CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-015

ADMINISTRATIVE DOCUMENTS

ODE III ACTION PACKAGE TABLE OF CONTENTS

Application # NDA 21-015 Drug Name: AndroGel (testosterone gel)

Applicant: Unimed Pharmaceuticals Chem./Ther. Type: 3S

CSO/PM: Colangelo Phone: x74252 HFD-580

Original Application Date: April 28, 1999 Original Receipt Date: April 29, 1999

CURRENT USER FEE GOAL DATE: February 29, 2000
Date Table of Contents Completed: 2/28/00

Section A: Administrative Information		X (completed), N/A (not applicable), or Comment
Tab A-1	Action Letter(s) Current Action: AP	X
Tab A-2	Phase 4 Commitments:	
	a. Copy of applicants communication committing to Phase 4	X
	b. Agency Correspondence requesting Phase 4 Commitments	X
Tab A-3	FDA revised Labels & Labeling and Reviews: (Separate each version/cycle with a colored sheet)	
	a. Package Insert	X
	b. Immediate Container and Carton Labels	X
Tab A-4	Original Proposed Labeling	X
Tab A-5	Foreign Labeling:	
	a. Foreign Marketing History	X
	b. Foreign Labeling and Review(s)	N/A
Tab A-6	Labeling and Nomenclature Committee's Tradename Review	X
Tab A-7	Summary Memoranda (e.g., Division Director, Group Leader, Office)	X - Group Ldr
Tab A-8	Copy of Patent Statement	X
	Exclusivity Checklist (and any requests for exclusivity)	X
	Debarment Statements	X
Tab A-9	Correspondences, Faxes, & Telecons	X
Tab A-10	Minutes of Meetings:	
	a. End-of-Phase II meeting	Feb. 18, 1997
	b. Pre-NDA meeting(s)	Nov. 3, 1998
	c. Filing meeting	May 21, 1999
	d. Other meetings	N/A
Tab A-11	Advisory Committee Meeting:	
	a. Questions Considered by the committee	N/A
	b. List of Attendees	N/A
	c. 24 hour alert memorandum	N/A
Tab A-12	Project Management Administrative Information (optional)	FinancialDisclosure; DDMACreviewPPI; labeling memo

ODE III ACTION PACKAGE TABLE OF CONTENTS (continued)

Application # NDA 21-015 Drug Name: AndroGel (testosterone gel)

Section B:	Clinical Information	X (completed), N/A (not applicable), or Comment
Tab B-1	Clinical Reviews and Memoranda	X
Tab B-2	Safety Update Reviews	See clinical review
Tab B-3	Pediatric Page	X
Tab B-4	Statistical (Clinical) Review and Memoranda	X
Tab B-5	Biopharmaceutics Review and Memoranda	X
Tab B-6	Abuse Liability Review	X
Tab B-7	DSI Audits	X
Tab B-8	Summary of Efficacy (from the summary volume of the application)	X
Tab B-9	Summary of Safety (from the summary volume of the application)	X

Section C:	Chemistry, Manufacturing, and Controls (CMC) Information	X (completed), N/A (not applicable), or Comment
Tab C-1	CMC Reviews and Memoranda	X
Tab C-2	DMF Reviews	X
Tab C-3	EA Reviews/FONSI	See Chemistry review
Tab C-4	Micro Review (validation of sterilization)	N/A
Tab C-5	Statistical Review of drug stability	N/A
Tab C-6	Inspection of facilities => Decision: acceptable Date: Feb. 25, 2000	X
Tab C-7	Methods Validation Information	X

Section D:	Pharmacology/Toxicology Information	X (completed), N/A (not applicable), or Comment
Tab D-1	Pharmacology/Toxicology Reviews and Memoranda	X
Tab D-2	Carcinogenicity Review (statistical)	N/A
Tab D-3	CAC/Executive Committee Report	N/A

ADDITIONAL NOTES:

Exclusivity Checklist

NDA: 21-015				
Trade Name: AndroGel				
Generic Name: testosterone gel				
Applicant Name: Unimed Pharmaceuticals				
Division: HFD-580; DRUDP				
Project Manager: Kim Colangelo				
Approval Date: Feb. 28, 2000				
PART I: IS AN EXCLUSIVITY DETERMINATION NEEDED?				
1. An exclusivity determination will be made for all original applications, but only for certain 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 an original NDA?	(Yes)		No	
b. Is it an effectiveness supplement?	Yes		(No)	
c. If yes, what type? (SE1, SE2, etc.)				
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.				
Explanation:				
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:				
Explanation:				
d. Did the applicant request exclusivity?	Yes		(No)	
If the answer to (d) is "yes," how many years of exclusivity did the applicant request?				
IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS.				
2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule previously been approved by FDA for the same use?	Yes		(No)	
If yes, NDA #				
Drug Name:				
IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE				

BLOCKS.		
3. Is this drug product or indication a DESI upgrade?	Yes	No (circled)
IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS (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.	Yes (circled)	No
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 (circled)	No

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

Drug Product	Androderm
NDA #	20-489
Drug Product	~~Theraderm~~ Testoderm
NDA #	19-762
Drug Product	Oreton Pellets
NDA #	4-1052

2. Combination product.	Yes	No (circled)
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).

Drug Product	
NDA #	
Drug Product	
NDA #	
Drug Product	
NDA #	

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY

Approved drug products containing the active moiety and, if known, the NDA #s (continued).

Drug Product: Delatestryl Injection
NDA 9-165

Drug Product: Depo-Testadiol
NDA 17-968

Drug Product: Testoderm AT
NDA 20-791

TO THE SIGNATURE BLOCKS. IF "YES," GO TO PART III.
PART III: THREE-YEAR EXCLUSIVITY FOR NDA'S 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.				
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. For the purposes of this section, studies comparing two products with the same ingredient(s) are considered to be bioavailability studies.				
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 BLOCKS.**				
Basis for conclusion:				
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 (circled)	
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:				
Investigation #1, Study #: UMD-96-017				
Investigation #2, Study #:				
Investigation #3, Study #:				
3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.				
a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")				
Investigation #1	Yes		No	✓
Investigation #2	Yes		No	
Investigation #3	Yes		No	
If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:				
Investigation #1 -- NDA Number				
Investigation #2 -- NDA Number				
Investigation #3 -- NDA Number				
b) For each investigation identified as "essential to the approval," does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?				
Investigation #1	Yes		No	✓
Investigation #2	Yes		No	
Investigation #3	Yes		No	
If you have answered "yes" for one or more investigations, identify the NDA in which a similar investigation was relied on:				
Investigation #1 -- NDA Number				
Investigation #2 -- NDA Number				
Investigation #3 -- NDA Number				
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"):				
Investigation #1 UMD-96-017				
Investigation #2				

Investigation #3	

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	Yes	✓	No	
IND#:				
Explain:				

Investigation #2	Yes		No	
IND#:				
Explain:				

Investigation #3	Yes		No	
IND#:				
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	
IND#:				
Explain:				

Investigation #2	Yes		No	
IND#:				
Explain:				

Investigation #3	Yes		No	
IND#:				
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	X
If yes, explain:				

BACK TO TOP

Signature of PM/CSO /S/
Date: 2/11/00

Signature of Division Director /S/
Date: 2/28/00

cc:
Original NDA ~~20~~ 21-015
Division File
HFD-93 Mary Ann Holovac

BACK TO TOP

APPEARS THIS WAY
ON ORIGINAL

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

APPLICATION TO MARKET A NEW DRUG, BIOLOGIC OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations, 314 & 601)

Form Approved: OMB No. 0910-0338
Expiration Date: April 30, 2000
See OMB Statement on page 2.

FOR FDA USE ONLY

APPLICATION NUMBER

APPLICANT INFORMATION

NAME OF APPLICANT	DATE OF SUBMISSION
Unimed Pharmaceuticals, Inc.	28 February 2000
TELEPHONE NO. (Include Area Code) (847) 541-2525	FACSIMILE (FAX) Number (Include Area Code) (847) 541-2569
APPLICANT ADDRESS (Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued): 2150 E. Lake Cook Road, Suite 210, Buffalo Grove, IL 60089	AUTHORIZED U.S. AGENT NAME & ADDRESS (Number, Street, City, State, ZIP Code telephone & FAX number) IF APPLICABLE

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER (If previously issued) 21-015

ESTABLISHED NAME (e.g., Proper name, USP/USAN name)	PROPRIETARY NAME (trade name) IF ANY
testosterone gel	AndroGel™

CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME (If any)	CODE NAME (If any)
Androst-4-en-3-one,17-hydroxy,(17β)-; 17β-hydroxyandrost-4-en-3-one	T-Gel

DOSAGE FORM:	STRENGTHS:	ROUTE OF ADMINISTRATION:
Gel	25 mg, 50 mg	Topical

(PROPOSED) INDICATION(S) FOR USE: Hormonal replacement therapy in males for conditions associated with a deficiency or absence of endogenous testosterone

APPLICATION INFORMATION

APPLICATION TYPE (check one)
☒ NEW DRUG APPLICATION (21 CFR 314.50) ☐ ABBREVIATED APPLICATION (ANDA, AADA, 21 CFR 31.94)
☐ BIOLOGICS LICENSE APPLICATION (21 CFR part 601)

IF AN NDA, IDENTIFY THE APPROPRIATE TYPE ☒ 505 (b) (1) ☐ 505 (b) (2) ☐ 507

IF AN ANDA, OR AADA, IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION
Name of Drug Holder of Approved Application

TYPE OF SUBMISSION (check one)
☐ ORIGINAL APPLICATION ☒ AMENDMENT TO A PENDING APPLICATION ☐ RESUBMISSION
☐ PRESUBMISSION ☐ ANNUAL REPORT ☐ ESTABLISHMENT DESCRIPTION SUPPLEMENT ☐ SUPAC SUPPLEMENT
☐ EFFICACY SUPPLEMENT ☐ LABELING SUPPLEMENT ☐ CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT ☒ OTHER

REASON FOR SUBMISSION: Response to request for information

PROPOSED MARKETING STATUS (check one) ☒ PRESCRIPTION PRODUCT (Rx) ☐ OVER THE COUNTER PRODUCT (OTC)

NUMBER OF VOLUMES SUBMITTED _____ THIS APPLICATION IS ☒ PAPER ☐ PAPER AND ELECTRONIC ☐ ELECTRONIC

ESTABLISHMENT INFORMATION

Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g. Final dosage form, Stability testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.

Cross References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMFs referenced in the current application)

FORM FDA 356h (7/97)

Created by Electronic Document Services/USDHHS, (301) 443-2454 EF

	This application contains the following items: *(Check all that apply)*
	1. Index
X	2. Labeling *(check one)* ☒ Draft Labeling ☐ Final Printed Labeling
	3. Summary (21 CFR 314.50(c))
	4. Chemistry section
	A. Chemistry, manufacturing, and controls information (e.g. 21 CFR 314.50(d) (1), 21 CFR 601.2)
	B. Samples (21 CFR 314.50 (e) (1), 21 CFR 601.2 (a)) (Submit only upon FDA's request)
	C. Methods validation package (e.g. 21 CFR 314.50 (e) (2) (i), 21 CFR 601.2)
	5. Nonclinical pharmacology and toxicology section (e.g. 21 CFR 314.50 (d) (2), 21 CFR 601.2)
	6. Human pharmacokinetics and bioavailability section (e.g. 21 CFR 314.50 (d) (3), 21 CFR 601.2)
	7. Clinical Microbiology (e.g. 21 CFR 314.50 (d) (4))
	8. Clinical data section (e.g. 21 CFR 314.50 (d) (5), 21 CFR 601.2)
	9. Safety update report (e.g. 21 CFR 314.50 (d) (5) (vi) (b), 21 CFR 601.2)
	10. Statistical section (e.g. 21 CFR 314.50 (d) (6), 21 CFR 601.2)
	11. Case report tabulations (e.g. 21 CFR 314.50 (f) (1), 21 CFR 601.2)
	12. Case report forms (e.g. 21 CFR 314.50 (f) (2), 21 CFR 601.2)
	13. Patent information on any patent which claims the drug (21 U.S.C. 355 (b) or (c))
	14. A patent certification with respect to any patent which claims the drug (21 U.S.C.355 (b) (2) or (j) (2) (A)
	15. Establishment description (21 CFR Part 600, if applicable)
	16. Debarment certification (FD&C Act 306 (k) (1))
X	17. Field copy certification (21 CFR 314.50(k) (3))
	18. User Fee Cover Sheet (Form FDA 3397)
	19. OTHER (Specify) Response to request for information

CERTIFICATION

I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including, but not limited to the following:

1. Good manufacturing practice regulations in 21 CFR 210 and 211, 606, and/or 820.
2. Biological establishment standards in 21 CFR Part 600.
3. Labeling regulations in 21 CFR 201, 606, 610, 660 and/or 809.
4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR 202.
5. Regulations on making changes in application in 21 CFR 314.70, 314.71, 314.72, 314.97, 314.99, and 601.12.
6. Regulations on Reports in 21 CFR 314.80, 314.81, 600.80 and 600.81.
7. Local, state and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.

The data and information in this submission have been review and, to the best of my knowledge are certified to be true and accurate.

Warning: a willfully false statement is a criminal offense, U.S. Code, title 18, section 1001.

SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT	TYPED NAME AND TITLE	DATE
Judy Athey	Judy Athey, Assistant Manager, Regulatory Affairs	28 Feb 2000

ADDRESS (Street, City, State, and ZIP Code)	Telephone Number
2150 E. Lake Cook Road, Suite 210, Buffalo Grove, IL 60089	(847) 541-2525

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FORM FDA 356h (7/97)

PEDIATRIC PAGE

(Complete for all original application and all efficacy supplements)

NDA/BLA Number:	21015	**Trade Name:**	ANDROGEL(TESTOSTERONE GEL) 25MG/50MG
Supplement Number:		**Generic Name:**	TESTOSTERONE GEL
Supplement Type:		**Dosage Form:**	GEL
Regulatory Action:	AP	**Proposed Indication:**	Androgel is indicated for replacement therapy in males for conditions associated with a deficiency or absence of endogenous testosterone.

ARE THERE PEDIATRIC STUDIES IN THIS SUBMISSION?

NO, No waiver and no pediatric data

What are the INTENDED Pediatric Age Groups for this submission?

____NeoNates (0-30 Days) ____Children (25 Months-12 years)

____Infants (1-24 Months) ____Adolescents (13-16 Years)

Label Adequacy	Adequate for ALL pediatric age groups
Formulation Status	-
Studies Needed	-
Study Status	-

APPEARS THIS WAY ON ORIGINAL

Are there any Pediatric Phase 4 Commitments in the Action Letter for the Original Submission? NO

COMMENTS:

2/18/00: Pediatric studies are deferred until March 1, 2001.

Deferred until March 1, 2001.

This Page was completed based on information from a PROJECT MANAGER/CONSUMER SAFETY OFFICER, KIM COLANGELO

/S/ 2/28/00

Signature Date

CONSULTATION RESPONSE

Office of Post-Marketing Drug Risk Assessment

Peter Tam—Safety Evaluator

(OPDRA; HFD-400)

DATE SENT: 1/31/00	DUE DATE: 2/7/00	OPDRA CONSULT #: 99-063

TO (Division):

Susan Allen, M.D.
Acting Director, Division of Reproductive and Urologic Drug Products
HFD-580

Through: Kim Colangelo, Project Manager

PRODUCT NAME:	MANUFACTURER: Unimed Pharmaceuticals, Inc.
Androgel® (testosterone gel) NDA #: 21-015	

OPDRA RECOMMENDATION:

OPDRA has no objections to the use of proprietary name "Androgel®.

/S/ 2/1/2000

Jerry Phillips
Associate Director for Medication Error Prevention
Office of Post-Marketing Drug Risk Assessment
Phone: (301) 827-3246
Fax: (301) 480-8173

/S/ 1/31/00

Peter Honig, MD
Deputy Director
Office of Post-Marketing Drug Risk Assessment
Center for Drug Evaluation and Research
Food and Drug Administration

WITHHOLD 29 PAGE (S)

WITHHOLD 28 PAGE (S)

Of Draft Labeling

WITHHOLD 49 PAGE (S)

OF Draft Labeling

Teleconference Minutes

Date: February 28, 2000 **Location:** Parklawn, 17B-45

NDA 21-015 **Drug:** AndroGel (testosterone gel)

Indication: hormone replacement

Sponsor: Unimed Pharmaceuticals

Type of Meeting: Information Request

Meeting Chair/Recorder:
Kim Colangelo – Regulatory Project Manager, Division of Reproductive and Urologic Drug Products (DRUDP; HFD-580)

External Attendee:
Judy Athey – Assistant Manager, Regulatory Affairs, Unimed

Meeting Objective: To convey labeling (package insert) comments for NDA 21-015 (AndroGel).

Discussion:

- Line 180: [redacted] should be revised to "Treatment Day"
- Line 215: [redacted]
- Line 235: the acronym "LHRH" should be defined (i.e., luteinizing hormone-releasing hormone)
- Line 342: [redacted] should be revised to "concentrations should be measured" to be consistent with **DOSAGE AND ADMINISTRATION**
- Line 462: the heading DOSAGE AND ADMINISTRATION should be bolded
- Lines 490-491: Strengths should be listed as 1% (x mg); and Package Size should be revised to "30 packets: X G per packet"

Action Items:

- Unimed will submit revised labeling *[received, February 28, 2000]*

/S/

Minutes Preparer, Chair

cc:
Original NDA 21-015
HFD-580/DivFile
HFD-580/Colangelo/Rumble

drafted: Colangelo, 02.28.00
concurrence: Rumble, 02.28.00
final: Colangelo, 02.28.00
MEETING MINUTES

Teleconference Minutes

Date: February 25, 2000 **Location:** Parklawn, 17B-45

NDA 21-015 **Drug:** AndroGel (testosterone gel)

Indication: hormone replacement

Sponsor: Unimed Pharmaceuticals

Type of Meeting: Information Request

Meeting Chair/Recorder:
Kim Colangelo – Regulatory Project Manager, Division of Reproductive and Urologic Drug Products (DRUDP; HFD-580)

External Attendee:
Judy Athey – Assistant Manager, Regulatory Affairs, Unimed

Meeting Objective: To request a Phase 4 commitment for NDA 21-015 (AndroGel).

Discussion:

- As discussed in our teleconfernence of February 16, 2000, evidence of no significant difference in the clinical delivery (as measured by testosterone levels) between the formulation used in Phase 3 and the to-be-marketed formulation is needed; as this evidence is not currently available, DRUDP requests that this evidence be provided as part of a Phase 4 commitment

Action Items:

- Unimed will submit the Phase 4 commitment in writing today (February 25, 2000)

/S/

Minutes Preparer, Chair

cc:
Original NDA 21-015
HFD-580/DivFile
HFD-580/Colangelo/Rumble

drafted: Colangelo, 02.25.00
concurrence: Rumble, 02.25.00
final: Colangelo, 02.25.00
MEETING MINUTES

Teleconference Minutes

Date: February 25, 2000 **Location:** Parklawn, 17B-45

NDA 21-015 **Drug:** AndroGel (testosterone gel)

Indication: hormone replacement

Sponsor: Unimed Pharmaceuticals

Type of Meeting: Information Request

Meeting Chair/Recorder:
Kim Colangelo – Regulatory Project Manager, Division of Reproductive and Urologic Drug Products (DRUDP; HFD-580)

External Attendee:
Judy Athey – Assistant Manager, Regulatory Affairs, Unimed
Kirk Rosemark – Director, Regulatory Affairs, Unimed

Meeting Objective: To convey labeling comments for NDA 21-015 (AndroGel).

Discussion:

- package insert: recommended text for the sentence beginning at Line 178: hypogonadal men who were appropriately titrated with AndroGel and who had sufficient data for analysis, — achieved an average serum testosterone within the normal range on Treatment Day 180."
- patient package insert: while DRUDP acknowledges Unimed's comments and concerns regarding the section entitled "**What are the possible side effects of AndroGel?**" and competitors patient package inserts, this section will be retained in the label to be consistent with the current format for patient package inserts adopted by the Agency; however, this section may be revised as follows:
  - in the section "AndroGel may cause the following side effects:"
    - combine the bullets regarding prostate enlargement and difficulty urinating (e.g., "prostate enlargement, sometimes accompanied by difficulty urinating)
    - delete bullets regarding —
  - in the section "Tell your doctor if you develop any of the following side effects:
    - delete bullets regarding —

Action Items:

- Unimed will submit proposals for the package insert and patient package inserts

/S/

Minutes Preparer, Chair

cc:
Original NDA 21-015
HFD-580/DivFile
HFD-580/Colangelo/Rumble

drafted: Colangelo, 02.25.00
concurrence: Rumble, 02.25.00
final: Colangelo, 02.25.00
MEETING MINUTES

Teleconference Minutes

Date: February 25, 2000 **Location:** Parklawn, 17B-45

NDA 21-015 **Drug:** AndroGel (testosterone gel)

Indication: hormone replacement

Sponsor: Unimed Pharmaceuticals

Type of Meeting: Information Request

Meeting Chair/Recorder:
Kim Colangelo – Regulatory Project Manager, Division of Reproductive and Urologic Drug Products (DRUDP; HFD-580)

External Attendee:
Judy Athey – Assistant Manager, Regulatory Affairs, Unimed

Meeting Objective: To request a Phase 4 commitment and discuss pending items for the review of AndroGel.

Discussion:

- as previously discussed on February 16 and 22, 2000, [redacted]
- a "483" was issued for the final manufacturing inspection; we will be confirming the impact, if any, on the final recommendation from the Office of Compliance
- responses from Unimed to our patient package insert recommendations will be submitted today

Action Items:

- Unimed will submit a Phase 4 commitment *[received, 02.25.00]*
- Unimed will submit responses regarding the patient package insert *[received, 02.28.00]*

/S/

Minutes Preparer, Chair

cc:
Original NDA 21-015
HFD-580/DivFile
HFD-580/Colangelo/Rumble

MEETING MINUTES

APPEARS THIS WAY
ON ORIGINAL

Teleconference Minutes

Date: February 16, 2000 **Location:** Parklawn, 17B-45

NDA 21-015 **Drug:** AndroGel (testosterone gel)

Indication: hormone replacement

Sponsor: Unimed Pharmaceuticals

Type of Meeting: Information Request

Meeting Chair/Recorder:
Kim Colangelo – Regulatory Project Manager, Division of Reproductive and Urologic Drug Products (DRUDP; HFD-580)

External Attendee:
Kirk Rosemark – Director, Regulatory Affairs, Unimed

Meeting Objective: To request information needed for the review of NDA 21-015 for AndroGel.

Discussion:

- evidence, beyond the *in vitro* data provided, is needed to show that the change in percentage of isopropyl myristate (from Phase 3 trial to to-be-marketed formulation) did not have an impact on testosterone levels
- if additional evidence, such as *in vivo* data or *in vitro/in vivo* correlation data, is not available, a Phase 4 commitment may be requested

Action Items:

- Unimed will verify the existence of such data and will notify Ms. Colangelo as soon as possible *[Phase 4 commitment; see telecon and sponsor correspondence of 2/25/00]*

/S/

Minutes Prepared, Chair

cc:
Original NDA 21-015
HFD-580/DivFile
HFD-580/Colangelo/Rumble

APPEARS THIS WAY ON ORIGINAL

drafted: Colangelo, 02.18.00
concurrence: Rumble, 02.28.00
final: Colangelo, 02.28.00
MEETING MINUTES

Teleconference Minutes

Date: February 16, 2000 **Location:** Parklawn, 17B-45

NDA 21-015 **Drug:** AndroGel (testosterone gel)

Indication: hormone replacement **Sponsor:** Unimed Pharmaceuticals

Type of Meeting: Guidance

Meeting Chair: David Lin, PhD **Meeting Recorder:** Kim Colangelo

FDA Attendees:
David Lin, PhD – Chemistry Reviewer, Division of New Drug Chemistry II @ Division of Reproductive and Urologic Drug Products (DRUDP; HFD-580)
Kim Colangelo – Regulatory Project Manager, DRUDP (HFD-580)

External Attendees:
Kirk Rosemark – Director, Regulatory Affairs, Unimed
Judy Athey – Assistant Manager, Regulatory Affairs, Unimed

Meeting Objective: To provide guidance regarding Chemistry issues related to NDA 21-015 for AndroGel; Unimed submitted responses dated February 11 and 15, 2000, to our January 24, 2000, letter containing Chemistry comments.

Discussion:

- regarding expiration dating: batch E687 has ——— stability data to support a ——— expiration date; however, batch E687 was produced using drug substance from a different supplier than the to-be-marketed product, therefore the data does not adequately support a ——— expiration; based on the data submitted, an expiration date of 18-months is supported; Unimed can submit a Chemistry supplement (review goal: 4 months) following approval of their product, or can submit additional stability information; written agreement from Unimed regarding an expiration date of 18-months will be needed for approval, if additional data supporting a longer expiration date are not submitted, reviewed and found to be acceptable
- a change in supplier of ——— will require a Prior Approval supplement due to the absorption of isopropyl myristate; Unimed will acknowledge this requirement
- the methods validation package has not been reviewed at this time, but will not be an approvability issue

Action Items:

- Unimed will either provide written acceptance of an 18-month expiration date, or will submit additional stability information to support a ——— expiration
- Unimed will submit written acknowledgement of the need for a Prior Approval supplement for changes in the ——— supplier

/S/

Minutes Preparer

/S/ 2/18/00

Concurrence, Chair

cc:
Original NDA 21-015
HFD-580/DivFile
HFD-580/Colangelo/Rumble/Rhee/Lin

drafted: Colangelo, 02.18.00
concurrence: Lin, Rumble, 02.18.00
final: Colangelo, 02.18.00
MEETING MINUTES

APPEARS THIS WAY
ON ORIGINAL

Colangelo

Teleconference Minutes

Date: February 11, 2000 **Location:** Parklawn, 17B-45

NDA 21-015 **Drug:** AndroGel (testosterone gel)

Indication: hormone replacement

Sponsor: Unimed Pharmaceuticals

Type of Meeting: Information Request

Meeting Chair/Recorder:
Kim Colangelo – Regulatory Project Manager, Division of Reproductive and Urologic Drug Products (DRUDP; HFD-580)

External Attendee:
Kirk Rosemark – Director, Regulatory Affairs, Unimed

Meeting Objective: To request information regarding Patient 1-08 for the review of NDA 21-015 for AndroGel.

Discussion:

- case report forms are needed for Patient 1-08, who underwent a bilateral mastectomy approximately two months after beginning AndroGel therapy
  - specifically, information on the patient's demographics (age, race, weight, past medical history, and past medication), baseline serum testosterone, DHT and estradiol levels, the investigator's name, any follow-up serum hormone levels, the dose of AndroGel, and the hospital records of the mastectomy
  - confirmation is needed that this adverse event was reported by the patient or investigator, and how it was classified (e.g., serious and treatment-related)

Action Items:

- Unimed will submit the requested information *[received, February 15, 2000]*

/S/ 2/18/00

Minutes Preparer, Chair

APPEARS THIS WAY
ON ORIGINAL

cc:
Original NDA 21-015
HFD-580/DivFile
HFD-580/Colangelo/Rumble

drafted: Colangelo, 02.18.00
concurrence: Rumble, 02.18.00
final: Colangelo, 02.18.00
MEETING MINUTES

Teleconference Minutes

Date: February 8, 2000 **Location:** Parklawn, 17B-45

NDA 21-015 **Drug:** AndroGel (testosterone gel)

Indication: hormone replacement

Sponsor: Unimed Pharmaceuticals

Type of Meeting: Information Request

Meeting Chair:
Lana Pauls, MPH – Associate Director, Division of Reproductive and Urologic Drug Products (DRUDP; HFD-580)

External Attendee:
Kirk Rosemark – Director, Regulatory Affairs, Unimed

Meeting Objective: To request information needed for the review of NDA 21-015 for AndroGel.

Discussion:

- additional information is needed on Patient 3-15, from Study UMD-98-035, who suffered a cerebral infarction on January 2, 1999:
  - baseline serum testosterone and baseline hemoglobin and hematocrit at the start of the Study
  - serum testosterone and hemoglobin/hematocrit from hospitalization on January 2, 1999
  - any follow-up serum testosterones or hemoglobin/hematocrits obtained at the 6-month study visit

Action Items:

- Unimed will submit the data by February 9, 2000 *[received February 10, 2000]*

/S/

Minutes Preparer

/S/

Concurrence, Chair

cc:
Original NDA 21-015
HFD-580/DivFile
HFD-580/Colangelo/Rumble

drafted: Colangelo, 02.22.00
concurrence: Pauls, 02.22.00
final: Colangelo, 02.25.00
MEETING MINUTES

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OF Draft Labeling

Kolangelo

Teleconference Minutes

Date: January 21, 2000 **Location:** Parklawn, 17B-45

NDA 21-015 **Drug:** Androgel (testosterone gel)

Indication: hormone replacement

Sponsor: Unimed Pharmaceuticals

Type of Meeting: Information Request

Meeting Chair/Recorder:
Kim Colangelo – Regulatory Project Manager, Division of Reproductive and Urologic Drug Products (DRUDP; HFD-580)

External Attendee:
Judy Athey – Assistant Manager, Regulatory Affairs, Unimed

Meeting Objective: To request information needed for the review of NDA 21-015 for Androgel.

Discussion:

- 17 patients in the 50 mg group were reported to have maximum testosterone levels (C_{max}) above the upper limit of normal on Day 30; a list of these 17 patients, with their respective Day 30 C_{max} values should be submitted
- Patient 7-07, from Study UMD-96-017, was admitted to the hospital on January 3, 1998; information on the patient's hemoglobin, hematocrit, and testosterone levels from the hospital admission should be submitted

Action Items:

- Unimed will submit the requested information via facsimile and original amendment to the NDA once available; the information is expected within one week *[received, 01.27.00]*

/S/

Minutes Preparer, Chair

cc:
Original NDA 21-015
HFD-580/DivFile
HFD-580/Colangelo/Rumble

APPEARS THIS WAY
ON ORIGINAL

drafted: Colangelo, 01.27.00
concurrence: Rumble, 01.28.00
final: Colangelo, 01.31.00
MEETING MINUTES

Safety Update Report review is contained in the Medical Officer Review dated February 15, 2000, on pages 46-51.

/S/ 2/18/00

APPEARS THIS WAY
ON ORIGINAL

Statistical Review not needed.

/S/ 2/17/00

APPEARS THIS WAY
ON ORIGINAL

PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

WK 8/27/1

TO (Division/Office): HFD-170 Corinne Moody, CPMS			FROM: HFD-580 (Division of Reproductive and Urologic Drug Products) Kim Colangelo	
August 23, 1999	IND NO.:	NDA NO.: 21-015	TYPE OF DOCUMENT:	DATE OF DOCUMENT:
NAME OF DRUG: Androgel (testosterone) gel	PRIORITY CONSIDERATION: standard		CLASSIFICATION OF DRUG: 3S	DESIRED COMPLETION DATE: October 12, 1999

NAME OF FIRM: Unimed Pharmaceuticals, Inc

REASON FOR REQUEST

I. GENERAL

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

II. BIOMETRICS

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

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: For abuse liability review. Please contact me if additional information is needed.

cc: Original NDA 21-015
HFD-580/Div. Files
HFD-580/Colangelo

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

8.9 Drug Abuse and Overdose

When used in normal physiologic doses in healthy persons, testosterone is usually not associated with significant side effects. However, supraphysiologic doses are associated with clinical effects which are related to the physiologic actions of androgen and its metabolites, or may be due to direct toxic effects particularly with large doses [1]. The 17 β-hydroxyl esters (testosterone propionate, testosterone cypionate, testosterone enanthate) must be injected intramuscularly because of extensive first-pass hepatic metabolism. The 17 α-alkylated oral preparations (methyltestosterone, fluoxymesterone, danazol) are more resistant to hepatic metabolism. Testosterone preparations used in transdermal delivery systems are absorbed over a 24-hour dosing period and avoid supraphysiologic peaks and variable serum testosterone levels associated with parenteral and oral administration. When considering the potential for abuse of any testosterone, one must take into account the formulation, how administered, and potential for achieving clinically significant, toxic levels.

Androgel, a 1% hydroalcoholic testosterone gel preparation, is a transdermal formulation that is applied topically without an occlusive patch. Testosterone is absorbed into the skin which serves as a reservoir for the slow release of testosterone into the systemic circulation, and there is no extensive first pass hepatic metabolism. In study UMD-96-017, the median time of the peak concentration on Day 1 was 22 hours for patients receiving 50 mg testosterone, and 16 hours for patients receiving 100 mg testosterone. Patients on daily maintenance dosing of 100 mg testosterone (the highest dose studied) achieved mean C_{max} levels of 670, 1106, and 1094 ng/dL, and highest C_{max} levels were 1974, 2728, and 3587 ng/dL for Days 1, 30, and 90, respectively. Levels associated with the eugonadal state in normal males range from 300 to 1000 ng/dL. The potential for achieving higher levels with higher doses was not evaluated, and there were no reports of overdose in study UMD-96-017 nor in any other Unimed-sponsored studies of Androgel.

Androgen abuse has become common among athletes and bodybuilders, and the compounds used and the patterns of administration vary. Multiple agents such as testosterone esters and oral agents may be used in combination and in progressively higher doses, and are administered up to 100 times the doses usually used for replacement therapy. Few data are available on the relative adverse effects and the specific compounds and doses used. Prolonged use of these agents particularly in high doses has been associated with serious hepatic adverse effects, including severe intrahepatic cholestasis and jaundice [2,3]. These cases typically involved individuals who were self-administering intramuscular and/or oral preparations in large doses. Other

reported complications include acne fulminans in three teenage males receiving testosterone enanthate for excessively tall stature [4], and a cerebrovascular accident in a 21-year old male receiving intramuscular testosterone for hypogonadism in which a testosterone level of 11,400 ng/dL was reported [5].

One case of topical testosterone abuse has been reported in a female patient who developed marked masculinization after self-treatment with up to 60 mg daily of a homemade preparation of topical testosterone ointment for vulvar lichen sclerosis [6]. The potential for abuse of Androgel is low, because it is unlikely that high testosterone levels associated with clinical complications can consistently be achieved over a significant period with a topical gel preparation. Testosterone has a relatively short half-life of approximately 10 minutes, which makes single doses of supraphysiologic amounts of Androgel an ineffective and impractical method for abuse. Oral or rectal ingestion of Androgel could be associated with significant levels acutely, but the rapid first-pass hepatic metabolism would negate any potential toxicity. Additionally, the widespread availability of oral and parenteral preparations renders a topical preparation such as Androgel both undesirable and inconvenient for abuse, particularly because of the need for repeated topical application of large quantities.

REFERENCES

1. Bagatell CJ, Bremner WJ. Androgens in men: uses and abuses. N Engl J Med 1996; 334: 707-14.

2. Yoshida EM, Erb SR, Scudamore CH, et al. Severe cholestasis and jaundice secondary to esterified testosterone, a non C-17 alkylated anabolic steroid. J Clin Gastroenterology 1994: 18: 268-270.

3. Gurakar A, et al. Androgenic/anabolic steroid-induced intrahepatic cholestasis: A review with four additional case reports. J Okla State Med Assoc 1994; 87 (9): 399-404.

4. Traupe H, et al. Acne of the fulminans type following testosterone therapy in three excessively tall boys. Arch Dermatol 1988; 124: 414-417.

5. Nagelberg SB, et al. Cerebrovascular accident associated with testosterone therapy in a 21 year old hypogonadal man (letter). N Engl J Med 1986; 314a: 649-650.

6. Punch MR, Ansbacher R. Autogenic masculinization. Amer J Obs & Gynecol 1990; 163: 114-116.

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II. RESULTS (by site):

NAME	CITY, STATE	ASSIGNED DATE	RECEIVED DATE	CLASSIFICATION/ FILE NUMBER
Adrian Dobs, M.D.	Baltimore, MD	6.24.99	9.21.99	VAI-RR/07041
Ronald Swerdloff, M.D.	Torrance, CA	6.24.99	12.29.99	VAI/02633
Ali Iranmanesh, M.D.	Salem, VA	6.24.99	*	

* This inspection request was never received by the Baltimore District Office (DO). This Summary is based on the two inspections that were completed.

Site #1
Adrian S. Dobs, M.D.
Johns Hopkins University
School of Medicine
1830 E. Monument Street, Suite 333
Baltimore, MD 21205

Acceptable

a. The field investigator reviewed 6 records of 22 subjects enrolled in protocol UMD-96-017 at Dr. Dobs' site.

b. There were no limitations on the inspection.

c. The inspection of this site noted several deviations from protocol: (1) failure to follow protocol in that diagnostic tests required by the protocol were not done; (2) one ineligible subject was entered into the study; (3) drug accountability records were incomplete; (4) the protocol was modified without IRB notification; and (5) adequate and accurate records were not maintained regarding blood sample handling and storage. The sponsor's response to these deficiencies indicated that appropriate changes would be made to ensure that these deficiencies would not be repeated in other studies.

Ronald Swerdloff, M.D.
Harbor-UCLA Medical Center
1000 W. Carson Street
Torrance, CA 90509

Acceptable

a. The field investigator inspected the records for 10 of the 26 subjects enrolled in protocol UMD-96-017 at Dr. Swerdloff's site.

b. There were no limitations on the inspection.

c. The inspection of this site noted two deviations from protocol: (1) one subject was entered into the study who did not meet weight requirements, and (2) a non-compliant subject was not dropped from the study.

Site #3
Ali Iranmanesh, M.D.
Veterans Affairs Medical Center
1970 Roanoke Blvd
Salem, VA 24153
***Inspection not done**

*Per the above note, this inspection request was not received by the Baltimore District Office, and no inspection was performed. The Summary is based exclusively on the inspections of Drs. Dobs and Swerdloff.

III. OVERALL ASSESSMENT OF FINDINGS AND GENERAL RECOMMENDATIONS

Overall, the violations observed at both sites were minor in scope and would not affect the reliability or integrity of the data submitted in support of this NDA.

Follow-up action: None needed

Roy Blay, Ph.D., Clinical Reviewer
DSI/GCPBI

CONCURRENCE:

David Lepay, M.D., PhD. 2/17/00
Division Director
Division of Scientific Investigations

WITHHOLD 3 PAGE (S)

13.0 PATENT INFORMATION

This section is not applicable since no patent exists for Unimed's testosterone gel product.

14.0 PATENT CERTIFICATION

This section is not applicable. This application is submitted under 505(b)(1) of the Federal Food, Drug and Cosmetic Act.

16.0 DEBARMENT CERTIFICATION

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

3.3 FOREIGN MARKETING HISTORY

Unimed is not aware of the marketing of testosterone gel outside of the U.S. Unimed does not market testosterone in any foreign country. Unimed Pharmaceuticals, Inc. has not applied for marketing approval of testosterone in any foreign country.

The above statements also apply to any derivative of testosterone, dosage form or complex of the drug.

Methods Validation package submitted (received February 15, 2000). Review will be completed post-action.

/S/ 2/18/00

Carcinogenicity studies were not required for this product.

/S/ 2/11/00

Carcinogenicity studies were not required for this product.

/S/ 2/11/00

Environmental Assessment review is in Chemistry Review #1, pages 20-21.

/S/ 2/11/00

Microbiology review of Sterility not needed.

/S/ 2/11/00

Statistical review of stability data not needed for this product per Dr. David Lin.

/S/ 2/11/00

Application: NDA 21015/000
Stamp: 29-APR-1999
Regulatory Due: 29-FEB-2000
Applicant: UNIMED PHARMS
2150 EAST LAKE COOK RD STE 210
Priority: BUFFALO GROVE, IL 60089
Org Code: 3S

Action Goal:
District Goal: 31-DEC-1999
Brand Name: ANDROGEL(TESTOSTERONE GEL) 25MG/50MG
Estab. Name:
Generic Name: TESTOSTERONE GEL

Dosage Form: (GEL)
Strength: 25, 50 MG

FDA Contacts: K. COLANGELO (HFD-580) 301-827-4260 , Project Manager
D. LIN (HFD-580) 301-827-4230 , Review Chemist
M. RHEE (HFD-580) 301-827-4237 , Team Leader

Overall Recommendation: ACCEPTABLE on 25-FEB-2000 by S. ADAMS (HFD-320) 301-594-0095

Establishment: [redacted]

DMF No: [redacted] AADA:
Responsibilities: [redacted] URER
Profile: CSN OAI Status: NONE
Estab. Comment: [redacted] (on 22-SEP-1999 by D. LIN (HFD-580) 301-827-4230)

Milestone Name	Date	Req. Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	23-SEP-1999				LINDAV
OC RECOMMENDATION	23-SEP-1999			ACCEPTABLE BASED ON PROFILE	EGASM

Establishment: [redacted]

DMF No: AADA:
Responsibilities: [redacted]
Profile: OIN OAI Status: NONE
Estab. Comment: [redacted] (on 22-SEP-1999 by D. LIN (HFD-580) 301-827-4230)

Milestone Name	Date	Req. Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	23-SEP-1999				LINDAV
SUBMITTED TO DO	23-SEP-1999	GMP			EGASM
ASSIGNED INSPECTION	23-SEP-1999	GMP			EGASM
INSPECTION SCHEDULED	23-NOV-1999		23-FEB-2000		IRIVERA
INSPECTION PERFORMED	24-FEB-2000		23-FEB-2000		IRIVERA
DO RECOMMENDATION	25-FEB-2000			ACCEPTABLE INSPECTION	ADAMSS
BASED ON 483 OC RECOMMENDATION	25-FEB-2000			ACCEPTABLE DISTRICT RECOMMENDATION	ADAMSS

Establishment: [redacted]

DMF No: AADA:

31-DEC-1999

29-FEB-2000
UNIMED PHARMS
3S
580
Priority:
Org Code:
Application Comment:
Responsibilities: FINISHED DOSAGE MANUFACTURER
FINISHED DOSAGE RELEASE TESTER
Profile: OIN OAI Status: NONE
Estab. Comment: PERFORMS MANUFACTURING AND QUALITY CONTROL TESTING OF DRUG PRODUCT GEL. (on 23-SEP-1999 by D. LIN (HFD-580) 301-827-4230)

Milestone Name	Date	Req. Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	23-SEP-1999				LINDAV
SUBMITTED TO DO	23-SEP-1999	GMP			EGASM
ASSIGNED INSPECTION	23-SEP-1999	GMP			EGASM
INSPECTION SCHEDULED	16-NOV-1999		17-DEC-1999		IRIVERA
DO RECOMMENDATION	24-FEB-2000			ACCEPTABLE	ADAMSS
OC RECOMMENDATION	24-FEB-2000			INSPECTION ACCEPTABLE DISTRICT RECOMMENDATION	ADAMSS

Establishment: [redacted]
DMF No: AADA:
Responsibilities: [redacted]
Profile: CTL OAI Status: NONE
Estab. Comment: [redacted] (on 22-SEP-1999 by D. LIN (HFD-580) 301-827-4230)

Milestone Name	Date	Req. Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	23-SEP-1999				LINDAV
SUBMITTED TO DO	23-SEP-1999	GMP			EGASM
ASSIGNED INSPECTION	23-SEP-1999	GMP			EGASM
INSPECTION SCHEDULED	10-NOV-1999		23-NOV-1999		IRIVERA
INSPECTION PERFORMED	23-NOV-1999		22-NOV-1999		EGASM
DO RECOMMENDATION	25-FEB-2000			ACCEPTABLE	ADAMSS
OC RECOMMENDATION	25-FEB-2000			INSPECTION ACCEPTABLE DISTRICT RECOMMENDATION	ADAMSS

CONSULT REQUEST-ABUSE LIABILITY

DIVISION OF ANESTHETIC, CRITICAL CARE, AND ADDICTION DRUG PRODUCTS (HFD-170)

REQUESTING DIVISION: Division of Reproductive and Urologic Drug Products (HFD-580)

DATE OF REQUEST: August 23, 1999

NDA # : 21-015

DRUG PRODUCT: Androgel (Testosterone) Gel

SPONSOR: Unimed Pharmaceuticals, Inc.

SUMMARY:

Sponsor amended NDA 21-015, with justification that the product be listed in Schedule III of the Controlled Substances Act.

The active ingredient is testosterone which is already listed in Schedule III (21 CFR 1300.01[b][4][xxvi] and 21 CFR 1308.13[f][1]) of the CSA. All mixtures and preparations of testosterone are listed in Schedule III, unless an exemption is requested and accepted by the DEA with FDA concurrence (per procedures in 21 CFR 1308.33).

CONCLUSION:

Androgel (Testosterone) Gel is a Schedule III product and the product labeling should indicate its control with the CIII symbol.

/S/

Michael Klein, Ph.D.
Team Leader, Controlled Substance Evaluation Team

October 14, 1999

cc:
Original NDA # 21-015
Division File
HFD-170/C.McCormick/MKlein/C.Moody
HFD-580/L.Rarick/K.Colangelo

APPEARS THIS WAY
ON ORIGINAL

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6 PAGES

Meeting Minutes

Date: May 21, 1999 **Time:** 3:00-3:35 p.m. EDT **Location:** Parklawn, 17B-43

NDA 21-015 **Drug:** Androgel (testosterone) **Indication:** testosterone replacement

Sponsor: Unimed

Type of Meeting: NDA Filing

Meeting Chair: Lisa Rarick, MD

Meeting Recorder: Kim Colangelo, BS

FDA Attendees:

Lisa Rarick, MD – Director, Division of Reproductive and Urologic Drug Products (DRUDP; HFD-580)
Lana Pauls, MPH – Associate Director, DRUDP (HFD-580)
Mark Hirsch, MD - Urologist, Medical Officer, DRUDP (HFD-580)
Norman Marks, MD - Urologist, Medical Officer, DRUDP (HFD-580)
Moo-Jhong Rhee, PhD - Chemistry Team Leader, Division of New Drug Chemistry II (DNDC-II) @ DRUDP (HFD-580)
Amit Mitra, PhD – Chemist, DNDC II @ DRUDP (HFD-580)
John Hunt – Deputy Director, Division of Pharmaceutical Evaluation II (DPE II; HFD-870)
Ameeta Parekh, PhD - Clinical Pharmacology and Biopharmaceutics Team Leader, DPE II @ DRUDP (HFD-580)
Dhruba Chatterjee, PhD - Clinical Pharmacology and Biopharmaceutics Reviewer, DPE II @ DRUDP (HFD-580)
Venkat Jarugula, PhD - Clinical Pharmacology and Biopharmaceutics Reviewer, DPE II @ DRUDP (HFD-580)
David Hoberman, PhD – Statistical Reviewer, Division of Biometrics II (DOB II) @ DRUDP (HFD-580)
Terri Rumble, BSN - Chief, Project Management Staff, DRUDP (HFD-580)
Kim Colangelo, BS – Regulatory Project Manager, DRUDP (HFD-580)
Gus Turner – Division of Scientific Investigations (DSI; HFD-344)

Meeting Objective: To determine the fileability of NDA 21-015 for Androgel, received on April 29, 1999.

Background: Androgel is a testosterone gel indicated for testosterone replacement in hypogonadal men; Unimed submitted one pivotal trial with 223 patients, 149 of whom received Androgel vs. Androderm TTS, an approved testosterone patch to support safety and efficacy.

Discussion:

- all disciplines report that the NDA is fileable
- possible review issues raised:
  - only 33 patients exposed to drug over 6 months
  - formulation changed -——— to sachets
  - superiority claims were not prospectively defined; support for superiority of efficacy may be difficult to support because the doses are not equivalent between the investigational product and the comparator
- safety appears acceptable with only six serious adverse events reported and few drop-outs
- a request for DSI audits is pending
- priority review was requested based on new dosage form (gel) and superior adverse event profile; since acceptable treatments for this non-life-threatening condition are available, priority review is not warranted
- the financial disclosure information submitted is acceptable

Decisions made:

- NDA is fileable
- a priority review is not warranted

Unresolved decisions: None.

Action Items:

- Ms. Colangelo will contact the Division of Addiction, Anesthetics, and Critical Care Drug Products regarding information needed for scheduled drug products

[After the filing meeting, it was noted that microbiology information had not been submitted. Unimed was contacted, and the information requested has been submitted.]

/S/

Minutes Prepared

/S/

Concurrence, Chair

cc:
Original NDA 21-015
HFD-580/DivFile
HFD-580/Colangelo/Rumble/Kammerman/Hoberman/Pauls
HFD-580/Rarick/Mann/Shames/Hirsch/Jordan/Rhee/Mitra/Parekh/Chatterjee/Jarugula

drafted: Colangelo, 06.14.99
concurrence: Rhee, Hirsch, Mitra, 06.16.99; Marks, Rarick, Chatterjee, 06.17.99; Rumble, Parekh, 06.21.99; Pauls, 06.22.99; Jarugula, 06.28.99
comments requested but not received: Hoberman
final: Colangelo, 08.04.99

MEETING MINUTES

Meeting Minutes

Date: November 3, 1998 **Time:** 1:00-2:30 p.m. EST **Location:** Chesapeake Room, Parklawn

IND ——— **Drug:** testosterone gel (T-Gel) **Indication:** testosterone replacement therapy

Sponsor: Unimed Pharmaceuticals

Type of Meeting: Pre-NDA

Meeting Chair: Marianne Mann, M.D., Deputy Director, Division of Reproductive and Urologic Drug Products (DRUDP, HFD-580)

External Lead: Robert Dudley, Ph.D., Senior Vice President, Unimed Pharmaceuticals

Meeting Recorder: Kim Colangelo, BS, Project Manager, DRUDP (HFD-580)

FDA Attendees:
Marianne Mann, MD, Deputy Director, DRUDP
Dan Shames, MD, Urology Team Leader, DRUDP
Mark Hirsch, MD, Urologist, Medical Officer, DRUDP
Phil Hanno, MD, Urologist, Medical Officer, DRUDP
Norman Marks, MD, Urologist, Medical Officer, DRUDP
Moo-Jhong Rhee, PhD, Chemistry Team Leader, Division of New Drug Chemistry II (DNDC II) @ DRUDP
David Lin, PhD, Chemistry Reviewer, DNDC II @ DRUDP
Venkat Jarugula, PhD, Pharmacokinetic Reviewer, Division of Pharmaceutical Evaluation II (DPE II) @ DRUDP
Lisa Kammerman, PhD, Statistical Team Leader, Division of Biometrics II (DB II) @ DRUDP
Barbara Elashoff, ScD, Statistician, DB II @ DRUDP
Terri Rumble, BSN, Acting Chief, Project Management Staff, DRUDP
Kim Colangelo, BS, Project Manager, DRUDP

External Attendees:
Robert Dudley, Ph.D., Senior Vice President
Gary Ringham, Ph.D., Director, Clinical Development
Georrge Kottayil, Ph.D., Associate Director, Pharmaceutical Development
Sandy Faulkner, R.N., Associate Director, Clinical Development
Donald Peckels, Director, Regulatory Affairs
Judy Athey, Regulatory Affairs Associate
Ronald Swerdloff, M.D., Consultant, Harbor-UCLA Medical Center

Meeting Objective:
To review prior agreements, define contents of NDA and clarify open issues.

Discussion:

- brief presentation by Unimed (copies of slides attached)
- Chemistry
  - trademark not yet determined
  - reference to the ——— drug master file is acceptable; ——— material was used for the pharmacokinetic study
  - although both sources of testosterone meet USP specifications, the impurity profile and HPLC chromatograms should be provided; Unimed also intends to submit chemical equivalence data with comparison of stability data
  - drug product stability data for 18 months on one lot for both package sizes at 25°/60% humidity and 40°/75% humidity will be included in the NDA; DRUDP cautioned if the data shows any negative findings, there may be difficulty in establishing an expiry date; stability data on four lots in bottles vs. to-be-marketed data are considered supportive
  - [redacted]
  - Unimed will implement *in vitro* release specifications immediately (including the stability lots), and will include the data in the NDA as per DRUDP recommendation; a copy of the guidance document relating to *in vitro* release testing will be provided to Unimed
  - Unimed confirmed that there are no other changes in the formulation other than the increase in isopropyl myristate
  - Unimed will investigate child resistant packaging, [redacted]
  - dose-delivery reproducibility and overfill of packages will be supported by a study of six people who each emptied 20 packages of T-Gel using one hand; data is based on the weight of gel collected, not amounts of testosterone
- Pharmacology/Toxicology
  - pharmacology/toxicology data section as proposed is acceptable
- Clinical and Statistics
  - primary sites for application of the product are arms and shoulders; secondary site is abdomen if needed; [redacted]
  - three month efficacy data for study UMD-96-017 is acceptable; Unimed estimates ~106 patients will have data through 6 months at submission
  - four month safety update will include data attained through approximately February, 1999; the safety update will include safety data for ~180 patients through 6 months and the final study report for UMD-96-017, to be submitted approximately 4 months and 2 weeks after NDA submission; key tables will be updated in the Integrated Summary of Efficacy
  - DRUDP cautioned of the risk of only submitting data for the 100 and 50 mg doses (75 mg dose data to be submitted later) if data does not support these dose levels (e.g., if serum testosterone levels are above or below the limit of normal); Unimed will be

- a separate study with appropriate blinding to support product superiority can be submitted as a labeling supplement after initial approval
- a clear and well-defined statistical plan prior to breaking the blind for both T-Gel and the comparator needs to be developed by Unimed and submitted for statistical review
- electronic text should be submitted in Microsoft Word (Office 97 or Window 95) format

Unresolved decisions:
None

Action Items:
- a copy of the guidance document relating to in vitro release testing will be provided to Unimed *[done; November 6,1998]*
- DRUDP comments on the transfer study will be provided within a week *[done; November 10, 1998]*

/S/

Minutes Preparer

/S/

Concurrence, Chair
12/4/98

cc:
Original IND 50,377
HFD-580/DivFile
HFD-580/Colangelo/Rumble/Pauls
HFD-580/Rarick/Mann/Shames/Hirsch/McNerney/Jordan/Rhee/Lin/Parekh/Jarugula
HFD-715/Kammerman/Elashoff

drafted: Colangelo, 11.13.98
concurrence: Hirsch, Mann, Rhee, 11.13.98; Shames, 11.17.98; Jarugula, Lin, 11.18.98; Kammerman, 11.19.98; Rumble, 11.20.98
final: Colangelo, 12.03.98

MEETING MINUTES

Unimed Consultants

- **Ronald Swerdloff, M.D.**
-

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Agenda

1:00 - 1:15	Overview of T-Gel Program
	• Meeting Objectives
	• T-Gel Indication
	• Premise for NDA
	• Content of NDA
	• Issues for Clarification
1:15 - 2:45	Open Discussion
2:45 - 3:00	Conclusions

4

Meeting Objectives

1) Review prior agreements with HFD-580;
2) Define contents of NDA based upon these agreements; and
3) Clarify open issues

5

T-Gel Indication

Testosterone replacement therapy in men for conditions associated with a deficiency or absence of endogenous testosterone.

6

NDA Premise #1

As previously agreed with HFD-580, preclinical section of original NDA will consist of:

- Comprehensive summary of key preclinical T literature
- Two preclinical studies that show T-gel is not an irritant or sensitizer
  - Acute dermal irritation in rabbit
  - Sensitization in guinea pig

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NDA Premise #2

As previously agreed with HFD-580, original NDA will include:

- Three-month efficacy & safety data from pivotal study (UMD-96-017)
  - Two T-gel doses v. T-Patch (Androderm®)
  - N = 75 enrolled/group
- All additional available safety data through cutoff date (10/16/98)

8

Clinical Overview of T-Gel

Current Therapies

- **Patches:** irritating, aesthetically unappealing, adhesive problems
- **IM Injections:** uncomfortable, inconvenient
- **Oral:** potential hepatotoxicity

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Clinical Overview of T-Gel (Cont.)

Projected Profile of T-Gel

- Consistent T plasma levels over 24 hours with once-daily application
- Ability to titrate doses
- Compliance
  - Ease of Application
  - Painless
  - Invisible
- Non-irritating, non-inflammatory transdermal product

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Clinical Overview of T-Gel (Cont.)

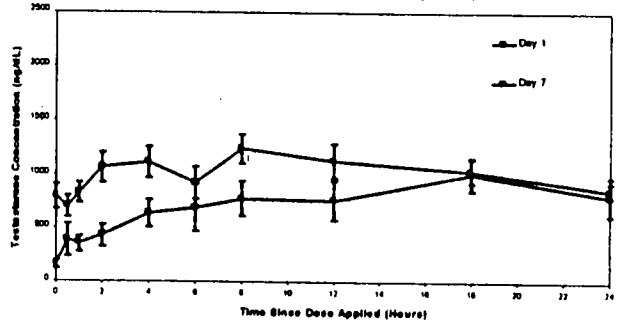
Overall Expected Clinical Outcomes

- Once daily dose → T levels within normal range
  → Consistent T levels over 24 hours
- Secondary endpoints improved from baseline
- Dermal safety profile better than patch

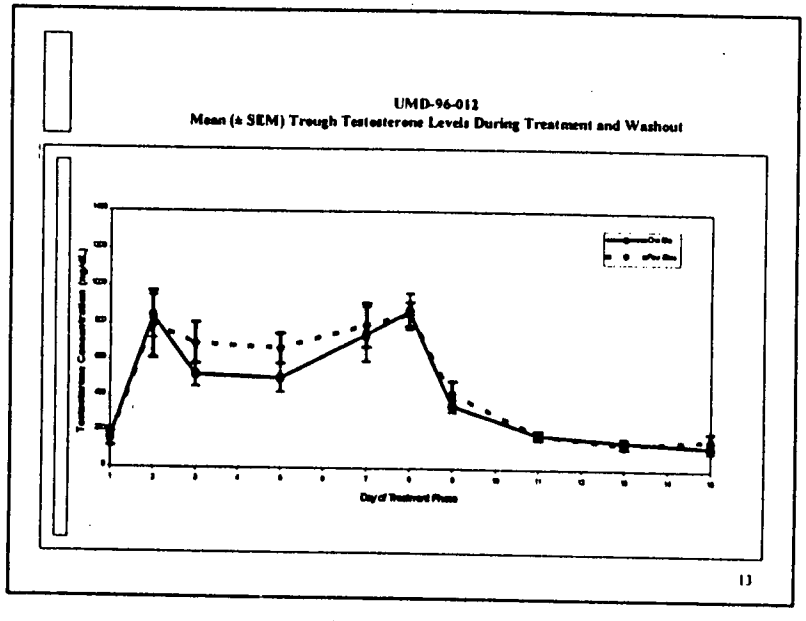
11

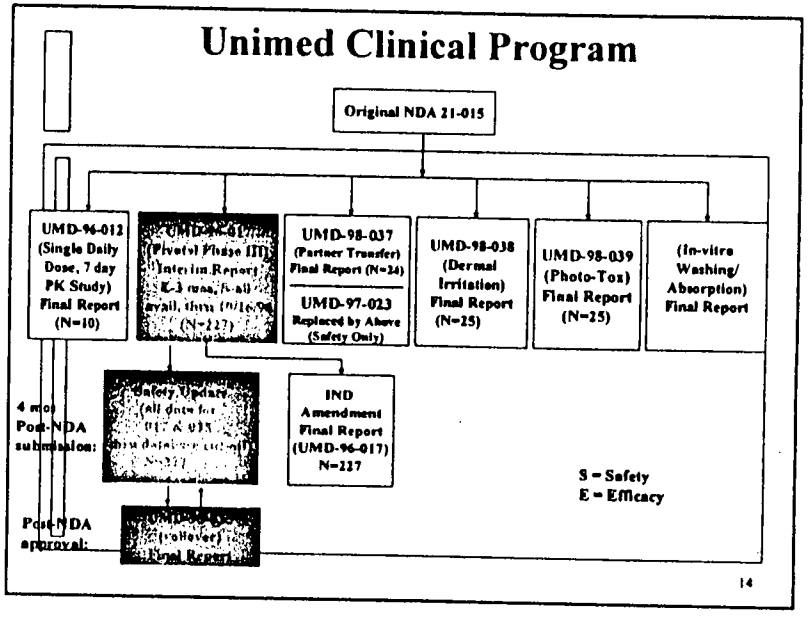
UMD-96-012

Mean (± SEM) 24-Hour Testosterone Levels
After Once Daily Application of 100 mg (N = 9)



12


UMD-96-012
Mean (± SEM) Trough Testosterone Levels During Treatment and Washout
13


Unimed Clinical Program
Original NDA 21-015
UMD-96-012 (Single Daily Dose, 7 day PK Study) Final Report (N=10)
UMD-98-037 (Partner Transfer) Final Report (N=24)
UMD-97-023 Replaced by Above (Safety Only)
UMD-98-038 (Dermal Irritation) Final Report (N=25)
UMD-98-039 (Photo-Tox) Final Report (N=25)
(In-vitro Washing/ Absorption) Final Report
IND Amendment Final Report (UMD-96-017) N=227
4 mos Post-NDA submission:
Post-NDA approval:
S = Safety
E = Efficacy
14

Issue for Clarification

[redacted] DMF Will Not Be Cross Referenced In NDA

- <5% of testosterone USP for clinical use sourced from [redacted] Chemical equivalence to [redacted] will be demonstrated.
- >95% of the testosterone USP for clinical use and that proposed for commercial use sourced from [redacted] The NDA will cross reference only [redacted] DMF.

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Issue for Clarification

Drug Product Stability at Time of Submission

Original NDA:

- >Two years stability in clinical supply packages (amber glass bottles)
- 18-month data for one lot (foil packets)
- 6-month data (per ICH protocol) for three lots (foil packets)

Amendment:

- One year data (per ICH protocol) for three lots (foil packets)

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Issue for Clarification

Provision of Electronic Documents

- Unimed plans to provide data on diskettes with the original hard copies of the NDA as outlined in the 10/2/98 briefing document
- Does the FDA have any additional electronic data requirements?

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Conclusion

Clinical development plan (completed and ongoing studies) will support filing of T-Gel NDA for the following indication:

Testosterone replacement therapy in men for conditions associated with a deficiency or absence of endogenous testosterone.

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MEMORANDUM OF MEETING MINUTES

DATE: February 18, 1997 **TIME:** 2:00-3:30 pm **LOCATION:** 17B-43

IND [redacted] **Indication:** Hypogonadism
50,377 — Androgel-T (testosterone)

Sponsor: Unimed Pharmaceuticals, Inc.

Type Of Meeting: Guidance/ Phase 2/3

Meeting Chair: Heidi Jolson, M.D., M.P.H., Deputy Director, Division of Urologic and Reproductive Drug Products, (DRUDP; HFD-580)

External Participant Lead: Robert E. Dudley, Ph.D., President and CEO, Unimed Pharmaceuticals, Inc.

Meeting Recorder: Terri Rumble, Project Manager, DRUDP; HFD-580

FDA Attendees:

Lisa D. Rarick, M.D., Director, DRUDP; HFD-580
Heidi Jolson, M.D., M.P.H., Deputy Director, DRUDP; HFD-580
Jean Fourcroy, M.D., Medical Officer, DRUDP; HFD-580
Daniel Shames, M.D., Medical Officer, DRUDP; HFD-580
Baldeo Taneja, Ph.D., Reviewing Statistician, Division of Biometrics II (DBII) @ DRUDP (HFD-580)
Alexander Jordan, Ph.D. - Pharmacology Team Leader, DRUDP; HFD-580
Mary Ellen McNerney, Ph.D. - Pharmacologist, DRUDP; HFD-580
Moo-Jhong Rhee, Ph.D. - Chemistry Team Leader, Division of New Drug Chemistry II (DNDC II) @ DRUDP (HFD-580)
K. Gary Barnette, Ph.D. - Pharmacokinetics Reviewer, Division of Pharmaceutical Evaluation II (DPE II) @ DRUDP (HFD-580)
Terri Rumble, B.S.N., Project Manager, DRUDP; HFD-580

External Constituents:

Robert E. Dudley, Ph.D., President and CEO, Unimed Pharmaceuticals, Inc.
Sandy Faulkner, R.N., B.S., Manager, Clinical Development, Unimed Pharmaceuticals, Inc.
Donald R. Peckels, Director, Regulatory Affairs, Unimed Pharmaceuticals, Inc.
Ronald S. Swerdloff, M.D., Chief, Division of Endocrinology & Metabolism, Harbor-UCLA Medical Center, Torrance, CA

Meeting Objectives: to review Phase 1 data and to discuss the proposed Phase 2/3 protocols planned for the investigations of Androgel-T and [redacted]

Background Information: These INDs are for 2 gels, manufactured in France, and used for the treatment of hypogonadal men. T- has a more specific mode of action.

Sponsor Presentation: (See attached overheads and questions)

FDA Discussion Points:

- the AUC levels for testosterone in normal men should be provided to the Division
- FDA has concerns regarding the long-term effect on the body of higher DHT levels causing suppression of T levels; high DHT effects are not known
- exclusion criteria could be modified to use older-age cut-offs for PSA levels
- some of the theoretical issues related to long-term claims, i.e., effects on the prostate, should be addressed now during the period of data collection
- primary endpoints for both studies need to be adequately defined
- the plan to rollover patients from Phase 2 into Phase 3 study is acceptable for testosterone if there are adequate washout, sample size, duration, and number of sites proposed;

- for chemistry requirements, all samples should be analyzed to determine impurities and qualify anything greater than 1.0%
- data on the photochemical stability studies for approval of the glass bottle used in the clinical trials should be submitted
- primary stability studies are needed for both the bottle and the packets; data on final packaging for marketed product is also needed
- a DMF for is required
- since a weight-based dose effect is seen, the protocol should be modified to stratify T dose by weight; the 100 mg dose seems to produce T levels too high (consider decreasing maximum dose to 50 or 75 mg)
- study should be designed to determine minimally effective dose vs. titrating to optimum dose; dose selection guidance for labeling will be important
- the protocol states the sample size was powered based on the lean body mass rather than T levels; the sample size is usually based on the primary endpoint, but this would not allow for enough subjects to assess safety
- potential abuse by women and athletes should be addressed during the approval process

- the psychosocial questionnaire(s) should be submitted to the INDs
- person-to-person transfer has not been seen as significant since the product dries quickly

Sponsor Discussion Points:

- higher androgens may lead to a lower CV risk (epidemiologic support)
- for T study, would titrate dose,
- plan to propose one large T study of 6 months, 3 months at a fixed dose and 3 months on a modified dose (titrated to individualize) based on the initial portion of the study, addressing the concern of body weight
- question regarding change relevant to excipient will be addressed by the sponsor

Summary:

- the T protocol requires modification
-
-

Action Items:

- Unimed will submit a modified T proposal for the Phase 3 study addressing the issues noted, such as, sample size proposed and dose selection based on individual responses
-
-

- Unimed will provide a letter of authorization to the DMF for the
- Unimed will provide the AUC levels for testosterone in normal men
- Unimed will submit the psychosocial questionnaire to the INDs

/S/ /S/

Minutes Preparer Concurrence, Chair

Attachments: Unimed Pharmaceuticals, Inc. Overheads and Questions

CC:
Original IND
Original IND
HFD-580/DivFile//Jolson/Fourcroy/Shames/Jordan/McNerney/Rhee/Rumble/Mercier
HFD-715/Kammerman/Taneja
HFD-870/Dorantes/Barnette

drafted: Rumble/February 24, 1007/wpfiles/minutes/ind
concurrences: Rarick,2.28.97/Jolson,2.25.97/Fourcroy,2.26.97/Shames,2.28.97/Taneja,/Rhee, /Jordan,2.28.97/McNerney,3.3.97/Barnette,3.4.97/Pauls,2.26.97
final: Rumble,3.4.97

MEETING MINUTES

**APPEARS THIS WAY
ON ORIGINAL**

Unimed Pharmaceuticals, Inc.
and
Division of Reproductive & Urologic Drug Products

February 18, 1997

Meeting Agenda

Subject: [redacted] *and IND* [redacted] *(Androgel™)*

Introduction (5 min.)..... Robert E. Dudley, PhD

Overview of Phase I Study Results (15 min.)..... Ronald Swerdloff, MD
[redacted] & UMD-96-012 (T-Gel)]

Discussion of Questions Included in 1/23/97 Information Package (30 min.)..... All

Wrap Up (10 min.)..... All

WITHHOLD 1 PAGE (S)

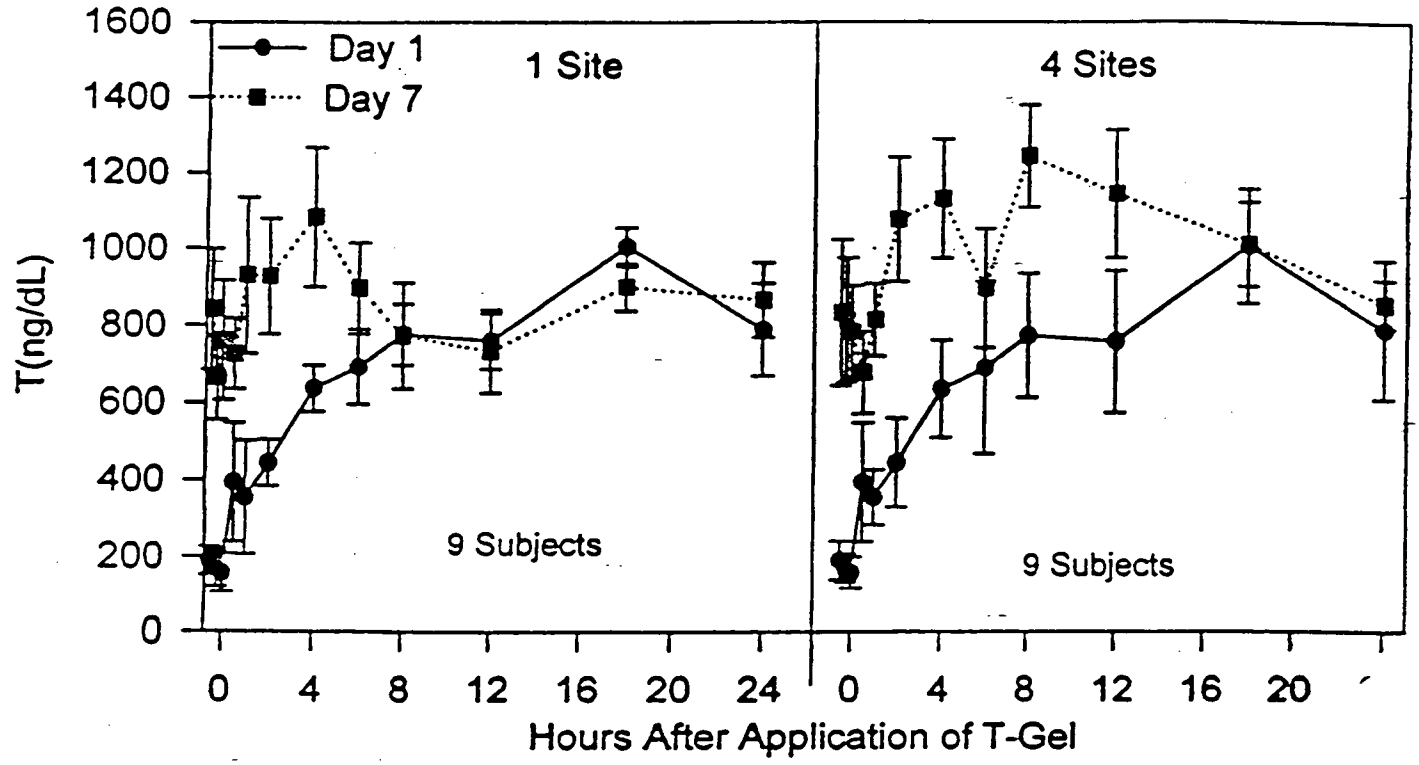
Testosterone-Gel (Androgel™) (UMD-96-012)

- Study Design
  - One vs. multiple sites, same dose cross-over comparison study
  - Subjects: hypogonadal men age 18 - 60
  - Dose: 100 mg T applied once daily
    - One site: 4 repeated applications of 25 mg T to one arm and shoulder
    - Multiple sites: 4 applications (25 mg T to each site)

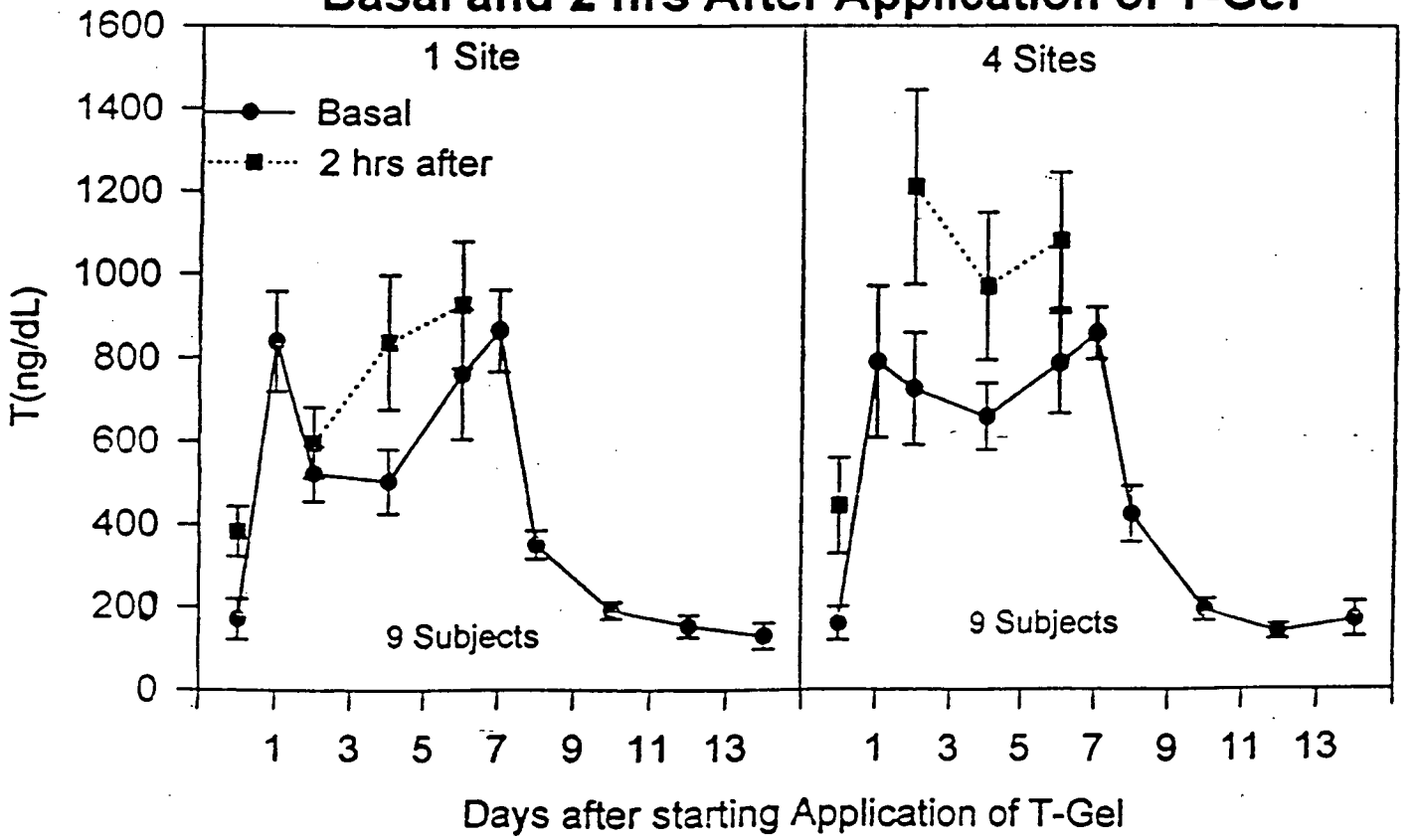
Testosterone-Gel (Androgel™) (UMD-96-012)

- Results
  - 100 mg dose of T-gel produced:
    - Serum T levels in the upper normal range
    - Serum levels 24 hours after application were maximal by day 1
    - Multiple sites gave more consistent levels than 1 site
  - Dried quickly without apparent residue
  - Good patient acceptability
  - No adverse effects
    - No skin reaction
    - No systemic complaints

Testosterone Levels After Application of T-Gel (Group Mean ± SEM)

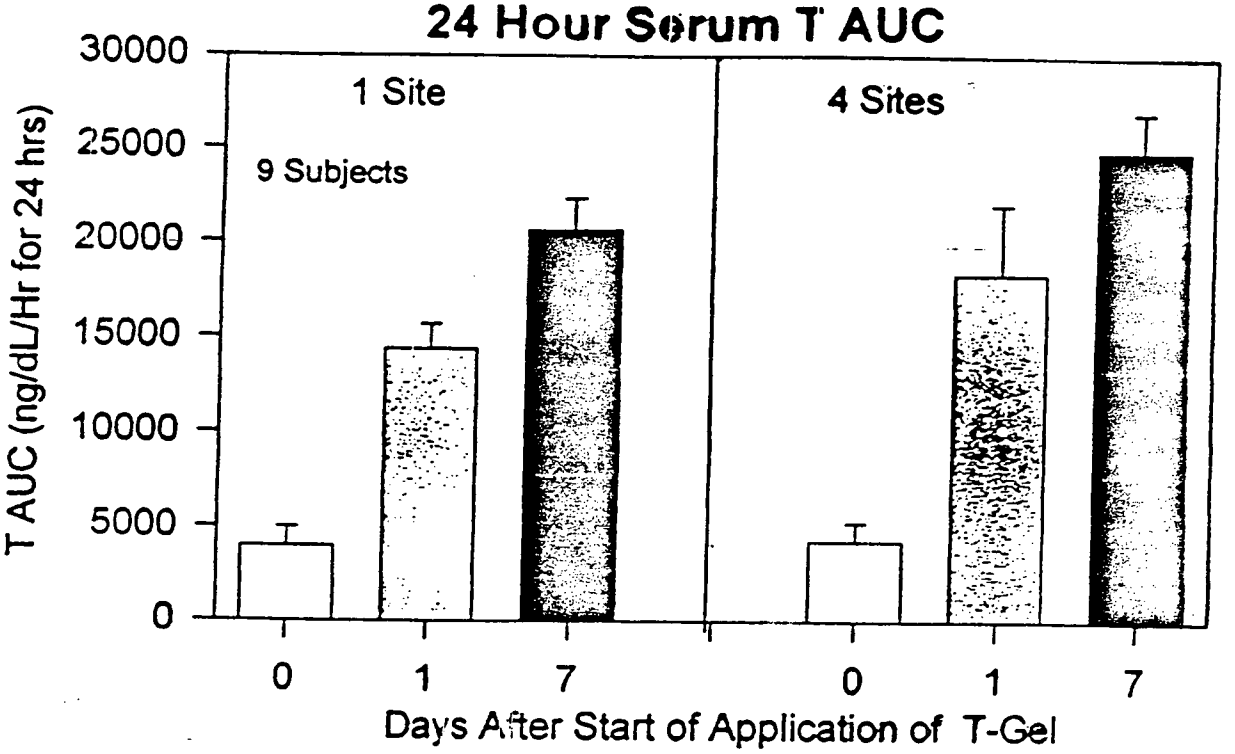


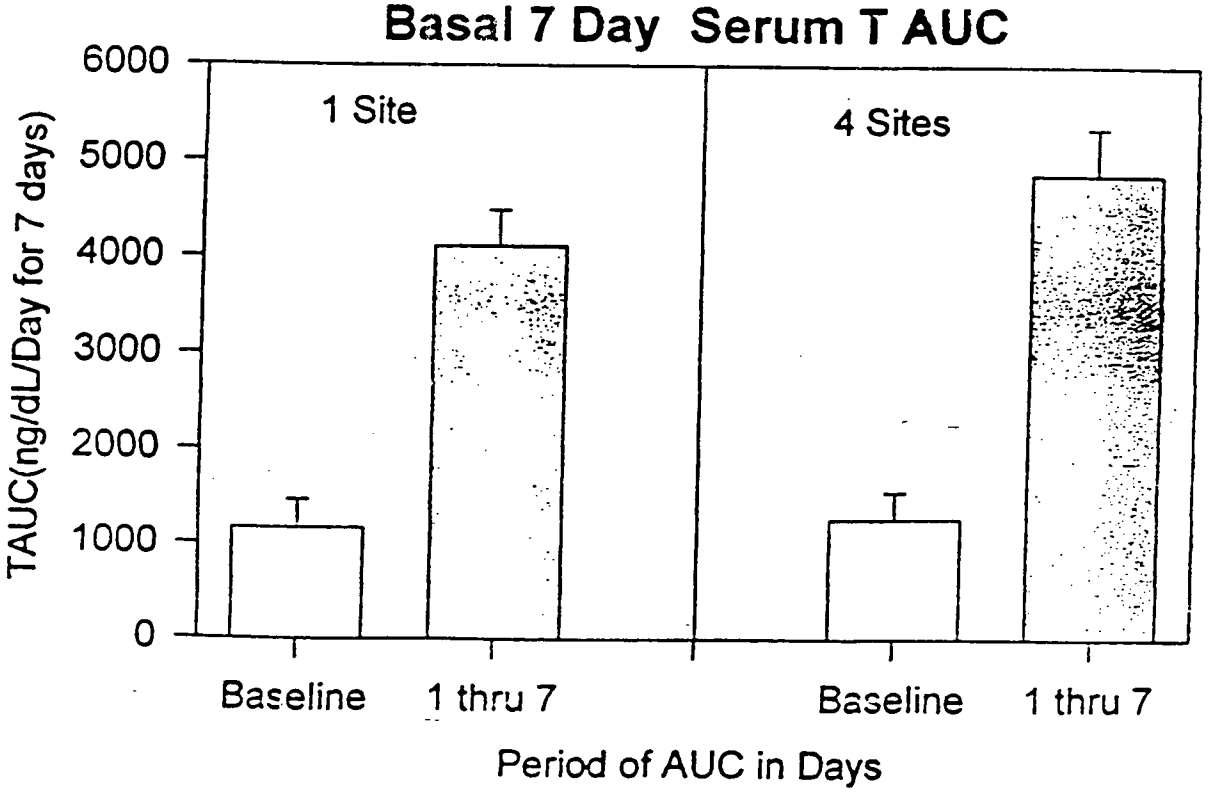
Basal and 2 hrs After Application of T-Gel



1/13/97[avgt.spw]

Testosterone Area Under the Curve After Application of T-Gel (Group Mean + SEM)





1/13/97[avgtauc.spw]

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Planned Phase II/III T and [ ] Studies

A PHASE II/III EVALUATION OF THE SAFETY AND EFFICACY OF TESTOSTERONE-GEL FOR HORMONAL REPLACEMENT IN HYPOGONADAL MEN

PROTOCOL NO.: UMD-96-017

Study Flow Chart

Parameter	Screening	Day 0 (Baseline)	Day 1	Day 30	Day 60	Day 90
T-Gel / T-Patch Application			→	→	→	→
Physical Examination	+[f]	+		+	+	+
Medical History	+					
Urine Flow	+[f]					+
Prostate Evaluation: Digital Rectal Exam + PSA	+[f]					+
CBC/Clinical Chem./Lipids/Urinalysis	+[f]		+[g]	+[g]	+[g]	+[g]
Serum Prolactin + Total T	+[aa]					
Skin Irritation Assessment		+	+	+	+	+
Serum Total T and Free T[a]		+	+	+	+[b]	+
Serum DHT, E_2, SHBG, LH, FSH[b]		+		+	+	+
DEXA [Body Composition (at least 3 sites)]		+				+
DEXA [Bone mineral density (at least 3 sites)][i]		+				
Muscle Strength (at least 3 sites)[h]		+				+
Serum Bone Formation Markers[c]		+		+		+
Urine Bone Markers[d]		+		+		+
Psychosexual Questionnaires[e]	→		→	→	→	→

[a] Multiple samples at -30 and -15 minutes before T-gel application and 0, 2, 4, 8, 12,16 (selected sites) and 24 hours after T-gel application.
[aa] Single morning sample at approximately 8:00 am.
[b] Single blood sample before dosing at approximately 8:00 am.
[c] Serum bone specific alkaline phosphatase, osteocalcin, type-1 procollagen and PTH.
[d] Timed two-hour fasting urine for calcium, creatinine, and type-1 collagen cross-linked N-telopeptide.
[e] Daily diary to be kept by subjects (7-day period prior to each clinic visit on Day 0, 30, 60 and 90).
[f] Values to serve as baseline.
[g] To be obtained at time '0', after an overnight fast.
[h] One repetition maximum technique will be used at 3 or more study sites to measure arm and leg muscle strength in bench press and seated leg press exercises.
[i] Lumbar spine and left hip regions.

A PHASE II/III EVALUATION OF THE SAFETY AND EFFICACY OF TESTOSTERONE-GEL FOR HORMONAL REPLACEMENT IN HYPOGONADAL MEN

PROTOCOL NO.: UMD-96-017

Inclusion Criteria

- Males, 18 - 60 yrs. requiring T replacement
- Morning serum T < 350 ng/dL
- General good health, no significant systemic or psychiatric illness
- Naïve to androgen replacement *or* washout of 6 weeks following IM T injections or 4 weeks following oral or transdermal T replacement
- Stable doses of endocrine replacement hormones for 14 days prior to entry; stable doses of tranquilizers and lipid lowering agents for 30 days prior to entry

Exclusion Criteria

- Urine flow rate of < 12 mL/sec
- Abnormal prostate as evidenced by prostatic symptoms, masses, or induration
- PSA > 4 mcg/mL
- Hematocrit > 50%
- Active alcoholism or history of drug abuse
- Concomitant therapy with antiandrogens, estrogens, p450 enzyme inducers, barbiturates, antidepressants

WITHHOLD 8 PAGE (S)

NDA 21-015

FEB 28 2000

MEDICAL OFFICER'S MEMO

FROM: Mark S. Hirsch, MD /S/ 2/28/00
Medical Officer

TO: Susan Allen, MD
Acting Division Director, HFD-580

THROUGH: Dan Shames, MD /S/ 2/28/00
Urology Team Leader, HFD-580

DATE: February 28, 2000

RE: Resolution of all outstanding labeling and clinical issues related to the clinical review of NDA 21-015, AndroGel™

The purpose of this memorandum is to inform the Acting Division Director that all relevant clinical issues regarding AndroGel (NDA 21-015) have been resolved. The final package insert and patient package insert are considered acceptable from a clinical perspective.

In the opinion of this reviewer, there are no outstanding clinical issues.

FEB 25 2000

~~FEB 24 2000~~

Medical Group Leader Memorandum Regarding OCPB Phase IV Commitment

NDA:	21-015
Product Trade Name:	ANDROGEL™
Active Ingredient/s:	Testosterone
Indication:	Testosterone Replacement Therapy (in hypogonadal men)
Submission Date:	April 29, 1999
Sponsor:	Unimed Pharmaceuticals Inc.
Type of Submission:	Original NDA, 3S
OCPB Reviewer:	Dhruba J. Chatterjee, Ph.D.
Consultant OCPB Reviewer:	Venkat Jarugula, Ph.D.
OCPB Team Leader:	Ameeta Parekh, Ph.D.
Urology Group Leader Memo:	2/25/00

Recommendation by OCPB

Based on the review, NDA 21-015 is acceptable from a Clinical Pharmacology and Biopharmaceutics perspective. Review of the PK data in this submission resulted in certain changes in the appropriate sections of the product label. The suggested changes have been appropriately incorporated in the label.

The following Phase IV commitment should be communicated to the sponsor:
Sponsor is requested to submit relevant evidence (post-approval) that there is no difference in clinical delivery of T (based on serum T levels) from the marketed ANDROGEL™ batches as compared to the clinical trial formulation.

I concur with the recommendation of the OCPB staff regarding the Phase IV commitment for ANDROGEL™

/S/

Daniel A. Shames MD
Team Leader, Urology
DRUDP/CDER/FDA

APPEARS THIS WAY
ON ORIGINAL

MEMORANDUM

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

DATE: February 18, 2000 FEB 1 8 2000

FROM: Kim Colangelo /S/
Regulatory Project Manager
Division of Reproductive and Urologic Drug Products (HFD-580)

SUBJECT: Comments on Sponsor's proposed labeling

TO: NDA 21-015

The following comments were received regarding the sponsor's minor labeling amendment containing revisions to the proposed package insert, submission dated February 9, 2000.

Comments from Mark Hirsch, MD – Medical Officer
Clinical Review begins on Line 167.
Line 171: O.K.

Line 172: O.K.

Line 176: O.K.

Line 178: O.K.

Line 178: O.K.

Line 191: O.K.

Line 196: O.K.

Line 199: O.K.

Line 203: O.K., except, *Question to sponsor:* Is the standard deviation for Cmax for 100 mg group accurate?

Line 205: O.K.

Line 209:

Line 233: O.K.

Line 234: increases over time ——————— in total body mass and total body lean mass, while total ...

Line 236: O.K.

Line 250: O.K.

Line 261: ——— ——————— ——————————— ———
Androgel treatment at 5 g/day and 10 g/day produced positive effects on mood and ——— fatigue.

Line 264: O.K.

Line 299: O.K.

Line 302: O.K.

Line 315: O.K.

Line 319: ...study conditions ——————— unprotected female partners had – a ———
serum testosterone concentration ——— >2 times baseline value at some time during the study.

Line 445: O.K.

Line 504: Adverse events possibly, probably or definitely related to ——— the use of Androgel and reported by ...

Line 508: Adverse Events Possibly, Probably or Definitely Related to Use of Androgel ———
———

> *Comment to sponsor:* We're concerned that there were absolutely no reports of "abnormal lab tests" (including increased hemoglobin, increased hematocrit, decreased HDL-cholesterol, increased PSA), "rash", or "arthralgias" that were considered even possibly-related to AndroGel in the controlled clinical trial. We're also concerned that none of the "headaches" in the 100 mg group were considered even possibly-related to Androgel. We're concerned that some GU events were considered "definitely not related" to Androgel. If any adverse event report term was even possibly-related to Androgel and ≥1% in incidence in the trial, it should appear in this Table. If any adverse event report term was even possibly-related to Androgel and <1% in incidence in the trial, it should appear in the text that follows the table.

Line 510: O.K.

Line 518: O.K. but unnecessary in the middle of a table.

Line 523: The following adverse events ——————————— possibly related to the use of AndroGel occurred in fewer... (*Note to sponsor*: replace these words)

Line 529: [redacted]

Line 536: [redacted] Delete figure

Line 552: ...cerebral hemmorhage, convulsion (neither of which were considered related to AndroGel administration)...

Line 560: No AndroGel patients discontinued due to skin reactions. [redacted]

Line: 572: ...clinical trial. The preliminary safety results from this study are consistent with those reported for the controlled clinical trial. Table ✓ summarizes those adverse events [redacted] possibly, probably or definitely related to the use of Androgel and reported by at least 1%...

Line 577: Table 4: Incidence of Adverse Events Possibly, Probably or Definitely Related to the Use of AndroGel in the Long-Term, Follow-Up Study

Comments to sponsor:

1. We're concerned that there were absolutely no reports of "hypertension"or "arthralgias" that were considered even possibly-related to AndroGel in the long-term, follow-up study. When these terms are assessed without regard to causality, they appear to be dose-related. In addition, there is a significant change-from-baseline in systolic BP in the 75 mg/daily group.
2. The AE term "Lab Test Abnormal" should be defined in the label.

Line 587: O.K.

Line 604: O.K.

Line 614:...Serum testosterone should be measured approximately -14 days after initiation of therapy to ensure proper dosing.

Line 617: O.K.

Line 626: O.K.

Comments from Dhruba Chatterjee, PhD – Clinical Pharmacology/Biopharmaceutics Reviewer
Review of lines 85 - 152
Line 85: [redacted] should be changed to "...all patients showed... within normal range within 4 hours after the initial application."

Line 104 : Remove newly proposed text [redacted]

Line 151 should be revised as follows: " [redacted] DHT/T ratio during 180... remained within normal limits (as determined by the analytical laboratory involved with this clinical trial) and ranged from 0.23...."

cc: Original NDA 21-015
HFD-580/Div. File

FEB 1 5 2000

Group Leader Memorandum

NDA:	**21-015**
Drug substance:	**testosterone**
Drug Product:	**testosterone gel**
Trade name:	**Androgel™**
Dose:	**25mg and 50mg**
Indication:	**Male hypogonadism**
Sponsor:	**Unimed Pharmaceuticals, Inc. Buffalo Grove, IL.**
Date received:	**4/30/99**
Review completed:	**2/15/999**

Background: Testosterone is an endogenous androgen produced by the Leydig cells of the testis under the influence of leutinizing hormone (LH) secreted by the pituitary gland. Testosterone is the metabolic precursor for two other important hormones, dihydrotestosterone, another important androgen, and estradiol. Androgens effect many important physiologic functions in men. These include the development of male sexual characteristics and effects on bones, lipids, proteins, erythropoieses and certain immune responses. In the adult male, normal plasma testosterone concentrations are in the range of approximately 300 to 1000 ng/dL, depending on the laboratory. The endogenous production of testosterone averages 6 to 7 mg/ day. Ninety percent of this comes from the testes, the remainder from the adrenal gland.

Male hypogonadism is a condition in which the endogenous secretion of testosterone is insufficient to maintain "normal" levels of testosterone and therefore may be associated with symptoms of testosterone deficiency. This condition may arise from a failure of the testis to produce testosterone (primary hypogonadism) or a failure of pituitary/hypothalamic stimulation of the testis (hypogonadotropic hypogonadism). Hypogonadism can result from identifiable conditions such as testicular torsion, orchitis, Klinefelter's syndrome, pituitary tumors, and exposure to toxins, or can be idiopathic. Signs and symptoms that may be associated with this condition include changes in mood, sexual desire, regression of male secondary sexual characteristics, osteoporosis and anemia.

It is important to note that inappropriately high levels of androgen could result in detrimental conditions such as polycythemia, negative mood changes, abnormal lipid

profiles or adverse effects on the prostate (benign or malignant growth), gynecomastia, or increased blood pressure.

Testosterone replacement is currently available in three forms, oral, intramuscular injection and dermal patches. Oral forms of testosterone are absorbed well but undergo extensive first-pass metabolism, which results in low availability and perhaps liver toxicity. The are various forms of intramuscular testosterone that must be administered from daily to every 2 to 3 weeks. In the last several years scrotal and non-scrotal trans- dermal patches have received Agency approval for hypogonadism. The sponsor believes that the transdermal route of administration avoids the discomfort and inconvenience of injectable forms of testosterone. The sponsor further believes that the current "patches" cause significant skin irritation and difficulties with adhesion. The sponsor concludes that Androgel™ is superior to the dermal patch comparator because Androgel™ demonstrated higher blood levels (and therefore increased efficacy)and less skin irritation in the submitted central comparative controlled trial.

Clinical Trials: In support of the proposed indication, the sponsor submitted one clinical trial (N=227) supported by smaller trials that add confirmatory efficacy or safety evidence. The central trial was a randomized, active-controlled, parallel-group, multicenter (U.S.), study comparing 50,75 and 100 mg of Androgel™ applied daily to a non-scrotal testosterone patch (2 patches applied daily, 5 mg absorbed testosterone) in hypogonadal men for six months. The study was double-blind with respect to the random assignment of the Androgel doses but open-label with respect to the patch. During the "initial treatment period" (from baseline to day 90) three treatments were administered : Androgel 5G (contains 50 mg of testosterone), Androgel 10 G (contains 100 mg of testosterone) and 2 testosterone patches (5 mg absorbed testosterone) all applied daily.

At day 91, a fourth treatment group was added, 7.5 G of Androgel™ daily(containing 75 mg of testosterone). Androgel™ patients who had a serum concentration of testosterone within the normal range during the first 90 days, and all testosterone patch patients remained in their treatment groups for another three months ("Extended Treatment Period"). However, Androgel™ 100 mg patients who exceeded the normal range or Androgel™ 50 mg patients who were below the normal range were titrated to receive Androgel™ 75 mg in an open label fashion for the "Extended Treatment Period" (days 90-180).

The primary efficacy endpoint was "the proportion of patients in each treatment group with both C_{avg} and C_{min} within the normal range" on day 30. This was one of several endpoints considered by The Division and was designed to capture subjects that had sufficient testosterone replacement to remain above the minimal normal range. Serum testosterone is used as a surrogate for the remediation of the clinical problems that can accompany hypogonadism. The endpoint agreed to in this trial has the disadvantage of allowing patients with occasional testosterone levels above the normal range to succeed in making the endpoint. Therefore preparations that cause higher levels of serum testosterone will "win" more than those that produce lower levels. However there is no evidence that higher levels of testosterone within the normal range are beneficial to the patient. On the contrary,

there is evidence (in this submission and elsewhere) that sustained testosterone levels above the normal range may be detrimental.

Efficacy Results: The primary endpoint was defined as the proportion of patients with both C_{avg} and C_{min} for total testosterone on day 30 within the normal range. The proportion that "succeeded" in making this endpoint was 38/73(53%) for Androgel™ 50 mg, 48/78 (62%) for Androgel™ 100mg and 17/76 (22%) for testosterone patch.

Table 1 presents the mean Cmax, Cmin, Cavg and Tmax calculated for each treatment group.

Table 1. Testosterone Pharmacokinetic Parameters, by Initial Treatment Randomization Group, on Day 30 (Mean ± SD)

	Androgel 50 mg (N=66)	Androgel 100 mg (N=74)	T Patch (N=70)
Cmax (ng/dL)	876 ± 466	1200 ± 482	576 ± 280
Cmin (ng/dL)	361 ± 149	505 ± 233	235 ± 132
Cavg (ng/dL)	566 ± 262	792 ± 294	419 ± 163
Tmax (hr)	7.9	7.8	11.3

A patient was classified as a treatment failure if either the Cavg or Cmin was outside the normal range (from 298 ng/dL to 1043 ng/dL). Table 2 presents the numbers of patients with Cavg or Cmin outside the normal range on Day 30 for each treatment group.

Table 2. Number of patients with Cavg or Cmin outside the normal range on Day 30.

	Cmin below normal range	Cmin above normal range	Cavg below normal range	Cavg above normal range
Androgel 50 mg	25	1	6	3
Androgel 100 mg	12	2	1	15
T patch	53	0	17	0

Table 3 presents the number of patients with Cmax outside the normal range for each treatment group.

Table 3. Number of patients with Cmax outside the normal range on Day 30.

	Cmax below normal range	Cmax above normal range
Androgel 50 mg	2	17
Androgel 100 mg	1	43
T patch	5	3

The above tables demonstrate that while the primary endpoint used in this study is a good way to "describe" the ability of each preparation to replace testosterone, it is not perfect. Neither The Division nor the experts in this area have been able to describe an easy method for defining testosterone "replacement". The reviewer must examine all the

pharmacokinetic parameters available. In addition, because most preparations of testosterone are titratable, individual patient variability will alter the final dose of this and other testosterone preparations.

Although it did not effect the 30-day endpoint, it should be noted that the label of the testosterone patch used in this study discusses lowering or raising the dose administered (reducing to one patch or increasing to three patches) based on individual patient response. The sponsor failed to titrate the "patch" while it allowed titration in the gel arms. One would expect that an "efficacious" dose of testosterone could be reached in an individual patient by measuring serum testosterone at the appropriate time and titrating either patch or gel accordingly. This reviewer believes that Androgel™ will be efficacious for the treatment of testosterone deficiency in hypogonadal men.

Safety Analysis: Important safety concerns noted during the studies described in this submission fell into one of three categories; 1. Physiologic and adverse effects of testosterone, 2. Skin irritation issues of gel versus patch, 3. Partner transfer issues.

Because Androgel™ tended to cause higher levels of testosterone (occasionally well above upper limits of normal), there were more adverse events related to androgenic effects in the gel group. These included urogenital disorders, emotional liability, hypertension, polycythemia and worsening lipid profile. This reviewer believes that the adverse events related to testosterone can be minimized by proper monitoring and titration of Androgel™as described in the label.

The sponsor believes that Androgel™ is better tolerated than the comparator testosterone patch because the patients on the gel reported fewer skin tolerability problems compared to the patch and there were no discontinuations in the gel group compared to about 20% in the patch group. There appeared to be a trend in terms of tolerability in this single unblinded trial. A double blind, double-dummy design with rigorous evaluation of skin irritation could confirm this finding if the sponsor wants a label claim of superiority. Superiority claims regarding skin tolerability would be inappropriate in the current label for Androgel™.

Androgel™ can clearly be transferred to the patient's partner by skin contact. The sponsor demonstrated that this could result in significantly increased testosterone levels in some females. This can pose some risk to females but even more risk to developing fetuses. Both these issues are addressed in the label and techniques to reduce risk are discussed.

Conclusion: I agree with the primary reviewer that Androgel™ should be approved for replacement therapy in males for conditions associated with a deficiency or absence of endogenous testosterone.

/S/

Daniel A. Shames MD
Team Leader, Urologic Drugs
DRUDP, HFD-580
CDER/FDA

Office of Post-Marketing Drug Risk Assessment
HFD-400; Rm 15B03
Center for Drug Evaluation and Research

PROPRIETARY NAME REVIEW

Date of Review: 1/27/00

NDA#: 21-015

Name of Drug: Androgel®

NDA Holder: Unimed Pharmaceuticals, Inc.

I. INTRODUCTION

This consult was written in response to a request from the Division of Reproductive and Urologic Drug Products (HFD-580) on December 2, 1999, to review the proposed proprietary drug name, Androgel® in regard to potential name confusion with existing proprietary/generic drug names.

The Labeling and Nomenclature Committee (LNC) had **NOT** reviewed this proprietary name. This consult was forwarded to OPDRA for final clearance prior to approval of NDA. The goal date is 2/29/00.

PRODUCT INFORMATION

Androgel® (testosterone gel) is a clear, colorless hydroalcoholic gel containing 1% testosterone. Androgel provides continuous transdermal delivery of testosterone, the primary circulating endogenous androgen, for 24 hours following a single approach to intact, clean, dry skin of the shoulders, upper arms and/or abdomen. Approximately 10% of the applied testosterone dose is absorbed across skin of average permeability during a 24-hour period.

Androgel (testosterone) is rapidly absorbed into the skin, which serves as a reservoir for the sustained release of testosterone into the systemic circulation. Increases in serum testosterone are observed within 30 minutes; serum concentrations within the normal range are achieved one hour after initial application. Testosterone is metabolized through two different pathways, and excreted mainly through urine.

Androgel will be supplied in aluminum packets containing 25 mg and 50 mg testosterone in cartons of 30.

II. RISK ASSESSMENT

In order to determine the potential for medication errors and to find out the degree of confusion of the proposed proprietary name, Androgel® with other drug names, the medication error staff of OPDRA searched Micromedex online, PDR (1999 Edition), American Drug Index (43rd Edition), Drug Facts and Comparison (update monthly), the Electronic Orange Book, and US Patent and Trademark Office online database. In addition, OPDRA also searched several FDA databases for potential sound-alike and look-alike names to approved/unapproved drug products through DPR, Medline online, Decision Support System (DSS), Establishment Evaluation System, and LNC database. A drug expert group was conducted to review all the findings from the searches. OPDRA also conducted studies of written and verbal analysis of the proposed proprietary name employing health practitioners within FDA to evaluate potential errors in handwriting and verbal communication of the name. This exercise was conducted to simulate an actual practice setting.

A. STUDY CONDUCTED BY OPDRA

Methodology:

This study involved 92 health professionals consisting of physicians, nurses and pharmacists within FDA to determine the degree of confusion of Androgel® with other drug names due to the similarity in handwriting and verbal pronunciation of the name. OPDRA staff member wrote two outpatient prescriptions, each consisting of a known drug product and a prescription for Androgel®. These prescriptions were scanned into the computer and a random sample of the written orders were then delivered to the participating health professionals via e-mail. Outpatient prescriptions and inpatient orders were sent to 30 and 31 participants for review. In addition, one pharmacist with a foreign accent recorded the outpatient orders on voice mail. The voice mail messages were then sent to 31 participating health professionals for their review and interpretation. After receiving either the written or verbal prescription orders, the participants sent their interpretations of the orders via e-mail to the medication error staff.

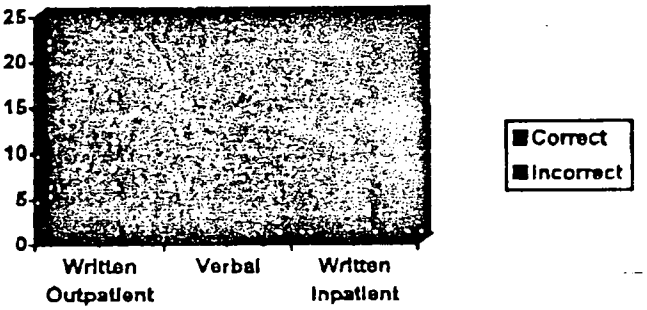
Results:

We received responses from 62 participants, Fifty-six of which interpreted the name correctly. Thirty interpreted outpatient prescriptions and thirty-one each interpreted verbal and inpatient orders.

The results are summarized in Table I.

Table I

Study	# of Sample	# of Responses (%)	Correctly Interpreted	Incorrectly Interpreted
Written Outpatient	30	20 (67%)	20	0
Verbal	31	21 (68%)	15	6
Written Inpatient	31	21 (68%)	21	0



Ninety percent of the participants responded with the correct name Androgel®. The incorrect written and verbal responses are as follows in Table II :

Table II

	Incorrectly Interpreted
Written	0
Verbal	Androga (2)
	Androzet
	Androgil
	Androget
	Androja

B. OPDRA EXPERT GROUP DISCUSSION:

The group did not uncover any existing drug names that could cause confusion with Androgel®, and thus pose a significant safety risk. However, concern were

voiced that "gel" sounded like a topical skin gel, and the name sounds alike with an existing proprietary name that is currently marketed "Androderm®" which contains 12.2 mg testosterone in a transdermal patch. Concern also raised that Androgel® sounds alike to Amphojel® which is an antacid containing aluminum hydroxide.

B. EXECUTIVE SUMMARY:

The results of the verbal and written analysis studies show fifty-six out of sixty-two participants interpreted the proprietary name Androgel® correctly. There are high scores of correct interpretation for all written prescriptions for this new proposed proprietary name Androgel®. There were only six incorrect verbal responses. These responses pose little concern since these products are currently not marketed. Furthermore, our study did not substantiate the concern raised by the OPDRA EXPERT GROUP that Androderm® and Amphojel® might pose potential for medication errors due to sound- alike and look-alike similarity. Finally, the studies and searches conducted within FDA did not reveal any existing drug names that would render the proposed proprietary name, Androgel®, objectionable.

III. RECOMMENDATIONS

OPDRA has no objections to the use of the proprietary name Androgel®.

Should you have any questions concerning this review, please contact Peter Tam at 301-827-3241

/S/

Peter Tam, RPh.
Safety Evaluator
Office of Post-Marketing Drug Risk Assessment

Concur

/S/ 2/1/2000

Jerry Phillips, RPh.
Associate Director for Medication Error Prevention
Office of Post-Marketing Drug Risk Assessment

C.C.

NDA-21-015
Office File
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APPEARS THIS WAY
ON ORIGINAL