CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20-791

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW
Division of Pharmaceutical Evaluation II

NDA:	**20-791**
Compound:	Testoderm® TTS (Testoderm®-II, Testoderm AT) Non-scrotal transdermal testosterone delivery system (60 cm^2, 5mg/24hr)
Sponsor:	ALZA
Type of Submission:	Original NDA and Amendments
Date of Submission:	December 19, 1996 February 14, 1997 November 3, 1997 (BC) November 19, 1997 November 26,1997 (BZ)
Reviewer:	Sam H. Haidar, R.Ph., Ph.D.

DEC 17 1997

Synopsis:

The ALZA Corporation submitted NDA 20-791 for Testoderm™ TTS on December 19, 1996. Testoderm™ TTS is a non-scrotal transdermal delivery system indicated for testosterone replacement therapy in males for conditions associated with a deficiency in endogenous testosterone, i.e., primary hypogonadism (congenital or acquired) and hypogonadotropic hypogonadism. Each patch is 60 cm^2 in size and contains 328 mg of testosterone, of which less than 2% is delivered over a 24-hour period. The patch is to be applied to the upper buttocks, back or upper arm, for controlled release of testosterone through the skin.

Seven pharmacokinetics studies were provided in the original NDA 20-791; two pivotal and five supportive studies. The pivotal studies, C-95-044 and C-95-045, evaluated single and multiple dose pharmacokinetics, dose proportionality and site of application in hypogonadal men. A cross-study comparison was performed to evaluate the effect of patient demographics on testosterone concentrations. Additionally, Study C-96-048 was submitted to support a two-year shelf life for Testoderm™ TTS.

In vitro drug release testing, *in vitro* skin permeation and adhesion data were submitted in an amendment to NDA 20-791, dated February 14, 1997 and eighteen-month stability data were submitted in an amendment dated November 3, 1997.

The sponsor's response to issues discussed in a teleconference on November 13, 1997, was submitted in an amendment to NDA 20-791, dated November 19, 1997. The main three topics covered in this amendment were dose calculation, release media for the analytical method, and justification for the release rate specification.

Five major issues were identified during the review of NDA 20-791.

1) The Division of Scientific Investigations uncovered problems with sample handling and analytical procedures during an audit of the analytical sites: this lead to the exclusion of free testosterone, dihydrotestosterone, and estradiol data from pharmacokinetic analysis. Therefore, no pharmacokinetic evaluation was performed for the above analytes.

2) The sponsor calculated the dose delivered using an equation based on two assumptions: a) fraction of dose absorbed from Testoderm™ TTS is the same as the fraction absorbed (bioavailability) from the previously approved scrotal patch (Testoderm®); b) systemic clearance of testosterone is the same regardless of which patch is applied. The first assumption (equal fraction absorbed) was not acceptable because it did not account for differences in permeability to testosterone in scrotal versus non-scrotal skin, or the first pass metabolism which takes place in scrotal skin. The estimated doses delivered to each patient using this method varied from mg/24hr. Subsequently, on November 19, 1997, the sponsor proposed an alternative method of dose calculation using the average testosterone clearance obtained from previous studies with the Androderm® patch (Theratech) to estimate dose absorbed based on individual AUC values (not corrected for baseline) following application of Testoderm™ TTS. This method of dose calculation was acceptable, although it is only an approximation. When this method was applied to the two pivotal pharmacokinetic studies, a mean dose of 5mg/24hr (±1.6 mg) was obtained. Thus, it was requested that labeling and package be changed to reflect the new dose delivered by Testoderm™ TTS.

3) After 24 months of storage (using accelerated stability conditions), the *in vitro* testosterone release rate from Testoderm™ TTS was more than 100% greater than the release rate from freshly produced patches. Furthermore, review of study C-96-048 showed there was insufficient data to determine that the 24 month old patches had similar bioavailability profiles as freshly produced patches. Therefore, the potential lack of stability of Testoderm™ TTS and the clinical significance thereof, was in question. During a teleconference on November 21, 1997 the sponsor accepted an 18 month shelf- life; additionally, the sponsor agree to conduct a Phase IV bioequivalence study, comparing freshly produced patches with those that have been in storage for a period of 24 months (actual time) to support a two year shelf-life.

4) The *in vitro* drug release specifications proposed by the sponsor were based on the mean + 15% of the release from the 5 month old systems (using accelerated stability conditions) for the upper limit and 85% of the mean release from the fresh patches to define the lower limit of the specifications. The end result was that the specifications were very wide and included data from accelerated release systems with inadequate *in vivo* testing. In the November 21, 1997 teleconference, the above concerns were communicated to the sponsor

and they agreed to submit new narrower specifications. which would support the 18 month shelf-life.

5) The proposed upper and lower limits of the normal physiological range for testosterone serum concentrations were based on the 95% confidence interval around the mean of baseline levels measured in healthy normal volunteers (n = 50) over 24 hours. Blood sampling in this study was more frequent when testosterone levels are at the lower range of the circadian rhythm and very sparse (1 sample) when testosterone levels are at the upper range. This has produced an overall profile for testosterone which does not show the magnitude of fluctuations reported in the literature. This issue is currently under discussion with the sponsor and will be resolved prior to the action date for NDA 20-791.

Recommendation:

The Office of Clinical Pharmacology and Biopharmaceutics/Division of Pharmaceutical Evaluation II (OCPB/DPEII) has reviewed NDA 20-791, submitted on December 19, 1997, and the amendments submitted on February 14, November 3, November 19, and November 26, 1997. Based on the review of the pharmacokinetic and biopharmaceutics studies submitted, OCPB/DPEII finds this NDA acceptable. However, the reviewer has the following comments:

1. The proposed label is acceptable from the Clinical Pharmacology/Biopharmaceutics perspective, provided the following changes to the proposed labeling are incorporated:

In a teleconference on December 15, 1997, the sponsor accepted all the above changes.

2. The proposed *in vitro* release specifications are not acceptable, and will be discussed with the sponsor prior to the action date for NDA 20-791

3. The sponsor should submit a proposed protocol for the Phase IV, bioequivalence study to compare newly prepared systems with those that have been stored for 24 months (actual

time) in order to obtain a 24 month shelf-life for their product. The protocol should be submitted within 3 months of approval date and prior to the initiation of the study. The study's final report and data should be submitted within 1 year of approval date.

Comment 3 should be communicated to the sponsor as appropriate.

Sam H. Haidar, R.Ph., Ph.D.
Office of Clinical Pharmacology and Biopharmaceutics
Division of Pharmaceutical Evaluation II

RD initialed by K. Gary Barnette, Ph.D., Acting Team Leader KGB 12/8/97
FT signed by K. Gary Barnette, Ph.D., Acting Team Leader 12/17/97

cc:
NDA 20-791
HFD-870 (M. Chen, A. Dorantes, S. Haidar)
HFD-580 (T. Rumble, M. Hirsch)
CDR (Barbara Murphy For Drug)

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Attachments

Study Summary

Background:

Testosterone is the primary endogenous androgen secreted by the male testis. Endogenous androgens are responsible for the normal growth and development of the male sex organs and for the maintenance of secondary sexual characteristics. Testosterone is active intracellularly in tissues, such as muscles. It is also converted to the more potent dihydrotestosterone (DHT) by 5-α-reductase enzyme found in the skin and the prostate. Normal adult men produce about 4 to 9 mg of testosterone per day. The serum levels of testosterone fluctuate widely in a circadian fashion. The highest levels are usually observed in the morning (8 a.m.) while the lowest levels are usually observed in the evening (7 - 10 p.m.). Older men tend to have lower serum levels of testosterone and a less apparent circadian rhythm.

Alza's Testoderm™ TTS is a non-scrotal transdermal patch (60 cm^2) designed to deliver physiological amounts of testosterone when applied to the upper arm, back or upper buttocks. The proposed indication for Testoderm™ TTS is replacement therapy in males for conditions associated with a deficiency of endogenous testosterone: primary hypogonadism (congenital or acquired) and hypogonadotropic hypogonadism.

Formulation and Administration

Testoderm® TTS patch components and ingredients are listed below. A diagram of the patch and its components is outlined in Figure 1.

Table I. System components of Testoderm® TTS.

Backing	Transparent polyester/ethylene-vinyl acetate copolymer film
Drug reservoir	Testosterone USP (328 mg)
Enhancer	Alcohol USP (1.2 mL)
Adhesive (Controls rate of release)	Ethylene-vinyl acetate coated with polyisobutylene
Protective liner	Silicone-coated polyester

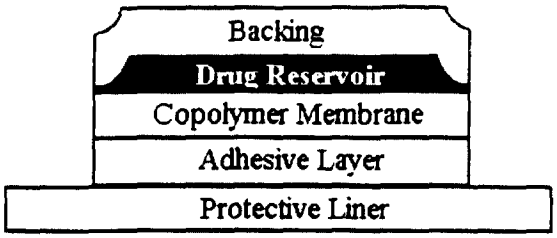


Figure 1. Schematic diagram of Testoderm™ TTS transdermal patch.

Reviewer Comment

1. The clinically tested formulation and the "to be marketed" formulation are the same and were manufactured at the same site.

In Vitro Drug Release

The *in vitro* release methodology and the proposed specifications for Testoderm TTS are presented in Table II. Table III provides *in vitro* release data for the clinically tested batches.

Table II. Proposed Drug Release Method and Release Rate Specifications.

Apparatus Type	USP Apparatus 7. Reciprocating Holder (cylinder option)	
Media		
Volume		
Shaker Frequency		
Sampling Times		
Dissolution Analytical Method		
Proposed Specifications*	**Time Intervals (hours)**	**Specification (mg/system)**
Cumulative amount of testosterone released per system over a time interval		
Release rate		mg/hr

* Specification values for the upper limit were obtained by taking the mean of the accelerated stability patches (fast release) and adding 15%, and for the lower limit by taking 85% of the mean of newly manufactured patches (slow release).

Table III. Clinically tested batches and their mean *in vitro* cumulative release (mg). All systems were 60 cm^2 and contained 328 mg of testosterone.

Control Number	Stability Study Number	Clinical Study Number	Batch Size (Systems)	Time (hour)			
				0 - 4	0 - 12	0 - 18	0 - 24
819395	SS1444	C-95-044 C-95-045 C-96-005 C-96-022 C-96-025 C-96-026					
864796	SS1577	C-96-048					

* These systems were part of stability study SS1444 and were stored at 40 °C/75% humidity for 5 months to simulate storage at room temperature for 24 months.

Reviewer Comments

1. The proposed *in vitro* dissolution method is acceptable.

2. The proposed release specifications are not acceptable. This recommendation was communicated to the sponsor in teleconferences held on November 13 and 21, 1997. Subsequently, the sponsor agreed to submit additional data and new specifications to support a shelf-life of 18 months.

3. *In vitro* testosterone release rate increases significantly with storage time, suggesting a possible stability problem.

4. *In vitro* dissolution data did not correlate with *in vivo* absorption data.

Analytical Methodology

Table IV. Testosterone assay validation.

	Nominal Testosterone Concentration (ng/dL)			
Intra-assay	**33.3**	**100**	**300**	**800**
Mean Precision (%CV) Accuracy (%)	36.2	107	350	810
Inter-assay				
Mean Precision (%CV) Accuracy (%)	35.6	110	317	843

Reviewer Comments

1. The analytical method and validation for the estimation of total testosterone concentrations in serum are acceptable.

2. Due to sample handling and assay irregularities, serum levels of DHT, free testosterone and estradiol were not acceptable for pharmacokinetic evaluation.

Pharmacokinetics:

Table V. Summary of clinical studies.

Study No.	Study Design	Dosage Form	Subjects
	Pivotal Pharmacokinetic Studies		
C-95-044	Open-label, placebo lead-in, three-treatment cross-over	Testoderm-TTS Testoderm®	
C-95-045	Open-label, randomized, three-treatment cross-over	Testoderm-TTS	
	Supportive Studies		
C-96-005	Open-label, randomized, two period, two-treatment cross-over (Wearing Acceptability)	Testoderm-TTS Androderm®	
C-96-022	Open-label (Skin irritation)	Testoderm-TTS	
C-96-025	Open-label, placebo controlled (Topical Safety)	Testoderm-TTS	
C-96-026	Open-label, placebo controlled (Topical Safety)	Testoderm-TTS	
C-96-048	Open-label (Accelerated release patches)	Testoderm-TTS	

The single dose and multiple dose pharmacokinetics of Testoderm® TTS patches were evaluated in study C-95-045. Thirteen hypogonadal men applied daily a single Testoderm®

TTS patch to the upper buttocks for five days. The pharmacokinetics of the patch were determined in each patient on Days 1 and 5 of the treatment. Comparison of the PK parameters after a single dose (Day 1) and multiple dosing (Day 5) showed that there was no accumulation with repeat dosing. Additionally, no significant differences in the PK parameters were observed. The PK parameters following a single dose and repeat dosing of Testoderm® TTS are listed in Table VI below.

Table VI. Mean (±SD) pharmacokinetic parameters for serum testosterone on Day 1 and Day 5 following application of Testoderm® TTS to Upper Buttocks.

Parameters	Day 1	Day 5
C_{max} (ng/dL)	**482** (149)	**473** (148)
*T_{max} (hr)	**3.9** (6.8)	**3.0** (5.5)
C_{min} (ng/dL)	**164** (104)	**189** (86)
*T_{min} (hr)	**0.0** (10)	**0.0** (7.2)
k (hr^{-1})	**0.52** (0.62)	**0.46** (0.36)
$t_{1/2}$ (hr)	**3.3** (2.4)	**2.3** (1.72)
AUC_{0-27} (ng.hr/dL)	**9560** (2651)	**8578** (2185)
AUC_{0-24} (ng.hr/dL)	**8712** (2323)	**7921** (1994)
Δ AUC_{0-27} (ng.hr/dL)	**4808** (2631)	**3826** (2528)
Δ AUC_{0-24} (ng.hr/dL)	**4488** (2318)	**3697** (2259)
C_{avg} (ng/dL)	N/A	**330** (83)
Δ C_{avg} (ng/dL)	N/A	**154** (94)

* Median values
Δ Baseline adjusted

Reviewer Comments

1. The study design was adequate to compare the pharmacokinetics of testosterone following single and multiple dose application of Testoderm® TTS to the upper buttocks.

2. Comparison of AUC_{0-24} on Day 1 and Day 5 after daily application of Testoderm® TTS patches to the upper buttocks showed that there was no accumulation of testosterone with repeat (daily) dosing.

Relative Bioavailability and Dose Calculation:

Study C-95-044 evaluated the bioavailability of Testoderm® TTS, a non-scrotal transdermal patch relative to Testoderm® (6mg/day), Alza's marketed scrotal patch. This study had a randomized cross-over design with a lead-in placebo. It was performed in hypogonadal men (N = 19). The results suggest greater bioavailability of Testoderm® TTS relative to

Testoderm® as reflected by the higher C_{max} and AUC values. Mean profiles for the different treatments are shown in Figure 2; the PK parameters are listed in Table VII below.

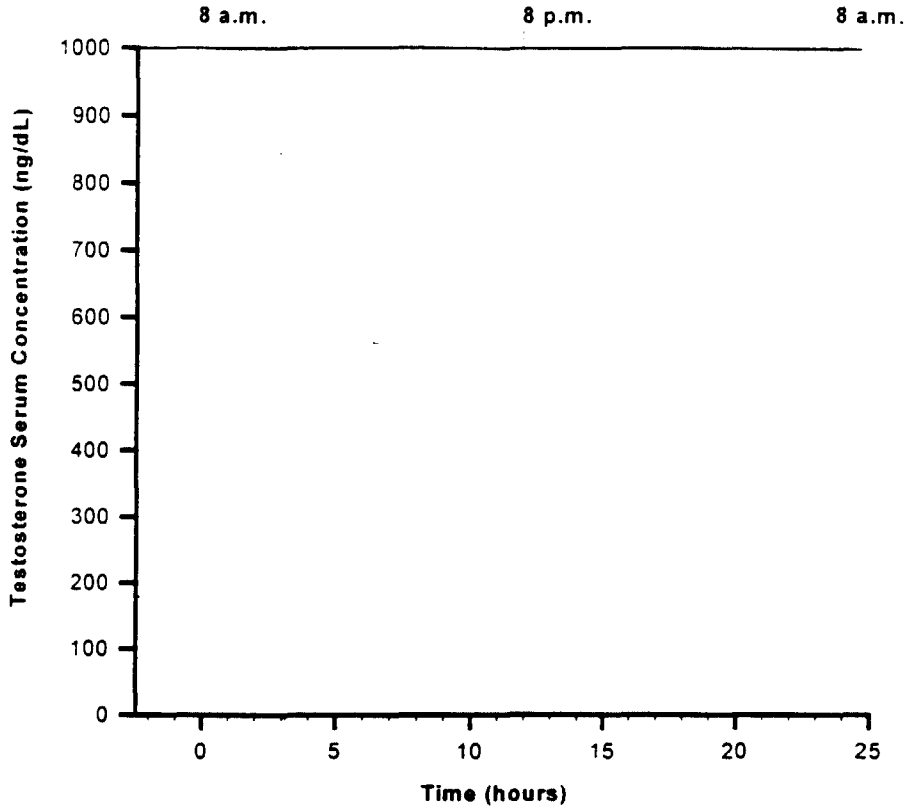


Figure 2. Mean (SD) steady state testosterone serum levels at baseline and following a single application of placebo (baseline), Testoderm (scrotal), and Testoderm TTS (non-scrotal) patch (over 24 hours).

Table VII. Mean (SD) pharmacokinetic parameters for serum testosterone concentrations after three treatments: Placebo, Testoderm® and Testoderm® TTS.

Parameter	Placebo	Testoderm® (Scrotal)	Testoderm®-II (Non-scrotal)
C_{max} (ng/dL)	**157** (172)	**403** (205)	**570** (225)
*T_{max} (hr)	**13.0**	**3.0**	**3.0**
C_{min} (ng/dL)	**51** (50)	**161** (112)	**201** (125)
*T_{min} (hr)	**4.0**	**13.1**	**0.0**
k (hr^{-1})	**N/A**	**0.68** (0.42)	**0.74** (0.72)
$t_{1/2}$ (hr)	**N/A**	**1.79** (1.26)	**1.62** (0.96)
AUC_{0-24} (ng·hr/dL)	**2,302** (2361)	**6,179** (3424)	**9,378** (3170)
C_{avg}(ng/dL)	**96** (98)	**257** (143)	**391** (132)
Δ AUC_{0-24} (ng·hr/dL)	**Ref.**	**3,877** (2948)	**7,075** (3653)
Δ C_{avg}(ng/dL)	**Ref.**	**162** (123)	**295** (152)

* median values; Δ baseline corrected.

Reviewer Comments

1. The study design was adequate to determine the bioavailability of Testoderm® TTS (non-scrotal, applied to the upper buttocks) relative to Testoderm (scrotal patch).

2. The sponsor estimated the dose (6mg/24hr) delivered for the Testoderm® TTS patches by taking the geometric mean of doses calculated using equation (1) below:

$$\text{Equation (1)} \qquad \text{Dose} = \frac{\Delta AUC_{\text{Testoderm - II}}}{\Delta AUC_{\text{Testoderm}}} \bullet \text{Dose}_{\text{Testoderm}}$$

The major problems identified with this approach are listed below:

   1) Testoderm® (scrotal) dose, was estimated by taking the difference between testosterone content of used systems and the mean testosterone system content of unused systems (residual method). The sponsor did not provide a correlation between the dose estimated by the residual method and an *in vivo* parameter, i.e., AUC. When this correlation was performed by the reviewer (dose vs. AUC), the correlation was less than adequate ($R^2 = 0.39$; Attachment B). The poor correlation casts uncertainty about the value of the estimated dose of Testoderm®; this in turn translates into uncertainty regarding the Testoderm® TTS dose.

   2) Equation (1) assumes the fraction of testosterone absorbed is the same regardless whether a scrotal or non-scrotal patch is applied. This assumption is unlikely to be true: scrotal skin is about five times more permeable to testosterone than non-scrotal skin, and there is a first pass effect in the scrotal skin. The result is more uncertainty regarding the estimated dose of testosterone delivered by the Testoderm® TTS system.

   3) The large variability in the testosterone dose delivered from the Testoderm® TTS systems suggests that the dose of 6 mg provided in the label is highly misleading. Comparison of the highest dose of Testoderm® TTS delivered (90.8 mg, subject) to the lowest dose (0.2 mg, subject results in a difference. The high variability could not be explained by the adherence scores.

3. The above concerns regarding the dose calculation method were communicated to sponsor in a teleconference on November 13, 1997. The sponsor then submitted an alternative method for dose calculation (Submission dated November 19, 1997). The new approach uses average testosterone clearance values obtained from previous studies with the Androderm® patch to estimate dose absorbed:

$$\text{Equation (2)} \qquad \text{Dose Absorbed} = CL^T * AUC^T$$

where CL^T is systemic clearance for testosterone, and AUC^T is the area under the curve for total testosterone levels, *uncorrected* for baseline. This method was applied to the two

pivotal pharmacokinetic studies (C-95-044 and C-95-045) and a mean dose of 5 mg 24 hours was obtained. The sponsor has agreed to change the product's package and labeling to reflect this new value for dose.

Dose Proportionality:

The dose proportionality between one (60 cm^2) and two (2 x 60 cm^2) Testoderm® TTS systems was evaluated in study C-95-044. Nineteen hypogonadal men applied to the upper buttocks one or two Testoderm® TTS systems in a randomized cross-over design following a lead-in placebo. Mean profiles for the various treatments are shown below (Figure 3).

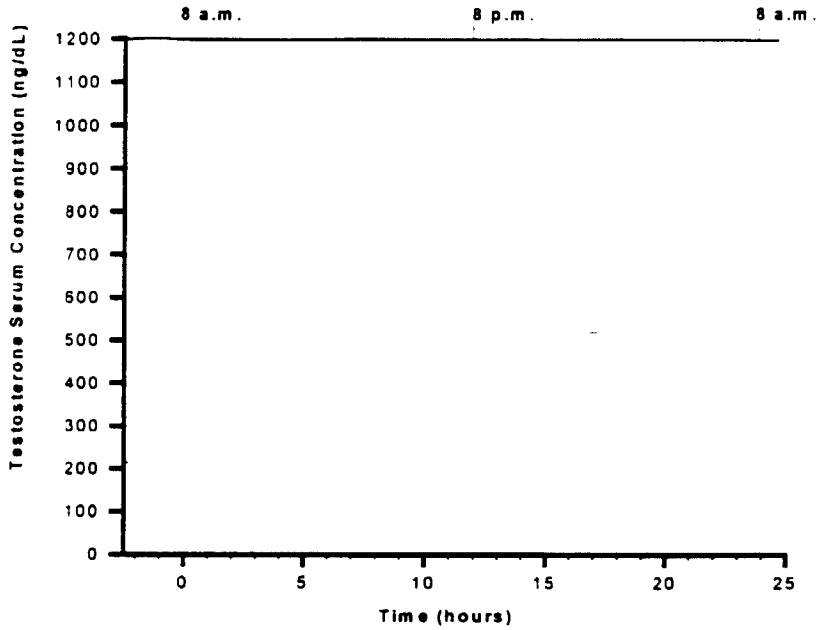


Figure 3. Mean (SD) testosterone serum levels at baseline and following a single application of Testoderm™ TTS, and 2 x Testoderm™ TTS.

Table VIII. Summary of pharmacokinetic parameters for serum testosterone concentrations after: Placebo, Testoderm® TTS, and 2 x Testoderm® TTS (N = 19).

Parameter	Placebo	Testoderm® TTS	2 x Testoderm® TTS
C_{max} (ng/dL)	**157** (172)	**570** (225)	**941** (382)
*T_{max} (hr)	**13.0**	**3.0**	**3.0**
C_{min} (ng/dL)	**51** (50)	**201** (125)	**326** (160)
k (hr^{-1})	**N/A**	**0.74** (0.72)	**0.50** (0.25)
$t_{1/2}$ (hr)	**N/A**	**1.62** (0.96)	**1.75** (0.98)
AUC_{0-24} (ng·hr/dL)	**2,302** (2361)	**9,378** (3170)	**14,003** (5721)
C_{avg} (ng/dL)	**96** (98)	**391** (132)	**583** (238)
Δ AUC_{0-24} (ng·hr/dL)	**Ref.**	**7,075** (3653)	**11,700** (6147)
Δ C_{avg} (ng/dL)	**Ref.**	**295** (152)	**488** (256)

* Median values; Δ baseline corrected.

Table IX. Statistical comparison of dose proportionality between Testoderm® TTS and 2 x Testoderm® TTS patches.

Parameter	Comparison	p-value	Ratio (%)
ΔAUC_{0-24}	*2 x Testoderm® TTS/ Testoderm® TTS	0.79	95.0

*Dose normalized

Reviewer Comments

1. The pharmacokinetics of one versus two Testoderm® TTS patches appear to be linear.

Anatomical Application Site:

Study C-95-045 compared the pharmacokinetics of Testoderm® TTS following application to the upper arm, back, or upper buttocks in 13 hypogonadal men in a randomized cross-over design. The results of the study are shown below.

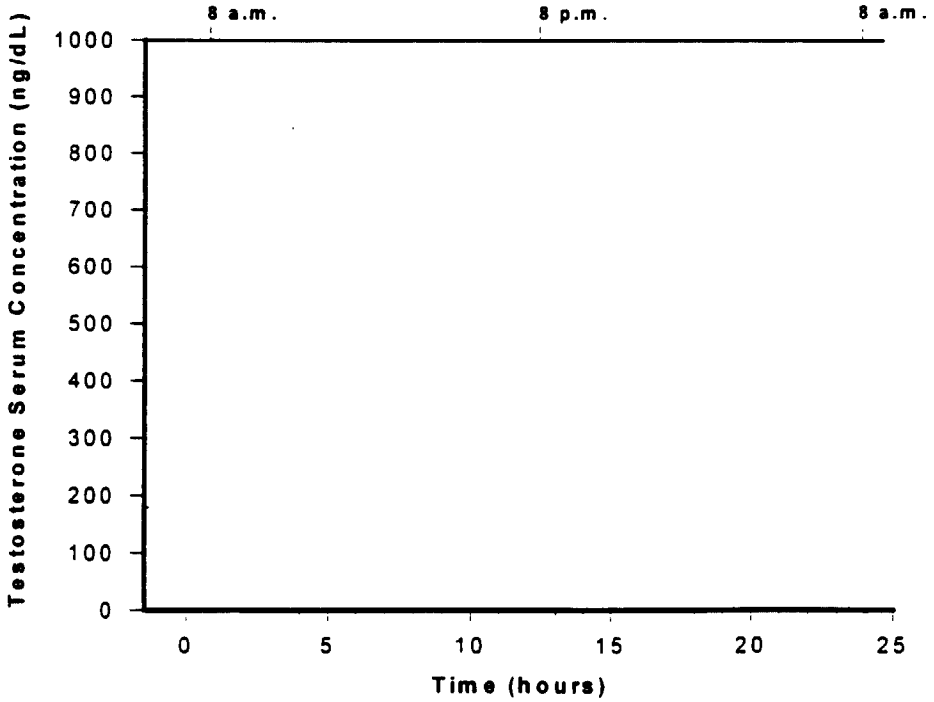


Figure 4. Mean (SD) testosterone serum levels at baseline and following a single application of Testoderm™ TTS to three different body sites (over 24 hours).

Table X. Mean (SD) of pharmacokinetic parameters for serum testosterone concentrations after a single dose application of Testoderm® TTS to different body sites.

Parameter	Baseline	Upper Buttocks	Upper Arm	Back
C_{max} (ng/dL)	**229** (145)	**482** (149)	**462** (150)	**499** (220)
$^{\bullet}T_{max}$ (hr)	**4.0**	**3.9**	**4.0**	**3.9**
C_{min} (ng/dL)	**129** (98)	**164** (104)	**135** (89)	**156** (116)
$^{\bullet}T_{min}$ (hr)	**17.0**	**4.3** (10.0)	**5.0** (10.1)	**5.7** (10.7)
k (hr^{-1})	**N/A**	**0.52** (0.62)	**0.52** (0.27)	**0.57** (0.58)
$t_{1/2}$ (hr)	**N/A**	**3.3** (2.40)	**2.07** (1.42)	**2.73** (2.01)
AUC_{0-27} (ng.hr/dL)	**4,752** (3207)	**9,560** (2651)	**8,651** (2962)	**8,988** (3616)
C_{avg}	**176** (119)	N/A	N/A	N/A
Δ AUC_{0-27} (ng.hr/dL)	**Ref.**	**4,808** (2631)	**3,899** (2453)	**4,236** (3572)

$^{\bullet}$ Median value
Δ Difference from baseline

Table XI. Statistical analysis of pharmacokinetic parameters for (natural) log transformed serum testosterone following administration of Testoderm® TTS to three different body sites.

Parameter	Contrast	Ratio (%)	p Value	Power	Lower (90% C.I)	Upper (90% C.I)
AUC_{0-27} (ng.hr/dL)	Arm/Buttocks	87.8	0.067	88.8		
	Back/Buttocks	89.9	0.127	88.8		
	Arm/Back	97.7	0.723	88.8		
C_{max} (ng/dL)	Arm/Buttocks	94.9	0.512	76.6		
	Back/Buttocks	100.5	0.947	76.6		
	Arm/Back	94.4	0.472	76.6		
ΔAUC (ng.hr/dL)	Arm/Buttocks	82.0	0.401	14.8		
	Back/Buttocks	83.6	0.473	13.6		
	Arm/Back	98.1	0.939	13.6		

Δ Baseline corrected.

A cross-study (C-95-044, C-95-045 and C-96-048) analysis was performed to determine the influence of different covariates on serum testosterone C_{avg}. It was determined that the inverse of body weight had the most significant effect (in terms of R^2). The results of the regression analysis are listed in Table XII below.

Table XII. The contribution of different covariates to the variability of serum testosterone C_{avg} following Testoderm® TTS treatment for studies C-95-044, C-95-045 and C-96-048 (n = 40).

Covariate	R^2	Slope (SE)	p-value
Inverse of Body Weight	0.323	37700 (8900)	<0.001
Lean Body Mass	0.298	-7.89 (1.96)	<0.001
Total Body Water	0.298	-10.79 (2.68)	<0.001
Body Surface Area	0.288	-0.0189 (0.0048)	<0.001
Body Weight	0.274	-3.90 (1.03)	<0.001
Body Mass Index	0.230	-12.6 (3.7)	0.002
Fat	0.195	-3.97 (1.30)	0.004
Age	0.081	2.75 (1.51)	0.076
Height	0.077	-6.45 (3.62)	0.083
Ideal Body Weight	0.077	-6.01 (3.38)	0.083
Lean Body Mass	0.076	-8.75 (4.94)	0.085
Ethnic Origin	0.013	-	-

Reviewer Comments:

1. Bioequivalence was demonstrated for Back/Buttocks and Arm/Back; Arm/Buttocks failed in terms of extent of absorption, but passed on the rate of absorption between the two sites. The reviewing medical officer of HFD-580, Dr. Mark Hirsch, however, judged the difference in the extent of absorption between the arm and buttocks not clinically significant.

2. Following an audit by the Division of Scientific Investigations, it was recommended that data from Subject should not be used for calculating pharmacokinetic parameters. It was discovered that Subject violated the inclusion criteria because his last testosterone injection occurred 4 weeks prior to the start of the study instead of the required six weeks. Recalculation of the mean AUC's for the Arm treatment showed that including or excluding data from Subject did not have a statistically significant effect on the mean AUC (See Attachment C). Therefore, it was decided to utilize the data generated for this subject.

3. The Division of Scientific Investigations also recommended against using free testosterone, estradiol and dihydrotestosterone (DHT) levels generated by this study for pharmacokinetic analysis because of improper sample handling and assay procedures. The free testosterone, estradiol and DHT levels, however, were adequate for diagnostic or efficacy evaluations. The DHT levels following application of Testoderm® TTS were in the normal range.

4. Linear regression of the relationship of different covariates on serum testosterone C_{avg} determined that covariates which contained a weight component (covariates 1 - 6 in Table

XII) produced regression lines with slopes significantly different from zero, using an alpha of 0.05. Information regarding the effect of weight on serum testosterone C_{avg} was not included in the labeling.

Stability:

The sponsor reported that testosterone *in vitro* release from Testoderm® TTS increased as a function of storage time (See Figure 5 below). The cumulative amount released from freshly produced Testoderm® TTS patches between 0 to 4 hours was 2.59 mg, compared with 7.38 mg for patches stored at 40 °C/75% humidity (simulating storage for 24 months at room temperature). Study C-96-048 was performed to see if a faster *in vitro* release rate lead to greater *in vivo* absorption. In the above study, eight hypogonadal men applied daily a single faster release patch over four days. The pharmacokinetics of aged (fast release) patches were determined in each patient on day 4 of the study. The results of the study are shown below.

To evaluate the bioequivalence between fresh and aged systems, a statistical comparison using ANOVA and 90% confidence intervals, of fresh and aged systems was performed by Karen Higgins (OEB/QRMS) , at the request of this reviewer (Attachment D). The results are shown in Table XIV. It should be noted, however, that the results are inconclusive because the data came from different studies and the power is not appropriate.

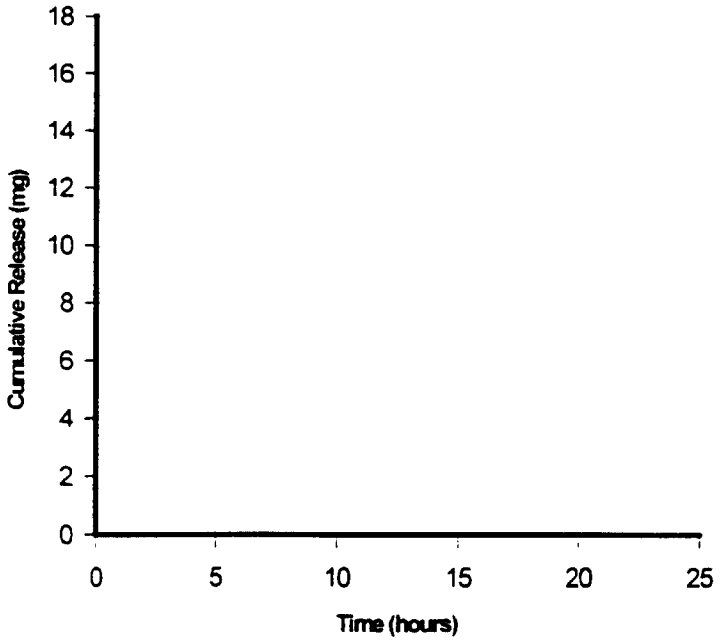


Figure 5. ***In vitro*** **cumulative release for freshly produced patches (SS1444) and aged patches from a stability study, 5 months at 40 °C and 75% humidity, simulating 24 months storage at room temperature (SS 1577).**

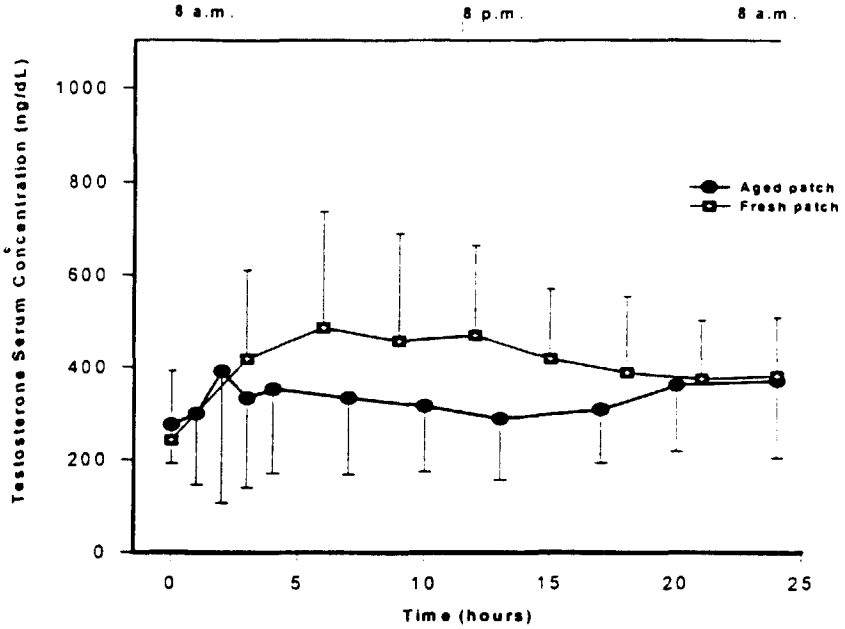


Figure 6. Mean testosterone concentration over 24 hours following application of slow release, fresh patch (SS 1444, n = 19), and a fast release, aged patch (SS 1577, n = 8).

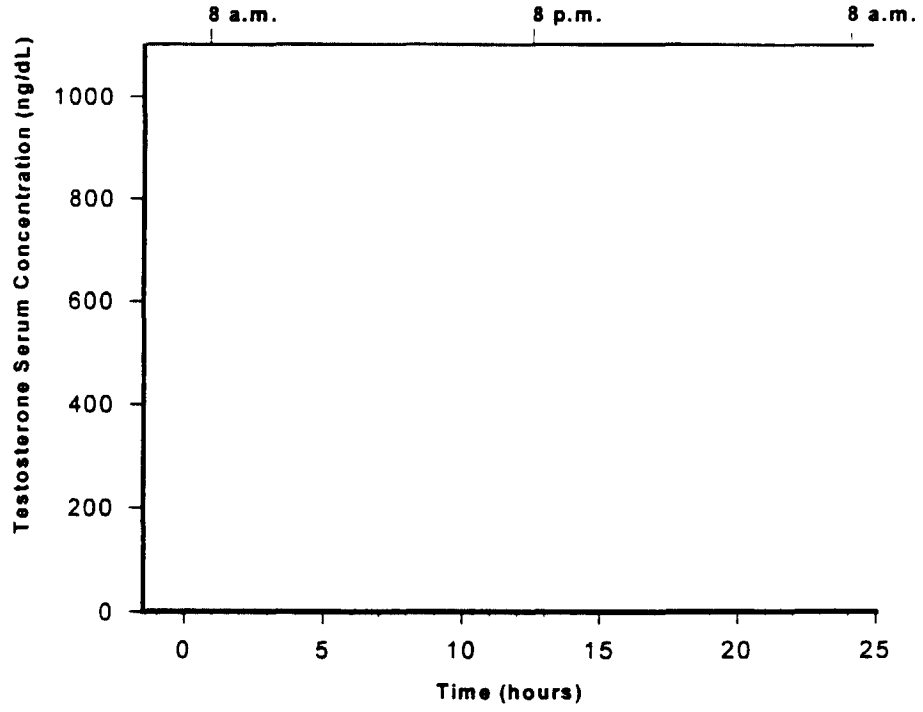


Figure 7. Individual serum testosterone concentration profiles (N = 8) following application of a single fast release Testoderm™ TTS on Day 4 of treatment (Study C-96-048).

Table XIII. Mean (SD) pharmacokinetic parameters from studies C-95-044 (fresh patches) and C-96-048 (aged patches).

Study	C_{max} (ng/dL)	C_{min} (ng/dL)	C_{avg} (ng/dL)	AUC_{0-24} (ng•hr/dL)
C-95-044 (N = 19)	**570** (225)	**201** (125)	**391** (132)	**9378** (3170)
C-96-048 (N = 8)	**452** (242)	**262** (132)	**331** (148)	**7933** (3552)

Table XIV. Statistical analysis of pharmacokinetic parameters for (natural) log transformed serum testosterone following administration of freshly produced Testoderm® TTS patches (C-95-044) aged patches (C-96-048).

Parameter	Contrast	p Value	Lower (90% C.I)	Upper (90% C.I)
AUC (ng.hr/dL)	C-96-048/ C-95-044	0.29		
C_{max} (ng/dL)	C-96-048/ C-95-044	0.21		

Reviewer Comments:

1. Examination of individual testosterone levels versus time profiles (Figure 7) showed that five of the eight patients had levels lower than or borderline with the normal lower physiological level for testosterone. This suggested a lower bioavailability for the accelerated release patches.

2. Bioequivalence testing of C_{max} and AUC values for studies C-96-048 and C-95-044 showed the two patches to be bioinequivalent (Table XIV above). It should be noted that the data came from different studies and Study C-96-048, N = 8, is not powered for bioequivalence testing. Nevertheless, the results indicate a tendency for lower bioavailability in the fast release patches.

3. The sponsor used the results of this study to justify a two year shelf-life for Testoderm® TTS, suggesting there was no difference in the pharmacokinetic parameters obtained using the fast release patch and freshly produced patches with slower *in vitro* release rates. However, it was concluded that due to the small sample size in study C-96-048 and the possibility for lower bioavailability, the results of this study do not support a two-year shelf-life. In a teleconference on November 21, 1997, the sponsor agreed to perform an adequate bioequivalence study, as a Phase IV commitment, to support a two-year shelf-life.

Attachment A

NDA 20-791

Audit Report: Division of Scientific Investigations

MEMORANDUM

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

DATE: August 21, 1997

FROM: Heather S. Forusz, Ph.D.
Pharmacologist
Division of Scientific Investigations (HFD-345)

Jacqueline A. O'Shaughnessy, Ph.D.
Pharmacologist
Division of Scientific Investigations (HFD-345)

and

Michael F. Skelly, Ph.D.
Pharmacologist
Division of Scientific Investigations (HFD-345)

THROUGH: C.T. Viswanathan, Ph.D. MF Skelly for
Associate Director
Division of Scientific Investigations (HFD-345)

SUBJECT: Review of an EIR Covering NDA 20-791, Testoderm II (Testosterone Transdermal System)
Sponsored by Alza Corporation, Palo Alto, CA

TO: Lisa D. Rarick, M.D.
Director
Division of Reproductive and Urologic Drug Products
(HFD-580)

As requested by HFD-580, the Division of Scientific Investigations initiated an audit of the following bioequivalence studies:

C-95-044: Bioavailability of a New Transdermal Therapeutic System of Testosterone Relative to Testoderm®

C-95-045: Pharmacokinetic Evaluation of Testoderm II Comparison of Site of Application and First and Fifth Day of Application

Study C-95-044 compared the kinetics of testosterone and its metabolites following Testoderm® applied to the scrotum, Testoderm II applied to the upper buttock, and 2 x Testoderm II applied to the upper buttock. Study C-95-045 compared the

kinetics of testosterone and its metabolites following Testoderm II applied to the back, upper arm, and upper buttock.

The clinical portions of study C-95-044 were conducted at:

..

The clinical portions of study C-95-045 were conducted at:

The analytical portions of both studies were performed by

Study C-95-044

Following the inspection, Form 483 was issued at the
No Form 483 was issued at
The inspectional findings at the
are summarized below:

1. **There were no documents to show how the six subjects' serum samples were handled, stored, and disposed of.**

2. **Lack of freezer temperature records for storing the above serum samples.**

The conditions of sample storage could not be verified. Some duplicate samples were stored at this location for 5 to 7 additional weeks before shipping to the analytical laboratory.

Additional findings included: failure to document nurses' training; the occasional lack of signatures or initials; failure to document some IRB approvals of protocol amendments; and minor unclear statements in the consent form. While these items are objectionable and need to be corrected, they are unlikely to have influenced the outcome of the study.

Study C-95-045

Following the inspections, Form 483 was issued at the

The inspectional findings at the
are summarized below:

1. **Failure to meet the inclusion criteria for subjects with respect to documentation of serum testosterone level.**

Documentation of prestudy serum testosterone levels was not available during the inspection; the clinical investigator subsequently provided data for both subjects from an earlier Alza-sponsored study. This documentation showed that subjects met the inclusion criterion for history of testosterone deficiency.

2. **The actual number of patches worn by the patients could not be verified due to the following:**

   a. **No documentation for patches worn during the outpatient portion of treatment B.**

   b. **Failure to document the number of patches used.**

3. **Failure to maintain the original dispensing record on site.**

4. **Failure to document the return of used and unused Testoderm II patches to the Sponsor.**

During the outpatient phase of treatment B (Testoderm II applied to the upper buttocks), subjects were responsible for applying and removing the patches. Upon their return to the clinic, the investigator failed to document that the subjects actually wore the patches. No record documented the return of used and unused patches to the sponsor. Therefore, the correct dosing of subjects could not be verified during the treatment B comparison of pharmacokinetic parameters after the first and fifth day of application.

5. **Failure to maintain temperature and inventory logs for the freezer storage of serum samples.**

The conditions of sample storage could not be verified.

Additional inspectional findings included minor inconsistencies between raw data and case report forms, and failure to consistently record the date of blood draw and patient identification on the nurses' notes. While these items are objectionable and need to be corrected, they are unlikely to have affected the study outcome.

The inspectional findings at the
are summarized below:

1. A comparison of clinic records and case report forms (CRF) for all eight study subjects revealed that test article application dates and times recorded on the case report forms were not consistently supported by data in the clinic records.

In eight instances the application times were written directly on the CRFs and not in the subjects' clinical records. This is unlikely to have affected the outcome of the study.

2. Subject - The subject's CRF indicates that his last testosterone injection was on 1/18/96. His medical record indicates that he was given an injection of testosterone on 2/8/96. The subject began participation in the study on 3/6/96. The protocol requires that the last testosterone injection be 6 weeks prior to participation in the study.

The protocol inclusion criteria required that for subjects "currently [using] other androgen therapeutic regimens ... must discontinue therapy prior to study initiation as follows: testosterone enanthate or cypionate injections, six weeks." This subject's medical record states that he received a 2 cc (400 mg) deep muscular testosterone injection, but does not mention whether a long-acting ester was used. We are unaware of testosterone formulations at 200 mg/cc, other than the long-acting enanthate and cypionate esters, being available commercially. The subject's baseline testosterone value on 3/6/96 was 245 ng/dL, meeting the inclusion criterion of being below 300 ng/dL; however we recommend that data from this subject should be excluded from analysis.

Following the inspection of the analytical portion of both studies at a Form 483 was issued. The inspectional findings are summarized below:

1. The estradiol assay validation was incomplete in that:

a. Charcoal-treated and lyophilized serum fractions were used for both calibration standards and quality control (QC) specimens. It was not demonstrated that these were equivalent to frozen serum for evaluations of accuracy, specificity, sensitivity, and precision.

b. Documentation of the assay procedure that was used during validation was not available for inspection.

c. reports ("Total counts") during six runs of the assay validation were inconsistent as to whether the was always diluted

* The estradiol assay validation did not demonstrate accuracy, precision, specificity, sensitivity, or stability during storage, and lacked proper quality controls. We recommend that the estradiol data from both studies should not be accepted.

2. The stability of the four analytes (total testosterone, free testosterone, dihydrotestosterone, and estradiol) in serum during frozen storage or through freezing and thawing was not demonstrated. Stability of extracts for reassay of total testosterone and dihydrotestosterone was not demonstrated.

   a. The locations and conditions of storage of serum samples (Projects 807-141 and 807-142) or of serum extracts (Projects 807-141, Runs 44A-26, 44A-28, 44A-33, and 44A-34) were not recorded.

   b. During assay validation, none of the four analytes was demonstrated to be stable during storage or during freezing and thawing.

   c. Stability during storage and freeze/thaw cycles was not demonstrated by documented concurrent storage of quality control specimens prepared in similar matrix.

The stability of these analytes during storage was not demonstrated by these alternative strategies (items a and b, , or c), and the conditions of sample storage at some of the clinical sites were not documented. However, according to published literature, total testosterone and dihydrotestosterone (DHT) concentrations are usually very stable during frozen storage and through freezing and thawing. It is therefore likely that the total testosterone and DHT were stable during the present studies and we recommend that the data for total testosterone should be accepted.

The stability of free testosterone concentrations and sex hormone binding globulin are not well supported by the literature. Due to the lack of records of the location, temperature, and number of freeze/thaw cycles for each serum sample, and lack of control samples, the concentrations of free testosterone and the percentage bound to protein cannot be ascertained with confidence.

3. **The accuracy and sensitivity of the free testosterone assay were not demonstrated in that nominal concentrations of free testosterone in the quality control specimens provided by the manufacturer were not determined by an independent methodology, but by**

Without independent verification of the QC concentrations, the accuracy of the assay for free testosterone cannot be verified. We recommend the accuracy of the free testosterone assay should not be regarded as having been validated.

4. **The accuracy and sensitivity of the testosterone and dihydrotestosterone assays were not demonstrated in that the purity of the testosterone reference material had not been determined more recently than 3/18/86, before use on 1/14/94, and the purity of the dihydrotestosterone reference material had not been determined.**

Testosterone in the pure form is generally stable, therefore it is likely that the testosterone reference material had adequate purity for this use. No information was available on the purity of the DHT reference material, therefore the reported concentrations of DHT and the ratios of DHT to testosterone cannot be verified.

5. **Dihydrotestosterone assays runs were accepted even though they failed predetermined acceptance/rejection criteria (Project 807-141, Runs 44A-007R, 44A-013, and 44A-035; Project 807-142, Run 45A-008). For example, in Runs 44A-007R and 45A-008, both "High Control" specimens failed, but the runs were accepted.**

We recommend that the data from these runs should not be accepted. Samples assayed in these runs are listed below:

Subject	Treatment	Sample Number	Run Number
	C	62327	35
	D	41339, 43715, 70292	13
	B	69979, 35291*, 72443	13 and 35*
	D	45155, 61210, 47586	7R
	B	33130	7R
	D	42176, 46172	13

	B	55307	35
	D	61823, 62291	7R
	C	56036	35
	B	39873, 61940, 42905	8
	B	33158, 62462, 59899	8

Conclusions:

We recommend that the total testosterone data from these studies, except for subject ___ should be accepted for your review. We recommend that free testosterone and dihydrotestosterone data should not be used for pharmacokinetic purposes; however, these data may be adequate for diagnostic (efficacy) evaluations. We recommend that the estradiol data from these studies should not be accepted for your review.

After you have reviewed this transmittal memo, please append it to the original NDA submission.

Heather S. Forusz, Ph.D.

Jacqueline A. O'Shaughnessy, Ph.D.

Michael F. Skelly, Ph.D.

cc:
HFA-224
HFD-340 Lepay
HFD-341 CF/RF
HFD-345 Viswanathan
HFD-580 Rumble
HFD-870 Dorantes/Haidar
HFR-MA150 Rashti
HFR-MA250 Rose/Gion
HFR-PA3540 Mattson
HFR-SW450 Ausfahl
HFR-SW1540 Robinson
Class: NAI(San Antonio Regional Hospital)
NAI(Bethesda Hospital)
VAI(University of Pennsylvania)
VAI(Oregon Health Sciences University)
VAI(Maryland Regional Impotence Center)
VAI(Covance)
Draft:HSF:7/18/97
Edited:MFS:8/19/97
File:5144;O:\BE\20791alz.tes

Attachment B

NDA 20-791

Correlation Between AUC and Dose of Testoderm®

(Scrotal Patch) Estimated by Residual Analysis

Correlation between Dose and AUC for Testoderm patch.

AUC (ng*hr/dL)	Dose (mg)
3290	3.2
162	1.5
2828	3.5
4385	2.4
1218	3.2
5322	3.7
9401	1.9
5888	3.2
6216	6
113	1.4
728	2.3
2330	1.8
6763	4.8
1043	1.7
5560	4.5
6188	4.6
8766	5.6
3679	1.8

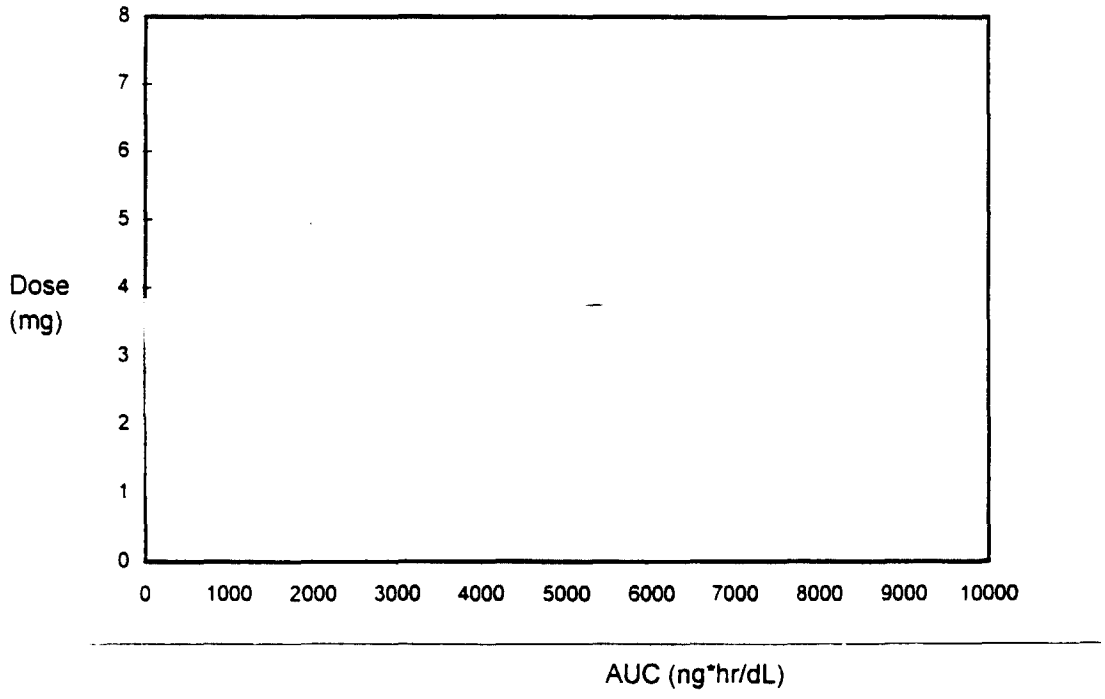
SUMMARY OUTPUT

Regression Statistics	
Multiple R	0.624587
R Square	0.390109
Adjusted R Square	0.35199
Standard Error	1.164516
Observations	18

ANOVA

	df	*SS*	*MS*	*F*	*Significance F*
Regression	1	13.87855	13.8785	10.2342	0.0056
Residual	16	21.69757	1.3561		
Total	17	35.57611			

	Coefficient	*andard Err*	*t Stat*	*P-value*	*Lower 95%*	*pper 95*
Intercept	1.873946	0.489933	3.824904	0.00149	0.835335132	2.912557
X Variable 1	0.000316	9.89E-05	3.19909	0.00559	0.000106704	0.000526



Attachment C

NDA 20-791

Comparison of Mean AUC Values With and

Without Subject

Study C-95-045 (Arm Treatment)

NDA 20-791
Sponsor: Alza Corporation

Study C-95-045
Arm Treatment

	Subject included		Subject not included	
	Subject	**AUC**	**Subject**	**AUC**
		5364		5364
		5314		5314
		10334		10334
		4001		4001
		6147		6147
		11747		11747
		14175		14175
		9411		9411
		9525		9525
		9003		9003
		7092		
		11581		11581
		9116		9116
Average		**8678**		**8810**
S.D.		**2964**		**3056**
C.V.(%)		**34**		**34**

t-Test: Two-Sample Assuming Equal Variances

	Variable 1	*Variable 2*
Mean	8677.692	8809.83
Variance	8787705	9338955
Observations	13	12
Pooled Variance	9051346	
Hypothesized Mean Difference	0	
df	23	
t Stat	-0.10972	
P(T<=t) one-tail	0.456793	
t Critical one-tail	1.71387	
***P(T<=t) two-tail**	**0.913586**	
t Critical two-tail	2.068655	

*** No significant difference whether or not subject is included in the analysis.**

Attachment D

NDA 20-791

Evaluation of Bioequivalence Between C-95-044 (Slow release patches)

And C-96-048 (fast release patches)

Analysis Performed by Karen Higgins (OEB/QMRS)

NDA 20-791
Testoderm-II, Transdermal Testosterone System
ALZA Corporation

AUC, analysis on log transformed variable

```
Two sample T for lauc048 vs lauc044
          N      Mean     StDev   SE Mean
lauc048   8     8.903     0.405      0.14
lauc044  19     9.087     0.363     0.083

90% CI for mu lauc048 - mu lauc044: ( -0.48,  0.112)
T-Test mu lauc048 = mu lauc044 (vs not =): T= -1.12  P=0.29  DF=  11

90% confidence interval of AUC 048 - AUC 044: (.62, 1.12)
```

Cmax, analysis on log transformed variable

```
Two sample T for lcmax048 vs lcmax044
           N      Mean     StDev   SE Mean
lcmax048   8     6.008     0.472      0.17
lcmax044  19     6.265     0.432     0.099

90% CI for mu lcmax048 - mu lcmax044: ( -0.60,  0.089)
T-Test mu lcmax048 = mu lcmax044 (vs not =): T= -1.32  P=0.21  DF=  12

90% confidence interval of Cmax 048 - Cmax 044:(.55, 1.09)
```

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pages of trade

secret and/or

confidential

commercial

information

Attachment F

NDA 20-791

Review of Individual Studies

Study No.: C-95-044

Study Title:
Bioavailability of a New Testosterone Transdermal Therapeutic System Relative to Testoderm®

Objectives:

- Estimate the bioavailability of Testoderm®-II (applied to the upper buttocks) using data from Testoderm® Testosterone Transdermal System (applied to the scrotum) as the reference.
- Evaluate the dose relationship of one (60 cm^2) and two (2 x 60 cm^2) Testoderm® -II systems (applied to the upper buttocks).
- Evaluate topical effects of Testoderm® II.

Study Design:

This study was a randomized, open label, four-period, crossover design with a lead-in placebo treatment followed by three active transdermal testosterone treatments that lasted 1 week each. Baseline hormone measurements were obtained from all patients during the placebo treatment period.

Treatments:

Treatment A: placebo transdermal system 60 cm^2, containing no drug, worn on the scrotum (1 day)

Treatment B: Testoderm® 60 cm^2, containing 15 mg testosterone with a nominal delivery of 6mg/day, worn on the scrotum (7 days)

Treatment C: Testoderm®-II 60 cm^2 containing 328 mg testosterone with a nominal delivery of 4 to 7 mg/day, worn on the upper buttocks (7 days)

Treatment D: Two Testoderm®-II 60 cm^2, each containing 328 mg testosterone with a nominal delivery of 4 to 7 mg/day/system (8 to 14 mg total), worn on the upper buttocks (7 days)

Twenty-two hypogonadal male patients (age range: years) were enrolled. 19 subjects completed the study.

Blood Sampling:

Blood samples were collected immediately prior to system application (hour 0) and at 1, 2, 3, 4, 7, 10, 13, 17, 20, 24 hours (system removed), and at 24.5, 25, and 27 hours.

Serum testosterone (total), DHT, free testosterone and estradiol concentrations were measured by

Pharmacokinetic Analysis:

Non-compartmental analysis was performed on testosterone serum concentrations to estimate C_{max}, C_{avg}, T_{max}, C_{min}, T_{min}, AUC_{0-24}, AUC_{0-27} and apparent $t_{1/2}$. Testosterone AUC values were determined by the linear trapezoidal method. According to the sponsor, the change in AUC_{0-24} testosterone values was calculated as the difference between the values at baseline and after active treatments. The average concentration (C_{avg}) was defined by $AUC_{0-24}/24$. The terminal half-life ($t_{1/2}$) was calculated using 0.693/k; k, which is the elimination rate constant, was estimated using linear regression of the log (natural) transformed, baseline corrected testosterone serum levels during the log linear terminal phase after system removal.

Testoderm®-II dose was calculated using the following equation:

$$\text{Dose} = \frac{\Delta AUC_{\text{Testoderm - II}}}{\Delta AUC_{\text{Testoderm}}} \bullet \text{Dose}_{\text{Testoderm}} \qquad (1)$$

where ΔAUC represents baseline-corrected AUC for the respective patches and Dose is the amount of testosterone delivered from Testoderm-II over 24 hours.

Free testosterone, DHT, and estradiol concentrations were calculated and compared to normal ranges.

Statistical Analysis:

Testosterone pharmacokinetic parameters, as well as the ratio of testosterone to DHT, for placebo and the three treatments were examined using analysis of variance (ANOVA). The variance model included period, patient within sequence, and treatment effect.

According to the sponsor, the log-transformed, normalized (by surface area) ΔAUC_{0-24} of testosterone for Testoderm®-II and 2 x Testoderm®-II was used to examine the dose proportionality by ANOVA.

Results:

Table V. Summary of pharmacokinetic parameters for serum testosterone concentrations after the four treatments: Placebo, Testoderm®, Testoderm®-II, and 2 x Testoderm®-II (N = 19).

Parameter	Placebo	Testoderm® (Scrotal)	Testoderm®-II (Non-scrotal)	2 x Testoderm®-II (Non-scrotal)
C_{max} (ng/dL)	157	403	570	941
*T_{max} (hr)	13.0	3.0	3.0	3.0
C_{min} (ng/dL)	51	161	201	326
*T_{min} (hr)	4.0	13.1	0.0	0.0
k (hr^{-1})	N/A	0.68	0.74	0.50
$t_{1/2}$ (hr)	N/A	1.79	1.62	1.75
AUC_{0-27} (ng·hr/dL)	2,302	6,179	9,378	14,003
C_{avg}(ng/dL)	96	257	391	583
Δ AUC_{0-27} (ng·hr/dL)	Ref.	3,877	7,075	11,700
Δ C_{avg}(ng/dL)	Ref.	162	295	488

*Median values.

Table VI. Dose proportionality between Testoderm®-II and 2 x Testoderm®-II patches.

Parameter	Comparison	p-value	Ratio (%)
Log ΔAUC_{0-24}	*2 x Testoderm®-II/ Testoderm®-II	0.79	95.0

*Dose normalized

Reviewer Comments:

1. The study design was adequate to determine the bioavailability of Testoderm®-II (non-scrotal) relative to Testoderm (scrotal patch) and the dose relationship of one (60 cm^2) and two (2 x 60 cm^2) Testoderm®-II systems (applied to the upper buttocks).

2. The sponsor estimated the dose (6mg/24hr) delivered for the Testoderm-II patches by taking the geometric mean of doses calculated using equation (1) above. The major problems identified with this approach are listed below:

1) Testoderm® (scrotal) dose, estimated by taking the difference between testosterone content of used systems and the mean testosterone system content of unused systems (residual method). The sponsor did not provide a correlation between the dose estimated by the residual method and an *in vivo* parameter, i.e., AUC. When this correlation was performed by the reviewer (dose vs. AUC), the correlation was less than adequate (R^2 = 0.39). The poor correlation casts uncertainty about the value of the estimated dose of Testoderm®; this in turn translates into uncertainty regarding the Testoderm®-II dose.

2) Inherent in equation (1) are two assumptions which the sponsor did not provide: first, F, or fraction absorbed, is the same between the scrotal and non-scrotal patches; and second, testosterone clearance is the same. The first assumption is unlikely to be true: scrotal skin is about five times more permeable to testosterone than non-scrotal skin, and there is a first pass effect in the scrotal skin; the second assumption may or may not be true, given that testosterone is metabolized differently in the scrotal skin as reflected by the higher DHT levels. The result is more uncertainty regarding the estimated dose of testosterone delivered by the Testoderm®-II system.

3) The large variability in the testosterone dose delivered from the Testoderm®-II systems suggests that the dose of 6 mg provided in the label is highly misleading. Comparison of the highest dose of Testoderm®-II delivered (90.8 mg, subject to the lowest dose (0.2 mg, subject results in a difference. The high variability could not be explained by the adherence scores.

3. The above concerns regarding the dose calculation method were communicated to sponsor in a teleconference on November 13, 1997. The sponsor then submitted an alternative method for dose calculation (Submission dated November 19, 1997). The new approach uses average testosterone clearance values obtained from previous studies with the Androderm® patch to estimate dose absorbed:

$$\text{Dose Absorbed} = CL^T * AUC^T \qquad (2)$$

where CL^T is systemic clearance for testosterone, and AUC^T is the area under the curve for total testosterone levels, *uncorrected* for baseline. This method was applied to the two pivotal pharmacokinetic studies (C-95-044 and C-95-045) and a mean dose of 5 mg/24 hours was obtained. The sponsor has agreed to change the package and labeling to reflect this new value for dose.

Study No. : C-95-045

Study Title:

Pharmacokinetic Evaluation of Testoderm® -II: Comparison of Site of Application and First and Fifth Day of Application.

Objectives:

- Determine the pharmacokinetics of testosterone concentrations resulting from Testoderm®-II application to the upper buttocks, upper arm, and back
- Compare testosterone serum concentrations with and without Testoderm®-II application
- Compare pharmacokinetic parameters of testosterone on the first and fifth days of application
- Evaluate topical safety.

Study Design:

This was a four-treatment, open-label, baseline lead-in, followed by a randomized three-treatment crossover design. The study was carried out in healthy, hypogonadal volunteers (N = 13).

The treatments were as follows:

A. Baseline (no system application) blood sampling was done periodically (at the same time intervals as for other treatments) for the entire 24 hours of the first day of the study.
B. Testoderm®-II, 60 cm^2, containing 328 mg testosterone with a nominal delivery of 4-7 mg/day, was applied to the upper buttocks and worn 24 hours. After a 2-day drug washout, daily applications were repeated for 5 days.
C. Testoderm®-II, 60 cm^2, containing 328 mg testosterone with a nominal delivery of 4-7 mg/day, was applied to the upper arm and worn 24 hours.
D. Testoderm®-II, 60 cm^2, containing 328 mg testosterone with a nominal delivery of 4-7 mg/day, was applied to the back and worn 24 hours.

Adhesion was assessed according to the following scale:

0 = System adhered to at least 90% of the area and no edges detached
1 = System between 75 and 90% adhered
2= System between 50 and 75 % adhered
3 = System less than 50% adhered or system no longer adhered to skin

Blood Sampling and Analysis : (hours)

Baseline: 0 (8:00 a.m.), 1, 2, 3, 4, 7, 10, 13, 17, 20, 24.

Treatment B, day 1: 0, 1, 2, 3, 4, 7, 10, 13, 17, 20, 24 (patch removed), 24.5, 25, 27; trough levels days 6 and 7; Day 8: 0, 1, 2, 3, 4, 7, 10, 13, 17, 20, 24 (patch removed), 24.5, 25, 27.

Treatments C and D: 0, 1, 2, 3, 4, 7, 10, 13, 17, 20, 24 (patch removed), 24.5, 25, 27.

Serum testosterone, free testosterone, dihydrotestosterone and estradiol concentrations were measured using

Pharmacokinetic Analysis:

Non-compartmental analysis was performed on testosterone serum concentrations to estimate C_{max}, C_{avg}, T_{max}, C_{min}, T_{min}, AUC_{0-24}, AUC_{0-27} and apparent $t_{1/2}$.

Testosterone AUC values were determined by the linear trapezoidal method. According to the sponsor, the change in AUC_{0-27} testosterone values was calculated as the difference between the values at baseline and after active treatments. The average concentration (C_{avg}) was defined by $AUC_{0-24}/24$. The terminal half-life ($t_{1/2}$) was calculated using 0.693/k; k, which is the elimination rate constant, was estimated using linear regression of the log (natural) transformed, baseline corrected testosterone serum levels during the log linear terminal phase after system removal.

The accumulation index was determined for the upper buttocks application by taking the ratio of the AUC_{0-24} for the fifth dose to the AUC_{0-24} of the first dose.

Free testosterone, DHT, and estradiol concentrations were calculated and compared to normal ranges.

Statistical Analysis:

Single dose pharmacokinetic parameters (AUC_{0-27}, C_{max}) were examined using analysis of variance (ANOVA) of log transformed serum concentrations of testosterone. The variance model included sequence, patient within sequence, treatment times sequence, and treatment effect. For each paired treatment comparison, the 90% confidence interval of the mean ratio was constructed using the residual error from the ANOVA model.

Results:

Table VII. Summary of pharmacokinetic parameters for serum testosterone concentrations after a single dose application (Day 1) of Testoderm®-II to different body sites.

Parameter	Baseline	Upper Buttocks	Upper Arm	Back
C_{max} (ng/dL)	229	482	462	499
$^{*}T_{max}$ (hr)	4.0	3.9	4.0	3.9
C_{min} (ng/dL)	129	164	135	156
$^{*}T_{min}$ (hr)	17.0	0.0	0.0	0.0
k (hr^{-1})	N/A	0.52	0.52	0.57
AUC_{0-27} (ng.hr/dL)	4,752	9,560	8,651	8,988
C_{avg}	176	N/A	N/A	N/A
Δ AUC_{0-27} (ng.hr/dL)	Ref.	4,808	3,899	4,236

* Median value
Δ Difference from baseline

Table VIII. Comparison of pharmacokinetic parameters for serum testosterone on Day 1 and Day 5 following application of Testoderm® II to Upper Buttocks.

Parameters	Day 1	Day 5
C_{max} (ng/dL)	482	473
$^{*}T_{max}$ (hr)	3.9	3.0
C_{min} (ng/dL)	164	189
$^{*}T_{min}$ (hr)	0.0	0.0
k (hr^{-1})	0.52	0.46
$t_{1/2}$ (hr)	3.3	2.3
AUC_{0-27} (ng.hr/dL)	9560	8578
AUC_{0-24} (ng.hr/dL)	8712	7921
Δ AUC_{0-27} (ng.hr/dL)	4808	3826
Δ AUC_{0-24} (ng.hr/dL)	4488	3697
C_{avg} (ng/dL)	N/A	330
Δ C_{avg} (ng/dL)	N/A	154

* Median values
Δ Difference from baseline

Table IX. Statistical analysis of pharmacokinetic parameters for (natural) log transformed serum testosterone following administration of Testoderm® II to three different body sites.

Parameter	Contrast	Ratio (%)	p Value	Power	Lower (90% C.I)	Upper (90% C.I)
AUC_{0-27} (ng.hr/dL)	Arm/Buttocks	87.8	0.067	88.8		
	Back/Buttocks	89.9	0.127	88.8		
	Arm/Back	97.7	0.723	88.8		
C_{max} (ng/dL)	Arm/Buttocks	94.9	0.512	76.6		
	Back/Buttocks	100.5	0.947	76.6		
	Arm/Back	94.4	0.472	76.6		
T_{max} (hr)	Arm/Buttocks	117.9	0.642	9.2		
	Back/Buttocks	71.5	0.350	9.2		
	Arm/Back	164.8	0.171	9.2		
ΔAUC (ng.hr/dL)	Arm/Buttocks	82.0	0.401	14.8		
	Back/Buttocks	83.6	0.473	13.6		
	Arm/Back	98.1	0.939	13.6		

Adhesion scores were 75-90% or better for the wide majority of the patients. Tape was applied sparingly.

Reviewer Comments:

1. The study design was adequate to compare the pharmacokinetics of testosterone following application of Testoderm-II to the arm, back and upper buttocks.

2. Bioequivalence was demonstrated for Back/Buttocks and Arm/Back; Arm/Buttocks failed in terms of extent of absorption, but passed on rate of absorption between the two sites. The reviewing medical officer, Dr. Mark Hirsch, however, judged the difference in the extent of absorption between the Arm and Buttocks, not clinically significant.

3. Comparison of AUC_{0-24} on Day 1 and Day 5 after daily application of Testoderm II patches to the Upper Buttocks showed that there was no accumulation of testosterone with repeat (daily) dosing.

4. Following an audit by the Division of Scientific Investigations, it was recommended that data from Subject should not be used for calculating pharmacokinetic parameters. It was discovered that Subject violated the inclusion criteria because his last testosterone injection occurred four weeks prior to the start of the study instead of the required six weeks. Recalculation of the mean AUC's for the Arm treatment showed that including or excluding data from Subject did not

have a statistically significant effect on the mean AUC. Therefore, it was decided to utilize the data generated for this subject.

5. The Office of Scientific Investigations also recommended against using free testosterone, estradiol and dihydrotestosterone (DHT) levels generated by this study for pharmacokinetic analysis because of improper sample handling and assay procedures. The free testosterone, estradiol and DHT levels, however, were adequate for diagnostic or efficacy evaluations.

Study No. : C-96-048

Study Title:
Pharmacokinetics of Testosterone from Elevated Release-Rate Testoderm®-II

Objectives:

- To describe the steady-state serum testosterone pharmacokinetic parameters of an elevated release-rate Testoderm®-II system

- To assess topical effects after a 24-hour application

Study Design:

This was an open-label, multiple dose study lasting four days. Eight male hypogonadal patients were enrolled in this study. Each patient applied a Testoderm-II system, which had an elevated *in vitro* release rate, to the upper buttocks, upper arm, or upper back each morning of the study days. Blood samples were obtained on day 4 to determine steady state pharmacokinetics of testosterone.

Results:

Table X. Summary of pharmacokinetic parameters for serum testosterone concentrations at steady state following application of accelerated release-rate Testoderm-II systems.

Parameters	
C_{max} (ng/dL)	452
*T_{max} (hr)	10.2
C_{min} (ng/dL)	262
*T_{min} (hr)	2.6
C_{avg} (ng/dL)	331
AUC_{0-24} (ng.hr/dL)	7933

*Median value

Reviewer Comments:

1. Study design was acceptable to meet the goal of the study, namely to characterize the pharmacokinetics of the accelerated release patch in eight subjects.

2. The sponsor used the results of this study to justify a two-year shelf life for Testoderm-II, suggesting there was no difference in the pharmacokinetic parameters

obtained using the fast release patch and freshly produced patches with slower *in vitro* release rates. Freshly produced patches were used in study C-95-044.

3. Examination of individual testosterone levels versus time profiles showed that five of the eight patients had levels lower than or borderline with the normal lower limit of testosterone. This suggested a lower bioavailability for the accelerated release patches.

4. Bioequivalence testing of C_{max} and AUC values for studies C-96-048 and C-95-044 showed the two patches to be bioinequivalent. It should be noted that the former study (C-96-048, eight patients) is not powered for bioequivalence testing, but the results still confirmed the tendency for lower bioavailability in the fast release patches.

5. It was concluded that due to the small sample size in study C-96-048 and the possibility for lower bioavailability, the results of this study do not support a two-year shelf life. In a teleconference on November 21, 1997, the sponsor agreed to perform an adequate bioequivalent study, as a Phase IV commitment, to support a two-year shelf life.