CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:NDA 20-791

CORRESPONDENCE

alza

ORIGINAL

Noted Brinkley 9/3/97

Noted MH 9/2/97

REVIEWS COMPLETED	
CSO ACTION: ☐ LETTER ☐ N.A.I. ☐ MEMO	
CSO INITIALS	DATE

ORIG AMENDMENT

BC

NDA Number 20-791
Volume 4.1

August 26, 1997

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II
Division of Reproductive and Urologic Drug Products (HFD-580)
Attention: Document Control Room 17B-20
5600 Fishers Lane
Rockville, MD 20857

noted Arnt. 9-3-97

Attention: Lisa Rarick, M.D. , Director
Division of Reproductive and Urologic Drug Products

Subject: NDA Amendment: Testoderm® TTS (Testosterone Transdermal System)
Environmental Assessment - Categorical Exclusion

Dear Dr. Rarick,

In a discussion between Ms. Terri Rumble and Steve Ketchum on August 8th, it was suggested that ALZA submit an amendment to the NDA to request a categorical exclusion for the preparation of an Environmental Assessment for Testoderm® TTS based on the July 29, 1997 Federal Register Notice.

Therefore, in accordance with 21 CFR 25.15(d), ALZA requests a categorical exclusion for the preparation of an Environmental Assessment for Testoderm® TTS based on 21 CFR 25.31(b), the estimated concentration of testosterone, the active moiety, at the point of entry into the aquatic environment will be below part per billion. To ALZA's knowledge, no extraordinary circumstances exist.

Although the regulations are not effective until August 28, 1997, ALZA understands that, since the agency has not signed a finding of no significant impact (FONSI), we may amend the NDA claiming a categorical exclusion in accordance with 25.15(d). ALZA waives the claim for categorical exclusion if a FONSI has been signed on or before August 28, 1997.

ALZA CORPORATION, 950 PAGE MILL ROAD, P.O. BOX 10950, PALO ALTO, CA 94303-0802 (415) 494-5000 TELEX 345526

A field copy of this submission is provided to the San Francisco District Office. I hereby certify that the field copy is a true copy of the archival and review copies of this amendment.

If you have any questions, please do not hesitate to contact Steve Ketchum, Ph.D. at (415) 237-2510 or me at (415) 237-2537, or either of us by fax at (415) 237-2581.

Sincerely,

Katy Morton

Katy Morton
Associate Director, Regulatory Affairs

Desk Copies for:

Dr. Amit Mitra, Chemistry Reviewer, DRUDP, HFD-580
Ms. Terri Rumble, Project Manager, DRUDP, HFD-580

December 17, 1997

NDA Number 20-791

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II
Division of Reproductive and Urologic Drug Products (HFD-580)
Attention: Document Control Room 17B-20
5600 Fishers Lane
Rockville, MD 20857

Attention: Lisa Rarick, MD, Director
Division of Reproductive and Urologic Drug Products

Subject: **General Correspondence to NDA 20-791 for Testoderm® TTS (Testosterone Transdermal System):** Copies of Facsimiles Dated 12/5/97, 12/9/97, 12/10/97, 12/14/97 and 12/15/97

Dear Dr. Rarick:

Further to Ms. Terri Rumble's request of earlier today (Wednesday, December 17th) for good quality copies of certain facsimiles for use in assembling the action package, enclosed to this submission are hard copies of the following faxes which ALZA has sent to the Division over the past two weeks:

Date	Subject	Location in this Submission	
		Attachment	Page(s)
12/5/97	Copies of Faxed Clarifications to Questions Raised 12/5/97 Regarding the Specification, Product Dimensions, the In Vitro Release Rate Specifications, and the Established Name for Testoderm® TTS During Dr. Amit Mitra's Chemistry Review of Amendment 12.1 to the NDA (Submitted 12/3/97)	1	004 - 023
12/9/97	Copies of Faxed Clarifications to Questions Raised 12/9/97 Regarding the USP IR Identity Test and the In Vitro Release Rate Specifications for Testoderm® TTS During Dr. Amit Mitra's Chemistry Review and During Dr. Sam Haidar's Biopharm Review of Amendment 12.1 to the NDA (Submitted 12/3/97)	2	025 - 031
12/10/97	Preliminary Responses to the Division's 12/10/97 Labeling Comments for Testoderm® TTS and Requests for Clarification via Teleconference	3	033 - 039
12/14/97	ALZA Contact Number for 12/15/97 Teleconference	4	041
12/15/97	Copies of Clarifications to the Questions Raised During the 12/15/97 Teleconference Regarding the In Vitro Release Rate Specifications and the Pharmacokinetic Table/Figure for the Revised Labeling to Facilitate Brief Teleconference (on 12/15/97) with Dr. Sam Haidar	5	043 - 047

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ALZA CORPORATION 1010 JOAQUIN ROAD P.O. BOX 7210 MOUNTAIN VIEW CA 94039-7210 PHONE 650.962.4000 http://www.alza.com

A field copy of this submission is provided to the San Francisco District Office. I hereby certify that the field copy is a true copy of the archival and review copies of this application.

If you have any questions regarding the information provided in this submission, please do not hesitate to contact me at 650-237-2510 or via facsimile at 650-237-2581.

Sincerely,

Steve Ketchum

Steve Ketchum, PhD,
Associate Director, Regulatory Affairs

(Enclosures)
Copies: Archival (1)
Reviewer (3) for:
Clinical Reviewer
Pharmacokinetics Reviewer
Chemistry Reviewer
Desk (2) for:
Terri Rumble, BSN, Project Manager, DRUDP, HFD-580
San Francisco District Field Office

December 16, 1997

NDA Number 20-791
Volume 14.1

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II
Division of Reproductive and Urologic Drug Products (HFD-580)
Attention: Document Control Room 17B-20
5600 Fishers Lane
Rockville, MD 20857

Attention: Lisa Rarick, MD, Director
Division of Reproductive and Urologic Drug Products

Subject: NDA Amendment: Testoderm® TTS (Testosterone Transdermal System):
Copy of Revised Package Insert Further to 12/16/97 Phone Conversation

Dear Dr. Rarick:

Further to a conversation which Steve Ketchum (ALZA) had with Ms. Terri Rumble earlier today (Tuesday, December 16th), a revised copy of the package insert is provided in Attachment 1 to this submission. The following revisions are the only changes which have been made to the version that was submitted yesterday (Monday, December 15th) as Volume 13.1 to the NDA:

(1) Page 008 of this submission (page 5 of the label), in Table 1, below line 171:
has been revised to read to be consistent with the skin site terminology stated throughout the label.

(2) Page 009 of this submission (page 6 of the label), old figure, below line 190:
As discussed with Ms. Terri Rumble earlier today, the revision mode's horizontal line through the middle of this figure was intended to indicate that this old figure has been replaced by the new, agreed upon figure which appears on the next page of the label. To make this clearer, an "X" has been drawn through this old figure.

(3) Page 011 of this submission (page 8 of the label), lines 217-218:
The words were inadvertently left in the last version; therefore, this text has been revised to read ' to be consistent with the terminology used throughout the label.

(4) Page 014 of this submission (page 11 of the label), line 367:
The first letter of the starting word of this sentence was inadvertently left in lowercase in the last version; therefore, this has been revised to uppercase

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ALZA CORPORATION 1010 JOAQUIN ROAD P.O. BOX 7210 PHONE 650.962.4000
MOUNTAIN VIEW CA 94039-7210 http://www.alza.com

If you have any questions, please do not hesitate to contact me at 650-962-4282, or Steve Ketchum, Associate Director, Regulatory Affairs at 650-237-2510. We share the same facsimile number (650-237-2581).

Sincerely,

J. Wissel By S.K.

Janne Wissel
Vice President,
Quality Management,
and Regulatory Affairs

(Enclosures)
Copies: Archival (1)
Reviewer (3) for:
Clinical Reviewer
Pharmacokinetics Reviewer
Chemistry Reviewer
Desk (1) for:
Terri Rumble, BSN, Project Manager, DRUDP, HFD-580

December 15, 1997

NDA Number 20-791
Volume 13.1

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II
Division of Reproductive and Urologic Drug Products (HFD-580)
Attention: Document Control Room 17B-20
5600 Fishers Lane
Rockville, MD 20857

Attention: Lisa Rarick, MD, Director
Division of Reproductive and Urologic Drug Products

Subject: NDA Amendment: Testoderm® TTS (Testosterone Transdermal System): Responses to Topics Communicated Via Teleconference on 12/15/97

Dear Dr. Rarick:

ALZA Corporation's responses to the issues raised in two separate FDA/ALZA teleconferences today (Monday, December 15th) regarding the Chemistry, Biopharm and Labeling review of the Testoderm® TTS NDA are provided.

Chemistry / Biopharm Comment

Further to the teleconference this afternoon with Dr. Moo Jhong Rhee (Chemistry Team Leader) and Dr. Sam Haidar (Biopharm Reviewer), ALZA hereby acknowledges its acceptance of the Division's requested in vitro release specifications tabulated below:

Cumulative Release Specifications, in mg

Attribute	Current Specification
h	
h	
h	
h	

At a future date, ALZA intends to revise these specifications and extend the product's expiration dating period following completion of the Phase 4 commitment to conduct a study of newly manufactured versus aged Testoderm® TTS systems. We appreciate the Division's offer of keeping the channels of communication open for potential meetings in future to discuss data that falls out of these specifications during the shelf-life evaluation.

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ALZA CORPORATION 1010 JOAQUIN ROAD P.O. BOX 7210 MOUNTAIN VIEW CA 94039-7210 PHONE 650.962.4000 http://www.alza.com

Labeling Comments on the Package Insert

A revised copy of the package insert, incorporating all of the changes agreed upon by both ALZA and FDA during today's teleconferences, is provided in Attachment 1 to this submission. As requested, this revised version has been generated in the revision mode in order to facilitate the Division's review.

A field copy of this submission is provided to the San Francisco District Office. I hereby certify that the field copy is a true copy of the archival and review copies of this application.

If you have any questions, please do not hesitate to contact me at 650-962-4282, or Steve Ketchum, Associate Director, Regulatory Affairs at 650-237-2510. We share the same facsimile number (650-237-2581).

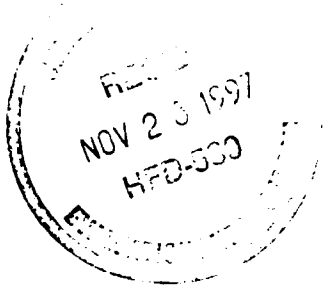
Sincerely,

Janne Wissel
Vice President,
Quality Management,
and Regulatory Affairs

(Enclosures)
Copies: Archival (1)
Reviewer (3) for:
Clinical Reviewer
Pharmacokinetics Reviewer
Chemistry Reviewer
Desk (2) for:
Terri Rumble, BSN, Project Manager, DRUDP, HFD-580
San Francisco District Office

alza

November 26, 1997 ORIGINAL



NDA Number 20-791
Volume 11.1

ORIG AMENDMENT
3L

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II
Division of Reproductive and Urologic Drug Products (HFD-580)
Attention: Document Control Room 17B-20
5600 Fishers Lane
Rockville, MD 20857

REVIEWS COMPLETED
CSO ACTION:
☐ LETTER ☐ N.A.I. ☐ MEMO
CSO INITIALS DATE

Attention: Lisa Rarick, MD, Director
Division of Reproductive and Urologic Drug Products

Subject: NDA Amendment: Testoderm® TTS (Testosterone Transdermal System): Responses to Topics Communicated via Teleconference on 11/21/97

Dear Dr. Rarick:

We are providing a response to the following three main topics which were discussed in our teleconference of November 21st, 1997:

1. Revisions to artwork to reflect the agreed upon dose of 5 mg/day
2. Addition of the delivery rate to the system backing print mat text
3. Justification of the proposed, initial expiration dating of 18 months

With regards to the Division's request to revise the current proposed labeling to reflect the dose of 5 mg/day, ALZA has incorporated this change into its most recent versions of the labeling. In view of the fact that additional labeling comments (dated November 25th, 1997) were received by facsimile yesterday, ALZA will provide copies of revised artwork to the Division as part of a separate formal response to that letter.

In response to Dr. Amit Mitra's request, ALZA hereby commits to adding the delivery rate (5 mg/day) to the system backing print mat text after completion of the currently planned manufacturing campaigns, and to effectuate this change via a formal submission to the NDA. ALZA will append a copy of the system backing print mat text in our response to the Division's labeling comments. This text will confirm for Dr. Mitra that, in addition to the Testoderm® TTS tradename, the generic identifier for the product is currently reflected on the system itself.

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In an attachment to this submission, ALZA has enclosed data generated to investigate the increase in release rates observed for the Testoderm® TTS product (Appendix A), and data which supports an 18 month initial expiration dating period for the product. In addition, ALZA hereby agrees to a Phase 4 commitment to conduct a clinical study of newly manufactured versus aged Testoderm® TTS systems. ALZA commits to providing a protocol to FDA within 6 months of final NDA approval, and to providing final clinical data for this study within 18 months of ALZA/FDA agreement on the study design. As discussed during our teleconference on November 21st, 1997, ALZA commits to conducting this study under special circumstances, since in vivo validation of the product specifications at the end of the shelf-life would not normally be required.

If you have any questions, please do not hesitate to contact me at 650-237-2510, or Sue Rinne, Director, Regulatory Affairs at 650-237-2523. We share the same facsimile number (650-237-2581).

Sincerely,

Steve Ketchum

Steve Ketchum, PhD
Associate Director, Regulatory Affairs

(Enclosures)
Copies: Archival (1)
Reviewer (3) for:
Clinical Reviewer
Pharmacokinetics Reviewer
Chemistry Reviewer
Desk (1) for:
Terri Rumble, BSN, Project Manager, DRUDP, HFD-580

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alza

REVIEWS COMPLETED

CSO ACTION:
☐ LETTER ☐ N.A.I. ☐ MEMO

CSO INITIALS DATE

CENTER FOR DRUG EVALUATION AND RESEARCH
REC'D
NOV 21 1997
HFD-580

November 19, 1997

NDA Number 20-791
Volume 10.1

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II
Division of Reproductive and Urologic Drug Products (HFD-580)
Attention: Document Control Room 17B-20
5600 Fishers Lane
Rockville, MD 20857

ORIG AMENDMENT
ORIGINAL 3C

Attention: Lisa Rarick, MD, Director
Division of Reproductive and Urologic Drug Products

Subject: NDA Amendment: Testoderm® TTS (Testosterone Transdermal System): Responses to Topics Communicated via Teleconference on 11/13/97

Dear Dr Rarick:

We are providing a response to the following three main topics which were discussed in our teleconference of November 13th, 1997:

1. Selection of method for dose calculation
2. Preferred release rate media for the analytical method
3. Justification for the release rate specification

This response is organized by topic, with our main response followed by copies of information referenced elsewhere in the NDA 20-791 for Testoderm®TTS (testosterone transdermal system) and NDA 19-762 for the scrotal Testoderm® products. You have also received via facsimile clarifications of topic 3 on November 17th, 1997 and of topic 2 on November 18th, 1997; copies of these facsimiles are also included here for completeness.

With regards to the question of the method for the calculation of the nominal dose for Testoderm® TTS, we are proposing a modification to the suggested Method B.2 for the calculation. The modified method was validated using previous study data. The method resolves the issue of first pass metabolism following scrotal application and uses the AUC value derived from both primary clinical studies (C-95-044 and C-95-045). The method results in a nominal dose of 5 mg/day, reduces variability within and between studies to about 30%, and considers the biological interaction of exogenous testosterone administration on endogenous testosterone levels.

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Sterile water will be the release rate media for the analytical method. This change to the document is expected to be completed this week.

We have provided a scientific rationale for the release rate specifications. The data in clinical study C-96-048 reflect the normal variability of testosterone concentrations seen in eugonadal men and justifies the upper bound of the release rate specification. Systems tested in this study, which were at the upper bound of the release rate specification, behave in a predictable manner and restore testosterone concentrations to the normal range.

We look forward to the discussion of these and any other topics at our teleconference scheduled for this Friday, November 21st at 1 pm EST. In addition, we are anxious to receive your comments on the package insert. If you have any questions, please do not hesitate to contact me at 650-237-2510 or via facsimile at 650-237-2581.

Sincerely,

Steve Ketchum

Steve Ketchum, PhD
Associate Director, Regulatory Affairs

(Enclosures)
Copies: Archival (1)
Reviewer (3) for:
Clinical Reviewer
Pharmacokinetics Reviewer
Chemistry Reviewer
Desk (8) for:
Lisa Rarick, MD, Director, DRUDP, HFD-580
Heidi Jolson, MD, MPH, Deputy Director, DRUDP, HFD-580
Mark Hirsch, MD, Medical Officer, DRUDP, HFD-580
Sam Haidar, PhD, Biopharmaceutics Reviewer, DPEII @ DRUDP, HFD-580
Angelica Dorantes, PhD, Pharmacokinetics Team Leader, DPEII, HFD-870
Amit Mitra, PhD, Chemistry Reviewer, HFD-580
Moo Jhong Rhee, PhD, Chemistry Team Leader,
Terri Rumble, BSN, Project Manager, DRUDP, HFD-580

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alza

ORIGINAL

November 3, 1997

NDA Number 20-791
Volume 9.1

ORIG AMENDMENT
BC

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II
Division of Reproductive and Urologic Drug Products (HFD-580)
Attention: Document Control Room 17B-20
5600 Fishers Lane
Rockville, MD 20857

Attention: Lisa Rarick, MD, Director
Division of Reproductive and Urologic Drug Products

Subject: NDA Amendment: Testoderm® TTS (Testosterone Transdermal System)
Stability Update

Dear Dr. Rarick:

Reference is made to our submission of October 14, 1997 (Volume 7.1) where we provided three months stability data for one lot and one month data on two lots of Testoderm® TTS packaged in pouchstock. As indicated, we are hereby providing three months data on all three validation lots (Attachment 1). The data indicate that systems packaged in pouchstock have similar performance to systems packaged in pouchstock.

In addition, as indicated in the referenced submission, we are providing updated stability data on the registration lots of Testoderm® TTS. We now have 18 months data for all five stability studies. The data, as presented in Attachment 2, support a shelf life of 24 months when the product is stored at or below 25°C (77°F).

A field copy of this submission is provided to the San Francisco District Office. I hereby certify that the field copy is a true copy of the archival and review copies of this application.

If you have any questions, please do not hesitate to contact me at (650) 237-2510 or Mirka Dunn, Director of Regulatory Affairs, at (650) 237-2524. We share the same facsimile number (650-237-2581).

Sincerely,

Steve Ketchum

Steve Ketchum, PhD
Associate Director, Regulatory Affairs

REVIEWS COMPLETED

CSO ACTION:
☐ LETTER ☐ N.A.I. ☐ MEMO

CSO INITIALS DATE

Desk Copies for:
Dr. Amit Mitra, Chemistry Reviewer, DRUDP, HFD-580
San Francisco District Office

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alza

ORIGINAL

October 14, 1997

ORIG AMENDMENT

NDA Number 20-791
Volume 7.1

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II
Division of Reproductive and Urologic Drug Products (HFD-580)
Attention: Document Control Room 17B-20
5600 Fishers Lane
Rockville, MD 20857

REVIEWS COMPLETED	
CSO ACTION: ☐ LETTER ☐ N.A.I. ☐ MEMO	
CSO INITIALS	DATE

Attention: Lisa Rarick, M.D. , Director
Division of Reproductive and Urologic Drug Products

Subject: NDA Amendment: Testoderm® TTS (Testosterone Transdermal System): Responses to Chemistry Reviewer's Requests Communicated on 7/25/97, 9/26/97, 10/1/97, and 10/2/97

Dear Dr. Rarick,

As requested in telephone conversations between Dr. Amit Mitra and Ms. Katy Morton or myself on July 25th, September 26th, and October 1st and 2nd of this year, ALZA is hereby providing the following information in response to the Chemistry Reviewer's requests:

(1) The results of adhesive peel force and release liner peel force testing on the registration lots of Testoderm® TTS

(2) A description of the content uniformity testing method

(3) The specifications and test methods for the materials used in the production of the

(4) Stability data for the validation lots packaged in pouchstock . Three months data on one lot, and one month data on the other two validation lots are enclosed. As indicated to Dr. Mitra and to Ms. Terri Rumble, three months data on the second and third validation lots will be available later this month and will be submitted to the Division. At that time, ALZA also plans to submit updated stability data on the registration lots.

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As discussed between Dr. Mitra and Ms. Morton on September 26th, 1997, ALZA is also taking this opportunity to update the specifications (ALZA Quality Standard [AQS]) for the drug product. A copy of the revised product specifications, as well as a description of the changes, is provided

A field copy of this submission is provided to the San Francisco District Office. I hereby certify that the field copy is a true copy of the archival and review copies of this application.

If you have any questions, please do not hesitate to contact me at 415-237-2510 or Mirka Dunn, Director of Regulatory Affairs, at 415-237-2524. We share the same facsimile number (415-237-2581).

Sincerely,

Steve Ketchum

Steve Ketchum, Ph.D
Associate Director, Regulatory Affairs

Desk Copies for:
Dr. Amit Mitra, Chemistry Reviewer, DRUDP, HFD-580
San Francisco District Office

alza

ORIGINAL

REVIEWS COMPLETED

CSO ACTION:
☐ LETTER ☐ N.A.I. ☐ MEMO

CSO INITIALS DATE

September 12, 1997

NDA Number 20-791
Volume 6.1

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II
Division of Reproductive and Urologic Drug Products (HFD-580)
Attention: Document Control Room 17B-20
5600 Fishers Lane
Rockville, MD 20857

Not in Comis
BL

ORIG AMENDMENT

Attention: Lisa Rarick, M.D., Director,
Division of Reproductive and Urologic Drug Products

Subject: **<u>Amendment to NDA 20-791</u>: Request for Review of Revised Proposed Labeling for Testoderm® TTS**

Dear Dr. Rarick:

Further to a telephone conversation with Ms. Terri Rumble on August 8, 1997, in which ALZA was informed of the FDA's concurrence as to the acceptability of the "Testoderm® TTS" tradename, please find enclosed to this submission the revised proposed labeling for the product pouch and carton. These revised samples replace the versions of the pouch and carton labeling which were enclosed to the original NDA (Volume 1.1, Pages 072 to 076 and 077 to 080, respectively). In addition, enclosed please find two new proposed labeling items, the demonstrator patch pouch and the system print mat text. Please note that behind each color version of the proposed labeling is a black and white copy with the identical text.

ALZA requests that the Division review the enclosed materials so that agreement can be reached on the final text for these labeling items. I am planning to contact Ms. Rumble the midweek of September 22, 1997, to elicit the Division's comments on the enclosed proposed labeling.

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Please contact me at (415) 237-2510, or by fax at 415-237-2581, if you have any questions regarding this submission. If you are unable to reach me, then please contact Sue Rinne, Director, Regulatory Affairs, at (415) 237-2523. We share the same facsimile number.

Sincerely,

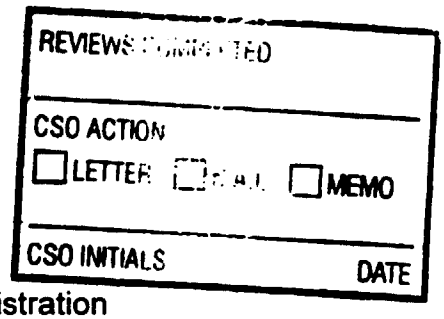
Steve Ketchum, Ph.D.
Associate Director
Regulatory Affairs

(Enclosures)

Copies: Archival (1)
Reviewer (3) for:
Chemistry Reviewer
Clinical Reviewer
Pharmacokinetics Reviewer
Desk (2) for:
Amit Mitra, Ph.D. (DRUDP; HFD-580)
Terri Rumble (DRUDP; HFD-580)

alza

ORIGINAL



September 12, 1997

NDA Number 20-791

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II
Division of Reproductive and Urologic Drug Products (HFD-580)
Attention: Document Control Room 17B-20
5600 Fishers Lane
Rockville, MD 20857

ORIG AMENDMENT

Attention: Terri Rumble, Project Manager
Division of Reproductive and Urologic Drug Products

Subject: Response to FDA Request for Proposed Labeling Information for Testoderm® TTS

Dear Ms. Rumble:

In response to your telephone request on August 9, 1997, enclosed are the electronic versions of the text for the proposed Patient Instructions and the Physician Insert (annotation deleted) that were included in the original NDA submission of December 19, 1996, for Testoderm® TTS. Please note that the enclosed diskette has been certified to be virus-free.

For your convenience, also enclosed are hard copies of the following documents.

- The proposed Patient Instructions (dated 12/17-18/96), which was included in the original NDA submission (Volume 1.1, Pages 065 to 071).
- The proposed Physician Insert (dated 12/17/96) with annotation deleted.
- The proposed Annotated Physician Insert (dated 12/17/96), which was included in the original NDA submission (Volume 1.1, Pages 042 to 063).

(sbk) g:\testoste\tts\nda\submittd\corespon\97_09_12\corresp1.doc (9/12/97)

ALZA CORPORATION, 950 PAGE MILL ROAD, P.O. BOX 10950, PALO ALTO, CA 94303-0802 (415) 494-5000 TELEX 345526

Please note that the electronic versions of the text for the proposed Patient Instructions and the Physician Insert (annotation deleted) do not include the diagrams, figures, and tables that are included in the corresponding hard copy documents listed above.

Please contact me at (415) 237-2510, or by fax at 415-237-2581, if you have any questions regarding this submission. If you are unable to reach me, then please contact Ray Lubecki, Manager, Regulatory Affairs, at (415) 237-2528. We share the same facsimile number.

Sincerely,

Ray Lubecki /for

Steve Ketchum, Ph.D.
Associate Director
Regulatory Affairs

(Enclosures)

alza

ORIGINAL

NDA Number 20-791
Volume 5.1

ORIG AMENDMENT
BI

August 28, 1997

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II
Division of Reproductive and Urologic Drug Products (HFD-580)
Attention: Document Control Room 17B-20
5600 Fishers Lane
Rockville, MD 20857

REVIEWS COMPLETED
CSO ACTION:
☐ LETTER ☐ N.A.I. ☐ MEMO
CSO INITIALS DATE

Attention: Lisa Rarick, M.D. , Director
Division of Reproductive and Urologic Drug Products

Subject: NDA Amendment: Testoderm® TTS (Testosterone Transdermal System)
Response to Microbiology Questions

Dear Dr. Rarick,

The following provides ALZA Corporation's response to issues raised in the July 30, 1997 letter to Ms. Janne Wissel regarding the microbiology review of the Testoderm® TTS NDA. For ease of review, FDA's comments are reproduced below in italics, followed by ALZA's response.

Question 1: *The submission was reviewed for microbiological issues concerning microbiological integrity. In regard to the microbial limits, the product does have microbiocidal properties, probably due to the* *in the product. However, this does not obviate the need to establish microbial limits for the product. Interestingly, bacterial spores may be stored in solutions containing* *Other microbes are also capable of adapting to, and contaminating very inhospitable environments.*

Accordingly, microbial limits should be set in a manner such that excursion above the limits may be indicative of process deviations. It will be necessary to use the established microbial limits as product release criteria. After generating a sufficient body of data indicating that microbial limits are unlikely to be exceeded, it may be possible to submit a supplemental application to reduce or eliminate testing.

Response: Although it was not indicated in the NDA, ALZA has established microbial limits for Testoderm® TTS systems as an in-house testing requirement. The microbial limits for this product are specified below:

- Total Aerobic Bacteria: colony forming units (CFU) per system
- Total Fungal Organisms: CFU per system
- No *S. aureus, P. aeruginosa,* and *E. coli* present

We established these in-house microbial purity specifications according to the USP-proposed specifications for topically applied products. If the bioburden of the finished product exceeds the limits of aerobic CFU per system or fungal CFU per system and these results are confirmed, then the contaminated batch of Testoderm ® TTS systems would be rejected and an investigation would be conducted to determine the source of this contamination. In addition, if *S. aureus, P. aeruginosa,* and *E. coli* were to be detected in any quantity in the finished product, then the batch would likewise be rejected.

To date, six lots (three registration and three validation) of Testoderm® TTS systems have been tested for microbial content according to AAM 6.127. The Testoderm® TTS systems were also tested for the absence of *S. aureus, P. aeruginosa,* and *E. coli,* according to AAMs 6.128 and 6.129. These test methods were generated in accordance with the principles in USP XXIII <61>, Microbial Limit Tests. Please note that these methods were provided in the original NDA under the Microbiology Section (volume 1.29, pages 048-078).

The bioburden levels of these lots were very low (Appendix 1). One lot showed contamination levels of 3 CFU per system tested. Further analysis of test results demonstrated the presence of gram positive *cocci*, which are non-pathogenic skin microorganisms. These common contaminants are present in most environments, including manufacturing facilities for non-sterile products. The contamination levels of the systems from other lots were below the maximum sensitivity of the test method, less than 3 CFU per system. In addition, the above indicated objectionable microorganisms were absent from all Testoderm® TTS systems tested.

As indicated in NDA 20-791, the viability of vegetative bacteria, yeast, and fungal spores was evaluated by directly exposing these organisms on the finished product and the final product formulation (gel). The results indicated that the tested organisms (*S. aureus* ATCC 6538, *E. coli* ATCC 8739, *P. aeruginosa* ATCC 9027, *C. albicans* ATCC 10237, and *A. niger* spores ATCC 16404) lost their viability after 2 days of exposure under the actual storage temperatures and conditions for the finished product and the final product formulation (gel).

In addition to performing the microbial limits testing and microbial challenge testing indicated above, a routine monitoring program is conducted at ALZA to ensure the

microbiological quality of the manufacturing facility. Testoderm® TTS systems are produced in Category III Clean Room Manufacturing Environments, defined as "work stations under bacterial retention filtered air, dress code consists of clean hair covering and lab coat." All equipment and utensils are cleaned with disinfectant solution before each lot of systems is manufactured.

We believe that the microbiological purity of Testoderm®TTS systems is assured by compliance with ALZA's Quality Control program, which consists of the following:

- Ensure that the finished product and the final formulation do not support microbial growth.
- Adhere to current GMP regulations in the manufacturing process.
- Monitor and control the manufacturing environment on a routine basis.
- Conduct microbial limits tests on the finished products.

At this time, we have concluded that conducting a microbial limits test on one batch of Testoderm® TTS systems annually will provide adequate confirmation of the microbiological purity of this product. This requirement has been added to the regulatory specifications.

Question 2: *In regard to microbial monitoring of stability samples, microbial limits should be monitored as a portion of the drug product stability protocol. After generating a sufficient body of data indicating that microbial limits are unlikely to be exceeded, it may be possible to submit a supplemental application to reduce or eliminate testing.*

Response: According to the previously submitted NDA Microbiology section (volume 1.29, pages 023-078), the microbial content of this product is expected to be continuously low based on these factors:

- Bactericidal property of the formulation
- Inability of vegetative organisms and fungal spores to maintain their viability on the product
- Microbiological controls over the manufacturing process
- Low bioburden profile of the finished products tested
- Historically controlled environmental microbial profile of the manufacturing facility

Therefore, there should be no concern regarding microbiological purity of the finished product unless the packaging (paper/foil/polymer pouch) is unable to maintain its integrity. Systems are individually packaged in these pouches by heat-sealing the polymer layers together. Appropriate controls have been established to assure proper sealing.

Alcohol, USP is incorporated into the final formulation of Testoderm® TTS systems at a target concentration of % (w/w). The ethanol content is controlled at lot release

and is measured on stability testing. Package failures would result in excessive ethanol loss from the systems with storage time. This is an adequate measure for monitoring package integrity over the duration and under the conditions of the stability studies. If the pouches can retain a volatile solvent (ethanol), they should be able to prevent ingress of microorganisms. Current stability studies results have shown little ethanol loss with time. Therefore, we have concluded that there is no value in including microbial limits testing on stability samples as one of the attributes of the stability protocol.

A field copy of this submission is provided to the San Francisco District Office. I hereby certify that the field copy is a true copy of the archival and review copies of this application.

If you have any questions, please do not hesitate to contact Steve Ketchum, Ph.D. at (415) 237-2510, or me at (415) 237-2537, or either of us by fax at (415) 237-2581.

Sincerely,

Katy Morton

Katy Morton
Associate Director, Regulatory Affairs

Desk Copies for:

Dr. Amit Mitra, Chemistry Reviewer, DRUDP, HFD-580
Ms. Terri Rumble, Project Manager, DRUDP, HFD-580

alza

NEW CORRESP

ORIGINAL

REVIEWS COMPLETED	
CSO ACTION: ☐ LETTER ☐ N.A.I. ☐ MEMO	
CSO INITIALS	DATE

August 1, 1997

NDA Number: 20-791

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II
Division of Reproductive and Urologic Drug Products (HFD-580)
Attention: Document Control Room 17B-20
5600 Fishers Lane
Rockville, MD 20857

CENTER FOR DRUG EVALUATION AND RESEARCH
REC'D
AUG 04 1997
HFD-580

Attention: Lisa Rarick, M.D., Director,
Division of Reproductive and Urologic Drug Products

Subject: **<u>Correspondence to NDA 20-791</u>: Follow-up to 7/31/97 Telephone Conversation: ALZA's Preference for, and Willingness to Accept, the Division's Proposed Alternate Tradename "Testoderm® TTS"**

Dear Dr. Rarick:

Further to ALZA's faxes dated 7/30/97, and in response to a request yesterday from Ms. Terri Rumble, ALZA hereby confirms its clear preference for, and willingness to accept, the "Testoderm® TTS" tradename that was proposed by the Division during the 7/30/97 teleconference as an acceptable alternative to for differentiating this new product (NDA 20-791) from the existing Testoderm® products. For business/commercialization reasons, ALZA has a strong preference for the "Testoderm® TTS" tradename over the other proposed alternative

In a phone conversation yesterday, Ms. Rumble communicated that the "TTS" suffix was not found to be acceptable by the Labeling and Nomenclature Committee at their meeting earlier that day because of a medication error issue that the Agency has apparently come across in the past with the 7-day transdermal product Catapress-TTS® (clonidine). Although the LNC apparently indicated that there have been a number of incidences of overdosing with that particular multi-day product when the "TTS" suffix has been misconstrued as meaning "Tuesday, Thursday, Saturday", we trust that the Division concurs with ALZA's view that this specific type of dosing confusion is not likely to be associated with, and would not present a safety issue for, ALZA's 1-day product.

Therefore, ALZA requests that the Division proceed with its deliberation of the "Testoderm® TTS" tradename. We look forward to working with you to come to closure on the tradename for NDA 20-791, and to receiving feedback from the Division on the "Testoderm® TTS" tradename by next Friday, August 8th, 1997, as you indicated during the teleconference on July 30th.

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Please contact me at (415) 237-2510, or by fax at 415-237-2581, if you have any questions regarding this letter.

Sincerely,

Steve Ketchum

Steve Ketchum, Ph.D.
Associate Director, Regulatory Affairs

Enclosures:
- Archival copy and Reviewer copies

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alza

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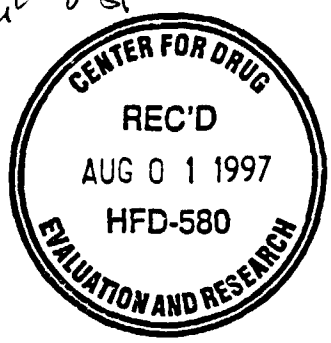
Mailed 8/6/97



July 30, 1997

NDA Number: 20-791 **NEW** CORRESP

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II
Division of Reproductive and Urologic Drug Products (HFD-580)
Attention: Document Control Room 17B-20
5600 Fishers Lane
Rockville, MD 20857

Faxed 8-7-97

8/6/97

Attention: Lisa Rarick, M.D., Director,
Division of Reproductive and Urologic Drug Products

Subject: **Correspondence to NDA 20-791: Follow-up to 7/30/97 Teleconference: Formal Request for an Expedited Trademark Consultation from the CDER Labeling and Nomenclature Committee (LNC) on the Division's Proposed Alternate Tradename "Testoderm® TTS"**

Dear Dr. Rarick:

As agreed during our teleconference this morning, I am writing this letter to confirm ALZA's acceptance of the "Testoderm® TTS" tradename that was proposed by the Division as an acceptable alternative to for differentiating this new product (NDA 20-791) from the existing Testoderm® products. ALZA hereby also formally requests an expedited trademark consultation from the CDER Labeling and Nomenclature Committee (LNC) and, as offered by Dr. Mark Askine (DDMAC), requests that the "Testoderm® TTS" tradename be placed on tomorrow's LNC meeting agenda.

Please contact me at (415) 237-2510, or by fax at 415-237-2581, if you have any questions regarding this letter. ALZA looks forward to working with you to come to closure on the tradename for NDA 20-791, and to receiving feedback from the Division on the "Testoderm® TTS" tradename by next Friday, August 8th, 1997, as you indicated during this morning's teleconference.

Sincerely,

Steve Ketchum

Steve Ketchum, Ph.D.
Associate Director, Regulatory Affairs

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REVIEWS COMPLETED

CSO ACTION:
☐ LETTER ☒ N.A.I. ☐ MEMO

8/6/97
CSO INITIALS DATE

Enclosures:

- Archival copy, Reviewer copies, plus desk copies for:
  Lisa Rarick, MD, Director, DRUDP, HFD-580
  Heidi Jolson, MD, MPH, Deputy Director, HFD-580
  Jean Fourcroy, MD, PhD, Medical Officer, HFD-580
  Mark Hirsch, MD, Medical Officer, HFD-580
  Moo Jhong Rhee, PhD, Chemistry Team Leader
  Amit Mitra, PhD, Chemistry Reviewer
  Lana Pauls, MPH, Chief, Project Management Staff
  Terri Rumble, BSN, Project Manager, DRUDP, HFD-580
  Mark Askine, MD, DDMAC, HFD-40

ALZA

ORIGINAL

ORIG AMENDMENT

REVIEWS COMPLETED	
CSO ACTION: ☐ LETTER ☐ N.A.I. ☐ MEMO	
CSO INITIALS	DATE

July 3, 1997

NDA Number 20-791
Volume 3.1

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II
Division of Reproductive and Urologic Drug Products (HFD-580)
Attention: Document Control Room 17B-20
5600 Fishers Lane
Rockville, MD 20857

Attention: Lisa Rarick, M.D. , Director
Division of Reproductive and Urologic Drug Products

Subject: NDA Amendment: Testoderm® AT (Testosterone Transdermal System)
Stability Update

Dear Dr. Rarick,

As discussed in a telephone conversation between myself and Dr. Amit Mitra on May 1, 1997, ALZA is providing this NDA Amendment to update the stability report. The original stability report filed in the Testoderm® NDA (Vol. 1.6/010) contained 6-9 month data on four registration lots (5 studies). The stability report has been updated to provide 12 month data on two studies and 15 month data on three studies.

The data, as presented in the attached stability update, supports a shelf life of 23 months when the product is stored at or below 25°C (77°F). Please note that one of the impurities, androstenedione (AD), has been shown to increase with time and temperature, but is projected to remain within the specification throughout the proposed shelf life at 25°C. AD is a natural occurring metabolite of testosterone and poses no clinical or safety concerns.

A field copy of this submission is provided to the San Francisco District Office. I hereby certify that the field copy is a true copy of the archival and review copies of this application.

If you have any questions, please do not hesitate to contact Dr. Steve Ketchum at (415) 237-2510 or me at (415) 237-2537, or either of us by fax at (415) 237-2581.

Sincerely,

Steve Ketchum for

Katy Morton
Associate Director
Regulatory Affairs

Enclosures: - Update to the Summary of the Stability of Testoderm®-II*
(*Note: Testoderm®-II is also referred to as Testoderm® AT and as TDC-15 is some of the documentation)
- Updated Stability Data Disk

Desk Copies for:
Dr. Amit Mitra, Chemistry Reviewer, DRUDP, HFD-580
San Francisco District Office
Ms. Terri Rumble, Project Manager, DRUDP, HFD-580