clinical safety concern. Data in the application shows that, at a dose of 5 gms, transfer to others is observed despite a simple t-shirt barrier. Therefore, the Clinical review team believes that a t-shirt has not been shown to effectively prevent transfer to others at doses above 2.5 gm. The Clinical review team seeks a simple, effective barrier, such as a t-shirt, as the key component for risk mitigation of transfer.

- The Clinical review team believes that a labeled recommendation (b) (4) (b) (4) (b) (4) (b) (4)

- 

- The Sponsor believes that spreading the dose out onto 3 or 4 sites should allow for the effective use of a t-shirt to prevent transfer. The Sponsor proposed another transfer study using 5 gm of Androgel 1.62% applied to both arms/shoulders and to the right and left abdomen with a t-shirt barrier. The Division stated that such a study seemed like a reasonable path forward, but if the 3- or 4-site regimen was successful in allowing effective use of a t-shirt at doses > 2.5gm, then PK data must be submitted to show comparable exposure of the new regimen to the rotating application regimen used in the Phase 3 study.

- The Sponsor asked whether PK data from the Phase 3 study in subjects who used a three- or four-site application regimen could provide the requested evidence of comparability. The Sponsor referred to these subjects as having minor protocol deviations. The Division stated that no commitments could be made until these data were submitted and briefly reviewed.

- The Sponsor informed the Division that they would submit additional information sometime in November in response to the Division's concern.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22309	ORIG-1	UNIMED PHARMACEUTICALS INC	ANDROGEL

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JEANNIE M ROULE
12/08/2009

MEMORANDUM

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

DATE: November 30, 2009

TO: NDA 22-309, Androgel 1.62%

FROM: Jeannie Roule

SUBJECT: Comments from the Microbiologist to Solvay Pharmaceuticals.

The following emails include comments that were sent to Solvay concerning the microbial limit test and acceptance criteria for NDA 22-309, Androgel 1.62% and the response received from Solvay.

Roule, Jeannie

From: Michael, Lincy [Lincy.Michael@solvay.com]
Sent: Wednesday, November 25, 2009 9:50 AM
To: Roule, Jeannie
Cc: Penhale-Unz, Kathryn
Subject: RE: NDA 22-309

Thank you Jeannie. I appreciate your quick response.

Best regards,
Lincy

From: Roule, Jeannie [mailto:Jeannie.Roule@fda.hhs.gov]
Sent: Wednesday, November 25, 2009 9:44 AM
To: Michael, Lincy; Penhale-Unz, Kathryn
Subject: RE: NDA 22-309

Thank you for this information. Please submit it to the NDA via edr.
The tcon for Monday is now cancelled.

Jeannie

From: Michael, Lincy [mailto:Lincy.Michael@solvay.com]
Sent: Wednesday, November 25, 2009 9:22 AM
To: Roule, Jeannie
Subject: FW: NDA 22-309
Importance: High

Dear Jeannie,

With regards to the comment from the microbiologist, we will add the microbial limit test and the acceptance criteria (as given in your e-mail) to the specifications listed in tables 2 and 3 in Section 3.2.P.5.1along with a statement that this is not a routine stability test, however, the drug product will comply with the acceptance criteria if tested at anytime during its shelf life (same as what was requested by the microbiologist).

If this is the only comment, I do not see a need to have a teleconference on Monday at 9:15 am. Of course, we will be available if you think that it is necessary to have this teleconference. So, please let me know.

Best regards,
Lincy

Lincy Michael
Asst.Director, Regulatory Affairs
Solvay Pharmaceuticals, Inc.
Phone: 770-578-5649
Fax: 770-578-5864
lincy.michael@solvay.com

From: Penhale-Unz, Kathryn
Sent: Tuesday, November 24, 2009 4:36 PM
To: Michael, Lincy
Subject: FW: NDA 22-309

Lincy,

I received the below note from FDA today. I have confirmed that we will have the tcon on Mon. Nov. 30th at 9:15.

Please set up a meeting room and lets discuss tomorrow who we should invite to this tcon.

I will be in the office tomorrow.

Kathryn Penhale-Unz
Director, Global Regulatory Affairs
tel. (770) 578-5796
fax (770) 578-5864

From: Roule, Jeannie [mailto:Jeannie.Roule@fda.hhs.gov]
Sent: Tuesday, November 24, 2009 2:41 PM
To: Penhale-Unz, Kathryn
Subject: NDA 22-309

Kathryn,

Below is a comment from the microbiologist. We will discuss this at the tcon on Monday, November 30 at 9:15 am.

Invite those that you think will be necessary to answer any questions. The attendees will be CMC and Micro people only.

Thanks,
Jeannie

The following is **not** a deficiency, but is only a comment.

It is acceptable to omit microbial limits testing for routine drug product release and stability testing. Nonetheless, the acceptance criteria for the microbiological quality of the drug product should be listed in Table 2 and Table 3, respectively, of the NDA submission Section 3.2.P.5.1, along with a statement that the drug product will comply with the acceptance criteria if tested at anytime during its shelf life. Examples of such acceptance criteria are shown in the following table:

Parameter	**Acceptance Criteria**
Total aerobic count	NMT 100 CFU/g
Total Yeast & Mold	NMT 10 CFU/g
S. aureus	Absent/1gram
P. aeruginosa	Absent/1gram

Jeannie Roule
Regulatory Project Manager
Division of 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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Merci d'informer immediatement l'expediteur par messagerie electronique et

d'ensuite detruire ce message.

Roule, Jeannie

From: Christner, Donna
Sent: Wednesday, November 25, 2009 9:38 AM
To: Roule, Jeannie; Mello, Robert
Cc: Shroff, Hitesh
Subject: RE: NDA 22-309

Hi Jeannie,

Since they are in agreement, I also do not see a need for a tcon. Please ask them to submit updated specification tables to the NDA.

Thanks, and have a great Thanksgiving,

Donna

-----Original Message-----
From: Roule, Jeannie
Sent: Wed 11/25/2009 9:35 AM
To: Mello, Robert; Christner, Donna
Subject: FW: NDA 22-309

Please read the email below and let me know if you still need a tcon on Nov 30.

Thanks,
Jeannie

From: Michael, Lincy [mailto:Lincy.Michael@solvay.com]
Sent: Wednesday, November 25, 2009 9:22 AM
To: Roule, Jeannie
Subject: FW: NDA 22-309
Importance: High

Dear Jeannie,

With regards to the comment from the microbiologist, we will add the microbial limit test and the acceptance criteria (as given in your e-mail) to the specifications listed in tables 2 and 3 in Section 3.2.P.5.1along with a statement that this is not a routine stability test, however, the drug product will comply with the acceptance criteria if tested at anytime during its shelf life (same as what was requested by the microbiologist).

If this is the only comment, I do not see a need to have a teleconference on Monday at 9:15 am. Of course, we will be available if you think that it is necessary to have this teleconference. So, please let me know.

Best regards,
Lincy

Lincy Michael
Asst.Director, Regulatory Affairs
Solvay Pharmaceuticals, Inc.
Phone: 770-578-5649
Fax: 770-578-5864
lincy.michael@solvay.com

From: Penhale-Unz, Kathryn
Sent: Tuesday, November 24, 2009 4:36 PM
To: Michael, Lincy
Subject: FW: NDA 22-309

Lincy,

I received the below note from FDA today. I have confirmed that we will have the tcon on Mon. Nov. 30th at 9:15.

Please set up a meeting room and lets discuss tomorrow who we should invite to this tcon.

I will be in the office tomorrow.

Kathryn Penhale-Unz

Director, Global Regulatory Affairs

tel. (770) 578-5796

fax (770) 578-5864

From: Roule, Jeannie [mailto:Jeannie.Roule@fda.hhs.gov]
Sent: Tuesday, November 24, 2009 2:41 PM
To: Penhale-Unz, Kathryn
Subject: NDA 22-309

Kathryn,

Below is a comment from the microbiologist. We will discuss this at the tcon on Monday, November 30 at 9:15 am.

Invite those that you think will be necessary to answer any questions. The attendees will be CMC and Micro people only.

Thanks,
Jeannie

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Parameter	Acceptance Criteria
Total aerobic count	NMT 100 CFU/g
Total Yeast & Mold	NMT 10 CFU/g
S. aureus	Absent/1gram
P. aeruginosa	Absent/1gram

Jeannie Roule
Regulatory Project Manager
Division of 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

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22309	ORIG-1	UNIMED PHARMACEUTICALS INC	ANDROGEL

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/s/

JEANNIE M ROULE
11/30/2009

MEMORANDUM

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

DATE: November 23, 2009

TO: NDA 022309, Androgel 1.62%

FROM: Jeannie Roule

SUBJECT: Proprietary Name Review

The attached emails discuss why there was not a formal review of the trade name Androgel 1.62%.
Specifically see email dated April 13, 2009 from Lori Cantin.

TEXT

NDA 22-309
Submit date: Nov 3, 2009
Rec date: Nov 3, 2009

Roule, Jeannie

From: Wasilik, Maria
Sent: Tuesday, November 03, 2009 3:47 PM
To: Roule, Jeannie
Subject: FW: NDA 22-309

Jeannie,
This is all i was able to find today. IF this is not enough for your package come over to my office and talk with me and Chris (TL) tomorrow.
maria

From: Cantin, Lori
Sent: Tuesday, November 03, 2009 3:34 PM
To: Wasilik, Maria; Milburn, Cherye
Subject: FW: NDA 22-309

From: Cantin, Lori
Sent: Monday, April 13, 2009 5:30 PM
To: 'kathryn.penhale-unz@solvay.com'
Cc: Milburn, Cherye; Arnwine, Kristina
Subject: RE: NDA 22-309

Kathryn,

You do not need to officially withdraw the request for a proprietary name review submission as was previously discussed. On our end, it is not necessary from an administrative standpoint. We will review the name as it pertains to the labels and labeling, however, a specific trade name review will not be conducted based on the information you have submitted.

Thank you,
Lori Cantin

From: Regulatory Submissions [mailto:Regulatory.Submissions@solvay.com]
Sent: Monday, April 13, 2009 5:11 PM
To: Cantin, Lori
Subject: FW: NDA 22-309

This message is sent on behalf of Kathryn Penhale-Unz, Director, Global Regulatory Affairs.

Hi Lori,

On March 25/09 you and I spoke regarding a "Request for Proprietary Name Review" for our product AndroGel® (testosterone gel) 1.62%. The cover letter of the trade name request was dated Feb. 11/09 and was submitted to NDA 22-309, sequence no. 0003.

You had called me together with Cherie Milburn, Project Manager, Trade Name Review because there was need for clarity regarding the requested trade name for the product. I advised that the 1.62% AndroGel application was a new improved formulation of the already approved AndroGel 1% product. I also advised that the requested trade name for the new improved formulation was "AndroGel® (testosterone gel) 1.62%"

You corrected me and clarified that the approved proprietary name for the AndroGel product is "AndroGel®". You stated that (testosterone gel) together with the strength (1% or 1.62%) is part of the established name of the product but the proprietary name for the product is simply "AndroGel®". Therefore, it was your opinion that since the proprietary name for the 1.62% NDA was already determined as "AndroGel®", the submitted "Request for Proprietary Name Review" was unnecessary and should be withdrawn.

Could you please confirm that the above summation is correct and that the tradename request for the AndroGel 1.62% application is unnecessary. I am requesting your written confirmation as proof that this issue is resolved as we move through the NDA review process. Once I receive your confirmation I will submit a letter requesting withdrawal of the Proprietary Name Review.

Many thanks,
Kathryn

Kathryn Penhale-Unz
Director, Global Regulatory Affairs
tel. (770) 578-5796
fax (770) 578-5864

Please respond to Kathryn Penhale-Unz, Director, Global Regulatory Affairs at the following email address: Regulatory.Submissions@solvay.com.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22309	ORIG-1	UNIMED PHARMACEUTICALS INC	ANDROGEL

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JEANNIE M ROULE
11/23/2009

MEMORANDUM

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

DATE: November 23, 2009

TO: NDA 022309, Solvay Pharmaceuticals

FROM: Jeannie Roule

SUBJECT: Information request sent to Solvay on November 18, 2009 regarding Androgel 1.62%

Atttached emails were sent to Kathryn Penhale-Unz

NDA 22-309
Submit: 11-18-09
Rec: 11-18-09

Roule, Jeannie

From: Roule, Jeannie
Sent: Wednesday, November 18, 2009 11:59 AM
To: 'Penhale-Unz, Kathryn'
Cc: 'Wojtanowski, Steven'
Subject: NDA 22-309 Information needed as soon as possible.

Attachments: IR requests from ClinPharm.doc

Dear Kathryn,

We continue to review your submission dated November 5, 2009, containing the following:

- Executive Summary
- Preliminary Headline Results Report for protocol S176.1.009, *entitled "An Open-Label, Parallel Group Study of Serum Testosterone Levels in Non-dosed Females after Secondary Exposure to Testosterone Gel 1.62%"*
- A Rationale document outlining supportive justifications regarding why the application scheme used in S176.1.009 to prevent transfer through a t-shirt should not adversely impact safety or efficacy conclusions from the previously completed pivotal S176.3.104

At this time we are requesting more information to help us with the review process (see attachment). In addition, if you have any other information that would help to bolster your argument that the efficacy and safety of the four site application is the same as the two site application, send that along as well.

After reviewing all of the requests in this email, please let me know the approximate date that we will be able to receive a reply.

Regards,
Jeannie

-see attached doc

IR requests from ClinPharm.doc...

Jeannie Roule
Regulatory Project Manager
Division of 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

We have a request for the following additional information:

1. You report that a subgroup of patients in Phase 3 has applied the testosterone 1.62 % gel to both abdomen & shoulders/upper arms on visit days (titration and PK-days).

   Per the Phase 3 study report included in NDA 22-309, patients were advised that "study drug NOT be applied prior to study visits" and that on PK days subjects apply the study gel "at the clinic under direct supervision of study staff".

   We therefore assume that dose application in those patients who used multiple application sites was also done in the clinic under supervision. In this regard, we request that you provide narratives/descriptions of the supervised dose application procedures for this subgroup of individuals, for each of the PK and titration days.

   This will be an important piece of information in our consideration of whether data obtained from this subgroup of patients would be a good representation of the multiple sites of application employed in your new transfer study S176.1.009 and (b) (4) included in your submission dated, November 5, 2009.

   If dosing to multiple sites in any or all of these individuals did not occur in the clinic under staff supervision and hence narratives are not available, comment on whether other records are available from those doses that can describe the method and sites of application. Any such records should be included in your response.

2. Comment as to why dosing to multiple application sites was employed in these patients and whether that was recorded as a protocol violation.

3. Provide a listing of the following information for all patients on each PK day who had applied dose to 3 or 4 application sites: Patient ID, PK day, dose, number and description of the application sites, whether dosing occurred at clinic, and PK parameters. Submit this information also for patients who used multiple sites of application on both the day before and on the day of PK. Also include plasma concentration-time profile data for these individuals. For subjects who applied dose to multiple application sites prior to a titration day provide a listing of their pre-dose concentrations. Please provide this information in SAS transport file format.

4. Comment on whether each of the patients in this subgroup was a responder or non-responder per final efficacy analyses (Day 112). Comment on whether any of these subjects were included in the list of testosterone outliers and whether this is attributable to the use of multiple drug application sites.

5. Submit the final study report for the new transfer study S176.1.009.

6. Clarify the volume of gel for each 1.25 g pump actuation.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22309	ORIG-1	UNIMED PHARMACEUTICALS INC	ANDROGEL

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/s/

JEANNIE M ROULE
11/23/2009

MEMORANDUM OF MEETING MINUTES

MEETING DATE:	September 25, 2009
TIME:	11:45-12:00 p.m.
LOCATION:	Room 5346
APPLICATION:	NDA 22-309
DRUG NAME:	Androgel 1.62%
TYPE OF MEETING:	T-con

MEETING CHAIR: Mark Hirsch, M.D.

MEETING RECORDER: Meredith Alpert, M.S.

FDA ATTENDEES:

Mark Hirsch, M.D.	Team Leader, Division of Reproductive and Urologic Products (DRUP)
Meredith Alpert, M.S.	Regulatory Project Manager, DRUP

EXTERNAL CONSTITUENT ATTENDEES:

Kathryn Penhale-Unz, Director, Regulatory Affairs, Solvay Pharmaceuticals

DISCUSSION POINTS:

- Dr. Mark Hirsch received a phone call from Kathryn Penhale-Unz, a representative of Solvay Pharmaceuticals, on September 25, 2009.

- Ms. Penhale-Unz inquired whether we had received Solvay's last two submissions for NDA 22-309, AndroGel 1.62% (the REMS document/additional information, and the response to the DRUP Information Request letter) and whether we had reviewed them. Dr. Hirsch replied that we had received them and we had reviewed them. Ms. Penhale-Unz asked if they were "helpful" and Dr. Hirsch replied that they were useful.

- The issue of drug transfer in Study 003 at the 5gm dose (Group B) was discussed. Dr. Hirsch stated that this was a continued and unresolved Clinical safety issue. Ms. Penhale –Unz questioned whether this issue could be resolved through labeling. Dr. Hirsh remarked that the 5gm transfer study remained an unresolved concern for the Clinical review team and that Solvay's idea about "spreading out the gel on 4 sites" and conducting another transfer study was intriguing.

- Dr. Hirsch mentioned that the Division would like to speak with Solvay and gain more details about the results from Study 003 and the 5gm transfer study.

- Ms. Penahle-Unz will call Jeannie on Monday or Tuesday to set up a tcon.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22309	ORIG-1	UNIMED PHARMACEUTICALS INC	ANDROGEL

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/s/

MEREDITH H ALPERT
09/29/2009

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 22-309 **INFORMATION REQUEST**

Unimed Pharmaceuticals, LLC
Attention: Kathryn Penhale-Unz
Director, Regulatory Affairs
901 Sawyer Road
Marietta, GA 30062

Dear Ms. Penhale-Unz:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for AndroGel® (testosterone gel) 1.62%.

We are reviewing the Chemistry, Manufacturing and Controls section of your submission and have the following comments and information requests. We request a written response by September 4, 2009, in order to continue our evaluation of your NDA.

- In support of the stability data provided in Sec. 3.2.P.8.3 (Lot# EG1179, EG1195 and EG 1194) submit the individual results of the Pump Performance - dose uniformity test in a tabular format for Androgel 1.62% at 25°C/60%RH and 40°C/75%RH. The data can be submitted in a form similar to what is provided in Sec. 3.2.P.2.Appendix 2-4 Pump Repro. Data for Androgel 1%.

- (b) (4) To ensure that the deliverable contents of each attenuation remains within acceptable criteria during the entire shelf life of the product, the Pump Performance - dose uniformity test based on USP <601> for metered-dose delivery systems for Androgel 1.62% at 25°C/60%RH should be performed during stability testing. Include the Pump Performance test with acceptance criteria and submit updated post approval stability specifications.

- Add the following statement to the post approval stability commitment in Section 3.2.P.8.2., and submit an updated Section 3.2.P.8.2.

    - Agree to withdraw from the market any lots that fall outside the approved drug product specifications. If the applicant has evidence that the deviation is a single occurrence that does not affect the safety and efficacy of the drug product the applicant should immediately discuss it with the reviewing division and provide justification for the continued distribution of that batch. The change or deterioration in the distributed drug product must be reported under 21 CFR 314.81(b)(1)(ii).

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

Sincerely,

{See appended electronic signature page}

Jennifer Mercier
Chief, Project Management Staff
Division of Reproductive and Urologic Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

JENNIFER L MERCIER
08/28/2009

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 22-309 **INFORMATION REQUEST**

Unimed Pharmaceuticals, LLC
Attention: Kathryn Penhale-Unz
Director, Regulatory Affairs
901 Sawyer Road
Marietta, GA 30062

Dear Ms. Penhale-Unz:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for AndroGel® (testosterone gel) 1.62%.

We are reviewing the Clinical section of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

We continue to have concerns regarding the issue of skin transfer and the efficacy of a T-shirt barrier in mitigating this risk. In Study S176.1.1003 which utilized 5 g of testosterone gel 1.62% (abdominal application) with abdomen to abdomen skin contact on Days 1 and 7, with and without a T-shirt barrier, the T-shirt barrier appears to have reduced female exposure by only about 50%. In Study S176.1.1008, in Group I (Treatments A and B), which utilized 2.5 g of testosterone gel 1.62% (abdominal application) with abdomen to abdomen skin contact occurring on Day 1 at 2 hours post dose, it appears that a T-shirt largely prevented female exposure. However, in two female subjects in that study (Subjects #27403 and #27419) there were still baseline-adjusted testosterone increases of 16.9 and 13.3 ng/dL at the maximum, respectively.

Therefore, the current data do not appear to support the conclusion that a T-shirt barrier is fully effective as a barrier to skin transfer of testosterone gel 1.62%, under the conditions of the transfer studies.

We will need you to provide information regarding the following concerns:

- The female subjects' baseline testosterone concentrations were established seven days prior to testosterone gel 1.62% dosing in male partners. Can the baseline values vary over time by subject?
- Comment on the differences between Studies 003 and 008 that may have led to differences in the transfer study results. Is transfer risk greater at the higher dose?
- Do you consider the transfer studies as a reasonable test of transfer risk under real-life conditions, or do you consider the conditions of the transfer study unrealistic?

- Comment upon the potential clinical significance of these transfer study results to a child. In responding, consider average and worst case scenarios based upon the transfer study results.

In addition, we continue to have concerns regarding the issue of skin transfer and the efficacy of skin application site washing in mitigating this risk. Study S176.1.1008, Group II (Treatments C and D), utilized 5 gm testosterone gel 1.62% applied to the male's abdomen with direct skin contact with female partner two hours post dose (C), and two hours post dose with skin application site washing before contact (D). The group mean averages appear to demonstrate that washing reduced female exposure by approximately 80-85 %. On an individual subject basis, for Subjects #27411 and #27405, there was more systemic exposure observed than for the other subjects. Serum T concentrations were also above baseline levels in Subjects #27399, #27402, #27404, and #27417.

Therefore, the current data do not appear to support the conclusion that skin washing fully eliminates the risk of transfer of testosterone gel 1.62% to the female partner.

We will need you to provide information regarding the following concerns:

- What were the application site washing instructions and procedures? Were the procedures consistently followed and their performance documented? Were other application site washing procedures considered?
- Do you consider the transfer studies as a reasonable test of transfer risk under real-life conditions, or do you consider the conditions of the transfer study unrealistic?
- Baselines T concentrations in the female subjects were obtained one week prior to the active treatment phase of the protocol. Is baseline shift of testosterone concentration a concern and how is this controlled for?
- Comment upon the potential clinical significance of this washing study results to a child. In responding, consider average and worst case scenarios based upon the washing study results.

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

Sincerely,

{See appended electronic signature page}

Jennifer Mercier
Chief, Project Management Staff
Division of Reproductive and Urologic Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

JENNIFER L MERCIER
08/28/2009

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

REQUEST FOR CONSULTATION

TO *(Office/Division)*: Controlled Substance Staff
Corinne Moody

REVISED FROM March 18,2009

FROM (*Name, Office/Division, and Phone Number of Requestor)*:
Jeannie Roule, Regulatory Project Manager
Division of Reproductive and Urologic Products
(301) 796-3993

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
08/07/09		22-309	Electronic	02-12-09

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
AndroGel 1.62% testosterone gel	Standard/ PDUFA is 12-12-09		10-14-09

NAME OF FIRM: Unimed Pharmaceuticals

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE / ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE-NDA MEETING
- ☐ END-OF-PHASE 2a MEETING
- ☐ END-OF-PHASE 2 MEETING
- ☐ RESUBMISSION
- ☐ SAFETY / EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☐ OTHER *(SPECIFY BELOW)*:

II. BIOMETRICS

- ☐ PRIORITY P NDA REVIEW
- ☐ END-OF-PHASE 2 MEETING
- ☐ CONTROLLED STUDIES
- ☐ PROTOCOL REVIEW
- ☐ OTHER (SPECIFY BELOW):
- ☐ CHEMISTRY REVIEW
- ☐ PHARMACOLOGY
- ☐ BIOPHARMACEUTICS
- ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE 4 STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL - BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG SAFETY

- ☐ PHASE 4 SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE, e.g., POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ NONCLINICAL

COMMENTS / SPECIAL INSTRUCTIONS: All of the documents for this NDA are available via edr.
This is a Class III controlled substance. Please review the language in the label with regard to scheduling and assure the information is correct.

SIGNATURE OF REQUESTOR	METHOD OF DELIVERY (Check one)
Jeannie Roule	☒ DFS ☐ EMAIL ☐ MAIL ☐ HAND
PRINTED NAME AND SIGNATURE OF RECEIVER	PRINTED NAME AND SIGNATURE OF DELIVERER

Linked Applications	Submission Type/Number	Sponsor Name	Drug Name / Subject
NDA 22309	ORIG 1	UNIMED PHARMS	ANDROGEL

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/s/

JEANNIE M ROULE
08/07/2009

DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service
Food and Drug Administration
Rockville, MD 20857

FILING COMMUNICATION

NDA 22-309

Unimed Pharmaceuticals, LLC
Attention: Kathryn Penhale-Unz
Director, Regulatory Affairs
901 Sawyer Road
Marietta, GA 30062

Dear Ms. Penhale-Unz:

Please refer to your new drug application (NDA) dated February 11, 2009, received February 12, 2009, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act, for AndroGel® (testosterone gel) 1.62%.

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 December 12, 2009.

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, 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 October 30, 2009.

During our filing review of your application, we identified the following potential Clinical and Clinical Pharmacology review issues:

Clinical:

1. The potential for secondary exposure of testosterone to women and children will be further considered. The results of transfer studies will be a review issue. Additional labeling may be requested, including information directed to patients to assure safe use.

2. We will conduct a detailed review of individual patients with serum testosterone level >2500ng/dL.

3. Hypertension was reported as a clinical adverse event (AE) in 6 drug treated patients and no placebo subjects. In one of these patients, worsening of hypertension may have been coincident with a rise in hematocrit. Provide an executive summary and analysis of hypertension as an AE and the relation of this AE to drug dose, systemic exposure, and duration of treatment. Include a discussion of potential worsening of pre-existing hypertension, and narratives for the patients involved. Your analysis should consider demographics, concurrent medications and concomitant medical diagnoses.

4. Syncope was reported as a clinical AE in 3 drug treated patients and no placebo patients in the double-blind period of Study S176.3.104. Provide an executive summary and analysis of syncope as an AE. Discuss related AEs, such as presyncope, and their relation to drug dose, systemic exposure, and the duration of treatment. Provide narratives for the patients involved. Your analysis should consider demographics, concurrent medications and concomitant medical diagnoses.

5. Five patients in the double-blind portion of Study S176.3.104 were reported to have an increase of hematocrit to greater than 54%. Provide an executive summary and analysis of these events in the double-blind and open label periods of Study S176.3.104, and their relation to drug dose, systemic exposure, and duration of treatment. Provide narratives for the patients involved. Your analysis should consider demographics, concurrent medications and concomitant medical diagnoses.

6. Twenty patients (9.8%) were observed to have “increased PSA”, defined as serum PSA > 4ng/dL or an increase from baseline in serum PSA of > 0.75ng/dL, during the double- blind period of Study S176.3.104. Provide an executive summary and analysis of these “increased PSAs” in the double-blind and open-label periods of Study S176.3.104. Provide a discussion of this event in relation to drug dose, systemic exposure, and duration of treatment. Provide narratives for the patients involved. Include information related to performance of prostate biopsies, biopsy results, and any changes in lower urinary tract symptoms in these patients. Your analysis should consider demographics, concurrent medications and concomitant medical diagnoses.

7. In two patients with serum testosterone level >2500 ng/dL, we note that the product was being used at more than the recommended dose, and in one patient with testosterone > 2500 ng/dL, the product was being used more frequently than advised. Provide an executive summary and analysis of all situations in the clinical studies where the recommended dose or frequency of dosing was exceeded. Consider proposing a strategy to limit these occurrences, which might include specific new instructions to patients.

8. It is not clear whether clinical AEs correlate with peak testosterone levels in Study S176.3.104. Provide an executive summary and analysis comparing clinical AEs and systemic exposure. Include all AEs, but pay special attention to hypertension, increased serum PSA and hemoglobin/hematocrit values.

Clinical Pharmacology:

9. The adequacy of the stability data provided in support of the 100% sample re-analysis that was conducted at (b) (4) will be a review issue.

10. Differences in systemic exposure appear to exist between the two application sites (shoulders/upper arms versus abdomen). Specific dosing instructions as they relate to the site of application will be a review issue.

11. Specific labeling instructions related to application site washing, use of moisturizer, and use of sunscreen will be a review issue.

We also request that you promptly submit the following Clinical Pharmacology information so that we may continue our review of the application:

1. As noted in your submission, "DHT has been shown to be stable in frozen human serum at 54.5 and 755 pg/mL using (b) (4) GC/MS (gas chromatography/mass spectrometry) Method MS 57 for a period of 2019 days at -20 °C. Data are stored on file at (b) (4). Provide relevant data in this regard.

2. You've also noted in your submission that "additional data demonstrating the stability of DHT in frozen human serum is being obtained by (b) (4) using LC/MS (liquid chromatography/mass spectrometry) methodology and data will be submitted to this report as an addendum". Clarify the anticipated date of this submission to the NDA.

3. For each of the analytes, confirm whether the range of quality controls evaluated in freeze/thaw and long-term stability studies would encompass the observed range of analyte concentrations in patients during the completed clinical trials for AndroGel® (testosterone gel)1.62%.

4. Quality controls (QCs) available in storage since May, 2003, were reportedly used for assessment of freeze/thaw and long-term stability (conducted in August, 2008). Clarify the source of these QCs and their storage location until the time of reanalysis (i.e. at (b) (4) Solvay, or (b) (4)). Comment on whether these were stored along with and under the same conditions as the study samples.

5. Provide the maximum number of freeze/thaw cycles that the study samples were subjected to while at (b) (4), Solvay and/or (b) (4) Clarify whether the available freeze/thaw stability data would encompass these sample handling conditions.

6. For the study S176.3.104, submit the serum testosterone pre-dose concentrations obtained during the titration phase on days 14, 28, and 42 for all subjects (analyzed by (b) (4) using RIA). Alternatively, provide their location in your NDA, if previously submitted. Clarify whether on dose titration days that overlapped with 24-hour PK days, pre-dose serum concentrations were assessed by both RIA (b) (4) and LC-MS/MS assays (b) (4)

7. Clarify the percentage of total serum samples that were available for re-analysis at the (b) (4) laboratory. State how many samples were missing from each study.

8. Serum analysis of the analyte SHBG appears to have been done by (b) (4) Elaborate on why these samples were not reanalyzed at (b) (4) along with other analytes.

We are providing the above comments to give you preliminary notice of potential review issues. Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review. Issues may be added, deleted, expanded upon, or modified as we review the application.

Please respond only to the above requests for additional 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.

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 in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We acknowledge receipt of your request for a full waiver of pediatric studies in children ages newborn to 17 years of age for this application. Once we have reviewed your request, we will notify you if the full waiver request is denied and a pediatric drug development plan is required.

If you have any questions, call Jeannie Roule, Regulatory Health 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

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/s/

George Benson

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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 22-309

NDA ACKNOWLEDGMENT

Unimed Pharmaceuticals, LLC
Attention: Kathryn Penhale-Unz
Director, Regulatory Affairs
901 Sawyer Road
Marietta, GA 30062

Dear Ms. Penhale-Unz:

We have received your new drug application (NDA) submitted under section 505(b)/pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA) for the following:

Name of Drug Product: AndroGel® (testosterone gel) 1.62%

Date of Application: February 11, 2009

Date of Receipt: February 12, 2009

Our Reference Number: NDA 22-309

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 April 13, 2009, in accordance with 21 CFR 314.101(a).

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 Drug Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

All regulatory documents submitted in paper should be three-hole punched on the left side of the page and bound. The left margin should be at least three-fourths of an inch to assure text is not obscured in the fastened area. Standard paper size (8-1/2 by 11 inches) should be used; however, it may occasionally be necessary to use individual pages larger than standard paper size. Non-standard, large pages should be folded and mounted to allow the page to be opened for review

without disassembling the jacket and refolded without damage when the volume is shelved. Shipping unbound documents may result in the loss of portions of the submission or an unnecessary delay in processing which could have an adverse impact on the review of the submission. For additional information, please see http:www.fda.gov/cder/ddms/binders.htm.

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

Sincerely,
{See appended electronic signature page}

Jennifer Mercier
Chief Project Management Staff
Division of Reproductive and Urologic Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

Jennifer L. Mercier
2/20/2009 03:04:49 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville, MD 20857

IND 50,377

Solvay Pharmaceuticals, Inc.
Attention: Steven Wojtanowski, RPh, MPH
Director, Regulatory Affairs
901 Sawyer Road
Marietta, GA 30062

Dear Mr. Wojtanowski:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for AndroGel (testosterone gel), 1.62%.

We also refer to your July 15, 2008, correspondence, requesting a meeting to discuss and clarify the Data Evaluation, Method Validation and Reassay Summary for Androgel (submitted via email on July 8, 2008) and dataset presentation to be submitted in the upcoming NDA submission.

We also refer to the meeting between representatives of your firm and the FDA on August 13, 2008.

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 at (301) 796-3993.

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

EXTERNAL PARTICIPANTS (continued):
Andrew Martin, PharmD. - Manager, Regulatory Affairs
Janet Benesh, Global Director - Global Project Management

BACKGROUND:

Solvay Pharmaceuticals currently markets AndroGel® (testosterone gel) 1% which was approved on February 28, 2000, for testosterone replacement in hypogonadal men. The sponsor has developed a new formulation of testosterone gel at a 1.62% concentration, which could reduce the volume of gel to be applied compared to the 1% formulation.

(b) (4)

(b) (4)

(b) (4)

Solvay has completed the clinical investigation of testosterone gel 1.62% under this IND. They are planning to submit NDA 22-309 to the FDA in the near future.Several data sets were generated for the clinical trials to address some "data validity concerns" which arose during the review by the Division of Metabolic and Endocrine Products (DMEP) o (b) (4)
(b) (4)

Solvay provided submissions on July 15, and July 30, 2008, which contained additional information, along with a request for a Type B meeting. Solvay requested to discuss and clarify the Data Evaluation, Method Validation and Reassay Summary for Androgel (submitted via email on July 8, 2008) and dataset presentation to be submitted in the upcoming NDA submission.

MEETING OBJECTIVES:

- Discuss why Solvay is proposing to amend the data analysis at this time and their rationale for the proposed changes.
- Discuss the path to be taken to resolve the deficiencies identified by the Division of Scientific Investigation's (DSI) audit of (b) (4) related to the data from all of their studies.
- Clarify the Data Evaluation, Method Validation, and Reassay Summary for AndroGel.
- Discuss a path forward for the filing of an NDA

DISCUSSION POINTS:

The following preliminary draft responses were provided to the sponsor on August 8, 2008, in response to the questions posed in the sponsor's meeting package update provided to the Division via email on July 29, 2008. 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.*

1. **Attachment 1 provides an overview of the circumstances and outcomes regarding the corrective actions taken to address deficiencies identified at the laboratory (b) (4) (b) (4) responsible for the majority of hormone analyses for this submission. These corrective actions led to the generation of multiple datasets for most studies.**

   Based on the background provided in Attachment 1, does the Division understand the need for the three data sets and their analyses under the originally approved SAP for the phase 3 Study S176.3.104 based on the findings as outlined in Attachment 1?

   Division Response: The Division understands the rationale for the three datasets and their analyses, but the information submitted to date does not resolve our concerns. See our Additional Comments below.

2. **Does the Division agree with how Solvay has placed the various datasets into the eCTD framework as outlined in Attachment 1?**

   Division Response: The placement of the datasets is not the issue of concern. See our response to Question 1 and the Additional Comments below.

Additional Comments

The minutes of the May 16, 2008, End-of-Review Meeting between Solvay and the Division of Metabolic and Endocrine Products (DMEP) state that DMEP did not agree that the data reevaluation and method revalidation work conducted by (b) (4) and Solvay had adequately

addressed or resolved the deficiencies identified by the Division of Scientific Investigation's (DSI) inspection of (b) (4)

According to the meeting packages submitted on July 15 and 30, 2008, (b) (4) served as the laboratory for most of the Phase 1 studies as well as the Phase 3 (S176.3.104) study evaluating the safety and efficacy of AndroGel 1.62% for NDA 22-309 (testosterone replacement in hypogonadal men), and the results of these studies were also affected by the inspection findings. Analytes specifically affected include testosterone, dihydrotestosterone (DHT), estradiol, and sex hormone-binding globulin. Despite the efforts of Solvay (b) (4), the Division of Reproductive and Urologic Products (DRUP) still finds the following deficiencies:

1. Assay Run Acceptance / Rejection Criteria: DRUP is concerned that the standard operating procedures (SOPs) for run acceptance/rejection criteria for samples in support of NDA 22-309, at the time of the analysis of the study samples, were not strictly adhered to by (b) (4) and were deficient. Consistent with what was stated by DMEP in the May 16, 2008, End-of Review meeting, DRUP also does not agree with the revision of acceptance/rejection criteria for already completed runs.

2. Method validation: DRUP does not agree that the post-study validation experiments (i.e., accuracy and precision) necessarily reflect assay performance during the analysis of the samples from the corresponding studies. Our concerns are summarized below:

    a. For the DHT assay, the specificity/selectivity evaluations conducted post-study do not necessarily reflect the condition of sample analysis at the time of the analysis of the study samples. For instance, earlier inspection findings included (but are not limited to):
        i. Lack of documentation on calibration standard stock solution and lots of antiserum used,
        ii. Replicate Quality Controls (QC) being rejected without justification,
        iii. Revised QC tables at least 3 times due to errors.

    b. The July 30, 2008, submission states that a review of the documentation associated with the testosterone LC-MS/MS method validation revealed that changes to the method occurred during the course of the method validation. It is unclear from the documentation whether the same method was used for study sample analysis. (b) (4) is proposing to conduct a revalidation of the testosterone method to address this ambiguity. However, it cannot be assured that the performance of the revalidated method reflects the performance of the testosterone assay used to analyze the study samples.

In support of our concerns, reference is made to the CDER Guidance to Industry: Bioanalytical Method Validation, which states that a bioanalytical method should be validated for the intended use or application. All experiments used to make claims or draw conclusions about the validity of the method should be presented in a method validation report. In order for a bioanalytical method to be considered valid, specific acceptance criteria should be set in advance and achieved for accuracy and precision for the validation of QC samples over the range of the standards.

Additional Discussion at the meeting::

- *The Sponsor believes that their application contains scientifically valid data and merits filing and review and that the NDA is ready to be submitted pending outcome of this meeting. The Sponsor has performed multiple audits of* (b) (4) *data and all bioanalytical reports have been amended to reflect corrective actions.*

- *The Division reiterated that Standard Operating Procedures (SOP) were not consistently followed at* (b) (4) *and that post-study method validation is not acceptable. Therefore, the review Division, the Division of Scientific Investigations (DSI), and the Office of Clinical Pharmacology (OCP) continue to have the same concerns and have not seen new data to allay those concerns.*

- *Solvay stated that they share the Division's concerns that post-study method validation is not optimal and that SOPs were not followed at* (b) (4) *but that the goal of this meeting was to discuss a path forward for this NDA.*

- *Solvay stated that 98% of all samples for all studies are available and are within the validated stability period. With this in mind, Solvay proposed several options for re-analysis of samples from the completed clinical trials. The sample re-analysis would be conducted at* (b) (4)*, using a validated method and following SOPs. The following options were discussed during the meeting:*
  - *Re-assay of Day 112 samples from the Phase 3 clinical trial only.*
  - *Re-assay of Day 112 and some other samples from the Phase 3 clinical trial with subsequent use of correlation analyses between the* (b) (4) *assay results to support use of the* (b) (4) *data as the primary source for NDA data.*
  - *Re-assay of all Phase 3 samples only.*
  - *Re-assay of all Phase 3 samples and all Phase 1 samples from studies critical for NDA review and labeling.*

- *The Division, DSI and OCP stated that all options for partial re-analyses were considered inadequate in resolving the pending deficiencies, as these will necessitate significant reliance on the* (b) (4) *data. The Division also noted that, in addition to the Phase 3 study, Phase 1 studies such as evaluation of transfer potential, site of application, and BA study, are expected to be critical for the NDA review and labeling of Androgel 1.62 % and that samples from these Phase 1 studies should also be re-analyzed at* (b) (4)*.*

- *Additional discussion ensued in regard to the value of a correlation analysis between samples analyzed by* (b) (4) *and samples analyzed previously by* (b) (4)

- *The Division, DSI and OCP reiterated that all Phase 3 samples and all Phase 1 samples from studies crucial to approval and labeling should be re-analyzed using a validated method and following SOPs (e.g., a* (b) (4) *that all options for partial re-analysis were inadequate, and that the correlation analysis would not resolve the concerns. Solvay*

agreed to consider moving forward in this manner (re-assaying all samples) if that were the Division's recommendation.

- *Sponsor stated that a correlation analysis report would be included in the application even if all samples were re-analyzed at* (b) (4) *The Division responded that it would review the new* (b) (4) *data for approval, and would not compare it to any other data from any of the other submissions. The correlation analysis report may or may not be reviewed.*

DECISIONS (AGREEMENTS) REACHED:

- Because a significant portion of the study samples were available for re-assay, the Division agreed to accept results from a complete re-assay of all available samples from all NDA studies for the three critical analytes (T, DHT and E2) at (b) (4) as an appropriate means of resolving the pending deficiencies. Efficacy and safety analyses would be based on the new (b) (4) results. The Sponsor may submit previous results, but (b) (4) data will be used as primary and (b) (4) data will be used as supportive evidence. The Sponsor is aware that this will require the re-writing of study reports and new datasets. The Sponsor agreed to consider this recommendation.

- The Sponsor was reminded that the NDA submission should provide data supporting acceptable stability of the re-assayed samples. This will be a review issue.

UNRESOLVED ISSUES OR ISSUES REQUIRING FURTHER DISCUSSION: None

ACTION ITEMS:

- Meeting minutes will be provided to the sponsor within 30 days.

ATTACHMENTS/HANDOUTS: Slide presentation presented at the meeting.

Pre-NDA Meeting
AndroGel 1.62%

August 13, 2008

Agenda

- Introductions
- Relevant Background and Timeline
- Solvay's corrective actions to date
- Differences in the AndroGel 1.62% application and [redacted] (b) (4)
- Regression analyses and correlation for T to support the AndroGel 1.62% data
- Agreement on path forward for filing the application

Background and Timeline

- May 2007: Solvay submits NDA for use of AndroGel 1% in the [redacted] (b) (4)
- [redacted] (b) (4)
- [redacted]
- [redacted] (b) (4) Solvay began audits of [redacted] (b) (4) to assess the impact of the 483
- [redacted] (b) (4)
- January 22, 2008: Pre-NDA meeting with DRUP for AndroGel 1.62%
- January 31, 2008: [redacted] (b) (4) complete response to FDA related to 483
- February 11, 2008: Solvay informs DRUP of the potential impact on the AndroGel 1.62% program and proposed corrective action

Corrective Actions for AndroGel 1.62% Program

- Audited [redacted] (b) (4) (100% review of the QC data, method validations)
- Engaged DRUP in dialogue to ensure transparency
- Worked with [redacted] (b) (4) to address the issues as completely as possible
- All study reports amended to reflect corrective action taken and re-analyses performed
- For the pivotal phase 3 study (S1763104), three datasets and analyses generated to show the robustness of results and correlation with initial data

Areas of Agreement

- Share FDA's concerns regarding the findings by DSI at [redacted] (b) (4)
  - SOP for run acceptance/rejection not adhered to
  - Incomplete pre-study method validation
  - Inadequate source documentation
- Agree the retrospective evaluation of analytical runs and the post study method validation are not optimal

Differences Between 1.62% and the 1% (Pediatric) Applications

- **AndroGel 1.62% Studies**
  - **Minimum overlap in time**

    [redacted] (b) (4)

    1.62%: 2006-2008
  - **More complete In-study documentation**
  - **More complete and traceable data contained within the bioanalytical reports**
  - **Different methods to analyze T and E2 (LCMS vs RIA)**

- **Product**
  - [redacted] (b) (4)
  - **Eight years safety experience in the intended adult population**
  - **More extensive safety and efficacy database**

Regression Analyses and Correlation for T to Support the AndroGel 1.62% Data

- **Pivotal phase 3 study (S1763104) original sample results vs. reassay results (due to run re-evaluations)**
  - **Excellent correlation demonstrates method reproducibility**

- **[redacted] RIA (titration and safety samples) vs. [redacted] LCMS (PK samples)**
  - **Good correlation despite the different methods**
  - **Studies S1761002 and S1763104**

- **Method comparison between the two LCMS assays used in the AndroGel 1.62% program [redacted]**
  - **Excellent correlation**
  - **Confirms accuracy of the [redacted] method**

Efficacy and Safety of AndroGel 1.62%

- **Primary efficacy**
  - Endpoint achieved
  - Robust results
- **Secondary efficacy**
  - Two of three endpoints achieved
  - None of the original T values >2500 ng/dL were affected by reevaluation and reassay
- **Safety profile of the data collected in the AndroGel 1.62% program are consistent with:**
  - Medical literature
  - Solvay's experience to date with AndroGel 1%

Path Forward

- Solvay desires to continue working with the review Division and DSI to resolve concerns/issues
- Solvay concludes the application contains scientifically valid data and merits filing and review
- Does DRUP agree?

Primary Success Criteria
Average Concentration within PK

- **75% of Subjects Cav 300-1000 ng/dL**
  - **Achieved 81.5% on Day 112**
  - **Achieved 75.1% and 83.2% on Days 14 and 56**
- **Lower bound of 95% CI $\geq$ 65%**
  - **Achieved 75.0% on Day 112**
  - **Achieved 68.6% and 76.9% on Days 14 and 56**

Secondary Success Criteria
PK Maximum T Concentrations

- **C_{max} ≤ 1500 ng/dL in ≥ 85% of subjects**
  Achieved on all PK days
- **C_{max} 1800-2500 ng/dL in ≤ 5% of subjects**
  Achieved on all PK days
- **C_{max} > 2500 ng/dL in none of the subjects**
  Previously discussed on January 22, 2008

Linked Applications	Sponsor Name	Drug Name
IND 50377	UNIMED PHARMACEUTICALS LLC	ANDROGEL (TESTOSTERONE)

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

/s/

MARK S HIRSCH
09/11/2008

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

IND 50,377

PRE-NDA MEETING MINUTES

Solvay Pharmaceuticals, Inc.
Attention: Steven Wojtanowski, R.Ph., M.P.H.
Assistant Director, Regulatory Affairs
901 Sawyer Road
Marietta, GA 30062

Dear Mr. Wojtanowski:

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 1.62%.

We also refer to the meeting between representatives of your firm and the FDA on January 21, 2008. The purpose of the meeting was to discuss your plans to submit a New Drug Application for testosterone gel 1.62%.

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 C. 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

BACKGROUND:
The Sponsor currently markets AndroGel® (testosterone gel) 1%, which was approved on February 28, 2000, for testosterone replacement in hypogonadal males. The Sponsor has developed a new formulation of testosterone gel at 1.62% concentration, which could reduce the volume of gel to be applied as compared to the 1% formulation. The Sponsor has conducted seven Phase 1 studies and one Phase 3 trial in support of an NDA for the new formulation. Another Phase 1 transference study is ongoing. The Sponsor requested this meeting to discuss the data to be submitted for filing a New Drug Application.

DISCUSSION POINTS:
The discussions that follow were generated from the Sponsor's specific questions. The Division's preliminary responses were conveyed to the Sponsor on January 16, 2008. After a brief slide presentation, which is attached, the responses to meeting questions were discussed.

1. *Through previous discussion and agreement with FDA, several phase I studies were conducted with testosterone gel 1.62%. Final synopses of the phase 1 studies (S176.1.004 is the final draft version) completed to date are included in this briefing book (Section 9). We believe that information provided within the prescribing information based on the data from these phase I studies will be sufficient to ensure safe use of the product in the intended population.*

   S176.1.001 *– evaluation of 3 new testosterone gel formulations*
   S176.1.002 *– dose ranging evaluation of 1.62% formulation*
   S176.1.003 *– testosterone transfer from dosed males to female partners*
   S176.1.004 *– cumulative irritation and sensitization study*
   S176.1.005 *– effect of washing application site*
   S176.1.006 *– effect of sunscreen/moisturizer in conjunction with gel*
   S176.1.007 *– evaluation of application sites*

   Does the Division agree that the data generated from these phase I studies completed to date are sufficient to file the initial application and that no additional phase I studies to assess specific product characteristics are required prior to NDA submission?

   Division Response: No. The final results from Study S176.1.008 (the follow-up transfer study) should be submitted at the time of NDA filing because the potential for transfer will be a major review issue.

   Clinical Pharmacology Comment: As long as the formulations used in Phase 1 and Phase 3 trials are the same as the to-be-marketed formulation, we agree that that no additional Phase 1 studies are required.

   Sponsor Response: The Sponsor agreed not to submit the initial NDA until Study S176.1.008 was finalized and included in the NDA submission. The Sponsor confirmed the formulation used in all Phase 1 and Phase 3 clinical studies was the "to-be-marketed formulation."

2a. *We have evaluated the results from Study S176.1.003 (transfer study) and Study S176.1005 (washing study). Results from S176.1.003 demonstrated that secondary exposure of testosterone to females was observed when the male did not wear a t-shirt, and that transfer was decreased by approximately 45% when the male wore a t-shirt. Results from S176.1.005 demonstrated that washing the application site as early as 2 hours post-dose had minimal effect on the bioavailability of testosterone gel 1.62% in hypogonadal men. Furthermore, based on the tape stripping data from S176.1.005, washing of the skin removes at least 80% of residual testosterone from the skin surface. Using data from both of these studies we anticipate the language in the labeling can be written such that the labeling would provide adequate information to healthcare providers and patients to ensure safe use of the product in the intended population.*

To further characterize the transfer potential of testosterone gel 1.62% and to evaluate measures to prevent or minimize secondary exposure to others, another phase I study, S176.1.008 is currently being conducted. The protocol for study S176.1.008 is included in this briefing book (Section 10) and was submitted on 16 November 2007. Data from this study is expected to provide additional guidance for the labeling regarding transfer potential and instruction on the prevention or minimization of secondary exposure.

Although we believe the data obtained from the above phase I studies would be sufficient to provide adequate information to educate healthcare providers and patients how to prevent or minimize secondary exposure of testosterone from treated males to others, the data generated from S176.1.008 will further strengthen the labeling information.

Does the Agency agree that the data from the phase I studies S176.1.003, S176.1.005 and S176.1.008 should provide sufficient data to address the information for inclusion in the prescribing information to adequately educate physicians and patients on how to prevent or minimize secondary exposure of testosterone from testosterone-treated skin to others?

Division Response: These three studies should suffice. However, the data collected will need to be reviewed to determine whether it is sufficient to address the issue.

Additional Discussion: The Division clarified that no additional studies were being requested at this time. Whether the data from these three studies is sufficient to address the issue of transference in labeling or risk management will be a review issue.

2b. *As noted, we intend to submit the NDA in February 2008; however, the final results from Study S176.1.008 will be provided with the 120-day safety update. Since the nature of this study is to further evaluate the potential of product transfer to others, Solvay does not believe it is part of the pivotal efficacy and safety information and therefore proposes to include the final study report in the 120-day safety update.*

Does the Agency agree that the submission of the S176.1.008 final study results can be submitted at the 120-day safety update with no impact to the PDUFA goal date?

Division Response: No. The final results from Study S176.1.008 should be submitted at the time of NDA filing.

Sponsor Response: Agreed by Sponsor.

3. *Preliminary results of Study S176.3.104, phase III pivotal evaluation of testosterone gel 1.62% in hypogonadal men are included in this briefing book (Section 11). These results demonstrate efficacy with > 81% of patients achieving the pre-defined endpoint of "75% of patients within the eugonadal range at Day 112 with the lower bound of the 95% confidence interval not less than 65%." Also of note, >75% and >83% of patients demonstrated efficacy by Day 14 and Day 56 respectively.*

   The enclosed "Critical C_{max} Subject Overview (Study S176.3.104)" (Section 12) identifies and summarizes 24 individual concentration values > 2500 ng/dL which were observed at various sample collection timepoints and dose levels across 16 total patients. Also provided are the 24-hour concentration-time profiles of observed testosterone for these 16 patients from Days 14, 56, 112 and 182. The aberrantly high, supraphysiologic concentrations do not consistently appear throughout the 24-hour sampling period or across study days or dose levels within each respective subject profile. Testosterone concentrations > 2500 ng/dL do not appear to be dose related and were rare occurrences representing < 0.5% of individual samples collected throughout the entire study and were observed in < 5% of subjects on any of the 4 pharmacokinetic days.

   Possible reasons for these elevated testosterone levels include contamination of serum samples by product remaining on the skin and individual variability in dose compliance, skin penetration and absorption, or metabolism. Adverse events are summarized in the "Critical C_{max} Subject Overview (Study S176.3.104)" for these 16 patients, and demonstrate there is no direct evidence of adverse events that correlate with the transiently elevated serum testosterone levels. We continue to evaluate other explanations for these elevated testosterone levels and will continue to provide the Agency with information if it becomes available.

   Testosterone concentration values > 2500 ng/dL were also observed in phase I studies S176.1.002 (n=2), S176.1.005 (n=9), and S176.1.007 (n=1). Phase I occurrences of testosterone > 2500 ng/dL appeared only with dose levels of 5 and 6.25 grams of gel per day. All dosing in the phase I studies was conducted at a fixed dose level and purposely evaluated the highest gel dose levels. Based on this, we believe testosterone concentrations > 2500 ng/dL observed in phase I have minimal impact on the overall safety evaluation of testosterone gel 1.62%.

   We believe testosterone concentrations in this supraphysiologic range can be addressed through dosing, monitoring, and titration instructions in the product label, including additional dose titration if monitoring reveals excessively high serum testosterone

concentrations. The proposed dosing recommendations would be to initiate therapy at a dose of 2.5 grams of gel per day and titrate as needed in 1.25 gram increments to maintain the patient within the eugonadal range.

Does the Agency believe the testosterone concentrations observed in the phase 3 study and/or the phase 1 studies would prohibit approval of this product despite the supporting safety data collected in these studies?

Division Response: Maximum serum T concentrations above 2500 ng/dL will be a major review issue for this NDA and should be addressed in great detail in the application.

Clinical Pharmacology Comment: It is premature to discuss this at this time. As communicated to you during the teleconference held on March 26, 2007, Study S176.1.007 did not demonstrate comparable PK across the application sites. The product would be labeled according to the Phase 3 usage only, provided the Phase 3 study result meet the pre-specified C_{avg} and C_{max} criteria. If the Phase 3 trial fails to meet the pre-determined criteria, it will not be possible to ascertain whether the failure was related to the site of application and therefore, salvaging the data under those circumstances would be difficult as the Phase 3 design doesn't allow stratification by site application. Decisions will be made after thorough review of the submitted data and information.

Additional Discussion: The Sponsor explained that while the primary endpoint was met, the secondary endpoint was not. There were 12 subjects who had C_{max} greater than 2500 ng/dL. The Sponsor provided several possible explanations for these outliers. The Division explained that the success criteria and cutpoints for C_{avg} and C_{max} endpoints were based on historical data, which have been consistently conveyed to Sponsors developing testosterone replacement therapies. Failure to totally meet these criteria does not preclude a review and does not categorically preclude approval of the NDA. The Sponsor was advised that it has the burden to explain and convince the Division that the elevated values are not an important safety issue. The Sponsor should provide as much detail as possible to provide evidence of a non-product cause for each case of C_{max} greater than 2500 ng/dL.

4. *As discussed during the 18 October 2006 end of phase 2 meeting, the phase 1 studies conducted in hypogonadal men (S176.1.001, S176.1.002, S176.1.005, S176.1.006, and S176.1.007) have been integrated and analyzed. The phase 3 safety data remains separate. We believe safety data collected from the seven completed phase I studies and the phase III trial representing a total of 370 hypogonadal men and 283 healthy male volunteers exposed to testosterone gel 1.62% for up to one year adequately demonstrates safety of this product.*

Does the Agency agree this amount of data is sufficient to support the safety of this product?

Division Response: With the understanding that skin safety data out to Day 182 from at least 50 subjects will be submitted at the time of NDA filing, we agree.

Sponsor Response: The stated that skin safety data from 179 subjects through Day 182 would be provided in the NDA.

Does the Agency agree with the presentation of the integrated phase I data separate from the phase III data are still adequate for this NDA?

Division Response: Yes.

5. *We propose to use the trade name "AndroGel® (1.62% testosterone gel)" as the trade name for the product once approved. Based upon FDA's response to a question at the EOP-2 meeting about the trade name for this product, Solvay would like to confirm that/clarify whether FDA will allow both the 1% and 1.62% products on the market at the same time, with both products having the trade name "AndroGel" provided that the trade name is accompanied by the strength of each product.*

Does the Agency agree?

Division Response: We do not recommend use of the strength or any other numbers in the proprietary name or established name of product. As recommended in the EOP2 meeting, the strength should be presented in conjunction with the established name as follows:

AndroGel® (testosterone gel) 1.62%	AndroGel® (testosterone gel) 1%

We have not identified any safety objections to having both strengths on the market at the same time, but please provide information on how you plan to minimize dispensing and administration errors of this new formulation as it is introduced into the market.

Sponsor Response: The Sponsor agreed to provide a separate section within the NDA to address how dispensing and administration errors can be prevented when both products are on the market. This should include such information as comparison of cartons, containers, labeling, and prescriber education materials.

6. *The NDA will be filed as an eCTD application. The submission will be made via the FDA portal or via DVD and will be fully compliant with eCTD guidance documents.*

Does the Agency have any additional requirements for this application format?

Division Response: No.

Clinical Pharmacology Comment: Submit the following for review:

a. A table including all of the clinical study numbers, titles, and formulation.
b. Phase 3 study raw data including individual 24 hr PK data plots for all subjects on each day assessed and a table of PK data summarized by BMI and site of applications, respectively.

Additional Discussion: The Sponsor should include a PK data plot for each day assessed for all subjects. The PK data should capture the application site associated with a particular PK day. The Sponsor may summarize the BMI (break down by quartiles) but the raw data should be included as well.

7. *As discussed during the 18 October 2006 meeting, we intend to submit the complete NDA with final study reports for all studies except S176.1.008 (follow-up transfer study). The initial submission will contain efficacy data through Day 112 and safety data through Day 182.*

   At the 120-day update we intend to submit the PK efficacy data through Day 182 and safety data through Day 266 (consisting of listings/tables, etc.) as well as the final study report for phase I study S176.1.008.

   The requested 7-month update will contain the final study report with one-year efficacy and safety data for Study S176.3.104.

   Does the Agency agree that this submission strategy and the information to be contained within each submission are acceptable?

   Division Response: No. As previously stated, final results from Study S176.1.008 (the follow-up transfer study) should be submitted at the time of NDA filing.

   In addition, we do not agree with your proposal to submit the final study report for the one-year efficacy and safety study S175.3.104 at Month 7, as such would present significant logistical problems for the review schedule. Instead, we now request that you submit **only** the required standard Safety Update on Day 120 and no others. Submit the final study report for Study S176.3.004 subsequent to this NDA action, either as an amendment to the IND or as a supplemental NDA if you wish to pursue additional labeling claims from the maintenance phase.

   Sponsor Response: The Sponsor agreed to provide tables and listings for only safety data through Day 364 as part of the 120-day safety update report.

8. *Datasets for the studies included in the application will be submitted as CDISC SDTM (version 3.1.1). An annotated CRF will be included with each dataset as appropriate (a blank CRF is contained within each study report). We intend to submit both SDTM and analysis datasets for each of the studies as well as the analysis dataset for the integrated dataset.*

Does the Agency agree with this strategy for submitting datasets within the application?

Division Response: Yes, we agree with your strategy, but we also like to remind that variable definition files for each analysis datasets must also be included in the submission.

Sponsor Response: Agreed by Sponsor

Additional CMC Comments:

- Complete drug substance information should be provided either in the application, by cross-reference to your approved NDA or in a Drug Master File (DMF) with the appropriate Letter of Authorization. If information is provided in a cross-referenced NDA or DMF, we request that the following information be provided in the NDA for ease of review: General information, physico-chemical properties, and Specifications.

- Complete information on the drug product should be provided in the NDA. For example, provide full information on formulations used throughout the clinical trials, and identify if there were any manufacturing site or process changes. Stability data should be provided generated on product in the to-be-marketed container closure. Clearly identify all manufacturing sites and their responsibilities in the NDA. Information for the carton and immediate container labels, including any logos and color, should be provided in order to allow full review of these labels.

Additional Discussion: The Sponsor was encouraged to reschedule the cancelled CMC specific pre-NDA meeting. The Sponsor explained that there was no new information and agreed to provide all requested CMC information within the NDA.

ACTION:

- The meeting minutes will be conveyed to the within 30 days.

ATTACHMENTS:

- Sponsor's slide presentation

Testosterone Gel 1.62%

Overview of Elevated Serum Testosterone Concentrations

Solvay
Pharmaceuticals

SOLVAY

T>2500 ng/dL in Phase 1

- Observed Testosterone >2500 ng/dL
  - 12 subjects
  - 17 samples
- Only at highest dose (5.0 g/d, 6.25 g/d)
- Fixed dosing schedule
- Only after application to Upper Arms/Shoulders
- Typically after multiple days of dosing
- Once per PK profile (1 exception)
- DHT/T ratio within the expected range

Primary Success Criteria
Average Concentration within PK

- 75% of Subjects Cav 300-1000 ng/dL
  - Achieved 81.5% on Day 112
  - Achieved 75.1% and 83.2% on Days 14 and 56
- Lower bound of 95% CI ≥ 65%
  - Achieved 75.0% on Day 112
  - Achieved 68.6% and 76.9% on Days 14 and 56

2

Secondary Success Criteria
PK Maximum T Concentrations

- C_{max} ≤ 1500 ng/dL in ≥ 85% of subjects
  Achieved on all PK days
- C_{max} 1800-2500 ng/dL in ≤ 5% of subjects
  Achieved on all PK days
- C_{max} > 2500 ng/dL in none of the subjects
  Discussion

3

T>2500 ng/dL in Phase 3

- Frequency
- Characteristics
- Possible causes
- Safety

Frequency of T>2500 ng/dL in Double Blind Phase

- 16/234 subjects assigned T
- 12/738 Cmax values
- 24/8060 T values

Characteristics of T>2500 ng/dL

- Sporadic
- Brief (not persistent within a PK profile)
- Inconsistent (between PK profiles)

Timing of T>2500 Occurrences

- Before any study drug administration (2 values)
- Pre-dose during the study (6 values)
- During a PK profile (16 values)

Likely Causes of Sporadic, Brief, Inconsistent T>2500 ng/dL

- Protocol violation
- Artifact of sampling protocol
- Acute increases in systemic absorption

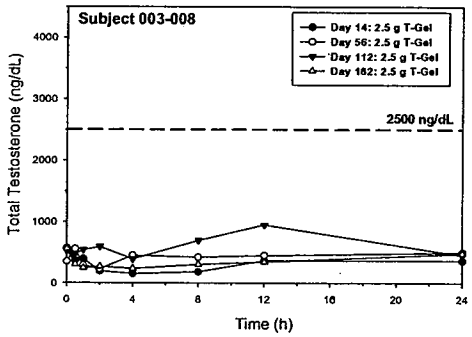
Protocol violation – Testosterone treatment against protocol

- Non-study drug administration
- Double dosing or excessive dosing with study drug prior to venipuncture

T>2500 before any study drug

Subject 003-008 (p. 142)

- **Baseline T = 3460 ng/dL**
- **DHT/T = 0.0078**

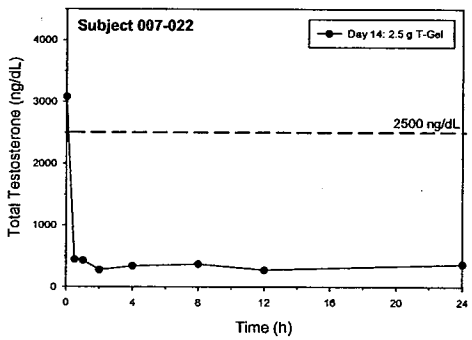


10

Pre-dose during study

Subject 007-022 (p. 125)

- **T = 3080 ng/dL**
- **2.5 g/d dose**
- **Day 14**
- **DHT/T = 0.015**



11

Physiologic and Anatomic Considerations (Relevant to Sampling Artifact)

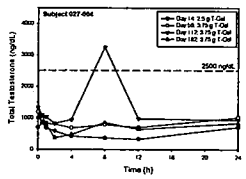
- **Skin is metabolically active**
  - Epidermis metabolizes T to DHT
  - Stratum corneum is not metabolically active
- **Skin is a reservoir for Testosterone (T)**
- **Substantial interstitial water in dermis**
  - Drained by lymphatics to venous system
  - Available for capillary absorption
  - Potential migration in extracellular space

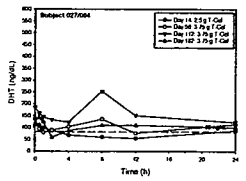
12

T>2500 during a 24 h PK profile

Subject 027-004 (p. 128)

- **T = 3240 ng/dL**
- **Day 112, 8 h post-dose**
- **3.75 g/d dose**
- **DHT/T = 0.078**





13

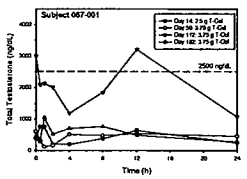
Acute increases in systemic absorption

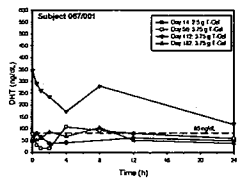
- **Capillary dilation and contraction**
  - Heat
  - Emotion
- **Lymphatic**
  - Increased hydration of dermis increasing pressure
  - Exercise/motion

Pre-dose and Post-dose during study

Subject 067-001 (p. 140)

- **Predose T = 2990 ng/dL**
- **Dose = 3.75**
- **Day = 112**
- **DHT/T = 0.116**





Safety

- Sporadic, Brief, and Inconsistent
- No TESAEs associated with T>2500 ng/dL
- No new safety signal identified after review of TEAEs and elevated T (Cmax>1500 ng/dL)
- Clinical safety experience similar to AndroGel® 1%

Summary

- T>2500 ng/dL occurred inconsistently
  - After all doses from 0 to 5.0 g/d
  - Throughout the 6 months of study (0 to 182 days)
  - At any time after a dose, but not persistently
  - Occasionally in the same subject or in the same PK profile
  - No associated TESAEs
- Compared with other T gel experience
  - Similar to medical literature
  - Safety profile consistent with AndroGel 1%

Discussion re T>2500 ng/dL

- Is this a sufficient level of detail for review of the application?
- As presented, does evidence of systemic absorption resulting in T>2500 ng/dL preclude approval of the product, given the safety experience?

Linked Applications	Sponsor Name	Drug Name
IND 50377	UNIMED PHARMACEUTICALS INC	ANDROGEL (TESTOSTERONE)

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

/s/

MARK S HIRSCH
02/19/2008

MEMORANDUM OF MEETING MINUTES

MEETING DATE: October 18, 2006 **TIME:** 9:30 am – 11 am

LOCATION: Food and Drug Administration
White Oak Building 22, Conference Room 1311
10903 New Hampshire Avenue
Silver Spring, MD 20993

APPLICATION: IND 50,377

DRUG NAME: Testosterone gel 1.62%

INDICATION: Testosterone replacement in hypogonadal males

TYPE OF MEETING: Type B, End-of-Phase 2

MEETING CHAIR: Mark Hirsch, M.D.

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

FDA ATTENDEES:
Mark Hirsch, M.D. – Acting Deputy Director, Division of Reproductive & Urologic Products (DRUP)
Harry Handelsman, D.O. – Medical Officer, DRUP
Stephan Ortiz, R.Ph., Ph.D. – Senior Clinical Pharmacologist, Office of Clinical Pharmacology
Donna Christner, Ph.D. – Pharmaceutical Assessment Lead, Pre-Marketing Assessment Division II (PMAD II), Office of New Drug Quality Assessment (ONDQA)
Rajiv Agarwal, Ph.D. – Chemistry Reviewer, PMAD II, ONDQA
David B. Lewis, Ph.D. – Pharmaceutical Assessment Lead, Branch III, Division of Post-Marketing Assessment (DPMA), Office of New Drug Quality Assessment (ONDQA)
Leslie McKinney, Ph.D. – Pharmacology/Toxicology Reviewer, DRUP
Eric Andreasen, Ph.D. – Pharmacology/Toxicology Reviewer, DRUP
Denise P. Toyer, Pharm.D. – Deputy Director, Division of Medication Errors and Technical Support, Office of Surveillance and Epidemiology
Margaret Kober, R.Ph., M.P.A. – Chief, Project Management Staff, DRUP
John Kim, R.Ph., J.D. – Regulatory Health Project Manager, DRUP

SOLVAY ATTENDEES:
Hjalmar Lagast, M.D. – VP, Clinical Development & Medical Affairs
John Brennan, Ph.D. – Group Director, Clinical Development
Michael Miller, Pharm.D. – Assistant Director, Clinical Development
Claire Pexman-Fieth, M.D. – Global Medical Affairs Director
Steven Wojtanowski, R.Ph., M.P.H. – Asst. Director Regulatory Affairs
Jodi Miller, Pharm.D., M.S.– Asst. Director, Clinical Development
Janet Benesh – Sr. Director, Project Leadership
Richard Oh, M.D. – Medical Director, Quintiles, Inc.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville, MD 20857

IND 50,377

MEETING MINUTES

Solvay Pharmaceuticals, Inc.
Attention: Steven Wojtanowski, R.Ph., M.P.H.
Assistant Director, Regulatory Affairs
901 Sawyer Road
Marietta, GA 30062

Dear Mr. Wojtanowski:

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 1.62%.

We also refer to the Type B meeting between representatives of your firm and the FDA on October 18, 2006. The purpose of this meeting was to discuss the results from the Phase 1/2 pharmacokinetic study, and to discuss the proposed Phase 3 protocol and the clinical development plan for the lower volume formulation.

The official minutes of that meeting are enclosed. You are responsible for notifying us of any significant differences in understanding regarding the meeting outcomes.

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

Sincerely,

{See appended electronic signature page}

Mark Hirsch, M.D.
Acting Deputy Director
Division of Reproductive and Urologic Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosure

BACKGROUND:
AndroGel® (testosterone gel) 1% was approved on February 28, 2000, for testosterone replacement in hypogonadal males. The Sponsor wishes to increase the concentration of testosterone in the currently market product from 1% to 1.62% so as to lower the volume of gel applied. The Sponsor conducted two Phase 1 pharmacokinetics studies and is requesting this meeting to discuss results from these studies and development plans for submission of a New Drug Application.

DISCUSSION POINTS:
The discussions that follow were generated from the Sponsor's specific questions, the Division's preliminary responses, and a slide presentation, which is attached.

8. Questions for the Agency
8.1. Preclinical Questions

8.1.1. *NDA 21-015 AndroGel® (testosterone gel) 1% characterized the toxicity of AndroGel at 1% testosterone concentration to sufficiently support approval by FDA. The intention of the current development program is to produce a product that delivers about the same amount of testosterone to the plasma in a smaller applied volume. Therefore, the new product will not have different systemic toxicity. However, in recognition of a possible local (dermal) response to the higher concentration, an appropriate irritation study in rabbits and a dermal sensitization study in guinea pigs were conducted (outlined below). Solvay concludes that these studies combined with the safety data from clinical studies are sufficient to characterize local responses and that no other non-clinical studies are required for approval of the NDA for the testosterone gel 1.62% product.* ***Does the Division agree?***

A Primary Skin Irritation Study in Rabbits with LVTG. (b) (4) Study No. QIT00001
Final Report submitted 31 March 2006 to IND 50,377, Serial #122
Groups of New Zealand White rabbits received a single dermal application of either placebo gel (containing 73.5% ethanol and 1% isopropyl myristate (IPM)), 4% testosterone gel (also containing 73.5% ethanol and 2.5% IPM) or testosterone gel 1.62% (also containing 73.5% ethanol and 1% IPM). Possible irritation at the skin test sites was scored for the subsequent 14 days after application. The test articles were judged to be nonirritating.

A Dermal Sensitization Study in Guinea Pigs with LVTG – Standard Buehler Design. (b) (4) Report No. QIT00002
Final Report Submitted 18 July 2006 to IND 50,377, Serial #125
Groups of Hartley-derived albino guinea pigs were treated with either placebo gel (containing 73.5% ethanol and 1% isopropyl myristate (IPM)), 4% testosterone gel (also containing 73.5% ethanol and 2.5% IPM) or testosterone gel 1.62% (also containing 73.5% ethanol and 1% IPM) according to the standard Buehler study design. This included nine induction exposures followed by a challenge exposure two weeks later, a re-challenge phase, and use of a positive DNCB control. Possible weak sensitization (scored as ± or 1) was observed in all three test groups, similar in response level for the placebo as for the active gels. The response could have been

due to ethanol because all test articles contained 73.5% ethanol, and it has been shown previously that ethanol has weak sensitization potential in the guinea pig.

Division Response: Yes, the nonclinical studies are sufficient to file an NDA, provided that there are no unexpected or unusual findings observed in clinical studies. Based upon your intent to conduct application site evaluations during the Phase 3 study (S1763013), and to conduct a dedicated sensitization/irritation potential study (S1761004), the generated data would be sufficient from a clinical perspective to assess irritation and sensitization in humans. You should define the application site evaluation procedures in the Phase 3 study in more detail. Also, for study S1761004, irritation potential should be assessed using the maximum to-be-approved dose.

Solvay Response: Division's response is acceptable and no follow-up discussion was necessary.

8.2. Clinical Development Program Questions

8.2.1. *Per the FDA Photosafety Testing Guidance for Industry (May 2003), photoirritation studies in humans should be considered for all drug substances and formulation components that absorb UVB, UVA, or visible radiation (290-700 nm). Testosterone gel 1.62% is composed of testosterone, ethanol, purified water, sodium hydroxide, carbomer 980 and isopropyl myristate (IPM). In order to assess the photoirritation potential of testosterone gel 1.62%, the formulation components with the highest potential for radiation absorption were evaluated via UV/VIS spectroscopic scans. The formulation components chosen for evaluation included the active ingredient, testosterone, and the* (b) (4), *IPM. The UV/VIS spectroscopic scans were performed using* (b) (4) (b) (4) *(major component in the formulation) mixture as diluent. The testosterone and IPM scans showed absorption maxima of 245 nm and 209 nm, respectively. There was no significant absorption observed between 290-700 nm. In addition, UV/VIS scans of the testosterone gel 1.62% formulation, a placebo formulation, and testosterone gel 1% formulation were also performed by* (b) (4). *The placebo formulation demonstrated no significant absorption, and both the 1.62% and 1% formulations demonstrated absorption at 244 nm corresponding to testosterone. None of the formulations have any significant radiation absorption between 290-700 nm. Please see Appendix 11.6 for the UV/VIS scans described above. Since the testosterone gel 1.62% formulation and active components do not absorb UVB, UVA, or visible radiation (290-700 nm), we believe that clinical photosafety studies are not necessary. However, please note a clinical study to evaluate the sensitization and irritation potential of repeated applications of testosterone gel 1.62% will be conducted (Study S176.1.004).* ***Does the Agency agree that clinical studies to evaluate photoirritation and photoallergy potential of testosterone gel 1.62% are not required?***

Division Response: Yes, we agree.

Solvay Response: No follow-up discussion was required.

8.2.2. ***Are the phase I studies outlined in Section 10.4, Table 7 (and in detail in Appendix 11.3) planned for submission in the NDA application acceptable to FDA as complete for the Division to file the initial application?***

Division Response: The Phase 1 clinical study concepts are generally acceptable, pending our review of the final protocols. However, we would like the results from the sunscreen interaction study (S1761006) submitted with the original NDA. In your final protocol for study S1761004, specify the dose to be used.

Additional Discussion: The Division clarified that the Sponsor can start these Phase 1 studies upon submission of the protocols, but a final review of the protocols is required for a definitive answer as to their acceptability. The Division recommended that the Sponsor should submit all future Phase 1 studies at same time and highlight any specific questions in the cover letter. In addition, the Division stated that the entire dose of the drug should be applied to determine irritation in the Phase 1 irritation study.

8.2.3. ***Is the phase I study (S176.1.006) outlined in Section 10.4, Table 7 (and in detail in Appendix 11.3) planned for post-approval acceptable to the FDA as part of Solvay's post-approval commitment?***

Division Response: No, you should submit the results of the sunscreen interaction study (S1761006) with the original NDA.

Solvay Response: Division's response is acceptable and no follow-up was discussion required.

8.2.4. *The rationale for the doses selected for efficacy and safety evaluation in the phase III program is outlined in Section 10.3.* ***Does the Division agree with this rationale and dose selection?***

Division Response: Yes; we agree with the doses selected and the rationale for their selection, but the proposed Phase 3 study still needs to be substantially revised to demonstrate that the labeled dose-titration regimen, not each dosage strength, is safe and effective (see also our responses to questions 8.2.5 and 8.2.8).

8.2.5. *The proposed Clinical Development Plan as outlined in Section 10.0 is based on a single phase III study evaluating the efficacy and safety of testosterone gel 1.62%.* ***Is this single study sufficient for FDA to file the application for review?***

Division Response: Yes, this NDA may be based upon a single Phase 2/3 study (S1763103); however, the protocol must be substantially revised. Of greatest importance is the inclusion of 24-hour pharmacokinetics in every subject during the dose-titration phase (the period that follows completion of the fixed-dose phase). This is necessary to provide assurance that the recommended dose-titration regimen in the DOSAGE & ADMINISTRATION section of the label is safe and effective. Dose titration should be based upon a single draw total serum T, but efficacy of the regimen must be judged by

24-hour PK profiles. We are willing to work with you to revise the proposed protocol to adequately meet this objective. Also, titration in the Phase 3 protocol and in the labeling should be based on serum T levels only.

Additional Discussion: Upon reviewing the Division's preliminary comments, the (b) (4) . The Division could not comment on the Sponsor proposal without adequate review. However, the Division suggested a simpler dosing scheme, starting with a 2.5 g fixed dose and titrating upward if a single-draw, steady-state trough level was < 300ng/dL. The Sponsor should also propose a downward titration criterion to prevent supraphysiological T levels. The Division reminded the Sponsor that any discontinued subjects would be included in an intent-to-treat (ITT) analysis. The primary efficacy will be based on 24-hour PK sampling 2-3 month after titrating to the optimal dose, with 150 subjects completing the study, but at least 50 subjects must complete the 6 month skin safety evaluation.

The Division suggested that the Sponsor submit a protocol outline for review prior to submitting the final Phase 3 protocol as a Special Protocol Assessment.

8.2.6. ***Is the indication as outlined in Section 3.0 of the Briefing Book and the Targeted Product Profile (TPP) found in Appendix 11.5 acceptable to the Division?***

Division Response: No. The indication for Androgel 1.62% will be the same as for all previously approved products in this class. (b) (4)

Solvay Response: Agreed.

8.2.7. ***Does the Division agree that a cut-off of total testosterone < 300 ng/dL classifies men as hypogonadal for the purpose of diagnosis and efficacy evaluation in the phase III study?***

Division Response: Yes.

8.2.8. ***Does the Division agree that the criteria to evaluate primary efficacy as outlined in the single phase III study in Appendix 11.2 is appropriate for the indication being studied?***

Division Response: We currently recommend the following efficacy endpoints for Phase 3 studies of T replacement products:

a. The primary endpoint should be: Percentage of "responders," defined as subjects with serum total testosterone $C_{avg(0-24)}$ within the normal range. Success in the trial may be claimed if ≥75% of subjects are responders (for the treatment regimen), with a lower bound of the 95% CI not less than 65%.

b. C_{max} should be assessed as a critical secondary endpoint. We would expect that serum total testosterone C_{max} will be ≤1500ng/dL in ≥85% of the subjects, be between 1800 and 2500ng/dL in ≤5% of the subjects, and be >2500ng/dL in none of the subjects.

The primary timepoint for assessing efficacy should not be Day 45 of the fixed-dose period, but rather at some timepoint following completion of the recommended titration procedures in the "titration phase." In reviewing the dose titration phase of your Phase 3 protocol, we advise obtaining a single sample serum T level at anticipated steady-state (i.e. 2 weeks) which could be used to titrate dose.

Additional Discussion: The Division clarified that a single patient above 2500 ng/dL would not represent total study failure if the Sponsor could provide an explanation as why the testosterone level was excessive (i.e. lab error, contamination). The Sponsor agreed to the efficacy endpoints.

8.2.9. ***Does the Division agree that the safety endpoints to be assessed as outlined in the single phase III study in Appendix 11.2 are appropriate to manage the safety of patients enrolled in this study?***

Division Response: Yes. The application site evaluations should be more thoroughly outlined.

Additional Discussion: Regarding skin safety assessment, the Division recommended that the Sponsor choose a specific skin assessment instrument and submit for review. The Division also recommended that digital rectal exams (DRE), serum liver function tests (LFTs), and weights should be performed every 3 months. Subjects should not have LFTs greater than 2 times upper limit of normal (ULN) and should be discontinued if these rise to greater than 3 times ULN. The Division agreed that the total testosterone, DHT, and estradiol levels would be required for the NDA.

8.2.10. ***Does the patient population as defined in the phase III Draft Protocol S176.3.103 (Appendix 11.2) support the indication to be studied?***

Division Response: The patient population is appropriate to support the existing indication for the class, (b) (4) Subjects on medical therapy for BPH symptoms should not be excluded. The exclusion criterion for BPH symptoms should be IPSS >15 points, not 19 points. Subjects with 2-fold increase in serum transaminases (not 3-fold), should be excluded. The washout period for intramuscular T should be 12 weeks, not 6 weeks.

Additional Discussion: The Division explained that the Phase 3 protocol should not exclude subjects who would not be excluded in the prescribing information. Therefore, subjects who are on alpha-blockers and 5-alpha-reductase inhibitors should not be excluded.

8.2.11. *Solvay believes 45-days of treatment for the entire patient population are adequate to evaluate the safety and efficacy of this testosterone gel 1.62% product. We plan to continue to evaluate the safety and efficacy of this product in the same controlled setting through 90 days of treatment. The remaining nine months will further assess safety and efficacy of treatment in an open-label manner without 24-hour pharmacokinetic sampling. Solvay proposes to submit the initial NDA with the 45-day efficacy and safety data for the entire patient population. The 90-day data will be submitted with the 120-day safety update to the NDA. Post-approval, we plan to submit the data from the open-label extension period to FDA for evaluation.* ***Is this strategy acceptable to the Division?***

Division Response: No. The application must be sufficiently complete at the time of filing in order to allow for approval in the first review cycle should the submitted information support approval. Therefore, at least 6 months data from the Phase 3 study should be submitted in the original NDA, for the following reasons:

- For purposes of assessing skin safety.
- To assess the efficacy of the dose regimen, using 24-hour PK assessments at the completion of the recommended dose-titration period.

We would accept the completed study report, including the full 1 year of data, with the 4-month Safety Update.

Additional Discussion: The Division agreed to accept interim results from the ongoing long-term extension in the 4-month safety update.

8.2.12. ***Does the Division accept data for product claims that are derived from well-controlled consumer-use testing of this testosterone gel 1.62% product?*** *Claims such as:*

(b) (4)

(b) (4)

8.2.13. ***Will FDA require safety data from the phase I studies be integrated with the phase III data into a single database for safety evaluation which would be then included in the initial NDA for testosterone gel 1.62%?***

Division Response: No. This would not be necessary. The NDA could contain a summary table for Phase 1 studies separate from the Phase 3 study.

8.2.14. *Solvay does not plan to integrate the safety data for testosterone gel 1.62% with the safety data from AndroGel® (testosterone gel) 1% for inclusion in the NDA to be submitted for this product.* ***Does the Division agree this is not required?***

Division Response: Yes, we agree that this is not required.

8.2.15. *The inclusion of 24-hour pharmacokinetic sampling at months 6 and 12 of the open label extension is under consideration. Accordingly, if 50% of patients at each titrated dose level have total testosterone Cmin and Cavg values at both time points that are within the eugonadal range of 300 - 1000 ng/*[redacted]

Division Response: As stated in our responses to questions 8.2.5 and 8.2.8, 24-hour PK assessments should be conducted after the recommended dose titration, to demonstrate the safety and efficacy of the treatment regimen [redacted]. Refer to our response to question 8.2.8 for the current standards of success for Phase 3 trials of testosterone replacement therapy products.

[redacted]

The Division's preliminary responses to the following Sponsor's questions (8.3.1 and 8.4.1-8.4.4) were acceptable and no further discussions were required.

8.3. Chemistry Manufacturing and Controls Questions

8.3.1. *At the time of submission, for stability requirements, Solvay plans to provide 12-month data from one* [redacted] *batch* [redacted] *and 9-month data from two additional batches at a minimum* [redacted] ***Does the Division agree with this approach?***

Division Response: Yes, we agree with this approach. At the time of submission, you must also submit the stability data using accelerated storage condition and intermediate conditions (if applicable). The shelf life will be based upon the review of the stability data.

8.4. Procedural Questions

8.4.1. *Based on previous conversations with the Division, Solvay does not plan to open a new IND for the development of testosterone gel 1.62%.* ***Does the Division agree?***

Division Response: Yes.

8.4.2. ***Does the Division agree that this testosterone gel 1.62% product will require a new NDA?***

Division Response: No. A supplement will be sufficient.

8.4.3. *It is planned that both the currently approved AndroGel 1% testosterone gel product and the investigational testosterone gel 1.62% product will be on the market at the same time (once approved). AndroGel 1% may be removed from the market once there is no longer demand for the 1% product. With this in mind, Solvay plans to retain AndroGel as part of the trade name for the testosterone gel 1.62% product [e.g. AndroGel® 1.62%*

(testosterone gel)]. ***Does the Division agree this is acceptable with the assumption that the modifier is submitted, reviewed and approved by FDA to ensure proper product selection at the pharmacy level for patient safety?***

Division Response: We do not recommend use of the strength or any other numbers in the proprietary names of products. However, we have no objections to the proprietary name AndroGel. We recommend that the strength be presented in conjunction with the established name. Thus, the format of presentation would be as follows:

AndroGel®	AndroGel®
(testosterone gel) 1.62%	(testosterone gel) 1%

8.4.4. *Because the approval for this testosterone gel 1.62% product is based on a full clinical development program it is our understanding that this product would be granted a three-year exclusivity period.* ***Does the Agency concur?***

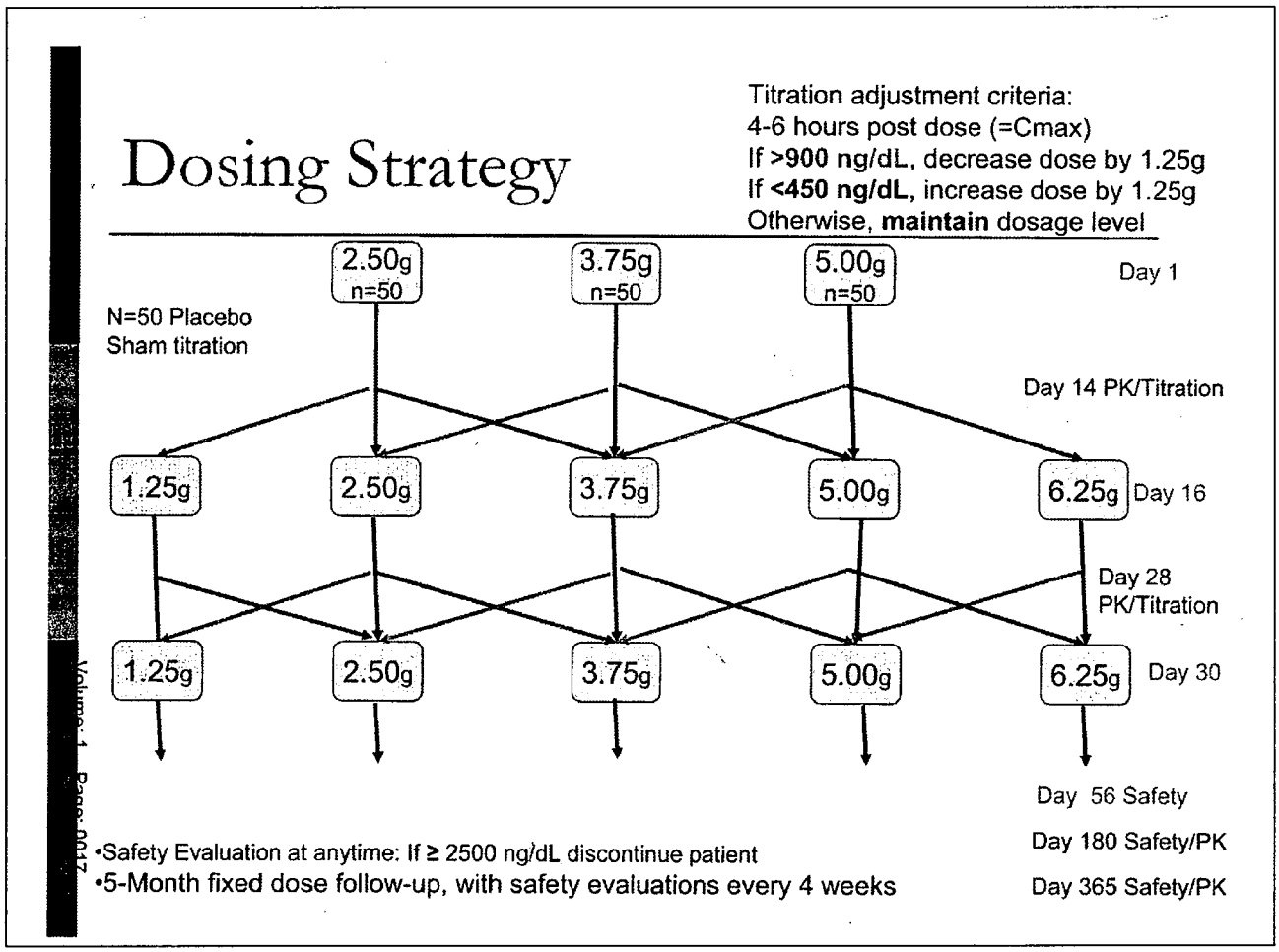
Division Response: Exclusivity determination is made by the Office of Generic Drugs upon approval of NDA, but this new formulation appears to meet the criteria for three-year exclusivity period.

ACTION ITEMS:

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

Signature: Meeting Chair
{See Appended Electronic Signature}
Mark Hirsch, M.D.
Acting Deputy Director

ATTACHMENTS:


Dosing Strategy
Titration adjustment criteria:
4-6 hours post dose (=Cmax)
If >900 ng/dL, decrease dose by 1.25g
If <450 ng/dL, increase dose by 1.25g
Otherwise, maintain dosage level
2.50g n=50
3.75g n=50
5.00g n=50
Day 1
N=50 Placebo
Sham titration
Day 14 PK/Titration
1.25g
2.50g
3.75g
5.00g
6.25g
Day 16
Day 28
PK/Titration
1.25g
2.50g
3.75g
5.00g
6.25g
Day 30
Day 56 Safety
Day 180 Safety/PK
Day 365 Safety/PK
•Safety Evaluation at anytime: If ≥ 2500 ng/dL discontinue patient
•5-Month fixed dose follow-up, with safety evaluations every 4 weeks

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/s/

Mark S. Hirsch
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