CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-015

CORRESPONDENCE

UNIMED

Unimed Pharmaceuticals, Inc.
2150 East Lake Cook Road
Buffalo Grove, Illinois 60089
847-541-2525
847-541-2569 FAX

approved
PI + PPI

FAX . . .

Date:	2/28/00	No. of Pages:	2532
To:	Kim Colangelo	From:	Judy Athey
	FDA Div. Urologic & Reproductive Products		Regulatory Affairs
Phone:	301-827-4260	Phone:	(847) 541-2525
Fax:	301-827-4267	Fax:	(847) 541-2569

RE: AndroGel™ (testosterone gel) NDA 21-015

Kim,

Attached please find the revised physician package insert incorporating revisions requested by telephone today.

Judy Athey

Judy Athey, Assistant Manager, Regulatory Affairs

2/28/00

Date

If You Experience Problems with this Transmission - Please Call the Number Listed Above

UNIMED

Unimed Pharmaceuticals, Inc.
2150 East Lake Cook Road
Buffalo Grove, Illinois 60089
847-541-2525
847-541-2569 FAX

FAX . . .

Date:	February 28, 2000	No. of Pages:	5
To:	Kim Colangelo	From:	*Judy Athey*
	FDA Div. Urologic & Reproductive Products		*Regulatory Affairs*
Phone:	301-827-4260	Phone:	*847-541-2525*
Fax:	301-827-4267	Fax:	*847-541-4827*

Dear Kim,

RE: **Androgel® (testosterone gel) NDA 21-015**

Following is the full text of the patient package insert incorporating all revisions requested by the agency and agreed to by Unimed Pharmaceuticals, Inc. Please contact me if you have questions.

Sincerely,

Judy Athey

Assistant Manager, Regulatory Affairs

If You Experience Problems with this Transmission - Please Call the Number Listed Above

WITHHOLD 4 PAGE (S)

WITHHOLD 12 PAGE (S)

WITHHOLD 4 PAGE (S)

WITHHOLD 34 PAGE (S)

UNIMED

Unimed Pharmaceuticals, Inc.
2150 East Lake Cook Road
Buffalo Grove, Illinois 60089
847-541-2525
847-541-2569 FAX

FAX . . .

Date:	2/25/00	No. of Pages:	22 25
To:	Kim Colangelo	From:	Judy Athey
	FDA Div. Urologic & Reproductive Products		Regulatory Affairs
Phone:	301-827-4260	Phone:	(847) 541-2525
Fax:	301-827-4267	Fax:	(847) 541-2569

RE: **AndroGel™ (testosterone gel) NDA 21-015**

Kim,

Attached please find the revised draft physician package insert incorporating all revisions discussed.

Please call if there are questions.

Judy Athey

Judy Athey, Assistant Manager, Regulatory Affairs

2/25/00

Date

If You Experience Problems with this Transmission - Please Call the Number Listed Above

UNIMED

Unimed Pharmaceuticals, Inc.
2150 East Lake Cook Road
Buffalo Grove, Illinois 60089
847-541-2525
847-541-2569 FAX

FAX . . .

Date:	2/25/00	No. of Pages:	3
To:	Kim Colangelo	From:	Judy Athey
	FDA Div_Urologic & Reproductive Products		Regulatory Affairs
Phone:	301-827-4260	Phone:	(847) 541-2525
Fax:	301-827-4267	Fax:	(847) 541-2569

RE: **AndroGel™ (testosterone gel) NDA 21-015**

Kim,

Following is a copy of the letter to the Agency which will be submitted today.

Please call if there are questions.

Judy Athey

Judy Athey, Assistant Manager, Regulatory Affairs

2/25/00

Date

REMARKS:	☐ FYI	☐ For your review	☐ Reply ASAP	☐ Please comment

UNIMED

Unimed Pharmaceuticals, Inc.
2150 East Lake Cook Road
Buffalo Grove, Illinois 60089
847-541-2525
847-541-2569 FAX

FAX . . .

Date:	2/25/00	No. of Pages:	3
To:	Kim Colangelo FDA Div. Urologic & Reproductive Products	From:	Judy Athey Regulatory Affairs
Phone:	301-827-4260	Phone:	(847) 541-2525
Fax:	301-827-4267	Fax:	(847) 541-2569

RE: AndroGel™ (testosterone gel) NDA 21-015

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Following is a copy of the letter to the Agency which will be submitted today.

Please call if there are questions.

Judy Athey

Judy Athey, Assistant Manager, Regulatory Affairs

2/25/00

Date

REMARKS:	☐ FYI	☐ For your review	☐ Reply ASAP	☐ Please comment

If You Experience Problems with this Transmission - Please Call the Number Listed Above

UNIMED

Unimed Pharmaceuticals, Inc.
2150 East Lake Cook Road
Buffalo Grove, Illinois 60089
847-541-2525
847-541-2569 FAX

FAX . . .

Date:	2/25/00	No. of Pages:	~~22~~ 25
To:	Kim Colangelo	From:	Judy Athey
	FDA Div. Urologic & Reproductive Products		Regulatory Affairs
Phone:	301-827-4260	Phone:	(847) 541-2525
Fax:	301-827-4267	Fax:	(847) 541-2569

RE: **AndroGel™ (testosterone gel) NDA 21-015**

Kim,

Attached please find the revised draft physician package insert incorporating all revisions discussed.

Please call if there are questions.

Judy Athey

Judy Athey, Assistant Manager, Regulatory Affairs

2/25/00

Date

********** -COMM. JOURNAL- ********** DATE OCT-07-1999 ***** TIME 13:21 *********

MODE = MEMORY TRANSMISSION START=OCT-07 13:20 END=OCT-07 13:21

FILE NO.=325

STN NO.	COMM.	ABBR NO.	STATION NAME/TEL NO.	PAGES	DURATION
001	OK	8	918475413706	001/001	00:00:42

-FDA/DRUDP

********** -FDA/DRUDP - ***** - 301 827 4267- **********

FACSIMILE TRANSMISSION RECORD

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II
Division of Reproductive and Urologic Drug Products (HFD-580)
Parklawn Building, Room 17B-45
5600 Fishers Lane, Rockville, Maryland 20857

1 Number of Pages (including cover sheet) **Date:** October 7, 1999

To: Donald R. Peckels
Director, Regulatory Affairs
UNIMED Pharmaceuticals, Inc.

Fax Number: 847-541-3706 **Voice Number:** 847-541-2525

From: Kim Colangelo
Project Manager

Fax Number: 301-827-4267 **Voice Number:** 301-827-4260

Message:

Electronic information requested:

1) All PK Study Summaries (i.e., Summary of Section 6 including figures/tables) - MS WORD version will be fine.
2) Individual Study Synopses (all PK Studies)- MS WORD version OK.
3) Draft Physician Package Insert (Label) - MS WORD version OK.
4) Raw Data (preferably in MS Excel) on:
a) PK (blood levels of T, DHT)
b) Secondary Clinical End Points & Safety Markers:
i) Phycosexual Scores
ii) Muscle Strength
iii) Body Composition/Bone Mineral Density
iv) Bone Markers
v) Patients Demographics (age, race, body wt., cause of T deficiency, etc.)
vi) Clincial Laboratory Evaluations (Hematology, Lipids, PSA)

/S/

Please note that we do not consider this a formal communication.

NOTE: If you do not receive a legible document, or do not receive all of the pages, please telephone us immediately at the voice number above.

UNIMED Pharmaceuticals, Inc.
2150 East Lake Cook Road
Buffalo Grove, IL 60089-1862
847-541-2525
Fax 847-541-2569

UNIMED

28 February 2000

Susan Allen, M.D., M.P.H., Acting Director
Division of Reproductive and
Urologic Drug Products, HFD-580
Center for Drug Evaluation and Research
Food and Drug Administration
Document Control Room17B-20
5600 Fishers Lane
Rockville, MD 20857

Dear Dr. Allen:

Re: **AndroGel™ (testosterone gel); NDA 21-015**
Response to requested information

Dear Dr. Allen:

This amendment to the above referenced NDA 21-015 provides information requested by the Agency on 25 Feb 2000. Specifically requested and provided herein are the full text of the AndroGel™ physician package insert and the patient package insert incorporating all revisions requested by the agency and agreed to by Unimed Pharmaceuticals, Inc.

A true copy of this amendment has been submitted to the Chicago District Field Office. Please contact me at 847-541-2525 should you need additional information.

Sincerely,

Judy Athey

Judy Athey
Assistant Manager, Regulatory Affairs

Enclosures

UNIMED Pharmaceuticals, Inc.
2150 East Lake Cook Road
Buffalo Grove, IL 60089-1862
847-541-2525
Fax 847-541-2569

UNIMED

28 February 2000

Susan Allen, M.D., M.P.H., Acting Director
Division of Reproductive and
Urologic Drug Products, HFD-580
Center for Drug Evaluation and Research
Food and Drug Administration
Document Control Room17B-20
5600 Fishers Lane
Rockville, MD 20857

Dear Dr. Allen:

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Response to requested information

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A true copy of this amendment has been submitted to the Chicago District Field Office. Please contact me at 847-541-2525 should you need additional information.

Sincerely,

Judy Athey

Judy Athey
Assistant Manager, Regulatory Affairs

Enclosures

UNIMED Pharmaceuticals, Inc.
2150 East Lake Cook Road
Buffalo Grove, IL 60089-1862
847-541-2525
Fax 847-541-2569

UNIMED

25 February 2000

Susan Allen, M.D., M.P.H., Acting Director
Division of Reproductive and
Urologic Drug Products, HFD-580
Center for Drug Evaluation and Research
Food and Drug Administration
Document Control Room17B-20
5600 Fishers Lane
Rockville, MD 20857

Dear Dr. Allen:

Re: **AndroGel™ (testosterone gel); NDA 21-015**
Response to requested information

Dear Dr. Allen:

This amendment to the above referenced NDA 21-015 provides information requested by the Agency on 25 Feb 2000. Specifically requested were: (1) revisions to the physician package insert; (2) revisions to the patient package insert; and (3) a Phase IV commitment.

(1) Lines 178-181 of the physician package insert ———— will now read: "Of 129 hypogonadal men who were appropriately titrated with AndroGel™ and who had sufficient data for analysis, 87% achieved an average serum testosterone level within the normal range on treatment day 180."

This makes the number of patients in the text exactly match the number of patients in Table 1. These data are taken from Vol. 4.4, Table 6.5, page 268-0002. The footnote to this same table explains the two-patient discrepancy between Table 1 and the previous language in line 178-180. Patients whose dose assignments at Day 180 reflected a departure from the protocol were excluded from the descriptive statistics presented for the extended treatment phase. This includes two patients (406 and 418) who were dose adjusted from 50 to 25 mg and 100 to 50 mg, respectively.

(2) The following revisions as requested by the Agency will be made to the patient package insert:

UNIMED PHARMACEUTICALS, INC.
25 FEB 2000
NDA 21-015

1. Under "**What are the possible side effects of AndroGel?**
   AndroGel may cause the following side effects:
   - Breast development and breast discomfort
   - Extra fluid in the body. This may cause serious problems for patients with heart, kidney, or liver damage.
   - Sleep disturbance call "sleep apnea". This is more likely in patients who are overweight or who have lung disease.
   - Prostate enlargement, sometimes accompanied by difficulty urinating
   - Emotional problems like depression
   - Changes in blood levels of cholesterol. This may be monitored and prevented by periodic blood tests.

   Tell your doctor if you develop any of the following side effects:
   - Penis erections that are too frequent or continue too long
   - Nausea, vomiting, yellow or darker skin (jaundice), or ankle swelling
   - Breathing problems, including problems breathing while sleeping
   - Any side effect that concerns you

In addition, the following statement will be placed at the end of the patient package insert:

Store at controlled room temperature 20-25°C (68-77°F).

(3) Phase IV commitment:

Unimed Pharmaceuticals, Inc. will provide evidence that there were no significant differences in testosterone absorption in the Phase III formulation and the marketed product.

Please contact me at 847-541-2525 should you need additional information.

Sincerely,

Judy Athey
Assistant Manager, Regulatory Affairs

UNIMED Pharmaceuticals, Inc.
2150 East Lake Cook Road
Buffalo Grove, IL 60089-1862
847-541-2125
Fax 847-541-2569

UNIMED

25 February 2000

Susan Allen, M.D., M.P.H., Acting Director
Division of Reproductive and
Urologic Drug Products, HFD-580
Center for Drug Evaluation and Research
Food and Drug Administration
Document Control Room17B-20
5600 Fishers Lane
Rockville, MD 20857

Dear Dr. Allen:

Re: **AndroGel™ (testosterone gel); NDA 21-015**
Response to requested information

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This makes the number of patients in the text exactly match the number of patients in Table 1. These data are taken from Vol. 4.4, Table 6.5, page 268-0002. The footnote to this same table explains the two-patient discrepancy between Table 1 and the previous language in line 178-180. Patients whose dose assignments at Day 180 reflected a departure from the protocol were excluded from the descriptive statistics presented for the extended treatment phase. This includes two patients (406 and 418) who were dose adjusted from 50 to 25 mg and 100 to 50 mg, respectively.

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25 FEB 2000
NDA 21-015

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Please contact me at 847-541-2525 should you need additional information.

Sincerely,

Judy Athey
Assistant Manager, Regulatory Affairs

WITHHOLD___1___PAGE (S)

DEPARTMENT OF HEALTH & HUMAN SERVICES

FEB 2 4 2000

NDA 21-015

Food and Drug Administration
Rockville MD 20857

Unimed Pharmaceuticals, Inc.
Attention: Judy Athey
Assistant Manager, Regulatory Affairs
2150 East Lake Cook Road
Buffalo Grove, IL 60089

Dear Ms. Athey:

Please refer to your April 28, 1999 new drug application for AndroGel™ (testosterone gel).

We are reviewing the proposed patient package insert in your submission and have the following comments and recommendations. (see attached patient package insert.) We need your prompt written response to continue our evaluation of your NDA.

If you have any questions or would like to discuss the recommendations in this letter, call Kim Colangelo, Regulatory Project Manager, at (301) 827-4260.

Sincerely,

/S/

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

Attachment:
Patient Information and Instructions for using ANDROGEL™ (testosterone gel)

cc:
Archival NDA 21-015
HFD-580/Div. Files
HFD-580/K.Colangelo
HFD-580/SAllen/MMann/DShames/MHirsch/TRumble/DChatterjee/Parekh
DISTRICT OFFICE

Drafted by: dsl/2.22.00
Initialed by: Hirsch, Shames, Chatterjee, Rumble, Mann, Parekh, 2.23.00
final: Spell-LeSane, 2.23.00
filename:

WITHHOLD 4 PAGE (S)

Draft Labeling

"rash" — All rashes involving the application sites of study drug were reported under "application site reactions", and all these events were considered related to study drug. Rashes on other parts of the body were reported as "rash". We have reconfirmed that none of the rashes was considered by the investigators to be related to study drug.

"arthralgia" — These adverse events primarily consisted of hip, knee, shoulder, or joint pain. We have reconfirmed that none of the events reported as arthralgias were considered by the investigators to be related to study drug.

"headache in the 100 mg group" —We have reconfirmed that no report of "headache" in the 100 mg group was considered related to AndroGel in the controlled clinical trial The majority of these events represented a single headache incidence and resolved while the patients remained on treatment.

"genitourinary events" —We have reconfirmed that some "genitourinary" events were considered not related to AndroGel. A review of these events shows that the majority were hematuria, urinary tract infections, or events that resolved while the patients remained on study drug.

Regarding revision request number 16, no reports of hypertension and arthralgia considered related to AndroGel in the long-term follow-up study:

"arthralgia" — These adverse events primarily consisted of hip, knee, shoulder, or joint pain. We have reconfirmed that none of these events were considered by the investigators to be related to study drug.

"hypertension" — As reported in the 4-Month Safety Update (Vol. 4.1, Summary Table 26, page 47), there was one adverse event of hypertension in the long-term follow-up study that was considered by the investigator to be related to AndroGel application. However, this was not included in Table 3 of the label because the incidence of such events was <1%. We have reconfirmed that none of the other reports of hypertension in the long-term follow-up study was considered by the investigator to be related to AndroGel application.

Please note that for consistency, footnotes were added to Table 2 (Adverse Events Possibly, Probably or Definitely Related to use of AndroGel™ in the Controlled Clinical Trial) for *lab test abnormal* and *prostate disorders.* This information was requested for Table 3 (Incidence of Adverse Events Possibly, Probably or Definitely Related to the use of AndroGel™ in the Long-Term, Follow-up Study).

REVIEWS COMPLETED
NDA approved 2/28/00
/S/ MEMO
3/1/00
DATE

UNIMED PHARMACEUTICALS, INC.
23 FEB 2000

Attached is the final draft of the physician package insert for AndroGel™ 1% (testosterone gel). Please contact me at 847-541-2525 should you need additional information.

Sincerely,

Judy Athey

Judy Athey
Assistant Manager, Regulatory Affairs

Enclosures

UNIMED Pharmaceuticals, Inc.
2150 East Lake Cook Road
Buffalo Grove, IL 60089-1862
847-541-2525
Fax 847-541-2569

UNIMED

ORIGINAL

18 February 2000

reviewed See Chem. Rev. #2 DTL 2/24/00

AMENDMENT

BC

Susan Allen, M.D. M.P.H., Acting Director
Division of Reproductive and
Urologic Drug Products (HFD-580)
Document Control 17B-20
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Re: AndroGel™ (testosterone gel), NDA 21-015
Response to Requested Information

Dear Dr. Allen:

The purpose of this submission is to provide the information requested via a teleconference on 16 February 2000 with Dr. David Lin, Reviewing Chemist, and Ms. Kim Colangelo, Project Manager, of the Food and Drug Administration and Mr. Kirk Rosemark and Ms. Judy Athey of Unimed Pharmaceuticals, Inc. (Unimed).

Specifically, Dr. Lin requested an acknowledgement from Unimed stating we would accept an approval based on 18 months expiry:

> Unimed Pharmaceuticals, Inc. will accept an approval for NDA 21-015, AndroGel™ (testosterone gel) based on 18 months expiry.

He also requested an acknowledgment that a prior approval supplement must be filed to utilize another supplier of the foil laminate:

> Unimed Pharmaceuticals, Inc. will submit a supplement for prior approval before utilizing another supplier of the foil laminate.

Dr. Lin pointed out that in Unimed's submission of 15 February 2000, responding to the agency's request for CMC information, response #11 and response #13 lacked specifications. The revised system suitability criteria provided under Attachments 3a and 3b in the responses should read:

Testosterone Assay:

In regard to the potential need for a phase IV commitment due to the change in percentage of isopropyl myristate from clinical packaging in glass bottles to the marketing packaging in foil laminate, we would like to highlight that the information provided in the original submission addresses the change. This information is located in Volume 1.1 page 3-55 in the Chemistry, Manufacturing, & Controls, Summary Section.

Unimed Pharmaceuticals, Inc. hereby certifies that a true copy of this submission has been submitted to the Chicago District Office. Should you have any additional questions, please contact me at 847-541-2525.

Sincerely,

Judy Athey

Judy Athey
Assistant Manager, Regulatory Affairs

6. Please revise Line 234 as follows:

7. Please revise Line 261 as follows:

   AndroGel treatment at 5 g/day and 10 g/day produced positive effects on mood and fatigue.

8. Please revise Line 319 as follows:

9. Please revise Line 504 as follows:
   Adverse events possibly, probably or definitely related to the use of Androgel and reported by ...

10. Please revise Line 508 as follows:

    We are 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 are also concerned that none of the "headaches" in the 100 mg group were considered even possibly-related to AndroGel. We are concerned that some genitourinary 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.

11. Please revise Line 523 as follows:
    The following adverse events possibly related to the use of AndroGel occurred in fewer...

12. Please delete Line 529 and Line 536 (Figure 3).

13. Please revise Line 552 as follows:
    ...cerebral hemorrhage, convulsion (neither of which were considered related to AndroGel administration)...

14. Please revise Line 560 as follows:
    No AndroGel patients discontinued due to skin reactions.

15. Please revise Line 572 as follows:

...clinical trial. The preliminary safety results from this study are consistent with those reported for the controlled clinical trial. Table – summarizes those adverse events ——— possibly, probably or definitely related to the use of AndroGel and reported by at least 1%...

16. Please revise Line 577 as follows:

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

We are 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 blood pressure in the 75 mg/daily group. Lastly, the adverse event term "Lab Test Abnormal" should be defined in the label.

17. Please revise Line 614 as follows:

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

If you have any questions or would like to discuss the recommendations in this letter, call Kim Colangelo, Regulatory Project Manager, at (301) 827-4260.

Sincerely,

/S/

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

ORIGINAL

UNIMED Pharmaceuticals, Inc.
2150 East Lake Cook Road
Buffalo Grove, IL 60089-1862
847-541-2525
Fax 847-541-2569

UNIMED

17 February 2000

Susan Allen, M.D. M.P.H., Acting Director ORIG AMENDMENT
Division of Reproductive and
Urologic Drug Products (HFD-580)
Document Control 17B-20
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

~~NEW CORRESP~~
BWL

Noted
Tx c gynecomastia
for 3 years
prior to surgery
and at least
4½ yrs prior
to Prostate
Ca Dx
MH
2/25/00

Re: AndroGel™ (testosterone gel), NDA 21-015
Requested Information

Dear Dr. Allen:

This submission is to provide additional information in response to a request via teleconference on 14 February 2000 between Ms. Kim Colangelo of the Food and Drug Administration and Mr. Kirk Rosemark of Unimed Pharmaceuticals, Inc.

All requested Information regarding patient 1-08 in Unimed study UMD-96-017 for testosterone gel, was submitted on 14 February 2000 with the exception of the patient hospital records. These records have been obtained are are enclosed.

If you have questions, please contact me at 847-541-2525.

Sincerely,

Judy Athey

Judy Athey
Assistant Manager, Regulatory Affairs

Enclosure

REVIEWS COMPLETED
NDA approved 2/28/00
K
KMC
DIVISION MEMO
3/1/00
DATE

UNIMED Pharmaceuticals, Inc.
2150 East Lake Cook Road
Buffalo Grove, IL 60089-1862
847-541-2525
Fax 847-541-2569

UNIMED

ORIG AMENDMENT

BC

15 February 2000

Susan Allen, M.D., M.P.H., Acting Director
Division of Reproductive and Urologic Drug Products, HFD-580
Center for Drug Evaluation and Research
Food and Drug Administration
Document Control Room 17B-20
5600 Fishers Lane
Rockville, MD 20857

See Chem. Rev. #2.
DTL 2/28/00

RE: AndroGel™ (testosterone gel); NDA 21-105
Response to Agency Request for Additional Information

Dear Dr. Allen,

The purpose of this correspondence is to amend the above referenced new drug application. Specifically, Unimed Pharmaceuticals, Inc. is amending the application to provide the information requested in the Agency's 24 January 2000 letter. To ease the review process, each of the Agency's requests is restated and followed by Unimed Pharmaceuticals' response. In addition, Unimed Pharmaceuticals, Inc. would like to take this opportunity to provide a revised Master Packaging Record for the foil sachets as well as revised sachet diagrams. The revised Master Packaging Record is provided under Attachment 7 and the revised sachet diagrams are provided under Attachment 8.

Agency Request #1:

Please clarify if the drug substance is fully tested according to USP 24 and the related substances residual solvents tests, or is accepted based on the supplier's Certificate of Analysis. If the drug substance is accepted based on the supplier's Certificate of Analysis, please state what release tests are performed.

Unimed Pharmaceuticals' Response:

The drug substance and all excipients used in the manufacture of the drug product are fully tested after receipt according to the current USP as described in the NDA (Vol.4, pp. 178 -184). However, European Pharmacopoeia (EP) specifications in conjunction with the current USP methods are used for determination of the specific gravity of alcohol.

REVIEWS COMPLETED
NDA approved 2/28/00
CSO NOTES:
NO
/S/ 3/1/00
CSO INITIALS DATE

Agency Request #2:

Please clarify if the excipients used in the manufacture of the drug product are fully tested according to the tests specified in the NDA, or accepted based on the supplier's Certificate of Analysis.

Unimed Pharmaceuticals' Response:

Please see the response to Request #1.

Agency Request #3:

Please provide representative Certificates of Analysis for components used in the manufacture of the stability batches.

Unimed Pharmaceuticals' Response:

The representative Certificates of Analysis for components used in manufacture of stability batch E 738 are provided under Attachment 1.

Agency Request #4:

Please clarify the discrepancy between the batch size of —— stated in the executed batch record for batch E738 in the original NDA and the batch size of —— in the November 19, 1999 amendment.

Unimed Pharmaceuticals' Response:

The executed batch record was for a batch size —— made prior to the time of the original NDA submission. Since then, the batch size has been increased to —— using the same equipment.

Agency Request #5:

Based on the number of drug product packets produced, there appears to be a loss of —— of drug product —— Please explain this loss of drug.

Unimed Pharmaceuticals' Response:

The loss of —— of drug product results from gel wasted in the set-up of the package form, fill and seal machine, collection of test samples and residual material loss in the feed hopper and transfer lines in the machine.

Agency Request #6:

Please provide executed batch records for all primary stability drug product batches.

Unimed Pharmaceuticals' Response:

Executed batch records for all six primary stability drug product batches are provided under Attachment 2.

Agency Request #7:

In Volume 1.4, page 4-295, it is stated that the Carbomer 940 excipient is added as a [redacted] There is no mention of a [redacted] component in the formulation of the drug product. Please explain this discrepancy.

Unimed Pharmaceuticals' Response:

This was an error. The statement is amended to say, "Carbomer is added to the dissolved testosterone to produce a gel. The final concentration of Carbomer is [redacted]

Agency Request #8:

Please clarify whether reprocessing operations will be conducted on the drug product.

Unimed Pharmaceuticals' Response:

Unimed Pharmaceuticals, Inc. certifies that no reprocessing will be conducted on the finished drug product.

Agency Request #9:

Please provide the sampling plan used to release the drug product gel.

Unimed Pharmaceuticals' Response:

[redacted]

Agency Request #10:

Based on the results of the batch analysis, the proposed related substances specifications should be revised as follows: Androstenedione

Unimed Pharmaceuticals' Response:

We will revise the drug product release specifications for related substances to Androstenedione ———— However, based on the stability data obtained for the drug product, we believe that expiry specifications for related substances (impurities) need to be retained as Androstenedione ————

Agency Request #11:

The capacity factor (k'), resolution (R_s), and tailing factor (T) should be included in the system suitability test for the HPLC assay and related substances methods.

Unimed Pharmaceuticals' Response:

The capacity factor (k'), resolution (R_s) and tailing factor (T) will be included in the system suitability test for the HPLC assay of testosterone. Since the peak areas are very low for androstenedione and the other related substances only the capacity factor (k') will be included. The revised system suitability criteria are provided under Attachment 3a.

Agency Request #12:

For the HPLC related substances method, please provide the procedure for preparing the testosterone calibration solution.

Unimed Pharmaceuticals' Response:

Agency Request #13:

Please provide the system suitability criteria for the isopropyl myristate content GC method and the ethyl alcohol content GC method.

Unimed Pharmaceuticals' Response:

The system suitability criteria for the isopropyl myristate analytical method are provided under Attachment 3b.

Agency Request #14:

It is recommended that reference to a DMF or similar information for the foil laminated package material be submitted.

Unimed Pharmaceuticals' Response:

The information regarding the foil laminated packaging material was provided to the Agency via an 11 February 2000 amendment of the pending new drug application.

Agency Request #15:

Please provide the 12-month microbial testing data that was referred to in the June 17, 1999 amendment.

Unimed Pharmaceuticals' Response:

A copy of the 12-month and 18-month microbial test data is provided under Attachment 4.

Agency Request #16:

Please submit a post-approval stability protocol.

Unimed Pharmaceuticals' Response:

A copy of the post-approval stability protocol is provided under Attachment 5.

Agency Request #17:

The proposed stability commitment should be revised as follows:

a) **Continue the stability studies as described in this application according to the attached protocol and report the results in the Annual Report.**

Unimed Pharmaceuticals' Response:

Unimed Pharmaceuticals, Inc. commits to continuing the stability studies described in this application in accordance with the Post Approval Stability Protocol provided under Attachment 5. In addition, Unimed Pharmaceuticals, Inc. commits to report the stability results to the Agency via the Annual Report process.

b) **The first three full-scale commercial production batches of testosterone 1% gel packaged in the marketed foil packets packaging should be placed on stability. Stability studies should be conducted in accordance with the post-approval protocol. In addition, a minimum of one representative lot should be selected annually for stability assessment at 25°C/60%RH.**

Unimed Pharmaceuticals' Response:

Unimed Pharmaceuticals, Inc. commits to placing the first three marketed batches of AndroGel 1% packaged in foil sachets in the on-going stability program. In addition, Unimed Pharmaceuticals, Inc. commits to placing at least one lot annually in the on-going stability program. The stability evaluations will be conducted in accordance with the Post Market Stability Protocol provided under Attachment 5 and the results of these evaluations will be provided to the Agency via the Annual Report process.

c) **The expiration dating could be extended based upon full shelf-life data obtained from the commercial batches covering the entire extended shelf life and tested according to the approved stability protocol.**

Unimed Pharmaceuticals' Response:

Unimed Pharmaceuticals, Inc. acknowledges that the expiry period may be extended based on stability data through the extended expiry period obtained from commercial batches and tested in accordance with the Post Approval Stability Protocol.

d) **Any lots found to fall outside the approved specifications for the drug product should be withdrawn from the market. If evidence indicates that the deviation is a single occurrence that does not affect the safety and efficacy of the drug product, you should immediately discuss it with us and provide justification for the continued distribution of that batch. The change or deterioration in the distributed drug product must be reported under 21 CFR 314.81(b)(1)(ii).**

Unimed Pharmaceuticals' Response:

Unimed Pharmaceuticals, Inc. commits to withdrawing from the market any lot of drug product that falls outside of the approved specifications. If evidence indicates that the deviation is a single occurrence that does not affect the safety and efficacy of the drug product, Unimed Pharmaceuticals, Inc. will immediately discuss it with the Agency and provide justification for the continued distribution of that lot. Any change or deterioration in the distributed drug product will be reported to the Agency in accordance with Title 21 CFR 314.81(b)(1)(ii).

Agency Request #18:

Please provide a description of the carton to be used to package the unit dose foil packets.

Unimed Pharmaceuticals' Response:

Unimed Pharmaceuticals, Inc. provided color layouts for both the sachet and carton (2.5 and 5 gram configurations) which contained revised text via a 21 January 2000 amendment.

Agency Request #19:

The proposed ——— expiration date is not acceptable. Based on the available stability data, an 18-month expiration date can be granted.

Unimed Pharmaceuticals' Response:

We request the approval of a ——— expiration date based on data obtained under accelerated conditions for the six lots on primary stability. The assay for testosterone remains well within specifications and no distinct increase in related substances is observed over the six month accelerated time period. Additionally, we have ——— room temperature data and ——— accelerated data available on lot E 687 in both package sizes. ——— room temperature data for the primary stability batches will become available July 2000.

Agency Request #20:

Please submit three copies of the final Method Validation Package. The Method Validation Package should include the regulatory specifications for the drug substance, but does not need to include the labeling.

Unimed Pharmaceuticals' Response:

A copy of the Method Validation Package is provided under Attachment 6. Three additional copies labeled as "Methods Validation Package" are provided with this amendment.

Unimed Pharmaceuticals, Inc. hereby certifies that a true copy of this submission has been submitted to the Chicago District Office. Should you have any additional questions or need more information please contact me at 847-541-2525.

Sincerely,

Kirk Rosemark
Director, Regulatory Affairs

UNIMED Pharmaceuticals, Inc.
2150 East Lake Cook Road
Buffalo Grove, IL 60089-1862
847-541-2525
Fax 847-541-2569

I will review my
desk copy
MK
2/22/00

UNIMED

ORIG AMENDMENT
BM

14 February 2000

Noted
DTC
2/23/00

2000
EVALUATION AND RESEARCH

Susan Allen, M.D., M.P.H., Acting Director
Center for Drug Evaluation and Research
Division of Reproductive and Urologic Drug Products, HFD-580
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

RE: AndroGel™ (testosterone gel), NDA 21-015
Requested Information

Dear Dr. Allen,

The purpose of this correspondence is to provide the information requested via a 14 February 2000 teleconference between Ms. Kim Colangelo of the Food and Drug Administration and Mr. Kirk Rosemark of Unimed Pharmaceuticals, Inc. Specifically, the following information was requested:

Ms. Colangelo requested information regarding patient 1-08: case report forms, demographic information, past medical history, past medications, baseline testosterone levels, baseline DHT levels, baseline estradiol levels, investigator name, follow-up levels, dose of AndroGel™, hospital records. Ms. Colangelo also asked if the surgical procedure (gynecomastia) was considered a serious adverse event.

The case reports forms, baseline testosterone, baseline DHT and baseline estradiol levels for patient 1-08 are provided under Attachment I. The patient's demographic information is as follows: Date of Birth [redacted] (entered study on 18 June 97, age 29), Race – Black, Weight 219 lbs. No follow-up testosterone, DHT or estradiol levels are available, as the patient did not enter the study extension phase due to a conflict with his work schedule. The investigator is Ronald Swerdloff, M.D. The patient was receiving a 10-gram dose of AndroGel™ with duration of approximately 97 days. The surgery was performed at approximately day 53 of treatment. The hospital records for this patient were not obtained as this surgery was performed as an outpatient procedure and was not considered an SAE. The patient has a history of Klinefelter's syndrome and gynecomastia (grade 4) at the start of study. The patient had no recent or concurrent medications other than testosterone injections from 1995 through 06 May 1997. The hospital records have been requested and will be provided upon receipt.

REVIEWS COMPLETED

/S/

CSO INITIALS

2/23/00

DATE

Should you have any additional questions or need more information please contact me at 847-541-2525.

Sincerely,

Kirk Rosemark
Director, Regulatory Affairs

ORIGINAL

UNIMED Pharmaceuticals, Inc.
2150 East Lake Cook Road
Buffalo Grove, IL 60089-1862
847-541-2525
Fax 847-541-2569

UNIMED

I have a dose of Mk 2/18/00

Sent via facsimile

ORIG AMENDMENT

11 February 2000

BM

Susan Allen, M.D., M.P.H., Acting Director
Division of Reproductive and Urologic Drug Products, HFD-580
Center for Drug Evaluation and Research
Food and Drug Administration
Document Control Room 17B-20
5600 Fishers Lane
Rockville, MD 20857

RE: AndroGeL™ (testosterone gel); NDA 21-105
Clinical Data Amendment

Dear Dr. Allen,

The purpose of this correspondence is to amend the above referenced new drug application. Specifically, Unimed Pharmaceuticals, Inc. (Unimed) is amending the application to correct an error in the DEXA database. The error occurred in the data that was provided to Unimed by ——— the company that interpreted the results of the DEXA scans. The data reported to us as "Total Body Lean Mass" was actually a combination of "Total Body Lean Mass" values and "Bone Mineral Content" values.

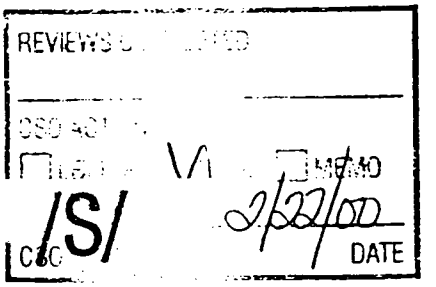
This error in the database also impacts the values reported for "Total Body Mass". "Total Body Mass" is calculated by summing the values reported for "Total Body Lean Mass", "Bone Mineral Content", and "Total Body Fat". As a result of the error, "Bone Mineral Content" values were included twice in the calculation.

A reanalysis of the corrected values for "Total Body Lean Mass" and "Total Body Mass" indicates that the overall results, conclusions and proposed labeling remains unchanged. Copies of the original and revised end-of-text tables which support the errors' negligible impact are provided under Attachments I and II, respectively. In addition, a letter from ——— noting the origination of the error is provided under Attachment III. Unimed will make the necessary revisions to the text, the end-of-text tables, and the data listings of the final report. This will be provided as an addendum to the final report (UMD-99-017 FR).

Should you have any additional questions or need more information please contact me at 847-541-2525.

Sincerely,

Kirk Rosemark
Director, Regulatory Affairs



UNIMED Pharmaceuticals, Inc.
2150 East Lake Cook Road
Buffalo Grove, IL 60089-1862
847-541-2525
Fax 847-541-2569

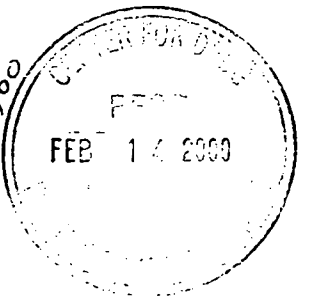
UNIMED

ORIG AMENDMENT

BC

See Chemistry Review #2
DTL
2/28/00

ORIGINAL



11 February 2000

Susan Allen, M.D., M.P.H., Acting Director
Division of Reproductive and
Urologic Drug Products, HFD-580
Center for Drug Evaluation and Research
Document Control Room 17B-20
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Dear Dr. Allen:

RE: AndroGeL™ (testosterone gel)
NDA 21-015
Response to Agency Request for Additional Information

The purpose of this correspondence is to amend the above referenced new drug application. Specifically, Unimed Pharmaceuticals, Inc., is amending the application to provide the information requested in the Agency's 24 January 2000 letter regarding the foil laminated packaging material. The requested information is provided in Attachment 1 of this correspondence. Please note that this information is in addition to the information presented in the original application (Volume 1.3, pages 4-191 through 4-206).

Should you have any additional questions or need more information, please contact me at 847-541-2525.

Sincerely,

Kirk Rosemark
Director, Regulatory Affairs

NDA approved 2/28/00
/S/
3/1/00
DATE

ORIGINAL

UNIMED Pharmaceuticals, Inc.
2150 East Lake Cook Road
Buffalo Grove, IL 60089-1862
847-541-2525
Fax 847-541-2569

UNIMED

ORIG AMENDMENT

11 February 2000

32

2000

Susan Allen, M.D., M.P.H., Acting Director
Division of Reproductive and Urologic Drug Products, HFD-580
Center for Drug Evaluation and Research
Food and Drug Administration
Document Control Room 17B-20
5600 Fishers Lane
Rockville, MD 20857

RE: AndroGeL™ (testosterone gel); NDA 21-105
Amendment to Provide Draft Labeling

Dear Dr. Allen,

The purpose of this correspondence is to amend the above referenced new drug application. Specifically, Unimed Pharmaceuticals, Inc. (Unimed) is amending the application to provide four copies of the revised draft package insert labeling. The labeling incorporates the revisions provided to the Agency via Umimed's 21 January and 09 February 2000 amendments. Please note that several other minor formating type corrections have also been captured in this revision.

Should you have any additional questions or need more information please contact me at 847-541-2525.

Sincerely,

Kirk Rosemark
Director, Regulatory Affairs

REVIEWS COMPLETED
IR letter sent 2/18/00
DSO ACTION
/S/ 2/18/00
DATE

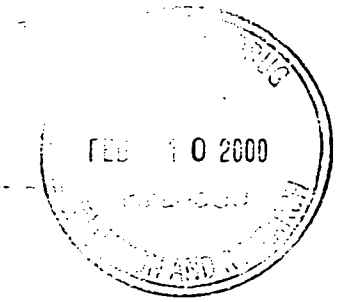
UNIMED Pharmaceuticals, Inc.
2150 East Lake Cook Road
Buffalo Grove, IL 60089-1862
847-541-2525
Fax 847-541-2569

UNIMED

ORIG AMENDMENT

BM

09 February 2000



Susan Allen, M.D., M.P.H., Acting Director
Center for Drug Evaluation and Research
Division of Reproductive and Urologic Drug Products, HFD-580
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

RE: AndroGel™ (testosterone gel), NDA 21-015
Requested Information

Dear Dr. Allen,

The purpose of this correspondence is to provide the information requested via teleconferences on 08 and 09 February 2000 between representatives of the Food and Drug Administration and Mr. Kirk Rosemark of Unimed Pharmaceuticals, Inc. Specifically, the following information was requested:

The medical officer requested the laboratory test results for hemoglobin; hematocrit and testosterone for patient 3-15 at baseline (start of study 035), time of hospitalization and at the six-month test interval. The available information for patient 3-15 is provided under Attachment I.

The classification (i.e. drug related, probably drug related or possibly drug related) of the adverse event data utilized to generate tables three and four in the package insert was requested. The adverse event data utilized to generate tables three and four included all adverse events deemed related, probably related or possibly related to drug use by the investigator that occurred in ≥1% of the patients.

Should you have any additional questions or need more information please contact me at 847-541-2525.

Sincerely,

Kirk Rosemark
Director, Regulatory Affairs

REVIEWS COMPLETED
/S/ NAI ☐ MEMO
2/17/00
DATE

ORIGINAL

UNIMED Pharmaceuticals, Inc.
2150 East Lake Cook Road
Buffalo Grove, IL 60089-1862
847-541-2525
Fax 847-541-2569

UNIMED

ORIG AMENDMENT

BL

09 February 2000

Susan Allen, M.D., M.P.H., Acting Director
Division of Reproductive and Urologic Drug Products, HFD-580
Center for Drug Evaluation and Research
Food and Drug Administration
Document Control Room 17B-20
5600 Fishers Lane
Rockville, MD 20857

RE: AndroGel™ (testosterone gel); NDA 21-105
Response to Proposed Labeling Revisions

Dear Dr. Allen,

The purpose of this correspondence is to amend the above referenced new drug application. Specifically, Unimed Pharmaceuticals, Inc. is amending the application to provide a response to the proposed labeling revisions outlined in the Agency's 28 January 2000 correspondence. Unimed Pharmaceuticals' response addresses only the areas in which alternative text is desired. Unimed Pharmaceuticals, Inc. accepts all of the revisions proposed in the above referenced correspondence that are not addressed in this amendment.

To ease the review process, a table of revisions which lists the current text, Unimed Pharmaceuticals' proposed revision and the rationale for the requested revision is provided under Attachment I. In addition, package insert references to the dose of AndroGel™ delivered have been revised from milligrams of testosterone to grams of AndroGel™ delivered. This revision was implemented to enhance the association between dosing and the finished product presentation. These additional revisions have also been captured in the above referenced table of revisions.

Should you have any additional questions or need more information please contact me at 847-541-2525.

Sincerely,

Kirk Rosemark
Director, Regulatory Affairs

REVIEWS COMPLETED
IR letter sent 2/18
☒ FTR ☐ N.A.I. ☐ MEMO
KMC 2/18/00
CASE INITIATED DATE

Colangelo

JAN 28 2000

NDA 21-015

INFORMATION REQUEST LETTER

Unimed Pharmaceuticals, Inc.
Attention: Judy Athey
Assistant Manager, Regulatory Affairs
2150 East Lake Cook Road
Buffalo Grove, IL 60089

Dear Ms. Athey:

Please refer to your April 28, 1999, new drug application for Androgel (testosterone gel) .

We also refer to your submission dated September 16, 1999.

We are reviewing the proposed package insert in your submission and have the following comments and information requests. We need your prompt written response to continue our evaluation of your NDA.

1. The trademark symbol (™) should be consistently utilized or removed throughout the package insert.

2. The structure of testosterone should be revised to be consistent with the USP structure.

3. Figure 1 should be revised to show testosterone levels at Day 30, with error bars added to show standard deviations.

4. Additional changes are recommended in the attached draft package insert. Deleted text is presented as strike-outs, and added text is underlined.

If you have any questions, call Kim Colangelo, Regulatory Project Manager, at (301) 827-4260.

Sincerely,

/S/ 1/28/00

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

ATTACHMENT

cc:
Archival NDA 21-015
HFD-580/Div. Files
HFD-580/K.Colangelo
HFD-580/Allen/Mann/Shames/Hirsch/Rhee/Lin/Parekh
HFD-580/Chatterjee/Rumble
HFD-820/DNDC Division Director
DISTRICT OFFICE

Drafted by: kmc/January 28, 2000
Initialed by: Rumble, 01.28.00
final: Colangelo, 01.28.00
filename: c:\mydocs\data\nda\21-015\irlabel.doc

INFORMATION REQUEST (IR)

UNIMED Pharmaceuticals, Inc.
2150 East Lake Cook Road
Buffalo Grove, IL 60089-1862
847-541-2525
Fax 847-541-2569

UNIMED

ORIG AMENDMENT

ORIGINAL

24 January 2000

BM

Noted
MH
2/1/00

Noted
2/2/00

Susan Allen, M.D., M.P.H., Acting Director
Division of Reproductive and
Urologic Drug Products, HFD-580
Center for Drug Evaluation and Research
Food and Drug Administration
Document Control Room17B-20
5600 Fishers Lane
Rockville, MD 20857

Dear Dr. Allen:

Re: **AndroGel™ (testosterone gel); NDA 21-105**
Response to requested information

Dear Dr. Allen:

This amendment to NDA 21-015 provides information requested by the agency on 21 Jan 2000. Specifically, the medical reviewer has requested a table identifying the 17 patients in the 50 mg T-gel group for whom C_{max} (serum Total Testosterone) on Day 30 was above the upper limit for normal. Also requested was additional information (hemoglobin, hematocrit and serum testosterone results) for Patient 7-07 at the time of his hospitalization.

Attached is a table listing both C_{max} and C_{avg} for each patient in the 50 mg T-gel group. Following this table, information is provided for hospitalized patient, 7-07.

Please contact me at 847-541-2525 should you need additional information.

Sincerely,

Judy Athey

Judy Athey
Assistant Manager, Regulatory Affairs

Enclosures

Colangelo

JAN 2 4 2000

NDA 21-015

DISCIPLINE REVIEW LETTER

Unimed Pharmaceuticals, Inc.
Attention: Judy Athey
Assistant Manager, Regulatory Affairs
2151 E. Lake Cook Road, Suite 210
Buffalo Grove, IL 60089

Dear Ms. Athey:

Please refer to your April 29, 1999, new drug application for Androgel (testosterone gel).

We also refer to your submissions dated June 17, November 19 and December 9, 1999.

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

1. Please clarify if the drug substance is fully tested according to USP 24 and the related substances residual solvents tests, or is accepted based on the supplier's Certificate of Analysis. If the drug substance is accepted based on the supplier's Certificate of Analysis, please state what release tests are performed.

2. Please clarify if the excipients used in the manufacture of the drug product are fully tested according to the tests specified in the NDA, or accepted based on the supplier's Certificate of Analysis.

3. Please provide representative Certificates of Analysis for the components used in the manufacture of the stability batches.

4. Please clarify the discrepancy between the batch size of 70 kg stated in the executed batch record for batch E 738 in the original NDA and the batch size of 75 kg in the November 19, 1999 amendment.

5. Based on the number of drug product packets produced, there appears to be a loss of ____ of drug product [redacted] Please explain this loss of drug.

6. Please provide executed batch records for all primary stability drug product batches.

7. [redacted]

8. Please clarify whether reprocessing operations will be conducted on the drug product.

9. Please provide the sampling plan used to release the drug product gel.

10. Based on the results of the batch analysis, the proposed related substances specifications should be revised as follows: [redacted]

11. The capacity factor (k'), resolution (R_s), and tailing factor (T) should be included in the system suitability test for the HPLC assay and related substances methods.

12. For the HPLC related substances method, please provide the procedure for preparing the testosterone calibration solution.

13. Please provide the system suitability criteria for the isopropyl myristate conten [redacted] method and the [redacted] method.

14. It is recommended that reference to a DMF or similar information for the foil laminated packaging material be submitted.

15. Please provide the 12-month microbial testing data that was referred to in the June 17, 1999 amendment.

16. Please submit a post-approval stability protocol.

17. The proposed stability commitment should be revised as follows:

    a) Continue the stability studies as described in this application according to the attached stability protocol and report the results in an Annual Report.
    b) The first three full-scale commercial production batches of testosterone 1% gel packaged in the marketed foil packet packaging should be placed on stability. Stability studies should be conducted in accordance with the post-approval protocol. In addition, a minimum of one representative lot should be selected annually for stability assessment at 25°C/60% RH.
    c) The expiration dating could be extended based upon full shelf-life data obtained from the commercial batches covering the entire extended shelf-life and tested according to the approved stability protocol.
    d) Any lots found to fall outside the approved specifications for the drug product should be withdrawn from the market. If evidence indicates that the deviation is a single occurrence that does not affect the safety and efficacy of the drug product, you should immediately discuss it with us and provide justification for the continued distribution of that batch. The change or deterioration in the distributed drug product must be reported under 21 CFR 314.81(b)(1)(ii).

18. Please provide a description of the carton to be used to package the unit dose foil packets.

19. The proposed 24-month expiration date is not acceptable. Based on the available stability data, an 18-month expiration date can be granted.

20. Please submit three complete copies of the final Method Validation Package. The Method Validation Package should include the regulatory specifications for the drug substance, but does not need to include the labeling.

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

If you have any questions, call Kim Colangelo, Regulatory Project Manager, at (301) 827-4260.

Sincerely,

/S/ 1/24/00

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

cc:
Archival NDA 21-015
HFD-580/Div. Files
HFD-580/K.Colangelo
HFD-580/SAllen/MHirsch/MRhee/D.Lin/T.Rumble
HFD-820/DNDC Division Director
DISTRICT OFFICE

Drafted by: kmc/January 19, 2000
Initialed by: Lin, Rhee, 01.21.00; Rumble, Allen, 01.24.00
final: Colangelo, 01.24.00
filename: c:\data\mydocs\nda\21-015\drchem.doc

DISCIPLINE REVIEW LETTER (DR)

UNIMED Pharmaceuticals, Inc.
2150 East Lake Cook Road
Buffalo Grove, IL 60089-1862
847-541-2525
Fax 847-541-2569

UNIMED

ORIGINAL
ORIG AMENDMENT

BL

please see my NDA review this was d/w chemistry
1/31/00

See Chemistry Review #2.
DTC
2/28/00

CENTER FOR DRUG EVALUATION AND RESEARCH
RECD
JAN 24 2000
HFD-580

21 January 2000

Susan Allen, M.D., M.P.H., Acting Director
Division of Reproductive and
Urologic Drug Products (HFD-580)
Document Control 17B-20
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Ref: AndroGeL™ (testosterone gel); NDA 21-015
Response to Requested Information

Dear Dr. Allen:

The purpose of this correspondence is to amend the above referenced new drug application. Specifically, Unimed Pharmaceuticals, Inc. is amending the application to provide revised draft labeling and to provide layouts of the revised draft labeling for the primary and secondary containers as requested by the Agency on the 05 January 2000.

A color layout of each piece of the labeling is attached. In addition, four copies of the draft labeling are provided in the review copy of this submission. To ease the review process, each revised piece is accompanied by a table, which lists the revisions to the draft labeling.

Should you require any additional information please do not hesitate to contact me at (847) 541-2525.

Sincerely,

Kirk Rosemark
Director, Regulatory Affairs

REVIEWS COMPLETED
NDA approved 2/28/00
CSO ACTION:
LETTER FINAL MEMO
/S/ 3/1/00
CSO INITIALS DATE

DEPARTMENT OF HEALTH & HUMAN SERVICES

Colangelo

Food and Drug Administration
Rockville MD 20857

DEC 29 1999

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

Dear Dr.Swerdloff:

The purpose of this letter is to inform you of our conclusions concerning your conduct of the clinical study (protocol #UMD-96-017) of Androgel that you conducted for Unimed Pharmaceuticals, Inc.

From September 20, 1999 to September 23, 1999, Mr. Armondo Chavez, representing the Food and Drug Administration (FDA), inspected the study identified above. This inspection is part of the FDA's Bioresearch Monitoring Program. This program includes inspections to determine the validity of clinical drug studies that may provide the basis for drug marketing approval and to assure that the rights and welfare of the human subjects who participated in those studies have been protected.

At the close of the inspection, Mr.Chavez provided you with his inspectional observations (i.e., Form FDA 483) and discussed these observations with you. We reviewed (a) the inspection report, (b) the documents copied during the inspection, and (c) your oral responses during the inspection to the inspectional observations. Based on our review, we find that you complied with most of the pertinent Federal regulations and with an acceptable standard of good clinical practice for the conduct of clinical studies of investigational new drugs and the protection of human subjects. Essentially, we find that you did not follow the protocol in all instances; in that, one subject was entered into the study who did not meet weight requirements and one non-compliant subject was not dropped from the study. We note your response to the observations and your assurance that corrective actions will be taken to prevent similar problems in your current and future studies.

We appreciate the cooperation shown Mr. Chavez during the inspection. Should you have any questions or concerns regarding this letter or the inspection, please contact me by letter at the address given below.

Sincerely yours,

/S/

Bette L. Barton, Ph.D., M.D., Chief
Good Clinical Practices Branch I, (HFD-46)
Division of Scientific Investigations
Office of Medical Policy
Center for Drug Evaluation and Research
7520 Standish Place, Suite 125
Rockville, MD 20855

WITHHOLD 1 PAGE (S)

ORIG AMENDMENT

BC

UNIMED Pharmaceuticals, Inc.
2150 East Lake Cook Road
Buffalo Grove, IL 60089-1862
847-541-2525
Fax 847-541-2569

UNIMED

ORIGINAL

See Chemistry Review #1.
DTC
2/28/00

CENTER FOR DRUG
RECD
DEC 10 1999
HFD-580
EVALUATION AND RESEARCH

December 9, 1999

Lisa Rarick, M.D., Director
Division of Reproductive and
Urologic Drug Products (HFD-580)
Attn: Division Document Room
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Re: Androgel™ (testosterone gel)
NDA 21-015/Amendment No. 6

Dear Dr. Rarick:

Unimed Pharmaceuticals, Inc. herewith submits an amendment to the above referenced pending New Drug Application 21-015 for Androgel™ (testosterone gel) under the provisions of 21CFR 314.60.

This amendment consists of changes to the chemistry, manufacturing, controls portion of the NDA. These changes consist of corrections or clarifications resulting from data audit and correction to manufacturing batch record for lot #738.

The original page numbers of Vols.1.1 through Vols. 1.4 are retained on the amended pages. All amended copy is highlighted by shading.

An exact copy of this submission is being provided to the FDA Chicago District Office.

Please contact me at 847-541-2525 if you have any questions concerning this submission.

Sincerely,

Judy Athey

Judy Athey
Assistant Manager, Regulatory Affairs

Enclosures

REVIEWS COMPLETED
NDA Approved 2/28/00
CSO ACTION:
X LETTER ☐ N.A.I. ☐ MEMO
/S/ 3/1/00
CSO INITIALS DATE

BC 12-17-99
10-01-99

ORIGINAL

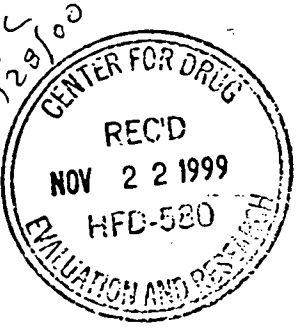
UNIMED Pharmaceuticals, Inc.
2150 East Lake Cook Road
Buffalo Grove, IL 60089-1862
847-541-2525
Fax 847-541-2569

UNIMED

November 19, 1999

See Chemistry Review #1.
DTC 2/28/00

ORIG AMENDMENT
BC



Lisa Rarick, M.D., Director
Division of Reproductive and
Urologic Drug Products (HFD-580)
Attn: Division Document Room
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Re: Androgel™ (testosterone gel)
NDA 21-015/Amendment No. 5

Dear Dr. Rarick:

Unimed Pharmaceuticals, Inc. herewith submits an amendment to the above referenced pending New Drug Application 21-015 for Androgel™ (testosterone gel) under the provisions of 21CFR 314.60.

This amendment consists of changes to the chemistry, manufacturing, controls portion of the NDA. While the changes are numerous, they are non-substantial on the whole. We do not view the changes as having any effect on the conclusions to be drawn from the review of the NDA nor do we view this amendment as a "major amendment" under the regulations. The changes essentially consist of corrections, clarifications, changes resulting from data audit, addition of longer-term stability data and replacement of the master manufacturing record.

The address change for Laboratoires Besins Iscovesco on page 122 is not a change of facility; it is simply a new mailing address for the same facility. The Organic Volatile Impurities specifications on pages 179 and 180 are updated to USP 24 requirements.

The original page numbers of Vols. 1.1, 1.2 and 1.4 are retained on the amended pages. All amended copy is highlighted by shading. In addition to the amended replacement pages, pages 143, 158, 164-166 and 172-174 are obsoleted. Pages 164-166 and 172-174 were submitted in error and are not part of the ———— master manufacturing record.

A copy of this submission is being provided to the FDA Chicago District Office.

Please contact me if you have any questions concerning this submission.

Sincerely,

Judy Athey

Judy Athey
Assistant Manager, Regulatory Affairs

Enclosures

REVIEWS COMPLETED
NDA approved 2/28/00
/S/ 3/1/00

ORIGINAL

NEW CORRESP

NC

UNIMED

UNIMED Pharmaceuticals, Inc.
2150 East Lake Cook Road
Buffalo Grove, IL 60089-1862
847-541-2525
Fax 847-541-2569

October 25, 1999

Lisa Rarick, M.D., Director
Division of Reproductive and
Urologic Drug Products (HFD-580)
Document Control 17B-20
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Ref: Androgel® (testosterone gel)
NDA 21-015
Correspondence

Dear Dr. Rarick:

This is to notify you that I will be the contact person for the above referenced NDA sponsored by Unimed Pharmaceuticals, Inc., until further notice.

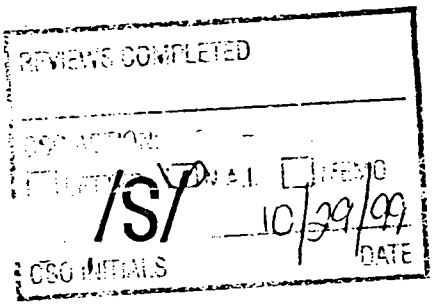
If you have questions, please contact me at 847-541-2525 extension 3023.

Sincerely,

Judy Athey

Judy Athey
Assistant Manager, Regulatory Affairs

Enclosure



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

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

OCT 21 1999

Dear Dr. Dobs:

The purpose of this letter is to inform you of our conclusions concerning your conduct of the clinical study (protocol #UMD-96-017) of T-Gel that you conducted for Unimed Pharmaceuticals, Inc.

Between August 9 and 19, 1999, Ms. Jeanne Diann Shaffer, representing the Food and Drug Administration (Agency), inspected the study identified above. This inspection is part of the Agency's Bioresearch Monitoring Program. This program includes inspections to determine the validity of clinical drug studies that may provide the basis for drug marketing approval and to assure that the rights and welfare of the human subjects who participated in those studies have been protected.

At the close of the inspection, Ms. Shaffer provided you her inspectional observations (i.e., Form FDA 483) and discussed these observations with you. We reviewed (a) the inspection report, (b) the documents copied during the inspection, and (c) your oral responses during the inspection to the inspectional observations. Based on our review, we concluded that you did not comply with all the pertinent Federal regulations and with acceptable standards of good clinical practice for the conduct of clinical studies of investigational new drugs and the protection of human subjects. We conclude that (a) you failed to follow the protocol in that diagnostic tests required by the protocol were not done, and one ineligible subject was entered into the study; (b) drug accountability records were incomplete; and (c) modification of the protocol was done without subsequent notification to the IRB. In addition you failed to prepare and maintain adequate and accurate records of all observations and other data pertinent to blood sample handling and storage.

We note your September 21, 1999, letter responding to the items listed on the FDA 483, especially those regarding dosage changes and ineligible subjects. We also note your intention to make appropriate changes in your procedures to assure that the findings noted above are not repeated in any of your ongoing or future studies. We agree with you that the lack of temperture recordings did not affect the integrity of the plasma samples, and that you are now recording the temperatures of refrigerators and freezers daily.

We appreciate the cooperation shown Ms. Shaffer during the inspection. Should you have any questions or concerns regarding this letter or the inspection, please contact me by letter at the address given below.

Sincerely yours,

/S/

Bette L. Barton, Ph.D., M.D.
Chief
Good Clinical Practices Branch I, (HFD-46)
Division of Scientific Investigations
Office of Medical Policy
Center for Drug Evaluation and Research
7520 Standish Place, Suite 125
Rockville, MD 20855

cc:
HFA-224
HFD-580 Doc. Rm. NDA #21-015
HFD-580 Review Div.Dir. Rarick
HFD-580 MO Hirsch
HFD-580 PM/CSO Colangelo
HFD- 45 Reading File
HFD- 46 Chron File
HFD- 46 CIB File #7041
HFD- 46 Turner
HFR-CE-250 DIB Draper
HFR-CE-2535 BIMO MONITOR Glasgow
HFR-CE-2535 FIELD INVESTIGATOR Shaffer

CFN: #1124626

Field Classification:VAI
Headquarters Classification:
_____1)NAI
2)VAI no response required
_____3)VAI-R response requested
_____4)VAI-RR adequate response received
_____5)OAI-W warning letter
_____6)OAI NIDPOE letter

If the Field and Headquarters classifications are different, explain why:

Deficiencies noted:
_____ inadequate consent form
_x___ inadequate drug accountability
_x___ deviations from protocol
_x___ inadequate and/or inaccurate records
_____ failure to report ADRs
_X___ failure to report protocol change to IRB

N:\GDT\DOBS1.GDT
drafted/(initials of GCPB1 reviewer)/(date)
reviewed/BLB/(10/7/99)
revised/GDT(10/19/99)
final/bc: 10/07/99
refinaled:nlp:10/20/99

Note to Review Division and DSI Recommendation:

The field investigator inspected the records for 6 of the 22 subjects enrolled in protocol UMD-96-017 at the Dobs site. The data appear acceptable for use in support of NDA 21-015. There were some minor protocol changes in the treatment of two subjects who developed high testosterone blood levels.

WITHHOLD 8 PAGE (S)

ORIGINAL

ORIG AMENDMENT

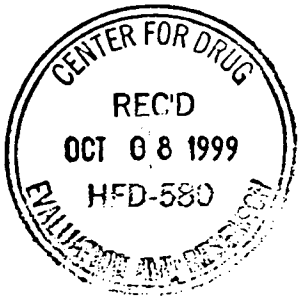
BM

UNIMED

UNIMED Pharmaceuticals, Inc.
2150 East Lake Cook Road
Buffalo Grove, IL 60089-1862
847-541-2525
Fax 847-541-2569

10/21/99

October 6, 1999



Lisa Rarick, M.D., Director
Division of Reproductive and
Urologic Drug Products (HFD-580)
Document Control Room 17B-20
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Ref: Androgel™ (testosterone gel)
NDA 21-015/Amendment No. 4

Dear Dr. Rarick:

Reference is made to Amendment 3 dated September 16, 1999 to NDA 21-015 for Androgel™ (testosterone gel). That amendment provided the final report (UMD-99-017-IR) for pivotal study UMD-96-017.

Enclosed in duplicate is a 100-MB zip drive cartridge that contains the end-of-text tables (file stattbls017.doc) and patient data listings (file DL017.doc for report UMD-99-017-IR. These data are the same as those provided in hard copy in the final report (UMD-99-017-FR) that was included in Amendment 3.

Please contact me directly if you have any questions concerning this submission.

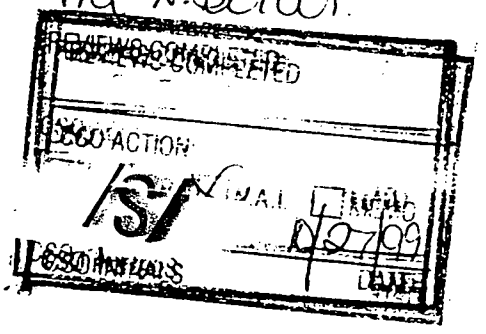
Sincerely yours,

DR Peckels

Donald R. Peckels
Director, Regulatory Affairs
(847) 541-2525 (ext. 3018)
(847) 541-3706 (fax)

drp/enclosures

Files available
via X:Drive



UNIMED Pharmaceuticals, Inc.
2150 East Lake Cook Road
Buffalo Grove, IL 60089-1862
847-541-2525
Fax 847-541-2569

UNIMED

ORIGINAL

ORIG AMENDMENT

BL

September 21, 1999

Ms. Kim Colangelo
Project Manager
Division of Reproductive and
Urologic Drug Products (HFD-580)
Room 17B-45
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Ref: Androgel® (testosterone gel)
NDA 21-015/Amendment No. 3

Dear Ms. Colangelo:

This is in reference to Unimed's amendment #3 to NDA 21-015 for Androgel™(testosterone gel) submitted September 16, 1999. Enclosed per our telephone conversation on September 21, 1999 are two copies of the revised, draft physician and patient package inserts that were included in the archival and review copies of that amendment. This labeling was inadvertently omitted from the two desk copies of the amendment.

Sincerely yours,

D R Peckels

Donald R. Peckels
Director, Regulatory Affairs
(847) 541-2525 (ext. 3018)
(847) 541-3706 (fax)

drp/enclosures

REVIEWS COMPLETED
Correspondence sent 10/1/99
CSO ACTION
LETTER FINAL MEMO
/S/ 10/4/99
CSO INITIALS DATE

ORIGINAL

AMENDMENT

SV

UNIMED

UNIMED Pharmaceuticals, Inc.
2150 East Lake Cook Road
Buffalo Grove, IL 60089-1862
847-541-2525
Fax 847-541-2569

See any review in final NDA
M.O. review
MH
3/7/00

September 16, 1999

Lisa Rarick, M.D., Director
Division of Reproductive and
Urologic Drug Products (HFD-580)
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Ref: Androgel® (testosterone gel)
NDA 21-015/Amendment No. 3

Dear Dr. Rarick:

Reference is made to NDA 21-015 for Androgel® (testosterone gel). Unimed Pharmaceuticals, Inc. is amending NDA 21-015 to provide for the following information:

- Revised physician and patient labeling (Volume 4.1),
- 4-Month Safety Update (Volumes 4.1 and 4.2),
- Final report for pivotal study UMD-96-017 (Volumes 4.3 through 4.20), and
- Interim database for long-term, follow-up study UMD-98-035.

The draft physician package insert has been updated from the version included in the original NDA 21-015 to reflect the 180-day safety and efficacy data for 50 mg, 75 mg and 100 mg Androgel that are included in this submission. The annotations to this labeling reflect the locations within this amendment and, where applicable, within the original submission where the supportive data are presented.

Substantive changes made to the draft patient package insert are:

- Verbiage regarding the role of testosterone in the body (first paragraph) was simplified to facilitate comprehension by the layman; and
- Corrections were made to the side effects information; this corrected information has been combined into the paragraph that immediately precedes the Precautions section.

The four-month Safety Update is in the form of a revised Integrated Summary of Safety report. This revised ISS includes safety data for 106 patients enrolled in the long-term, follow-up study UMD-98-035 (an extension study for patients completing the pivotal trial UMD-96-017). In addition, this ISS reflects the data presented in the final report for

study UMD-96-017 that is included in Volumes 4.3 through 4.20. The final report for this pivotal study is entitled, "A Phase II/III Evaluation of the Safety and Efficacy of Testosterone Gel for Hormonal Replacement in Hypogonadal Men" (# UMD-99-017-FR). Please note that the QA procedures for each hormonal assay are located in Volume 4.17; Volume 4.20 contains the corresponding assay validation reports for each parameter.

Portions of this amendment are submitted in electronic format (duplicate 100 MB zip drive cartridges). The labeling; updated ISS (4-month Safety Update); and the text and end-of-text figures for report UMD-99-017-FR are in MS Word97. The database for report UMD-99-017-FR and the interim database for study UMD-98-035 are provided in SAS v6.12. Unimed certifies that: 1) the electronic components of this amendment are exact duplicates of the technical information provided in hard copy and 2) these electronic data are virus-free.

Pursuant to 21 CFR, an archival and a review copy of this amendment are being submitted. Two extra copies of the revised ISS are also being submitted in a separate package to Ms. Kim Colangelo, Project Manager. In addition, an exact copy of the patient and physician labeling has been submitted to the FDA Chicago District Office. Please contact me directly if you have any questions concerning this submission.

Sincerely yours,

DRPeckels

Donald R. Peckels
Director, Regulatory Affairs
(847) 541-2525 (ext. 3018)
(847) 541-3706 (fax)

drp/enclosures

REVIEWS COMPLETED
Approved 2/28/00
CSO ACTION
INITIAL ☐ MEMO
/S/ 3/7/00
CSO INITIALS DATE

ORIGINAL NEW CORRESP

UNIMED Pharmaceuticals, Inc.
2150 East Lake Cook Road
Buffalo Grove, IL 60089-1862
847-541-2525
Fax 847-541-2569

Rationale is reasonable to me MM 8/23/99

UNIMED

Consult sent for abuse liability review (HFD-170) /S/ 8/23/99

August 18, 1999

Lisa Rarick, M.D., Director
Division of Reproductive and
Urologic Drug Products (HFD-580)
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

NOTED IC 8/25/99

REC'D AUG 19 1999 HFD-580 DIV DRUG EVALUATION AND RESEARCH

Ref: Androgel™ (testosterone gel)
NDA 21-015

MM 8-24-99

Dear Dr. Rarick:

Reference is made to NDA 21-015 for Androgel™ (testosterone gel), submitted April 28, 1999. Unimed Pharmaceuticals, Inc. is amending NDA 21-015 to provide justification for the classification of Androgel as a Schedule III controlled substance. This justification is summarized below:

- The active pharmacological ingredient in Androgel is testosterone. Androgel delivers physiologic amounts of testosterone into the body through the skin.

- In accordance with the Controlled Substance Act and 21 CFR 1308.02(b)(26), testosterone is classified as an anabolic steroid. The regulations (21 CFR 1308.13[f][1]) place testosterone into Schedule III

- All marketed testosterone products in the U.S. are labeled as Schedule III drugs, including transdermally applied patches. Since Androgel delivers testosterone transdermally, it would be reasonable to place the drug product into Schedule III. In addition, the Androgel draft physician package insert included in Sections 2.0, 3.1 and 4.4.3 of NDA 21-015 is comprised of several testosterone class labeling statements that were abstracted from the approved labeling for transdermally applied testosterone products, including Testoderm® TTS and Androderm® patches.

In consideration of the above information, Unimed Pharmaceuticals, Inc. hereby proposes that Androgel be placed into Schedule III of the Controlled substance Act. Please contact me directly if you have any questions or if you require any additional information.

Sincerely yours,

DR Peckels

Donald R. Peckels
Director, Regulatory Affairs
(847) 541-2525
(847) 541-3706 (fax)

cc: Dr. James R. Cooper
Associate Director for Medical & International Affairs
National Institute for Drug Abuse (NIDA)
5600 Fishers Lane
Rockville, MD 20857

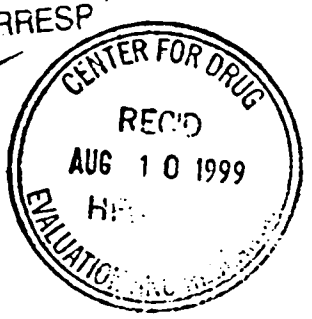
REVIEWS COMPLETED

CSO ACTION:
☐ LETTER ☒ N.A.I. ☐ MEMO

/S/ 8/26/99
CSO INITIALS DATE

Consult to HFD170 sent 8/23

ORIGINAL
NEW CORRESP



UNIMED

UNIMED Pharmaceuticals, Inc.
2150 East Lake Cook Road
Buffalo Grove, IL 60089-1862
847-541-2525
Fax 847-541-2569

August 9, 1999

Ms. Kim Colangelo, Consumer Safety Officer
Food and Drug Administration
Division of Reproductive and Urology Drugs
Center for Drug Evaluation and Research (HFD-580)
Attention Document Control Room #17B-20
5600 Fishers Lane
Rockville, MD 20857

RE: NDA 21-015
Androgel™ (testosterone gel)

Dear Kim:

Per your request via phone today, enclosed in an extra copy of volume 1.1 of the Androgel™ NDA for the Clinical Team Leader.

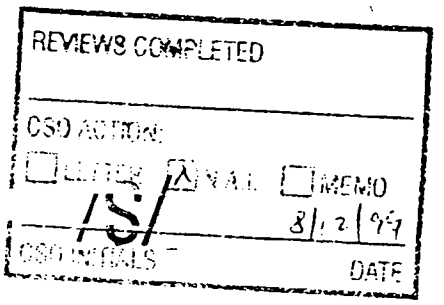
Please contact me if I can provide you with anything further.

Sincerely,

D R Peckels

Donald R. Peckels
Director, Regulatory Affairs
(847) 541-2525 ext. 3018
(847) 541-3706 (fax)

DRP/lc



Desk copy placed in Dr Hirsch's mail box. CAR

UNIMED Pharmaceuticals, Inc.
2150 East Lake Cook Road
Buffalo Grove, IL 60089-1862
847-541-2525
Fax 847-541-2569

UNIMED

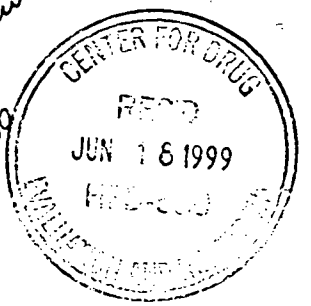
ORIGINAL

ORIG AMENDMENT

BI

See Chemistry Review #5

JTC 2/29/00



June 17, 1999

Lisa Rarick, M.D., Director
Division of Reproductive and
Urologic Drug Products (HFD-580)
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Ref: Androgel® (testosterone gel)
NDA 21-015/Amendment No. 1

Dear Dr. Rarick:

Reference is made to Unimed Pharmaceuticals, Inc.'s pending NDA 21-015 for Androgel® (testosterone gel) and to a telephone call on May 24, 1999 between Ms. Kim Colangelo and Mr. Donald R. Peckels of Unimed for information to prove the absence of pathogens on the release and stability testing of Androgel® (testosterone gel). This request originated from the Reviewing Chemist, Dr. Amit Mitra.

Unimed Pharmaceuticals, Inc. is herein amending NDA 21-015 to provide data for the microbiological evaluation of Androgel. The lots analyzed and time points tested are described in the following table:

Batch No.	T_0	3 Months	12 Months
E 733	Certificate of Analysis Attached	---	Data available June 99
E 734	Certificate of Analysis Attached	---	Data available June 99
E 735	Certificate of Analysis Attached	---	Data available June 99
E 736	Certificate of Analysis Attached	---	Data available June 99
E 737	Certificate of Analysis Attached	---	Data available June 99
E 738	Certificate of Analysis Attached	---	Data available June 99
E 766	Certificate of Analysis Attached	on-going	---
E 768	Certificate of Analysis Attached	on-going	---
E 772	Certificate of	on-going	---

Batch No.	T_0	3 Months	12 Months
	Analysis Attached		
E 773	Certificate of Analysis Attached	on-going	---
E 774	Certificate of Analysis Attached	on-going	---
E 776	Certificate of Analysis Attached	on-going	---
E 777	Certificate of Analysis Attached	on-going	---
E 778	Certificate of Analysis Attached	on-going	---
E 805	Certificate of Analysis Attached	---	---
E 806	Certificate of Analysis Attached	---	---
E 807	Certificate of Analysis Attached	---	---

The supplier of Androgel drug product (Laboratoires Besins Iscovesco, Montrouge, France) contracted this microbial testing to ———————— Please be advised that Unimed has revised the testing protocol for Androgel lots placed on stability in order to perform the microbial limits test at each time point. Enclosed are certificates of analysis (COAs) for all lots tested. In order to facilitate review, an English translation of the COA for a representative lot (lot # E 733) is appended as being representative of the wording used on all of the COAs. The test procedure was performed in accordance with Chapter 61 of USP XXIII (Microbial Limits Test). Twelve-month data will be submitted as an amendment to NDA 21-015 as soon as these data are available.

Please contact me directly if you have any questions concerning this submission.

Sincerely yours,

D R Peckels

Donald R. Peckels
Director, Regulatory Affairs
(847) 541-2525 (ext. 3018)
(847) 541-3706 (fax)

drp/enclosures

REVIEWS COMPLETED
NDA approved 2/28/00
CSO ACTION: ☒ LETTER ☐ N.A.I. ☐ MEMO
/S/ 3/1/00
CSO INITIALS DATE

MAY 2 8

Unimed Pharmaceuticals, Inc.
Attention: Donald R. Peckels
Director, Regulatory Affairs
2150 E. Lake Cook Road
Buffalo Grove, IL 60089

Dear Mr. Peckels:

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

Name of Drug Product: Androgel (testosterone) Gel

Therapeutic Classification: Standard (S)

Date of Application: April 28, 1999

Date of Receipt: April 29, 1999

Our Reference Number: 21-015

Unless we notify you within 60 days of our receipt date that the application is not sufficiently complete to permit a substantive review, this application will be filed under section 505(b) of the Act on June 28, 1999 in accordance with 21 CFR 314.101(a). If the application is filed, the primary user fee goal date will be February 29, 2000, and the secondary user fee goal date will be April 29, 2000.

Please cite the NDA number listed above at the top of the first page of any communications concerning this application. All communications concerning this NDA should be addressed as follows:

U.S. Postal/Courier/Overnight Mail:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Reproductive and Urologic Drug Products, HFD-580
Attention: Division Document Room
5600 Fishers Lane
Rockville, Maryland 20857

If you have any questions, contact Kim Colangelo, Project Manager, at (301) 827-4260.

Sincerely,

/S/ 5/25/99

Terri F. Rumble, BSN
Chief, Project Management Staff
Division of Reproductive and Urologic Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

cc:
Archival NDA 21-015
HFD-580/Div. Files
HFD-580/Colangelo
DISTRICT OFFICE

Drafted by: kmc/May 21, 1999
Initialed by: Rumble, 05.24.99
final: Colangelo, 05.27.99
filename: AC000.DOC

ACKNOWLEDGEMENT (AC)

UNIMED Pharmaceuticals, Inc.
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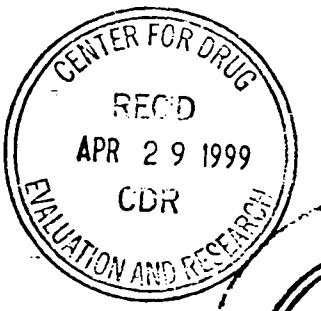

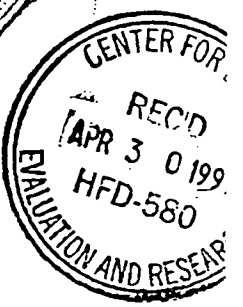

April 28, 1999

Lisa Rarick, M.D., Director
Division of Reproductive and
Urologic Drug Products (HFD-580)
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Ref: Androgel™ (testosterone gel)
NDA 21-015 (Original NDA)

Dear Dr. Rarick:

Unimed Pharmaceuticals, Inc. herein submits an original New Drug Application for Androgel™ (testosterone gel). Androgel is a topically applied transdermal product in a gel formulation for use as testosterone replacement therapy in hypogonadal men.

Androgel (50 and 100 mg testosterone) was compared to the Androderm®patch (2 x 2.5 mg testosterone/patch) in a large, multicenter, randomized, parallel-group, positive-controlled Phase III study (UMD-96-017) in 227 hypogonadal men. Unimed believes the results show that Androgel is more effective than Androderm based upon both primary and secondary measures of efficacy. Moreover, the pharmacokinetic profile associated with the use of Androgel, namely, achievement of both C_{avg} and C_{min} within the normal range (298 to 1043 ng/dL) for testosterone in the majority of patients, represents a substantial improvement over similar profiles observed in response to transdermal testosterone patches or injectable testosterone preparations.

Also noteworthy is the superior skin irritation profile of Androgel compared to Androderm. Study UMD-96-017 shows that Androgel had a dramatically lower incidence of skin-related adverse events at the application sites and a significantly lower rate of premature discontinuations. Thus, the use of Androgel reduces the incidence of a treatment-limiting drug reaction associated with a currently available product (i.e., the skin irritations associated with the use of Androderm). In addition, this study provides evidence of enhanced patient compliance with Androgel as compared to Androderm as shown by the differences in mean compliance rates at Days 1 to 90 for Androgel (93%) versus Androderm (65%). Therefore, in accordance with MAPP 6020.3, Unimed requests that NDA 21-015 be assigned a 3-P priority review classification.

Portions of this application are submitted in electronic format (on CDs and a zip drive 100 MB cartridge) as previously agreed by the FDA at the November 4, 1998 Pre-NDA Meeting. Two copies each of two CDs and a zip drive cartridge are enclosed. One of each is appended to the archival NDA copy; the other CDs and cartridge are appended to the reviewers' copy. In addition, the table of contents for Section 4 (CMC) and each of the volume tables of contents for Section 12 (CRFs) on the respective CDs contain hyperlinks to the section (or CRF pages) to help facilitate the NDA review. The electronic components are listed below:

Listing of Electronic NDA Components

Section	Contents	Format
1.0 Index	All pages	MS Word97 (zip drive cartridge)
2.0 Labeling	All pages	MS Word97 (zip drive cartridge)
3.0 Summary	All pages (excluding literature articles in Appendix)	MS Word97 (zip drive cartridge)
4.0 Chemistry, Manufacturing and Controls	All pages (Section table of contents contains hyperlinks to all major subsections)	CD
5.0 Preclinical Pharmacology & Toxicology	All text/tables: Sections 5.1 – 5.3	MS Word97 (zip drive cartridge)
6.0 Clinical Pharmacology	Text/tables/figures: Sections 6.1 - 6.6.4, 6.7 (ref. list, excluding articles); Text: Sections 6.6.5, 6.6.6 Databases: UMD-99-017-IR, UMD-98-012-R, UMD-99-037-R, UMD-98-023-R, UMD-98-038-R, UMD-99-039-R (Refer to database files in Section 8)	MS Word97 (zip drive cartridge) SAS v6.12 (zip drive cartridge)
8.0 Clinical Data	Text/tables/figures: Sections 8.1 - 8.3.1.3.3, 8.3.1.3.6 -8.3.1.3.8, 8.4.1 - 8.5.2.4, 8.7 - 8.13, 8.14 (ref. list, excluding articles); Text re: Sections 8.3.1.3.4, 8.3.1.3.5 Databases: UMD-99-017-IR, UMD-98-012-R, UMD-99-037-R, UMD-98-023-R, UMD-98-038-R, UMD-099-039-R	MS Word97 (zip drive cartridge) SAS v6.12 (zip drive cartridge)
10.0 Statistical Data	See Section 8	---
11.0 CRF Tabulations	---	Can be created from database for UMD-99-017-IR; refer to files in Section 8
12.0 CRFs	All pages (each volume table of contents contains hyperlinks to 1st page of each CRF)	CD

As previously discussed and agreed upon by the FDA:

- The report of pivotal study UMD-96-017 (report UMD-99-017-IR) provides three months of primary efficacy data and up to six months of safety data for 227 patients dosed with 50 or 100 mg Androgel. A final report of this six-month study will be submitted with revised labeling and a safety update to this NDA.

- Appendix 16.1.9 (statistical methods) for report UMD-99-017-IR is provided in the statistical section (section 10); this appendix is excluded from the paper copies of the report in the pharmacokinetic and clinical data sections (Sections 6 and 8).

- The patient data listings for reports UMD-98-012-R, UMD-99-017-IR, UMD-99-037R, UMD-99-039-R, and UMD-98-023-R are provided in lieu of the case report form tabulations in section 11. In addition, these listings are excluded from the paper copy of the report in Sections 6 and 8.

Unimed certifies that: 1) the electronic components of this NDA are exact duplicates of the technical information provided in hard copy (archival and review copies); and 2) the electronic data are virus-free.

Pursuant to 21 CFR, an archival and a review copy of this NDA are being submitted. In addition, an exact copy of Sections 1 through 4 has been submitted to the FDA Chicago District Office. Per the request of your Project Manager, Ms. Kim Colangelo, two extra copies of the following information are submitted in a separate package to Ms. Colangelo as desk copies: Volume 1.1, the ISS and the ISE.

Please contact me directly if you have any questions concerning this submission.

Sincerely yours,

D R Peckels

Donald R. Peckels
Director, Regulatory Affairs

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drp/enclosures